Remington's Pharmaceutical Sciences

Eighteenth Edition

Jeanne Forehand

Table of Metric Doses with Approximate Apothecary Equivalents

These ***approximate*** dose equivalents represent the quantities usually prescribed, under identical conditions, by physicians using, respectively, the metric system and the apothecary system of weights and measures. Statements of quantity or strength in the labeling of drug products, when expressed in the metric and apothecary systems, shall utilize ***exact*** equivalents.

When prepared dosage forms such as tablets, capsules, etc, are prescribed in the metric system, the pharmacist may dispense the corresponding ***approximate*** equivalent in the apothecary system and vice versa, as indicated in the following table.

For the conversion of specific quantities in converting pharmaceutical formulas, use the ***exact*** equivalents (see pages 75 and 76). For prescription compounding, use the exact equivalents rounded to three significant figures.

Liquid Measure

Metric	Approximate Apothecary Equivalents	Metric	Approximate Apothecary Equivalents	Metric	Approximate Apothecary Equivalents
1000 mL	1 quart	10 mL	2½ fluid drams	0.5 mL	8 minims
750 mL	1½ pints	8 mL	2 fluid drams	0.3 mL	5 minims
500 mL	1 pint	5 mL	1¼ fluid drams	0.25 mL	4 minims
250 mL	8 fluid ounces	4 mL	1 fluid dram	0.2 mL	3 minims
200 mL	7 fluid ounces	3 mL	45 minims	0.1 mL	1½ minims
100 mL	3½ fluid ounces	2 mL	30 minims	0.06 mL	1 minim
50 mL	1¾ fluid ounces	1 mL	15 minims	0.05 mL	¾ minim
30 mL	1 fluid ounce	0.75 mL	12 minims	0.03 mL	½ minim
15 mL	4 fluid drams	0.6 mL	10 minims		

Weight

Metric	Approximate Apothecary Equivalents	Metric	Approximate Apothecary Equivalents	Metric	Approximate Apothecary Equivalents
30 g	1 ounce	200 mg	3 grains	4 mg	1/15 grain
15 g	4 drams	150 mg	2½ grains	3 mg	1/20 grain
10 g	2½ drams	125 mg	2 grains	2 mg	1/30 grain
7.5 g	2 drams	100 mg	1½ grains	1.5 mg	1/40 grain
6 g	90 grains	75 mg	1¼ grains	1.2 mg	1/50 grain
5 g	75 grains	60 mg	1 grain	1 mg	1/60 grain
4 g	60 grains (1 dram)	50 mg	¾ grain	800 μg	1/80 grain
3 g	45 grains	40 mg	⅔ grain	600 μg	1/100 grain
2 g	30 grains (½ dram)	30 mg	½ grain	500 μg	1/120 grain
1.5 g	22 grains	25 mg	⅜ grain	400 μg	1/150 grain
1 g	15 grains	20 mg	⅓ grain	300 μg	1/200 grain
750 mg	12 grains	15 mg	¼ grain	250 μg	1/250 grain
600 mg	10 grains	12 mg	⅕ grain	200 μg	1/300 grain
500 mg	7½ grains	10 mg	⅙ grain	150 μg	1/400 grain
400 mg	6 grains	8 mg	⅛ grain	120 μg	1/500 grain
300 mg	5 grains	6 mg	1/10 grain	100 μg	1/600 grain
250 mg	4 grains	5 mg	1/12 grain		

NOTE: A milliliter (mL) is the approximate equivalent of a cubic centimeter (cc).

Table of Logarithms

Natural Numbers	0	1	2	3	4	5	6	7	8	9	Proportional Parts 1	2	3	4	5	6	7	8	9
10	0000	0043	0086	0128	0170	0212	0253	0294	0334	0374	4	8	12	17	21	25	29	33	37
11	0414	0453	0492	0531	0569	0607	0645	0682	0719	0755	4	8	11	15	19	23	26	30	34
12	0792	0828	0864	0899	0934	0969	1004	1038	1072	1106	3	7	10	14	17	21	24	28	31
13	1139	1173	1206	1239	1271	1303	1335	1367	1399	1430	3	6	10	13	16	19	23	26	29
14	1461	1492	1523	1553	1584	1614	1644	1673	1703	1732	3	6	9	12	15	18	21	24	27
15	1761	1790	1818	1847	1875	1903	1931	1959	1987	2014	3	6	8	11	14	17	20	22	25
16	2041	2068	2095	2122	2148	2175	2201	2227	2253	2279	3	5	8	11	13	16	18	21	24
17	2304	2330	2355	2380	2405	2430	2455	2480	2504	2529	2	5	7	10	12	15	17	20	22
18	2553	2577	2601	2625	2648	2672	2695	2718	2742	2765	2	5	7	9	12	14	16	19	21
19	2788	2810	2833	2856	2878	2900	2923	2945	2967	2989	2	4	7	9	11	13	16	18	20
20	3010	3032	3054	3075	3096	3118	3139	3160	3181	3201	2	4	6	8	11	13	15	17	19
21	3222	3243	3263	3284	3304	3324	3345	3365	3385	3404	2	4	6	8	10	12	14	16	18
22	3424	3444	3464	3483	3502	3522	3541	3560	3579	3598	2	4	6	8	10	12	14	15	17
23	3617	3636	3655	3674	3692	3711	3729	3747	3766	3784	2	4	6	7	9	11	13	15	17
24	3802	3820	3838	3856	3874	3892	3909	3927	3945	3962	2	4	5	7	9	11	12	14	16
25	3979	3997	4014	4031	4048	4065	4082	4099	4116	4133	2	3	5	7	9	10	12	14	15
26	4150	4166	4183	4200	4216	4232	4249	4265	4281	4298	2	3	5	7	8	10	11	13	15
27	4314	4330	4346	4362	4378	4393	4409	4425	4440	4456	2	3	5	6	8	9	11	13	14
28	4472	4487	4502	4518	4533	4548	4564	4579	4594	4609	2	3	5	6	8	9	11	12	14
29	4624	4639	4654	4669	4683	4698	4713	4728	4742	4757	1	3	4	6	7	9	10	12	13
30	4771	4786	4800	4814	4829	4843	4857	4871	4886	4900	1	3	4	6	7	9	10	11	13
31	4914	4928	4942	4955	4969	4983	4997	5011	5024	5038	1	3	4	6	7	8	10	11	12
32	5051	5065	5079	5092	5105	5119	5132	5145	5159	5172	1	3	4	5	7	8	9	11	12
33	5185	5198	5211	5224	5237	5250	5263	5276	5289	5302	1	3	4	5	6	8	9	10	12
34	5315	5328	5340	5353	5366	5378	5391	5403	5416	5428	1	3	4	5	6	8	9	10	11
35	5441	5453	5465	5478	5490	5502	5514	5527	5539	5551	1	2	4	5	6	7	9	10	11
36	5563	5575	5587	5599	5611	5623	5635	5647	5658	5670	1	2	4	5	6	7	8	10	11
37	5682	5694	5705	5717	5729	5740	5752	5763	5775	5786	1	2	3	5	6	7	8	9	10
38	5798	5809	5821	5832	5843	5855	5866	5877	5888	5899	1	2	3	5	6	7	8	9	10
39	5911	5922	5933	5944	5955	5966	5977	5988	5999	6010	1	2	3	4	5	7	8	9	10
40	6021	6031	6042	6053	6064	6075	6085	6096	6107	6117	1	2	3	4	5	6	8	9	10
41	6128	6138	6149	6160	6170	6180	6191	6201	6212	6222	1	2	3	4	5	6	7	8	9
42	6232	6243	6253	6263	6274	6284	6294	6304	6314	6325	1	2	3	4	5	6	7	8	9
43	6335	6345	6355	6365	6375	6385	6395	6405	6415	6425	1	2	3	4	5	6	7	8	9
44	6435	6444	6454	6464	6474	6484	6493	6503	6513	6522	1	2	3	4	5	6	7	8	9
45	6532	6542	6551	6561	6571	6580	6590	6599	6609	6618	1	2	3	4	5	6	7	8	9
46	6628	6637	6646	6656	6665	6675	6684	6693	6702	6712	1	2	3	4	5	6	7	7	8
47	6721	6730	6739	6749	6758	6767	6776	6785	6794	6803	1	2	3	4	5	5	6	7	8
48	6812	6821	6830	6839	6848	6857	6866	6875	6884	6893	1	2	3	4	4	5	6	7	8
49	6902	6911	6920	6928	6937	6946	6955	6964	6972	6981	1	2	3	4	4	5	6	7	8
50	6990	6998	7007	7016	7024	7033	7042	7050	7059	7067	1	2	3	3	4	5	6	7	8
51	7076	7084	7093	7101	7110	7118	7126	7135	7143	7152	1	2	3	3	4	5	6	7	8
52	7160	7168	7177	7185	7193	7202	7210	7218	7226	7235	1	2	2	3	4	5	6	7	7
53	7243	7251	7259	7267	7275	7284	7292	7300	7308	7316	1	2	2	3	4	5	6	6	7
54	7324	7332	7340	7348	7356	7364	7372	7380	7388	7396	1	2	2	3	4	5	6	6	7
55	7404	7412	7419	7427	7435	7443	7451	7459	7466	7474	1	2	2	3	4	5	5	6	7
56	7482	7490	7497	7505	7513	7520	7528	7536	7543	7551	1	2	2	3	4	5	5	6	7
57	7559	7566	7574	7582	7589	7597	7604	7612	7619	7627	1	2	2	3	4	5	5	6	7
58	7634	7642	7649	7657	7664	7672	7679	7686	7694	7701	1	1	2	3	4	4	5	6	7
59	7709	7716	7723	7731	7738	7745	7752	7760	7767	7774	1	1	2	3	4	4	5	6	7
60	7782	7789	7796	7803	7810	7818	7825	7832	7839	7846	1	1	2	3	4	4	5	6	6
61	7853	7860	7868	7875	7882	7889	7896	7903	7910	7917	1	1	2	3	4	4	5	6	6
62	7924	7931	7938	7945	7952	7959	7966	7973	7980	7987	1	1	2	3	3	4	5	6	6
63	7993	8000	8007	8014	8021	8028	8035	8041	8048	8055	1	1	2	3	3	4	5	5	6
64	8062	8069	8075	8082	8089	8096	8102	8109	8116	8122	1	1	2	3	3	4	5	5	6
65	8129	8136	8142	8149	8156	8162	8169	8176	8182	8189	1	1	2	3	3	4	5	5	6
66	8195	8202	8209	8215	8222	8228	8235	8241	8248	8254	1	1	2	3	3	4	5	5	6
67	8261	8267	8274	8280	8287	8293	8299	8306	8312	8319	1	1	2	3	3	4	5	5	6
68	8325	8331	8338	8344	8351	8357	8363	8370	8376	8382	1	1	2	3	3	4	4	5	6
69	8388	8395	8401	8407	8414	8420	8426	8432	8439	8445	1	1	2	2	3	4	4	5	6
70	8451	8457	8463	8470	8476	8482	8488	8494	8500	8506	1	1	2	2	3	4	4	5	6
71	8513	8519	8525	8531	8537	8543	8549	8555	8561	8567	1	1	2	2	3	4	4	5	5
72	8573	8579	8585	8591	8597	8603	8609	8615	8621	8627	1	1	2	2	3	4	4	5	5
73	8633	8639	8645	8651	8657	8663	8669	8675	8681	8686	1	1	2	2	3	4	4	5	5
74	8692	8698	8704	8710	8716	8722	8727	8733	8739	8745	1	1	2	2	3	4	4	5	5
75	8751	8756	8762	8768	8774	8779	8785	8791	8797	8802	1	1	2	2	3	3	4	5	6
76	8808	8814	8820	8825	8831	8837	8842	8848	8854	8859	1	1	2	2	3	3	4	5	5
77	8865	8871	8876	8882	8887	8893	8899	8904	8910	8915	1	1	2	2	3	3	4	4	5
78	8921	8927	8932	8938	8943	8949	8954	8960	8965	8971	1	1	2	2	3	3	4	4	5
79	8976	8982	8987	8993	8998	9004	9009	9015	9020	9026	1	1	2	2	3	3	4	4	5
80	9031	9036	9042	9047	9053	9058	9063	9069	9074	9079	1	1	2	2	3	3	4	4	5
81	9085	9090	9096	9101	9106	9112	9117	9122	9128	9133	1	1	2	2	3	3	4	4	5
82	9138	9143	9149	9154	9159	9165	9170	9175	9180	9186	1	1	2	2	3	3	4	4	5
83	9191	9196	9201	9206	9212	9217	9222	9227	9232	9238	1	1	2	2	3	3	4	4	5
84	9243	9248	9253	9258	9263	9269	9274	9279	9284	9289	1	1	2	2	3	3	4	4	5
85	9294	9299	9304	9309	9315	9320	9325	9330	9335	9340	1	1	2	2	3	3	4	4	5
86	9345	9350	9355	9360	9365	9370	9375	9380	9385	9390	1	1	2	2	3	3	4	4	5
87	9395	9400	9405	9410	9415	9420	9425	9430	9435	9440	0	1	1	2	2	3	3	4	4
88	9445	9450	9455	9460	9465	9469	9474	9479	9484	9489	0	1	1	2	2	3	3	4	4
89	9494	9499	9504	9509	9513	9518	9523	9528	9533	9538	0	1	1	2	2	3	3	4	4
90	9542	9547	9552	9557	9562	9566	9571	9576	9581	9586	0	1	1	2	2	3	3	4	4
91	9590	9595	9600	9605	9609	9614	9619	9624	9628	9633	0	1	1	2	2	3	3	4	4
92	9638	9643	9647	9652	9657	9661	9666	9671	9675	9680	0	1	1	2	2	3	3	4	4
93	9685	9689	9694	9699	9703	9708	9713	9717	9722	9727	0	1	1	2	2	3	3	4	4
94	9731	9736	9741	9745	9750	9754	9759	9763	9768	9773	0	1	1	2	2	3	3	4	4
95	9777	9782	9786	9791	9795	9800	9805	9809	9814	9818	0	1	1	2	2	3	3	4	4
96	9823	9827	9832	9836	9841	9845	9850	9854	9859	9863	0	1	1	2	2	3	3	4	4
97	9868	9872	9877	9881	9886	9890	9894	9899	9903	9908	0	1	1	2	2	3	3	4	4
98	9912	9917	9921	9926	9930	9934	9939	9943	9948	9952	0	1	1	2	2	3	3	4	4
99	9956	9961	9965	9969	9974	9978	9983	9987	9991	9996	0	1	1	2	2	3	3	3	4

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18

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Preface to the First Edition

The rapid and substantial progress made in Pharmacy within the last decade has created a necessity for a work treating of the improved apparatus, the revised processes, and the recently introduced preparations of the age.

The vast advances made in theoretical and applied chemistry and physics have much to do with the development of pharmaceutical science, and these have been reflected in all the revised editions of the Pharmacopoeias which have been recently published. When the author was elected in 1874 to the chair of Theory and Practice of Pharmacy in the Philadelphia College of Pharmacy, the outlines of study which had been so carefully prepared for the classes by his eminent predecessors, Professor William Procter, Jr, and Professor Edward Parrish, were found to be not strictly in accord, either in their arrangement of the subjects or in their method of treatment. Desiring to preserve the distinctive characteristics of each, an effort was at once made to frame a system which should embody their valuable features, embrace new subjects, and still retain that harmony of plan and proper sequence which are absolutely essential to the success of any system.

The strictly alphabetical classification of subjects which is now universally adopted by pharmacopoeias and dispensatories, although admirable in works of reference, presents an effectual stumbling block to the acquisition of pharmaceutical knowledge through systematic study; the vast accumulation of facts collected under each head being arranged lexically, they necessarily have no connection with one another, and thus the saving of labor effected by considering similar groups together, and the value of the association of kindred subjects, are lost to the student. In the method of grouping the subjects which is herein adopted, the constant aim has been to arrange the latter in such a manner that the reader shall be gradually led from the consideration of elementary subjects to those which involve more advanced knowledge, whilst the groups themselves are so placed as to follow one another in a natural sequence.

The work is divided into six parts. Part I is devoted to detailed descriptions of apparatus and definitions and comments on general pharmaceutical processes.

The Official Preparations alone are considered in Part II. Due weight and prominence are thus given to the Pharmacopoeia, the National authority, which is now so thoroughly recognized.

In order to suit the convenience of pharmacists who prefer to *weigh solids* and *measure liquids*, the official formulas are expressed, in addition to parts by weight, in *avoirdupois weight* and *apothecaries' measure*. These equivalents are printed in *bold type* near the margin, and arranged so as to fit them for quick and accurate reference.

Part III treats of Inorganic Chemical Substances. Precedence is of course given to official preparation in these. The descriptions, solubilities, and tests for identity and impurities of each substance are systematically tabulated under its proper title. It is confidently believed that by this method of arrangement the valuable descriptive features of the Pharmacopoeia will be more prominently developed, ready reference facilitated, and close study of the details rendered easy. Each chemical operation is accompanied by equations, whilst the reaction is, in addition, explained in words.

The Carbon Compounds, or Organic Chemical Substances, are considered in Part IV. These are naturally grouped according to the physical and medical properties of their principal constituents, beginning with simple bodies like cellulin, gum, etc, and progressing to the most highly organized alkaloids, etc.

Part V is devoted to Extemporaneous Pharmacy. Care has been taken to treat of the practice which would be best adapted for the needs of the many pharmacists who conduct operations upon a moderate scale, rather than for those of the few who manage very large establishments. In this, as well as in other parts of the work, operations are illustrated which are conducted by manufacturing pharmacists.

Part VI contains a formulary of Pharmaceutical Preparations which have not been recognized by the Pharmacopoeia. The recipes selected are chiefly those which have been heretofore rather difficult of access to most pharmacists, yet such as are likely to be in request. Many private formulas are embraced in the collection; and such of the preparations of the old Pharmacopoeias as have not been included in the new edition, but are still in use, have been inserted.

In conclusion, the author ventures to express the hope that the work will prove an efficient help to the pharmaceutical student as well as to the pharmacist and the physician. Although the labor has been mainly performed amidst the harassing cares of active professional duties, and perfection is known to be unattainable, no pains have been spared to discover and correct errors and omissions in the text. The author's warmest acknowledgments, are tendered to Mr A B Taylor, Mr Joseph McCreery, and Mr George M Smith for their valuable assistance in revising the proof sheets, and to the latter especially for his work on the index. The outline illustrations, by Mr John Collins, were drawn either from the actual objects or from photographs taken by the author.

Philadelphia, October, 1885 JPR.

Preface to the Eighteenth Edition

In anticipation of setting forth this *Preface* and prior to gathering thoughts on paper (or more accurately, the word processor!), this Editor paused to reread the preface to the first edition of *Remington*, published in 1885. Since it appears on the preceding page of this book it is recommended highly. The first paragraph would be just as suitable today as penned by Professor Remington 105 years ago.

Each decade transcends the previous one and the pharmaceutical and health sciences are not laggards. Every revision of *Remington* has encompassed new viewpoints, ideas, doctrines or principles which, perhaps, were inconceivable for the previous edition. It is a tribute to the authors and editors that they have kept abreast of the burgeoning literature in their respective fields of expertise.

Change not withstanding, the organization of this edition is similar to its immediate predecessors, being divided into 9 Parts, each subdivided into several chapters. Every chapter has been culled, revised and rewritten to update the material presented.

Two new chapters are evident; *Biotechnology and Drugs* (Chapter 74) and *Drug Education* (Chapter 99). Three chapters of the previous edition, which embraced *Interfacial and Particle Phenomena* and *Colloidal and Coarse Dispersions* have been winnowed and combined into a single chapter entitled, *Disperse Systems* (Chapter 19).

The current revision contains an additional 21 pages. A large amount of space (about 19 pages) gleaned from the review and condensation process, coupled with the extra pages, have been devoted primarily to expanding the contents of Part 6, *Pharmaceutical and Medicinal Agents* and Part 9, *Pharmaceutical Practice.*

Excessive duplication of text is the bane of any editor dealing with a multitude of authors. While some duplication in the discussion of rudimentary concepts is beneficial, there has been a special effort to cross-reference and eliminate unnecessary repetition. Space is at such a premium that it is hoped the reader will not be offended by being diverted to a different section of the text in order to obtain supplementary information.

Photographs which depicted the typical "black box" have been eliminated almost completely and replaced by line drawings or schematic diagrams which are instructive rather than picturesque.

Most of the drug monographs have been revamped not only as a means of updating, but to gain a degree of uniformity. All structural formulas are now in the standard *USAN* form. Duplication of chemical names has been minimized and the inclusion of trade names increased. No attempt has been made to ferret out every trade name by which a product is known, and only the most common are mentioned. The standard format for the major monographs is: Official Name, chemical name (*CAS*—inverted), trade name(s) and manufacturer(s), structural formula, *CAS* (*Chemical Abstracts System*) registry number (in brackets), molecular formula and formula weight (in parenthesis). This is followed by the method of preparation (or a reference if the method is lengthy), physical description, solubility, uses, dose and dosage forms.

The number of authors remains at 97, however, 36 new authors have joined as contributors to *Remington.* As the credentials of the new authors touch upon many areas of pharmacy, every section of the book has been invigorated by the incorporation of updated and fresh concepts.

As one primarily responsible for the production of a comprehensive text devoted to the science and practice of pharmacy, the wisdom of Dr Eric Martin, editor of the 13th Edition, in creating an Editorial Board to share the enormous burden, has been evident constantly. Each of the section editors labored diligently to comply with the logistics of maintaining a smooth flow of manuscripts and proofs. Also, each section editor doubled as an author or coauthor of one or more chapters. It would be remiss not to extend special mention to this group of dedicated people.

Four members of the Editorial Board are serving for the first time after having been authors for several editions. Dr Ara DerMarderosian of PCP&S, Editor for Part 1; Dr Daniel Hussar, also of PCP&S, Part 9; Dr Edward Rippie of the University of Minnesota, Part 2; and Dr Joseph Schwartz of PCP&S, Part 8. Each of the new members literally "jumped into the fray," gave much of their precious time and have become "blooded" members of the staff.

The stalwarts of the Editorial Board surviving the tribulations of one or more previous editions of this work demand singular attention. Dr Grafton Chase of PCP&S for Part 5, *Radioisotopes in Pharmacy & Medicine*; Dr Thomas Medwick of Rutgers University for Part 3, *Pharmaceutical Chemistry* and Part 4, *Testing and Analysis*; and Dr Gilbert Zink of PCP&S for Part 7, *Biological Products.*

Two dauntless, prolific contributors claim special recognition. Drs Stewart Harvey and Ewart Swinyard, both of the University of Utah, have served on the Editorial Board for twenty and twenty-five years respectively. They bear the burden of Part 6, *Pharmaceutical & Medicinal Agents*, which comprises over one-third of the book. Their diligence and meticulous attention to detail has eased the task of this Editor. Our relationship over the past several decades has been one of exceptional pleasure.

The Mack Publishing Company, through Messers Paul Mack and David Palmer, continues its unrelenting support, which has endured through many, many editions of this publication. Special commendation must be extended to Ms Nancy Smolock, of the Mack organization, as she was the person who interfaced with the Editorial Board. She was competent, cooperative and much too tolerant of the many requests made of her.

As with any publication a few of the editorial staff bear the brunt of the unglamorous, but absolutely essential, chores associated with the production of this voluminous tome. It mandates a close working relationship and, at times, restraint and concession to sustain the harmony necessary to function efficiently. One often encounters the aphorism usually attributed to administrators, "When three managers meet to discuss a problem there arise four points-of-view." Fortunately, this dilemma did not surface in the association of this Editor with Mr John Hoover and Ms Bonnie Packer.

After shepherding this publication through four editions, the Twelfth to Fifteenth, following a short hiatus for the Sixteenth, Mr Hoover returned in a lesser capacity with the Seventeenth revision. With the current edition he reassumes the role of Managing Editor and his experience in pharmacy, journalism and the publishing business, have provided the capabilities needed to translate a disarranged manuscript into a format acceptable by the publisher and pleasing to the reader.

Ms Packer accepted the assignment of scrutinizing every word of text in the proof stages. Combining her skills in the

health and social sciences, she assumed the charge of reading primarily for comprehension and clarity of presentation, while concurrently uncovering typographical, spelling and grammatical errors which, although unpardonable, are ever-present. As a consequence of her deliberations, passages were often rephrased and refined to portray a concept from the viewpoint of the student, for whom this work primarily is directed.

The *Index* was developed by Mr Hoover, with the assistance of Ms Packer. Much use was made of the computer in ensuring that a complete, practical and useful index was created. It is the opinion of this Editor that a major weakness encountered in most reference books is a perfunctory, casual index which amounts to little more than an expanded table of contents. Users of the index of this book will find it "friendly."

Philadelphia, February, 1990 ARG

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CHAPTER 19

Disperse Systems

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Interfacial Phenomena

Very often it is desirable or necessary in the development of pharmaceutical dosage forms to produce multiphasic dispersions by mixing together two or more ingredients which are not mutually miscible and capable of forming homogeneous solutions. Examples of such dispersions include suspensions (solid in liquid), emulsions (liquid in liquid) and foams (vapor in liquids). Because these systems are not homogeneous and thermodynamically stable, over time they will show some tendency to separate on standing to produce the minimum possible surface area of contact between phases. Thus, suspended particles agglomerate and sediment, emulsified droplets cream and coalesce and the bubbles dispersed in foams collapse, to produce unstable and nonuniform dosage forms. In this chapter the fundamental physical chemical properties of dispersed systems will be discussed, along with the principles of interfacial and colloidal physics and chemistry which underly these properties.

Interfacial Forces and Energetics

In the bulk portion of each phase, molecules are attracted to each other equally in all directions, such that no resultant forces are acting on any one molecule. The strength of these forces determines whether a substance exists as a vapor, liquid or solid at a particular temperature and pressure.

At the boundary between phases, however, molecules are acted upon unequally since they are in contact with other molecules exhibiting different forces of attraction. For example, the primary intermolecular forces in water are due to hydrogen bonds, whereas those responsible for intermolecular bonding in hydrocarbon liquids, such as mineral oil, are due to London dispersion forces.

Because of this, molecules situated at the interface contain potential forces of interaction which are not satisfied relative to the situation in each bulk phase. In liquid systems such unbalanced forces can be satisfied by spontaneous movement of molecules from the interface into the bulk phase. This leaves fewer molecules per unit area at the interface (greater intermolecular distance) and reduces the actual contact area between dissimilar molecules.

Any attempt to reverse this process by increasing the area of contact between phases, ie, bringing more molecules into the interface, causes the interface to resist expansion and to behave as though it is under a tension everywhere in a tangential direction. The force of this tension per unit length of interface generally is called the interfacial tension, except when dealing with the air–liquid interface, where the terms surface and surface tension are used.

To illustrate the presence of a tension in the interface, consider an experiment where a circular metal frame, with a looped piece of thread loosely tied to it, is dipped into a liquid. When removed and exposed to the air, a film of liquid will be stretched entirely across the circular frame, as when one uses such a frame to blow soap bubbles. Under these conditions (Fig 19-1*A*), the thread will remain collapsed. If now a heated needle is used to puncture and remove the liquid film from within the loop (Fig 19-1*B*), the loop will stretch spontaneously into a circular shape.

The result of this experiment demonstrates the spontaneous reduction of interfacial contact between air and the liquid remaining and, indeed, that a tension causing the loop to remain extended exists parallel to the interface. The circular shape of the loop indicates that the tension in the plane of the interface exists at right angles or normal to every part of the looped thread. The total force on the entire loop divided by the circumference of the circle, therefore, represents the tension per unit distance of surface, or the surface tension.

Just as work is required to extend a spring under tension, work should be required to reverse the process seen in Figs 19-1*A* and *B*, thus bringing more molecules to the interface. This may be seen quantitatively by considering an experiment where tension and work may be measured directly. Assume that we have a rectangular wire with one movable side (Fig 19-2). Assume further that by dipping this wire into a liquid, a film of liquid will form within the frame when it is removed and exposed to the air. As seen earlier in Fig 19-1, since it comes in contact with air, the liquid surface will tend to contract with a force, F, as molecules leave the surface for the bulk. To keep the movable side in equilibrium, an equal force must be applied to oppose this tension in the surface. We then may define the surface tension, γ, of the liquid as $F/2l$, where $2l$ is the distance of surface over which F is operating ($2l$ since there are two surfaces, top and bottom). If the surface is expanded by a very small distance, Δx, one can then estimate that the work done is

$$W = F\Delta x \tag{1}$$

and therefore

$$W = \gamma 2l\Delta x \tag{2}$$

Dr Zografi authored the section on *Interfacial Phenomena*. *Dr Schott* authored the section on Colloidal Dispersions. *Dr Swarbrick* authored the section on Particle Phenomena and Coarse Dispersions.

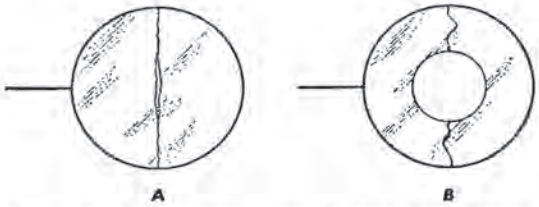


Fig 19-1. A circular wire frame with a loop of thread loosely tied to it: (*A*) a liquid film on the wire frame with a loop in it; (*B*) the film inside the loop is broken.[1]

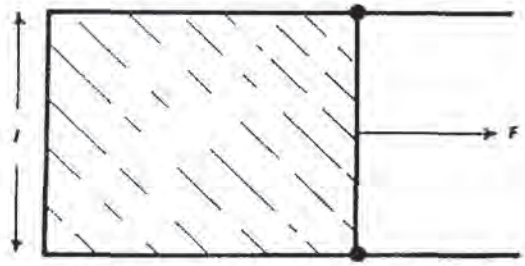


Fig 19-2. A movable wire frame containing a film of liquid being expanded with a force, *F*.

Since

$$\Delta A = 2l\Delta x \qquad (3)$$

where ΔA is the change in area due to the expansion of the surface, we may conclude that

$$W = \gamma\Delta A \qquad (4)$$

Thus, the work required to create a unit area of surface, known as the surface free energy/unit area, is equivalent to the surface tension of a liquid system, and the greater the area of interfacial contact between phases, the greater the free-energy increase for the total system. Since a prime requisite for equilibrium is that the free energy of a system be at a minimum, it is not surprising to observe that phases in contact tend to reduce area of contact spontaneously.

Liquids, being mobile, may assume spherical shapes (smallest interfacial area for a given volume), as when ejected from an orifice into air or when dispersed into another immiscible liquid. If a large number of drops are formed, further reduction in area can occur by having the drops coalesce, as when a foam collapses or when the liquid phases making up an emulsion separate.

Surface tension is expressed in units of dynes/cm, while surface free energy is expressed in ergs/cm^2. Since an erg is a dyne-cm, both sets of units are equivalent.

Values for the surface tension of a variety of liquids are given in Table I, while interfacial tension values for various liquids against water are given in Table II. Other combinations of immiscible phases could be given but most heterogeneous systems encountered in pharmacy usually contain water. Values for these tensions are expressed for a particular temperature. Since an increased temperature increases the thermal energy of molecules, the work required to bring molecules to the interface should be less, and thus the surface and interfacial tension will be reduced. For example, the surface tension of water at 0° is 76.5 dynes/cm and 63.5 dynes/cm at 75°.

As would be expected from the discussion so far, the relative values for surface tension should reflect the nature of intermolecular forces present; hence, the relatively large values for mercury (metallic bonds) and water (hydrogen bonds), and the lower values for benzene, chloroform, carbon tetrachloride and the *n*-alkanes. Benzene with π electrons exhibits a higher surface tension than the alkanes of comparable molecular weight, but increasing the molecular weight of the alkanes (and hence intermolecular attraction) increases their surface tension closer to that of benzene. The lower values for the more nonpolar substances, perfluoroheptane and liquid nitrogen, demonstrate this point even more strongly.

Table I—Surface Tension of Various Liquids at 20°

Substance	Surface tension, dynes/cm
Mercury	476
Water	72.8
Glycerin	63.4
Oleic acid	32.5
Benzene	28.9
Chloroform	27.1
Carbon tetrachloride	26.8
1-Octanol	26.5
Hexadecane	27.4
Dodecane	25.4
Decane	23.9
Octane	21.8
Heptane	19.7
Hexane	18.0
Perfluoroheptane	11.0
Nitrogen (at 75°K)	9.4

Table II—Interfacial Tension of Various Liquids against Water at 20°

Substance	Interfacial tension, dynes/cm
Decane	52.3
Octane	51.7
Hexane	50.8
Carbon tetrachloride	45.0
Chloroform	32.8
Benzene	35.0
Mercury	428
Oleic acid	15.6
1-Octanol	8.51

Values of interfacial tension should reflect the differences in chemical structure of the two phases involved; the greater the tendency to interact, the less the interfacial tension. The 20-dynes/cm difference between air–water tension and that at the octane–water interface reflects the small but significant interaction between octane molecules and water molecules at the interface. This is seen also in Table II, by comparing values for octane and octanol, oleic acid and the alkanes, or chloroform and carbon tetrachloride.

In each case the presence of chemical groups capable of hydrogen bonding with water markedly reduces the interfacial tension, presumably by satisfying the unbalanced forces at the interface. These observations strongly suggest that molecules at an interface arrange themselves or orient so as to minimize differences between bulk phases.

That this occurs even at the air–liquid interface is seen when one notes the relatively low surface-tension values of very different chemical structures such as the *n*-alkanes, octanol, oleic acid, benzene and chloroform. Presumably, in each case, the similar nonpolar groups are oriented toward the air with any polar groups oriented away toward the bulk phase. This tendency for molecules to orient at an interface is a basic factor in interfacial phenomena and will be discussed more fully in succeeding sections.

Solid substances such as metals, metal oxides, silicates and salts, all containing polar groups exposed at their surface, may be classified as high-energy solids, whereas nonpo-

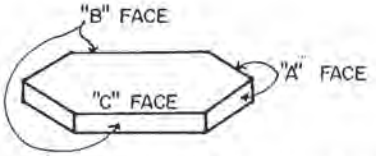


Fig 19-3. Adipic acid crystal showing various faces.[2]

Table III—Values of γ_{sv} for Solids of Varying Polarity

Solid	γ_{sv} (dynes/cm)
Teflon	19.0
Paraffin	25.5
Polyethylene	37.6
Polymethyl methacrylate	45.4
Nylon	50.8
Indomethacin	61.8
Griseofulvin	62.2
Hydrocortisone	68.7
Sodium Chloride	155
Copper	1300

lar solids such as carbon, sulfur, glyceryl tristearate, polyethylene and polytetrafluoroethylene (Teflon) may be classified as low-energy solids. It is of interest to measure the surface free energy of solids; however, the lack of mobility of molecules at the surface of solids prevents the observation and direct measurement of a surface tension. It is possible to measure the work required to create new solid surface by cleaving a crystal and measuring the work involved. However, this work not only represents free energy due to exposed groups but also takes into account the mechanical energy associated with the crystal (ie, plastic and elastic deformation and strain energies due to crystal structure and imperfections in that structure).

Also contributing to the complexity of a solid surface is the heterogeneous behavior due to the exposure of different crystal faces, each having a different surface free energy/unit area. For example, adipic acid, $HOOC(CH_2)_4COOH$, crystallizes from water as thin hexagonal plates with three different faces, as shown in Fig 19-3. Each unit cell of such a crystal contains adipic acid molecules oriented such that the hexagonal planes (faces) contain exposed carboxyl groups, while the sides and edges (A and B faces) represent the side view of the carboxyl and alkyl groups, and thus are quite nonpolar. Indeed, interactions involving these different faces reflect the differing surface free energies.[2]

Other complexities associated with solid surfaces include surface roughness, porosity and the defects and contamination produced during a recrystallization or comminution of the solid. In view of all these complications, surface free energy values for solids, when reported, should be regarded as average values, often dependent on the method used and not necessarily the same for other samples of the same substance.

In Table III are listed some approximate average values of γ_{sv} for a variety of solids, ranging in polarity from Teflon to copper, obtained by various indirect techniques.

Adhesional and Cohesional Forces

Of prime importance to those dealing with heterogeneous systems is the question of how two phases will behave when brought in contact with each other. It is well known, for instance, that some liquids, when placed in contact with other liquid or solid surfaces, will remain retracted in the form of a drop (known as a lens), while other liquids may exhibit a tendency to spread and cover the surface of this liquid or solid.

Based upon concepts developed to this point, it is apparent that the individual phases will exhibit a tendency to minimize the area of contact with other phases, thus leading to phase separation. On the other hand, the tendency for interaction between molecules at the new interface will offset this to some extent and give rise to the spontaneous spreading of one substance over the other.

In essence, therefore, phase affinity is increased as the forces of attraction between different phases (adhesional forces) become greater than the forces of attraction between molecules of the same phase (cohesional forces). If these adhesional forces become great enough, miscibility will occur and the interface will disappear. The present discussion is concerned only with systems of limited phase affinity, where an interface still exists.

A convenient approach used to express these forces quantitatively involves the use of the terms work of adhesion and work of cohesion.

The work of adhesion, W_a, is defined as the energy per cm^2 required to separate two phases at their boundary and is equal but opposite in sign to the free energy/cm^2 released when the interface is formed. In an analogous manner the work of cohesion for a pure substance, W_c, is the work/cm^2 required to produce two new surfaces, as when separating different phases, but now both surfaces contain the same molecules. This is equal and opposite in sign to the free energy/cm^2 released when the same two pure liquid surfaces are brought together and eliminated.

By convention, when the work of adhesion between two substances, A and B, exceeds the work of cohesion for one substance, eg, B, spontaneous spreading of B over the surface of A should occur with a net loss of free energy equal to the difference between W_a and W_c. If W_c exceeds W_a, no spontaneous spreading of B over A can occur. The difference between W_a and W_c is known as the spreading coefficient, S; only when S is positive will spreading occur.

The values for W_a and W_c (and hence S) may be expressed in terms of surface and interfacial tensions, when one considers that upon separation of two phases, A and B, γ_{AB} ergs of interfacial free energy/cm^2 (interfacial tension) are lost, but that γ_A and γ_B ergs/cm^2 of energy (surface tensions of A and B) are gained; upon separation of bulk phase molecules in an analogous manner, $2\gamma_A$ or $2\gamma_B$ ergs/cm^2 will be gained. Thus

$$W_a = \gamma_A + \gamma_B - \gamma_{AB} \tag{5}$$

and

$$W_c = 2\gamma_A \text{ or } 2\gamma_B \tag{6}$$

For B spreading on the surface of A, therefore

$$S_B = \gamma_A + \gamma_B - \gamma_{AB} - 2\gamma_B \tag{7}$$

or

$$S_B = \gamma_A - (\gamma_B + \gamma_{AB}) \tag{8}$$

Utilizing Eq 8 and values of surface and interfacial tension given in Tables I and II, S can be calculated for three representative substances—decane, benzene, and oleic acid—on water at 20°.

Decane:	$S = 72.8 - (23.9 + 52.3)$	$= -3.4$
Benzene:	$S = 72.8 - (28.9 + 35.0)$	$= 8.9$
Oleic acid:	$S = 72.8 - (32.5 + 15.6)$	$= 24.7$

As expected, relatively nonpolar substances such as decane exhibit negative values of S, whereas the more polar materials yield positive values; the greater the polarity of the mole-

cule, the more positive the value of S. The importance of the cohesive energy of the spreading liquid may be noted also by comparing the spreading coefficients for hexane on water and water on hexane:

$$S_{H/W} = 72.8 - (18.0 + 50.8) = \quad 4.0$$

$$S_{W/H} = 18.0 - (72.8 + 50.8) = -105.6$$

Here, despite the fact that both liquids are the same, the high cohesion and air–liquid tension of water prevents spreading on the low-energy hexane surface, while the very low value for hexane allows spreading on the water surface. This also is seen when comparing the positive spreading coefficient of hexane to the negative value for decane on water.

To see whether spreading does or does not occur, a powder such as talc or charcoal can be sprinkled over the surface of water such that it floats; then, a drop of each liquid is placed on this surface. As predicted, decane will remain as an intact drop, while hexane, benzene and oleic acid will spread out, as shown by the rapid movement of solid particles away from the point where the liquid drop was placed originally.

An apparent contradiction to these observations may be noted for hexane, benzene and oleic acid when more of each substance is added, in that lenses now appear to form even though initial spreading occurred. Thus, in effect a substance does not appear to spread over itself.

It is now established that the spreading substance forms a monomolecular film which creates a new surface having a lower surface free energy than pure water. This arises because of the apparent orientation of the molecules in such a film so that their most hydrophobic portion is oriented towards the spreading phase. It is the lack of affinity between this exposed portion of the spread molecules and the polar portion of the remaining molecules which prevents further spreading.

This may be seen by calculating a final spreading coefficient where the new surface tension of water plus monomolecular film is used. For example, the presence of benzene reduces the surface tension of water to 62.2 dynes/cm so that the final spreading coefficient, S_F, is

$$S_F = 62.2 - (28.9 + 35.0) = -1.7$$

The lack of spreading exhibited by oleic acid should be reflected in an even more negative final spreading coefficient, since the very polar carboxyl groups should have very little affinity for the exposed alkyl chain of the oleic acid film. Spreading so as to form a second layer with polar groups exposed to the air would also seem very unlikely, thus leading to the formation of a lens.

Wetting Phenomena

In the experiment described above it was shown that talc or charcoal sprinkled onto the surface of water float despite the fact that their densities are much greater than that of water. In order for immersion of the solid to occur, the liquid must displace air and spread over the surface of the solid; when liquids cannot spread over a solid surface spontaneously, and, therefore, S, the spreading coefficient, is negative, we say that the solid is not wetted.

An important parameter which reflects the degree of wetting is the angle which the liquid makes with the solid surface at the point of contact (Fig 19-4). By convention, when wetting is complete, the contact angle is zero; in nonwetting situations it theoretically can increase to a value of 180°, where a spherical droplet makes contact with solid at only one point.

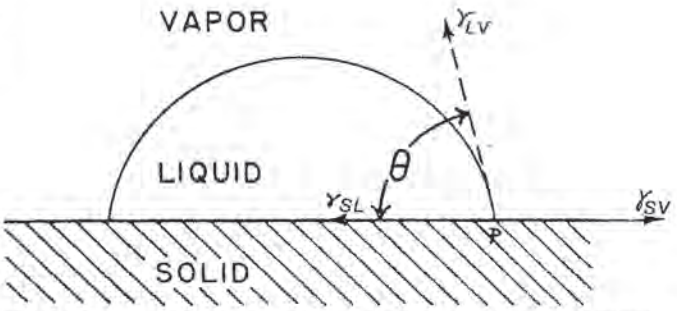


Fig 19-4. Forces acting on a nonwetting liquid drop exhibiting a contact angle of θ.[3]

In order to express contact angle in terms of solid–liquid–air equilibria, one can balance forces parallel to the solid surface at the point of contact between all three phases (Fig 19-4), as expressed in

$$\gamma_{SV} = \gamma_{SL} + \gamma_{LV} \cos \theta \qquad (9)$$

where γ_{SV}, γ_{SL}, and γ_{LV} represent the surface free energy/unit area of the solid–air, solid–liquid, and liquid–air interfaces, respectively. Although difficult to use quantitatively because of uncertainties with γ_{SV} and γ_{SL} measurements, conceptually the equation, known as the Young equation, is useful because it shows that the loss of free energy due to elimination of the air–solid interface by wetting is offset by the increased solid–liquid and liquid–air area of contact as the drop spreads out.

The $\gamma_{LV} \cos \theta$ term arises as the horizontal vectorial component of the force acting along the surface of the drop, as represented by γ_{LV}. Factors tending to reduce γ_{LV} and γ_{SL}, therefore, will favor wetting, while the greater the value of γ_{SV} the greater the chance for wetting to occur. This is seen in Table IV for the wetting of a low-energy surface, paraffin (hydrocarbon), and a higher energy surface, nylon, (polyhexamethylene adipamide). Here, the lower the surface tension of a liquid, the smaller the contact angle on a given solid, and the more polar the solid, the smaller the contact angle with the same liquid.

With Eq 9 in mind and looking at Fig 19-5, it is now possible to understand how the forces acting at the solid-

Table IV—Contact Angle on Paraffin and Nylon for Various Liquids of Differing Surface Tension

Substance	Surface tension, dynes/cm	Contact angle Paraffin	Nylon
Water	72.8	105°	70°
Glycerin	63.4	96°	60°
Formamide	58.2	91°	50°
Methylene iodide	50.8	66°	41°
α-Bromonaphthalene	44.6	47°	16°
tert-Butylnaphthalene	33.7	38°	spreads
Benzene	28.9	24°	"
Dodecane	25.4	17°	"
Decane	23.9	7°	"
Nonane	22.9	spreads	"

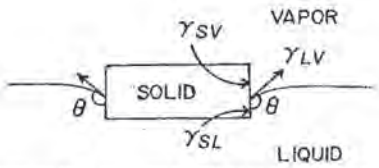


Fig 19-5. Forces acting on a nonwettable solid at the air+liquid+solid interface: contact angle θ greater than 90°.

Table V—Critical Surface Tensions of Various Polymeric Solids

Polymeric Solid	γ_c Dynes/cm at 20°
Polymethacrylic ester of ϕ'-octanol	10.6
Polyhexafluoropropylene	16.2
Polytetrafluoroethylene	18.5
Polytrifluoroethylene	22
Poly(vinylidene fluoride)	25
Poly(vinyl fluoride)	28
Polyethylene	31
Polytrifluorochloroethylene	31
Polystyrene	33
Poly(vinyl alcohol)	37
Poly(methyl methacrylate)	39
Poly(vinyl chloride)	39
Poly(vinylidene chloride)	40
Poly(ethylene terephthalate)	43
Poly(hexamethylene adipamide)	46

liquid-air interface can cause a dense nonwetted solid to float if γ_{SL} and γ_{LV} are large enough relative to γ_{SV}.

The significance of reducing γ_{LV} was first developed empirically by Zisman when he plotted cos θ vs the surface tension of a series of liquids and found that a linear relationship, dependent on the solid, was obtained. When such plots are extrapolated to cos θ equal to one or a zero contact angle, a value of surface tension required to just cause complete wetting is obtained. Doing this for a number of solids, it was shown that this surface tension (known as the critical surface tension, γ_c) parallels expected solid surface energy γ_{SV}; the lower γ_c, the more nonpolar the surface.

Table V indicates some of these γ_c values for different surface groups, indicating such a trend. Thus, water with a surface tension of about 72 dynes/cm will not wet polyethylene (γ_c = 31 dynes/cm), but heptane with a surface tension of about 20 dynes/cm will. Likewise, Teflon (polytetrafluoroethylene) (γ_c = 19) is not wetted by heptane but is wetted by perfluoroheptane with a surface tension of 11 dynes/cm.

One complication associated with the wetting of high-energy surfaces is the lack of wetting after the initial formation of a monomolecular film by the spreading substance. As in the case of oleic acid spreading on the surface of water, the remaining liquid retracts because of the low-energy surface produced by the oriented film. This phenomenon, often called autophobic behavior, is an important factor in many systems of pharmaceutical interest since many solids, expected to be wetted easily by water, may be rendered hydrophobic if other molecules dissolved in the water can form these monomolecular films at the solid surface.

Capillarity

Because water shows a strong tendency to spread out over a polar surface such as clean glass (contact angle 0°), one would expect to observe the meniscus which forms when water is contained in a glass vessel such as a pipet or buret. This behavior is accentuated dramatically if a fine-bore capillary tube is placed into the liquid (Fig 19-6); not only will the wetting of the glass produce a more highly curved meniscus, but the level of the liquid in the tube will be appreciably higher than the level of the water in the beaker.

The spontaneous movement of a liquid into a capillary or narrow tube due to surface forces is defined as capillarity and is responsible for a number of important processes involving the penetration of liquids into porous solids. In contrast to water in contact with glass, if the same capillary is placed into mercury (contact angle on glass: 130°), not

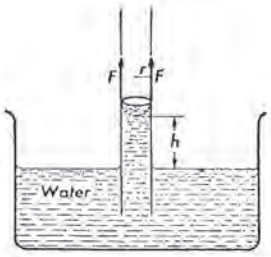


Fig 19-6. Capillary rise for a liquid exhibiting zero contact angle.[1]

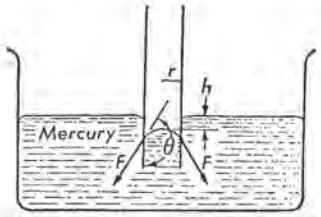


Fig 19-7. Capillary fall for a liquid exhibiting a contact angle, θ, which is greater than 90°.[1]

only will the meniscus be inverted (see Fig 19-7), but the level of the mercury in the capillary will be lower than in the beaker. In this case one does not expect mercury or other *nonwetting* liquids to easily penetrate pores unless external forces are applied.

To quantitate the factors giving rise to the phenomenon of capillarity, let us consider the case of a liquid which rises to a height, h, above the bulk liquid in a capillary having a radius, r. If (as shown in Fig 19-6) the contact angle of water on glass is zero, a force, F, will act upward and vertically along the circle of liquid–glass contact. Based upon the definition of surface tension this force will be equal to the surface tension, γ, multiplied by the circumference of the circle, $2\pi r$. Thus

$$F = \gamma 2\pi r \tag{10}$$

This force upward must support the column of water, and since the mass, m, of the column is equal to the density, d, multiplied by the volume of the column, $\pi r^2 h$, the force W opposing the movement upward will be

$$W = mg = \pi r^2 dgh \tag{11}$$

where g is the gravity constant.

Equating the two forces at equilibrium gives

$$\pi r^2 dgh = \gamma 2\pi r \tag{12}$$

so that

$$h = \frac{2\gamma}{rdg} \tag{13}$$

Thus, the greater the surface tension and the finer the capillary radius, the greater the rise of liquid in the capillary.

If the contact angle of liquid is not zero (as shown in Fig 19-8), the same relationship may be developed, except the

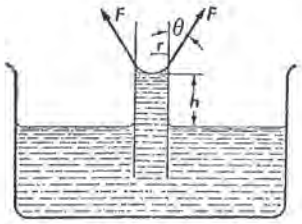


Fig 19-8. Capillary rise for a liquid exhibiting a contact angle, θ, which is greater than zero but less than 90°.[1]

vertical component of F which opposes the weight of the column is $F \cos \theta$ and, therefore

$$h = \frac{2\gamma \cos \theta}{rdg} \quad (14)$$

This indicates the very important fact that if θ is less than 90°, but greater than 0°, the value of h will decrease with increasing contact angle until at 90° ($\cos \theta = 0$), $h = 0$. Above 90°, values of h will be negative, as indicated in Fig 19-7 for mercury. Thus, based on these equations we may conclude that capillarity will occur spontaneously in a cylindrical pore even if the contact angle is greater than zero, but it will not occur at all if the contact angle becomes 90° or more. In solids with irregularly shaped pores the relationships between parameters in Eq 14 will be the same, but they will be more difficult to quantitate because of nonuniform changes in pore radius throughout the porous structure.

Pressure Differences across Curved Surfaces

From the preceding discussion of capillarity another important concept follows. In order for the liquid in a capillary to rise spontaneously it must develop a higher pressure than the lower level of the liquid in the beaker. However, since the system is open to the atmosphere, both surfaces are in equilibrium with the atmospheric pressure. In order to be raised above the level of liquid in the beaker and produce a hydrostatic pressure equal to hgd, the pressure just below the liquid meniscus, in the capillary, P_1, must be less than that just below the flat liquid surface, P_0, by hgd, and therefore

$$P_0 - P_1 = hgd \quad (15)$$

Since, according to Eq 14

$$h = \frac{2\gamma \cos \theta}{rgd}$$

then

$$P_0 - P_1 = \frac{2\gamma \cos \theta}{r} \quad (16)$$

For a contact angle of zero, where the radius of the capillary is the radius of the hemisphere making up the meniscus,

$$P_0 - P_1 = \frac{2\gamma}{r} \quad (17)$$

The consequences of this relationship (known as the Laplace equation) are important for any curved surface when r becomes very small and γ is relatively significant. For example, a spherical droplet of air formed in a bulk liquid and having a radius, r, will have a greater pressure on the inner concave surface than on the convex side, as expressed in Eq 17.

Another direct consequence of what Eq 17 expresses is the fact that very small droplets of liquid, having highly curved surfaces, will exhibit a higher vapor pressure, P, than that observed over a flat surface of the same liquid at P'. The equation (Eq. 18) expressing the ratio of P/P' to droplet radius, r, and surface tension, γ, is called the Kelvin equation where

$$\log P/P' = \frac{2\gamma M}{2.303RT\rho r} \quad (18)$$

and M is the molecular weight, R the gas constant in ergs per mole per degree, T is temperature and ρ is the density in g/cm^3. Values for the ratio of vapor pressures are given in Table VI for water droplets of varying size. Such ratios indicate why it is possible for very fine water droplets in clouds to remain uncondensed despite their close proximity to one another.

Table VI—Ratio of Observed Vapor Pressure to Expected Vapor Pressure of Water at 25° with Varying Droplet Size

P/P' [a]	Droplet size, μm
1.001	1
1.01	0.1
1.1	0.01
2.0	0.005
3.0	0.001
4.2	0.00065
5.2	0.00060

[a] P is the observed vapor pressure and P' is the expected value for "bulk" water.

This same behavior may be seen when measuring the solubility of very fine solid particles since both vapor pressure and solubility are measures of the escaping tendency of molecules from a surface. Indeed, the equilibrium solubility of extremely small particles has been shown to be greater than the usual value noted for coarser particles; the greater the surface energy and smaller the particles, the greater this effect.

Adsorption

Vapor Adsorption on Solid Surfaces

It was suggested earlier that a high surface or interfacial free energy may exist at a solid surface if the unbalanced forces at the surface and the area of exposed groups are quite great.

Substances such as metals, metal oxides, silicates, and salts—all containing exposed polar groups—may be classified as high-energy or hydrophilic solids; nonpolar solids such as carbon, sulfur, polyethylene, or Teflon (polytetrafluoroethylene) may be classified as low-energy or hydrophobic solids (Table III). Whereas liquids satisfy their unbalanced surface forces by changes in shape, pure solids (which exhibit negligible surface mobility) must rely on reaction with molecules either in the vapor state or in a solution which comes in contact with the solid surface to accomplish this.

Vapor adsorption is the simplest model demonstrating how solids reduce their surface free energy in this manner.

Depending on the chemical nature of the adsorbent (solid) and the adsorbate (vapor), the strength of interaction between the two species may vary from strong specific chemical bonding to interactions produced by the weaker more nonspecific London dispersion forces. Ordinarily, these latter forces are those responsible for the condensation of relatively nonpolar substances such as N_2, O_2, CO_2 or hydrocarbons.

When chemical reaction occurs, the process is called chemisorption; when dispersion forces predominate, the term physisorption is used. Physisorption occurs at temperatures approaching the liquefaction temperature of the vapor, whereas, for chemisorption, temperatures depend on the particular reaction involved. Water-vapor adsorption to various polar solids can occur at room temperature through hydrogen-bonding, with binding energies intermediate to physisorption and chemisorption.

In order to study the adsorption of vapors onto solid surfaces one must measure the amount of gas adsorbed/unit area or unit mass of solid, at different pressures of gas. Since such studies usually are conducted at constant temperature, plots of volume adsorbed vs pressure are referred to as adsorption isotherms. If the physical or chemical adsorption process is monomolecular, the adsorption iso-

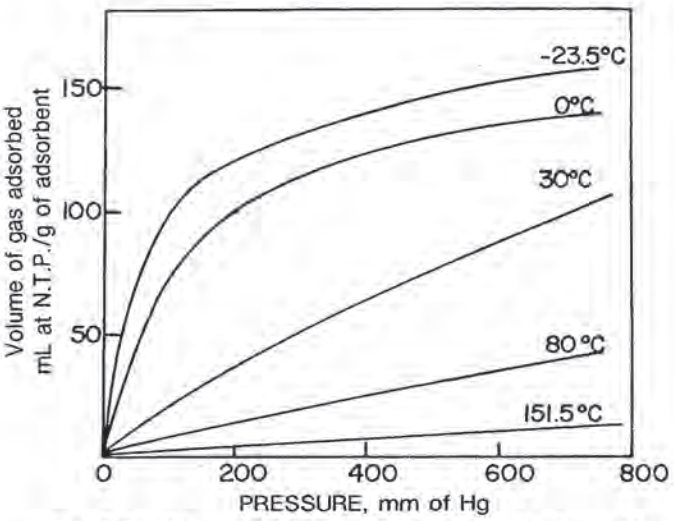


Fig 19-9. Adsorption isotherms for ammonia on charcoal.[4]

therm should look like those shown in Fig 19-9. Note the significant increase in adsorption with increasing pressure, followed by a leveling off. This leveling off is due either to a saturation of available specific chemical groups, as in chemisorption, or to the entire available surface being covered by physically adsorbed molecules. Note also the reduction in adsorption with increasing temperature which occurs because the adsorption process is exothermic. Often in the case of physical adsorption at low temperatures, after adsorption levels off, a marked increase in adsorption occurs, presumably due to multilayered adsorption. In this case vapor molecules essentially condense upon themselves as the liquefaction pressure of the vapor is approached. Figure 19-10 illustrates one type of isotherm generally seen with multilayered physisorption.

In order to have some quantitative understanding of the adsorption process and to be able to compare different systems, two factors must be evaluated; it is important to know what the capacity of the solid is or what the maximum amount of adsorption is under a given set of conditions and what the affinity of a given substance is for the solid surface or how readily does it adsorb for a given amount of pressure? In effect, this second term is the equilibrium constant for the process.

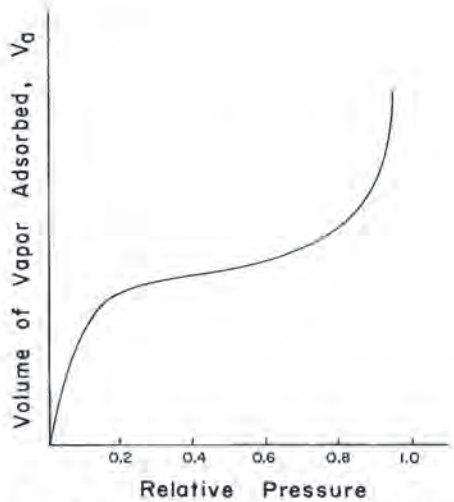


Fig 19-10. Typical plot for multilayer physical adsorption of a vapor on a solid surface.

A significant development along these lines was introduced by Langmuir when he proposed his theory of monomolecular adsorption. He postulated that for adsorption to occur a solid must contain uniform adsorption sites, each capable of holding a gas molecule. Molecules colliding with the surface may bounce off elastically or they may remain in contact for a period of time. It is this contact over a period of time that Langmuir termed adsorption.

Two major assumptions were made in deriving the equation: (1) only those molecules striking an empty site can be adsorbed, hence, only monomolecular adsorption occurs, and (2) the forces of interaction between adsorbed molecules are negligible and, therefore, the probability of a molecule adsorbing onto or desorbing from any site is independent of the surrounding sites.

The derivation of the equation is based upon the relationship between the rate of adsorption and desorption, since at equilibrium the two rates must be equal. Let μ equal the number of molecules striking each sq cm of surface/sec. From the kinetic theory of gases

$$\mu = \frac{p}{(2\pi mkT)^{1/2}} \tag{19}$$

where p is the gas pressure, m is the mass of the molecule, k is the Boltzmann gas constant, and T is the absolute temperature. Thus, the greater p, the greater the number of collisions. Let α equal the fraction of molecules which will be held by the surface; then $\alpha\mu$ is equal to the rate of adsorption on the bare surface. However, if θ is the fraction of the surface already covered, the rate of adsorption actually will be

$$R_a = \alpha\mu(1 - \theta) \tag{20}$$

In a similar manner the rate of molecules leaving the surface can be expressed as

$$R_d = \gamma\theta \tag{21}$$

where γ is the rate at which molecules can leave the surface and θ represents the number of molecules available to desorb. The value of γ strongly depends on the energy associated with adsorption; the greater the binding energy, the lower the value of γ. At equilibrium, $R_a = R_d$ and

$$\gamma\theta = \alpha\mu(1 - \theta) \tag{22}$$

Isolating the variable term, p, and combining all constants into k, the equation can be written as

$$\theta = \frac{kp}{1 + kp} \tag{23}$$

and, since θ may be expressed as

$$\theta = \frac{V_a}{V_m} \tag{24}$$

where V_a is the volume of gas adsorbed and V_m is the volume of gas covering all of the sites, Eq. 23 may be written as

$$V_a = \frac{V_m kp}{1 + kp} \tag{25}$$

A test of fit to this equation can be made by expressing it in linear form

$$\frac{p}{V_a} = \frac{1}{V_m k} + \frac{p}{V_m} \tag{26}$$

The value of k is, in effect, the equilibrium constant and may be used to compare affinities of different substances for the solid surface. The value of V_m is valuable since it indicates the maximum number of sites available for adsorption. In the case of physisorption the maximum number of sites is

actually the total surface area of the solid and, therefore, the value of V_m can be used to estimate surface area if the volume and area/molecule of vapor are known.

Since physisorption most often involves some multilayered adsorption, an equation, based on the Langmuir equation, the B.E.T. equation, is normally used to determine V_m and solid surface areas. Equation 27 is the B.E.T. equation:

$$V_a = \frac{V_m c p}{(p_0 - p)[1 + (C - 1)(p/p_0)]} \tag{27}$$

where c is a constant and p_0 is the vapor pressure of the adsorbing substance.[5] The most widely used vapor for this purpose is nitrogen, which adsorbs nonspecifically on most solids near its boiling point at −195° and appears to occupy about 16 Å²/molecule on a solid surface.

Adsorption from Solution

By far one of the most important aspects of interfacial phenomena encountered in pharmaceutical systems is the tendency for substances dissolved in a liquid to adsorb to various interfaces. Adsorption from solution is generally more complex than that from the vapor state because of the influence of the solvent and any other solutes dissolved in the solvent. Although such adsorption is generally limited to one molecular layer, the presence of other molecules often makes the interpretation of adsorption mechanisms much more difficult than for chemisorption or physisorption of a vapor. Since monomolecular adsorption from solution is so widespread at all interfaces, we will first discuss the nature of monomolecular films and then return to a discussion of adsorption from solution.

Insoluble Monomolecular Films

It was suggested above that molecules exhibiting a tendency to spread out at an interface might be expected to orient so as to reduce the interfacial free energy produced by the presence of the interface. Direct evidence for molecular orientation has been obtained from studies dealing with the spreading on water of insoluble polar substances containing long hydrocarbon chains, eg, fatty acids.

In the late 19th century Pockels and Rayleigh showed that a very small amount of olive or castor oil—when placed on the surface of water—spreads out, as discussed above. If the amount of material was less than could physically cover the entire surface only a slight reduction in the surface tension of water was noted. However, if the surface was compressed between barriers, as shown in Fig 19-11, the surface tension was reduced considerably.

Devaux extended the use of this technique by dissolving small amounts of solid in volatile solvents and dropping the solution onto a water surface. After assisting the water-insoluble molecules to spread, the solvent evaporated, leaving a surface film containing a known amount of solute.

Compression and measurement of surface tension indicated that a maximum reduction of surface was reached when the number of molecules/unit area was reduced to a value corresponding to complete coverage of the surface. This suggested that a monomolecular film forms and that surface tension is reduced upon compression because contact between air and water is reduced by the presence of the film molecules. Beyond the point of closest packing the film apparently collapses very much as a layer of corks floating on water would be disrupted when laterally compressed beyond the point of initial physical contact.

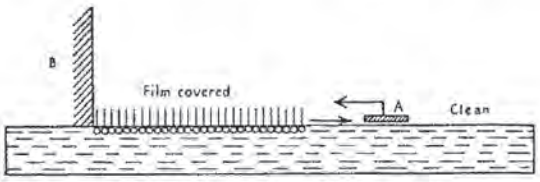


Fig 19-11. Insoluble monomolecular film compressed between a fixed barrier, *B*, and a movable barrier, *A*.[6]

Using a refined quantitative technique based on these studies, Langmuir[7] spread films of pure fatty acids, alcohols, and esters on the surface of water. Comparing a series of saturated fatty acids, differing only in chain length, he found that the area/molecule at collapse was independent of chain length, corresponding to the cross-sectional area of a molecule oriented in a vertical position (see Fig 19-11). He further concluded that this molecular orientation involved association of the polar carboxyl group with the water phase and the nonpolar acyl chain out towards the vapor phase.

In addition to the evidence for molecular orientation, Langmuir's work with surface films revealed that each substance exhibits film properties which reflect the interactions between molecules in the surface film. This is best seen by plotting the difference in surface tension of the clean surface, γ_0, and that of the surface covered with the film, γ, vs the area/molecule, A, produced by film compression (total area ÷ the number of molecules). The difference in surface tension is called the surface pressure, π, and thus

$$\pi = \gamma_0 - \gamma. \tag{28}$$

Figure 19-12 depicts such a plot for a typical fatty acid monomolecular film. At areas greater than 50 Å²/molecule the molecules are far apart and do not cover enough surface to reduce the surface tension of the clean surface to any extent and thus the lack of appreciable surface pressure. Since the molecules in the film are quite free to move laterally in the surface, they are said to be in a two-dimensional "gaseous" or "vapor" state.

As the intermolecular distance is reduced upon compression, the surface pressure rises because the air–water surface is being covered to a greater extent. The rate of change in π with A, however, will depend on the extent of interaction between film molecules; the greater the rate of change, the more "condensed" the state of the film.

In Fig 19-12, from 50 Å² to 30 Å²/molecule, the curve shows a steady increase in π, representative of a two-dimensional "liquid" film, where the molecules become more restricted in their freedom of movement because of interactions. Below 30 Å²/molecule the increase in π occurs over a narrow range of A, characteristic of closest packing and a two-dimensional "solid" film.

Any factor tending to increase polarity or bulkiness of the molecule—such as increased charge, number of polar groups, reduction in chain length, or the introduction of

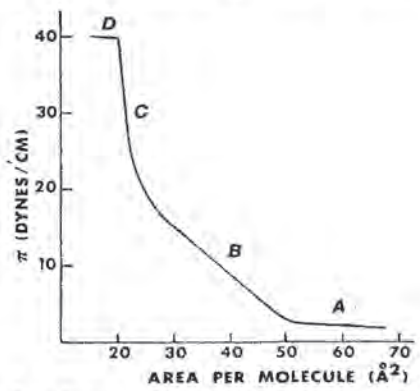


Fig 19-12. A surface pressure–area curve for an insoluble monomolecular film: Region *A*, "gaseous" film; Region *B*, "liquid" film; Region *C*, "solid" film; Region *D*, film collapse.

aromatic rings, side chains, and double bonds—should reduce molecular interactions, while the longer the alkyl chain and the less bulky the polar group, the closer the molecules can approach and the stronger the extent of interaction in the film.

Soluble Films and Adsorption from Solution

If a fatty acid exhibits highly "gaseous" film behavior on an aqueous surface, we should expect a relatively small change in π with A over a considerable range of compression. Indeed, for short-chain compounds—eg, lauric acid (12 carbons) and decanoic acid—not only is the change in π small with decreasing A but at a point just before the expected closest packing area the surface pressure becomes constant without any collapse.

If lauric acid is converted to the laurate ion, or if a shorter chain acid such as octanoic acid is used, spreading on water and compression of the surface produces no increase in π; the more polar the molecule (hence, the more "gaseous" the film), the higher the area/molecule where a constant surface pressure occurs.

This behavior may be explained by assuming that polar molecules form monomolecular films when spread on water but that, upon compression, they are caused to enter the aqueous bulk solution rather than to remain as an intact insoluble film. The constant surface pressure with increased compression arises because a constant number of molecules/unit area remain at the surface in equilibrium with dissolved molecules. The extent of such behavior will be greater for substances exhibiting weaker intermolecular interaction and greater water solubility.

Starting from the other direction, it can be shown that short-chain acids and alcohols (when dissolved in water) reduce the surface tension of water, thus producing a surface pressure, just as with insoluble films (see Eq 28). That dissolved molecules are accumulating at the interface in the form of a monomolecular film is suggested from the similarity in behavior to systems where slightly soluble molecules are spread on the surface. For example, compressing the surface of a solution containing "surface-active" molecules has no effect on the initial surface pressure, whereas increasing bulk-solution concentration tends to increase surface pressure, presumably by shifting the equilibrium between surface and bulk molecules.

At this point we may ask, why should water-soluble molecules leave an aqueous phase and accumulate or "adsorb" at an air–solution interface? Since any process will occur spontaneously if it results in a net loss in free energy, such must be the case for the process of adsorption.

A number of factors will produce such a favorable change in free energy. First, the presence of the oriented monomolecular film reduces the surface free energy of the air–water interface. Second, the hydrophobic group on the molecule is in a lower state of energy at the interface, where it no longer is as surrounded by water molecules, than when it is in the bulk-solution phase. Increased interaction between film molecules also will contribute to this process.

A further reduction in free energy occurs upon adsorption because of the gain in entropy associated with a change in water structure. Water molecules, in the presence of dissolved alkyl chains are more highly organized or "ice-like" than they are as a pure bulk phase; hence, the entropy of such structured water is lower than that of bulk water.

The process of adsorption requires that the "ice-like" structure "melt" as the chains go to the interface and, thus, an increase in the entropy of water occurs. The adsorption of molecules dissolved in oil can occur but it is not influenced by water structure changes and, hence, only the first factors mentioned are important here.

It is very rare that significant adsorption can occur at the hydrocarbon–air interface since little loss in free energy can occur by bringing hydrocarbon chains with polar groups attached to this interface; however, at oil–water interfaces the polar portions of the molecule can interact with water at the interface, leading to significant adsorption.

Thus, whereas water-soluble fatty acid salts are adsorbed from water to air–water and oil–water interfaces, their undissociated counterparts, the free fatty acids, which are water insoluble, form insoluble films at the air–water interface, are not adsorbed from oil solution to an oil–air interface, but show significant adsorption at the oil–water interface when dissolved in oil.

From this discussion it is possible also to conclude that adsorption from aqueous solution requires a lower solute concentration to obtain the same level of adsorption if the hydrophobic chain length is increased or if the polar portion of the molecule is less hydrophilic. On the other hand, adsorption from nonpolar solvents is favored when the solute is quite polar.

Since soluble or adsorbed films cannot be compressed, there is no simple direct way to estimate the number of molecules/unit area coming to the surface under a given set of conditions. For relatively simple systems it is possible to estimate this value by application of the Gibbs equation, which relates surface concentration to the surface-tension change produced at different solute activities. The derivation of this equation is beyond the scope of this discussion, but it arises from a classical thermodynamic treatment of the change in free energy when molecules concentrate at the boundary between two phases. The equation may be expressed as

$$\Gamma = -\frac{a}{RT}\frac{d\gamma}{da} \tag{29}$$

where Γ is the moles of solute adsorbed/unit area, R is the gas constant, T is the absolute temperature and $d\gamma$ is the change in surface tension with a change in solute activity, da, at activity a. For dilute solutions of nonelectrolytes, or for electrolytes when the Debye–Hückel equation for activity coefficient is applicable, the value of a may be replaced by solute concentration, c. Since the term dc/c is equal to $d \ln c$, the Gibbs equation is often written as

$$\Gamma = -\frac{1}{RT}\frac{d\gamma}{d \ln c} \tag{30}$$

In this way the slope of a plot of γ vs $\ln c$ multiplied by $1/RT$ should give Γ at a particular value of c. Figure 19-13 depicts typical plots for a series of water-soluble surface-active agents differing only in the alkyl chain length. Note the

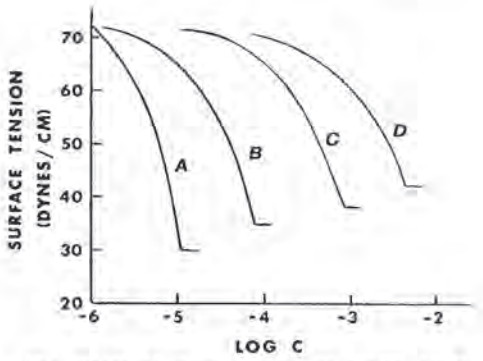


Fig 19-13. The effect of increasing chain length on the surface activity of a surfactant at the air–aqueous solution interface (each figure depicted to differ by two methylene groups with *A*, the longest chain, and *D*, the shortest).

greater reduction of surface tension that occurs at lower concentrations for longer chain-length compounds. In addition, note the greater slopes with increasing concentration, indicating more adsorption (Eq 30), and the abrupt leveling of surface tension at higher concentrations. This latter behavior reflects the self-association of surface-active agent to form micelles which exhibit no further tendency to reduce surface tension. The topic of micelles will be discussed later on page 268.

If one plots the values of surface concentration, Γ, vs concentration, c, for substances adsorbing to the vapor-liquid and liquid-liquid interfaces, using data such as those given in Fig 19-13, one generally obtains an adsorption isotherm shaped like those in Fig 19-9 for vapor adsorption. Indeed, it can be shown that the Langmuir equation (Eq 25) can be fitted to such data when written in the form

$$\Gamma = \frac{\Gamma_{max} k'c}{1 + k'c} \tag{31}$$

where Γ_{max} is the maximum surface concentration attained with increasing concentration and k' is related to k in Eq 25. Combining Eqs 29 and 31 leads to a widely used relationship between surface tension change Π (see Eq 28) and solute concentration, c, known as the Syszkowski equation:

$$\Pi = \Gamma_{max} RT \ln (1 + k'c) \tag{32}$$

Mixed Films

It would seem reasonable to expect that the properties of a surface film could be varied greatly if a mixture of surface-active agents were in the film. As an example, consider that a mixture of short- and long-chain fatty acids would be expected to show a degree of "condensation" varying from the "gaseous" state, when the short-chain substance is used in high amount, to a highly condensed state when the longer chain substance predominates. Thus, each component in such a case would operate independently by bringing a proportional amount of film behavior to the system.

More often, the ingredients of a surface film do not behave independently, but, rather, interact to produce a new surface film. An obvious example would be the combination of organic amines and acids which are oppositely charged and would be expected to interact strongly.

In addition to such polar-group interactions, chain–chain interaction will strongly favor mixed condensed films. An important example of such a case occurs when a long-chain alcohol is introduced along with an ionized long-chain substance. Together the molecules form a highly condensed film despite the presence of a high number of like charges. Presumably this occurs as seen in Fig 19-14, by arranging the molecules so that ionic groups alternate with alcohol groups; however, if chain–chain interactions are not strong, the ionic species often will be displaced by the more nonpolar unionized species and "desorb" into the bulk solution.

On the other hand, sometimes the more soluble surface-active agent produces surface pressures in excess of the collapse pressure of the insoluble film and displaces it from the surface. This is an important concept because it is the underlying principle behind cell lysis by surface-active agents and some drugs, and behind the important process of detergency.

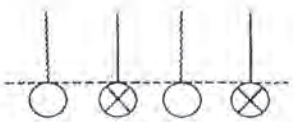


Fig 19-14. A mixed monomolecular film. ⊗: a long-chain ion; O: a long-chain nonionic compound.

Adsorption on Solid Surfaces From Solution

Adsorption to solid surfaces from solution may occur if the dissolved molecules and the solid surface have chemical groups capable of interacting. Nonspecific adsorption also will occur if the solute is surface active and if the surface area of the solid is high. This latter case would be the same as occurs at the vapor-liquid and liquid-liquid interfaces. As with adsorption to liquid interfaces, adsorption to solid surfaces from solution generally leads to a monomolecular layer, often described by the Langmuir equation or by the empirical, yet related, Freundlich equation

$$x/M = kc^n \tag{33}$$

where x is the grams of solute adsorbed by M grams of solid in equilibrium with a solute concentration of c. The terms k and n are empirical constants. However, as Giles[8] has pointed out, the variety of combinations of solutes and solids, and, hence the variety of possible mechanisms of adsorption, can lead to a number of more complex isotherms. In particular, adsorption of surfactants and polymers, of great importance in a number of pharmaceutical systems, is still not well understood on a fundamental level, and may in some situations even be multilayered.

Adsorption from solution may be measured by separating solid and solution and either estimating the amount of adsorbate adhering to the solid or the loss in concentration of adsorbate from solution.

In view of the possibility of solvent adsorption, the latter approach really only gives an apparent adsorption. For example, if solvent adsorption is great enough, it is possible to end up with an increased concentration of solute after contact with the solid; here, the term negative adsorption is used.

Solvent not only influences adsorption by competing for the surface but, as discussed in connection with adsorption at liquid surfaces, the solvent will determine the escaping tendency of a solute; eg, the more polar the molecule, the less the adsorption that occurs from water. This is seen in Fig 19-15, where adsorption of various fatty acids from water onto charcoal increases with increasing alkyl chain length or nonpolarity. It is difficult to predict these effects but, in general, the more chemically unlike the solute and solvent and the more alike the solid surface groups and solute, the

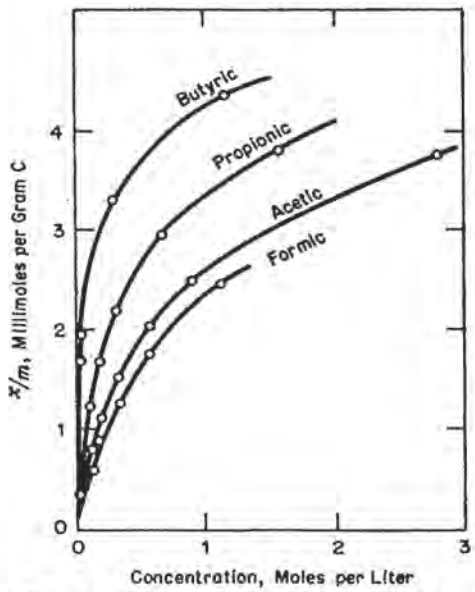


Fig 19-15. The relation between adsorption and molecular weight of fatty acids.[9]

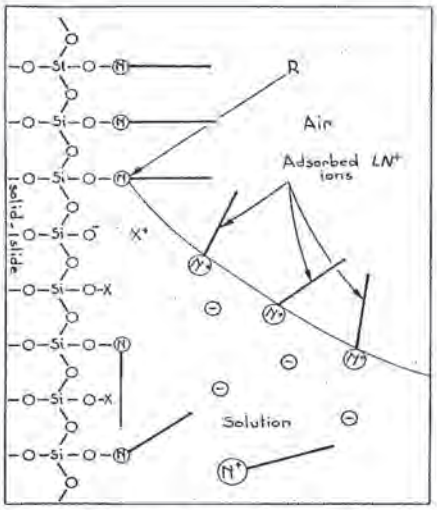


Fig 19-16. The adsorption of a cationic surfactant, LN^+, onto a negatively charged silica or glass surface, exposing a hydrophobic surface as the solid is exposed to air.[10]

greater the extent of adsorption. Another factor which must be kept in mind is that charged solid surfaces, such as polyelectrolytes, will strongly adsorb oppositely charged solutes. This is similar to the strong specific binding seen in gas chemisorption and it is characterized by significant monolayer adsorption at very low concentrations of solute. See Fig 19-16 for an example of such adsorption.

Surface-Active Agents

Throughout the discussion so far, examples of surface-active agents (surfactants) have been restricted primarily to fatty acids and their salts. It has been shown that both a hydrophobic portion (alkyl chain) and a hydrophilic portion (carboxyl and carboxylate groups) are required for their surface activity, the relative degree of polarity determining the tendency to accumulate at interfaces. It now becomes important to look at some of the specific types of surfactants available and to see what structural features are required for different pharmaceutical applications.

The classification of surfactants is quite arbitrary, but one based on chemical structure appears best as a means of introducing the topic. It is generally convenient to categorize surfactants according to their polar portions since the nonpolar portion is usually made up of alkyl or aryl groups. The major polar groups found in most surfactants may be divided as follows: anionic, cationic, amphoteric and nonionic. As we shall see, the last group is the largest and most widely used for pharmaceutical systems, so that it will be emphasized in the discussion that follows.

Types

Anionic Agents—The most commonly used anionic surfactants are those containing carboxylate, sulfonate, and sulfate ions. Those containing carboxylate ions are known as soaps and are generally prepared by the saponification of natural fatty acid glycerides in alkaline solution. The most common cations associated with soaps are sodium, potassium, ammonium, and triethanolamine, while the chain length of the fatty acids ranges from 12 to 18.

The degree of water solubility is greatly influenced by the length of the alkyl chain and the presence of double bonds. For example, sodium stearate is quite insoluble in water at room temperature, whereas sodium oleate under the same conditions is quite water soluble.

Table VII—Effect of Aerosol OT Concentration on the Surface Tension of Water and the Contact Angle of Water with Magnesium Stearate

Concentration, $m \times 10^6$	γ_{sv}	θ
1.0	60.1	120°
3.0	49.8	113°
5.0	45.1	104°
8.0	40.6	89°
10.0	38.6	80°
12.0	37.9	71°
15.0	35.0	63°
20.0	32.4	54°
25.0	29.5	50°

Multivalent ions, such as calcium and magnesium, produce marked water insolubility, even at lower alkyl chain lengths; thus, soaps are not useful in hard water which is high in content of these ions. Soaps, being salts of weak acids, are subject also to hydrolysis and the formation of free acid plus hydroxide ion, particularly when in more concentrated solution.

To offset some of the disadvantages of soaps, a number of long-alkyl-chain sulfonates, as well as alkyl aryl sulfonates such as sodium dodecylbenzene sulfonate, may be used; the sulfonate ion is less subject to hydrolysis and precipitation in the presence of multivalent ions. A popular group of sulfonates, widely used in pharmaceutical systems, are the dialkyl sodium sulfosuccinates, particularly sodium bis-(2-ethylhexyl)sulfosuccinate, best known as Aerosol OT or docusate sodium. This compound is unique in that it is both oil and water soluble and hence forms micelles in both phases. It reduces surface and interfacial tension to low values and acts as an excellent wetting agent in many types of solid dosage forms (see Table VII).

A number of alkyl sulfates are available as surfactants, but by far the most popular member of this group is sodium lauryl sulfate, which is widely used as an emulsifier and solubilizer in pharmaceutical systems. Unlike the sulfonates, sulfates are susceptible to hydrolysis which leads to the formation of the long-chain alcohol, so that pH control is most important for sulfate solutions.

Cationic Agents—A number of long-chain cations, such as amine salts and quaternary ammonium salts, are often used as surface-active agents when dissolved in water; however, their use in pharmaceutical preparations is limited to that of antimicrobial preservation rather than as surfactants. This arises because the cations adsorb so readily at cell membrane structures in a nonspecific manner, leading to cell lysis (eg, hemolysis), as do anionics to a lesser extent. It is in this way that they act to destroy bacteria and fungi.

Since anionic and nonionic agents are not as effective as preservatives, one must conclude that the positive charge of these compounds is important; however, the extent of surface activity has been shown to determine the amount of material needed for a given amount of preservation. Quaternary ammonium salts are preferable to free amine salts since they are not subject to effect by pH in any way; however, the presence of organic anions such as dyes and natural polyelectrolytes is an important source of incompatibility and such a combination should be avoided.

Amphoteric Agents—The major group of molecules falling into this category are those containing carboxylate or phosphate groups as the anion and amino or quaternary ammonium groups as the cation. The former group is represented by various polypeptides, proteins, and the alkyl betaines, while the latter group consist of natural phospholipids such as the lecithins and cephalins. In general, long-chain amphoterics which exist in solution in zwitterionic form are

more surface-active than ionic surfactants having the same hydrophobic group since in effect the oppositely charged ions are neutralized. However, when compared to nonionics, they appear somewhere between ionic and nonionic.

Nonionic Agents—The major class of compounds used in pharmaceutical systems are the nonionic surfactants since their advantages with respect to compatibility, stability, and potential toxicity are quite significant. It is convenient to divide these compounds into those that are relatively water insoluble and those that are quite water soluble.

The major type of compounds making up this first group are the long-chain fatty acids and their water-insoluble derivatives. These include (1) fatty alcohols such as lauryl, cetyl (16 carbons) and stearyl alcohols; (2) glyceryl esters such as the naturally occurring mono-, di- and triglycerides; and (3) fatty acid esters of fatty alcohols and other alcohols such as propylene glycol, polyethylene glycol, sorbitan, sucrose and cholesterol. Included also in this general class of nonionic water-insoluble compounds are the free steroidal alcohols such as cholesterol.

To increase the water solubility of these compounds and to form the second group of nonionic agents, polyoxyethylene groups are added through an ether linkage with one of their alcohol groups. The list of derivatives available is much too long to cover completely, but a few general categories will be given.

The most widely used compounds are the polyoxyethylene sorbitan fatty acid esters which are found in both internal and external pharmaceutical formulations. Closely related compounds include polyoxyethylene glyceryl, and steroidal esters, as well as the comparable polyoxypropylene esters. It is also possible to have a direct ether linkage with the hydrophobic group as with a polyoxyethylene–stearyl ether or a polyoxyethylene–alkyl phenol. These ethers offer advantages since, unlike the esters, they are quite resistant to acidic or alkaline hydrolysis.

Besides the classification of surfactants according to their polar portion, it is useful to have a method that categorizes them in a manner that reflects their interfacial activity and their ability to function as wetting agents, emulsifiers, solubilizers, etc. Since variation in the relative polarity or nonpolarity of a surfactant significantly influences its interfacial behavior, some measure of polarity or nonpolarity should be useful as a means of classification.

One such approach assigns a hydrophile–lipophile balance number (HLB) for each surfactant and, although developed by a commercial supplier of one group of surfactants, the method has received wide-spread application. The HLB value, as originally conceived for nonionic surfactants, is merely the percentage weight of the hydrophilic group divided by five in order to reduce the range of values. On a molar basis, therefore, a 100% hydrophilic molecule (polyethylene glycol) would have a value of 20.

Thus, an increase in polyoxyethylene chain length increases polarity and, hence, the HLB value; at constant polar chain length, an increase in alkyl chain length or number of fatty acid groups decreases polarity and the HLB value. One immediate advantage of this system is that to a first approximation one can compare any chemical type of surfactant to another type when both polar and nonpolar groups are different.

HLB values for nonionics are calculable on the basis of the proportion of polyoxyethylene chain present; however, in order to determine values for other types of surfactants it is necessary to compare physical chemical properties reflecting polarity with those surfactants having known HLB values.

Relationships between HLB and phenomena such as water solubility, interfacial tension, and dielectric constant have been used in this regard. Those surfactants exhibiting values greater than 20 (eg, sodium lauryl sulfate) demonstrate hydrophilic behavior in excess of the polyoxyethylene groups alone. Table XIX, page 304, presents HLB values for a variety of surface-active agents.

Surfactant Properties in Solution and Micelle Formation

As seen in Fig 19-13, increasing the concentration of surface-active agents in aqueous solution causes a decrease in the surface tension of the solution until a certain concentration where it then becomes essentially constant with increasing concentration. That this change is associated with changes also taking place in the bulk solution rather than just at the surface can be seen in Fig 19-17, which shows the same abrupt change in bulk solution properties such as solubility, equivalent conductance and osmotic pressure as with surface properties. The most reasonable explanation for these effects is that the solute molecules self-associate to form soluble aggregates which exhibit markedly different properties from the monomers in solution. Such aggregates (Fig 19-18*A*) appear to exhibit no tendency to adsorb to the surface since the surface and interfacial tension above this solute concentration do not change to any significant extent. Such aggregates, known as micelles, form over such a very narrow range of concentrations that one can speak of a critical micellization concentration (cmc). These micelles form for essentially the same reasons that cause molecules to be adsorbed; the lack of affinity of the hydrophobic chains for water molecules and the tendency for strong hydrophobic chain-chain interactions when the chains are oriented closely together in the micelle, coupled with the gain in entropy due to the loss of the ice-like structure of water when the chains are separated from water, lead to a favorable free energy change for micellization. The longer the hydrophobic chain or the less the polarity of the polar group, the greater the tendency for monomers to "escape" from the water to form micelles and, hence the lower the cmc (see Fig 19-13).

In dilute solution (still above the cmc) the micelles can be considered to be approximately spherical in shape (Fig 19-18*A* and *B*), while at higher concentrations they become

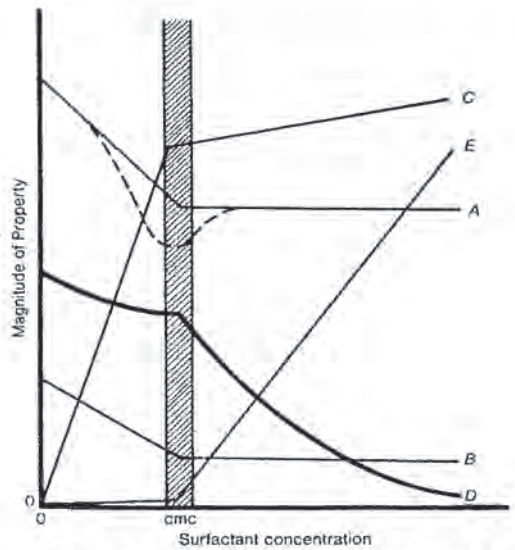


Fig 19-17. Effect of surfactant concentration and micelle formation on various properties of the aqueous solution of an ionic surfactant. *A:* Surface tension; *B:* interfacial tension; *C:* osmotic pressure; *D:* equivalent conductivity; *E:* solubility of compound with very low solubility in pure water.[11]

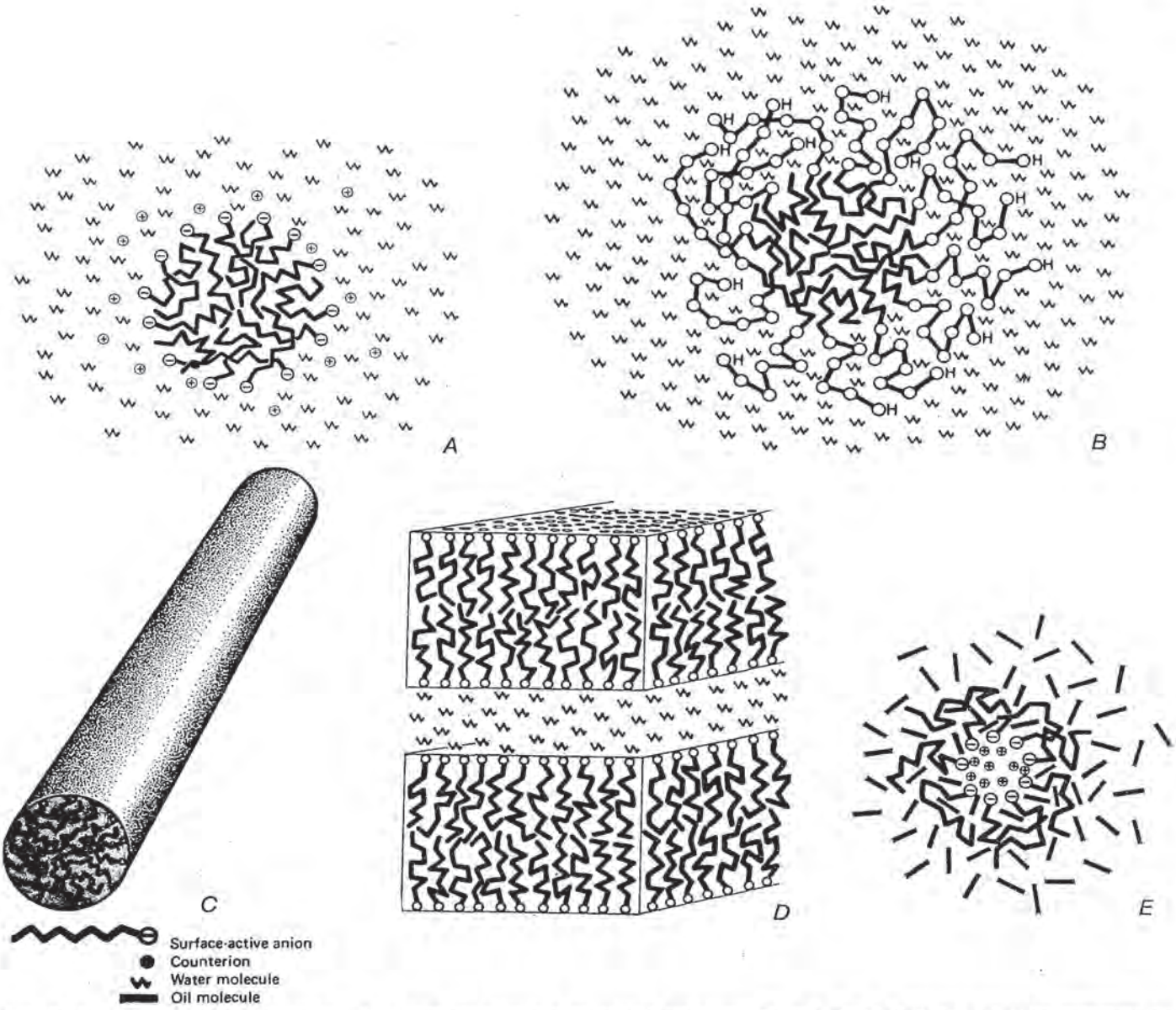


Fig 19-18. Different types of micelles. *A:* Spherical micelle of an anionic surfactant; *B:* spherical micelle of a nonionic surfactant; *C:* cylindrical micelle of an ionic surfactant; *D:* lamellar micelle of an ionic surfactant; *E:* reverse micelle of an anionic surfactant in oil.[11]

more asymmetric and eventually assume cylindrical (Fig 19-18*C*) or lamellar (Fig 19-18*D*) structures. It is important to recognize that equilibrium, and hence reversibility, exists between the monomers and the various types of micelles. The sizes of such micelles depend on the number of monomers per micelle and the size and molecular shape of the individual monomers. In Table VIII are given the cmc and number of monomers per micelle for different types of surfactants. Note for the nonionic surfactants that the longer the polyoxyethylene chain, and hence the more polar and bulkier the molecule, the higher the cmc, ie the less the tendency for micelle formation. It is also possible for oil-soluble surfactants to show a tendency to self-associate into "reverse micelles in nonpolar solvents, as depicted in Fig 19-18*E*, with their polar groups all oriented away from the solvent. In general these micelles tended to be smaller and to aggregate over a wider range of concentrations than seen in water, and therefore, to exhibit no well-defined cmc.

Micellar Solubilization

As seen in Fig 19-18, the interior of surfactant micelles formed in aqueous media consists of hydrocarbon "tails" in liquid-like disorder. The micelles, therefore, resemble miniscule pools of liquid hydrocarbon surrounded by shells of polar "head groups." Compounds which are poorly soluble in water but soluble in hydrocarbon solvents, can be dissolved inside these micelles, ie, they are brought homogeneously into an overall aqueous medium.

Being hydrophobic and oleophilic, the solubilized molecules are located primarily in the hydrocarbon core of the micelles (see Fig 19-19*A*). Even water-insoluble drugs usually contain polar functional groups such as hydroxyl, carbonyl, ether, amino, amide, and cyano. Upon solubilization, these hydrophilic groups locate on the periphery of the micelle among the polar headgroups of the surfactant in order to become hydrated (see Fig 19-19*B*). For instance,

Table VIII—Critical Micelle Concentrations and Micellar Aggregation Numbers of Various Surfactants in Water at Room Temperature

Structure	Name	CMC, mM/L	Surfactant molecules/ micelle
n-$C_{11}H_{23}COOK$	Potassium laurate	24	50
n-$C_8H_{17}SO_3Na$	Sodium octant sulfonate	150	28
n-$C_{10}H_{21}SO_3Na$	Sodium decane sulfonate	40	40
n-$C_{12}H_{25}SO_3Na$	Sodium dodecane sulfonate	9	54
n-$C_{12}H_{25}OSO_3Na$	Sodium lauryl sulfate	8	62
n-$C_{12}H_{25}OSO_3Na$	Sodium lauryl sulfate[a]	1	96
	Sodium di-2-ethylhexyl sulfosuccinate	5	48
n-$C_{10}H_{21}N(CH_3)_3Br$	Decyltrimethylammonium bromide	63	36
n-$C_{12}H_{25}N(CH_3)_3Br$	Dodecyltrimethylammonium bromide	14	50
n-$C_{14}H_{29}N(CH_3)_3Br$	Tetradecyltrimethylammonium bromide	3	75
n-$C_{14}H_{29}N(CH_3)_3Cl$	Tetradecyltrimethylammonium chloride	3	64
n-$C_{12}H_{25}NH_3Cl$	Dodecylammonium chloride	13	55
n-$C_{12}H_{25}O(CH_2CH_2O)_8H$	Octaoxyethylene glycol monododecyl ether	0.13	132
n-$C_{12}H_{25}O(CH_2CH_2O)_8H$[b]		0.10	301
n-$C_{12}H_{25}(CH_2CH_2O)_{12}H$	Dodecaoxyethylene glycol monododecyl ether	0.14	78
n-$C_{12}H_{25}O(CH_2CH_2O)_{12}H$[b]		0.091	116
t-C_8H_{17}-C_6H_4-$O(CH_2CH_2O)_{9.7}H$	Decaoxyethylene glycol mono-p,t-octylphenyl ether (octoxynol 9)	0.27	100

[a] Interpolated for physiologic saline, 0.154 M NaCl.
[b] At 55° instead of 20°.

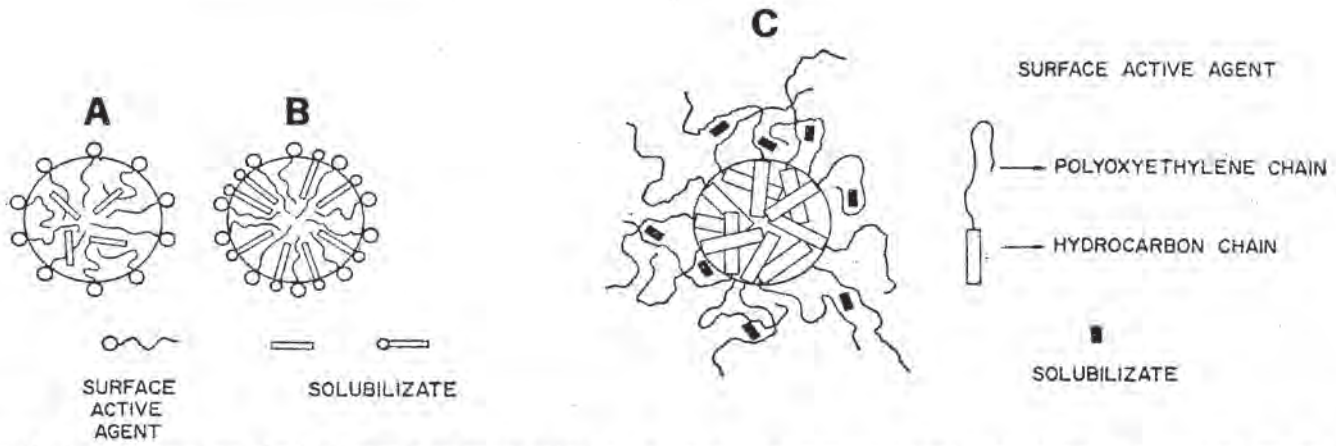


Fig 19-19. The locations of solubilizates in spherical micelles. A: Ionic surfactant (solubilized molecule has no hydrophilic groups); B: ionic surfactant (solubilized molecule has a hydrophilic group); C: nonionic surfactant (polar solubilizate).[12]

when cholesterol or dodecanol is solubilized by sodium lauryl sulfate, their hydroxyl groups penetrate between sulfate ions and are even bound to them by hydrogen bonds, while their hydrocarbon portions are immersed among the dodecyl tails of the surfactant which make up the core of the micelle.

Micelles of polyoxyethylated nonionic surfactants consist of an outer shell of hydrated polyethylene glycol moieties and a core of hydrocarbon moieties. Compounds like phenol, cresol, benzoic acid, salicylic acid, and esters of p-hydroxy and p-aminobenzoic acids have some solubility in water and in oils but considerable solubility in liquids of intermediate polarity like ethanol, propylene glycol or aqueous solutions of polyethylene glycols. When solubilized by nonionic micelles, they are located in the hydrated outer polyethylene glycol shell as shown in Fig 19-19C. Since these compounds have hydroxyl or amino groups, they frequently form complexes with the ether oxygens of the surfactant by hydrogen bonding.

Solubilization is generally nonspecific: any drug which is appreciably soluble in oils can be solubilized. Each has a solubilization limit, comparable to a limit of solubility, which depends on temperature and on the nature and concentration of the surfactant. Hartley distinguishes two categories of solubilizates. The first consists of comparatively large, asymmetrical and rigid molecules forming crystalline solids, such as steroids and dyes. These do not blend in with the normal paraffin tails which make up the micellar core; because of dissimilarity in structure, they remain distinct as solute molecules. They are sparingly solubilized by surfactant solutions, a few molecules/micelle at saturation (see Table IX). The number of carbon atoms in the micellar hydrocarbon core required to solubilize a molecule of steroid or dye at saturation is of the same order of magnitude as the number of carbon atoms of bulk liquid dodecane or hexadecane per molecule of steroid or dye in their saturated solutions in these liquids.

Since solubilization depends on the presence of micelles, it does not take place below the cmc. It can, therefore, be used to determine the cmc, particularly when the solubilizate is a dye or another compound easy to assay. Plotting the maximum amount of a water-insoluble dye solubilized by aqueous surfactant, or the absorbance of its saturated solutions, versus the surfactant concentration produces a straight line which intersects the surfactant concentration axis at the cmc. Above the cmc, the amount of solubilized dye is directly proportional to the number of micelles and, therefore,

Table IX—Micellar Solubilization Capacities of Different Surfactants for Estrone.[13]

Surfactant	Concentration range, molarity	Temp, °C	Moles surfactant/mole solubilized estrone
Sodium laurate	0.025–0.023	40	91
Sodium oleate	0.002–0.35	40	53
Sodium lauryl sulfate	0.004–0.15	40	71
Sodium cholate	0.09–0.23	20	238
Sodium deoxycholate	0.007–0.36	20	476
Diamyl sodium sulfosuccinate	0.08–0.4	40	833
Dioctyl sodium sulfosuccinate	0.002–0.05	40	196
Tetradecyltrimethylammonium bromide	0.005–0.08	20	45
Hexadecylpyridinium chloride	0.001–0.1	20	32
Polysorbate 20	0.002–0.15	20	161
Polysorbate 60	0.0008–0.11	20	83

proportional to the overall surfactant concentration. Below the cmc, no solubilization takes place. This is represented by Curve E of Fig 19-17.

The second category of compounds to be solubilized are often liquid at room temperature and consist of relatively small, symmetrical, and/or flexible molecules such as many constituents of essential oils. These molecules mix and blend in freely with the hydrocarbon portions of the surfactants in the core of the micelles, so as to become indistinguishable from them. Such compounds are extensively solubilized and in the process usually swell the micelles: they augment the volume of the hydrocarbon core and increase the number of surfactant molecules per micelle. Their solubilization frequently lowers the cmc.

Microemulsions[14-16]

Microemulsions are liquid dispersions of water and oil that are made homogeneous, transparent, and stable by the addition of relatively large amounts of a surfactant and a cosurfactant. *Oil* is defined as a liquid of low polarity and low miscibility with water, eg, toluene, cyclohexane, mineral or vegetable oils.

Microemulsions are intermediate in properties between micelles containing solubilized oils and emulsions. While emulsions are lyophobic and unstable, microemulsions are on the borderline between lyophobic and lyophilic colloids. True microemulsions are thermodynamically stable.[17] Therefore, they are formed spontaneously when oil, water, surfactants, and cosurfactants are mixed together. The unstable emulsions require input of considerable mechanical energy for their preparation, which may be supplied by colloid mills, homogenizers or ultrasonic generators.

Both emulsions and microemulsions may contain high volume fractions of the internal phase. For instance, some O/W systems contain 75% (v/v) of oil dispersed in 25% water, although lower internal phase volume fractions are more common.

At low surfactant concentrations, viz, low multiples of the cmc, micelles are spheres (Fig 19-18*A*, *B* and *E*) or ellipsoids. When an oil is solubilized by micelles in water, it blends into the micellar core formed by the hydrocarbon tails of the surfactant molecules (Fig 19-19) and swells the micelles.

Spherical or ellipsoidal micelles are nearly monodisperse, and their mean diameters are in the range of 25 to 60 Å. Microemulsion droplets also have a narrow droplet size distribution with a mean diameter range of approximately 60 to 1000 Å. Since the droplet diameters are less than ¼ of the wavelength of light (4200 Å for violet and 6600 Å for red light), microemulsions scatter little light and are, therefore, transparent or at least translucent.

Emulsions have very broad droplet size distributions. Only the smallest droplets, with diameters of about 1000 to 2000 Å, are below the resolving power of the light microscope. The upper size limit is 25 or 50 μm (250,000 or 500,000 Å). Because emulsion droplets are comparable in size, or larger than the wavelength of visible light, they scatter it more or less strongly depending on the difference in refractive index between oil and water. Thus, most emulsions are opaque.

The three disperse systems—micellar solutions, microemulsions, and emulsions—can be of the O/W (oil-in-water) or W/O type. Aqueous micellar surfactant solutions can solubilize oils and lipid-soluble drugs in the core formed by their hydrocarbon chains. Likewise, oil-soluble surfactants like sorbitan monooleate and docusate sodium form "reverse micelles" in oils (Fig 19-18*E*) capable of solubilizing water in the polar center. The solubilized oil in the former micelles and the solubilized water in the latter may in turn enhance the micellar solubilization of oil-soluble and water-soluble drugs, respectively.

Oil-soluble drugs have been incorporated into O/W emulsions by dissolving them in the oil phase before emulsification.[18] By the same token, it may be possible to dissolve oil-soluble drugs in a vegetable oil and make an oral or parenteral O/W microemulsion. The advantage of such microemulsion systems over conventional emulsions is their smaller droplet size and superior shelf stability. Aqueous micellar solutions[19] and O/W microemulsions[20] have both been used as aqueous reaction media for oil-soluble compounds.

Emulsions and micellar solutions of oils solubilized in aqueous surfactant solutions consist of three components, oil, water and surfactant. Microemulsions generally require a fourth component, called *cosurfactant*. Commonly used cosurfactants are linear alcohols of medium chain length, which are sparingly miscible with water. Since the cosurfactants as well as the surfactants are surface-active, they promote the generation of extensive interfaces through the spontaneous dispersion of oil in water, or vice-versa, resulting in the formation of microemulsions. The large interfacial area between oil and water permits the extensive formation of a mixed interfacial film consisting of surfactant and cosurfactant. This film is called the "interphase" because it is thicker than the surfactant monolayers formed at oil-water interfaces in emulsions. The interfacial tension at the oil-water interface in microemulsions approaches zero, which also contributes to their spontaneous formation. According to another viewpoint, microemulsions are regarded as micelles extensively swollen by large amounts of solubilized oil.

Typical formulations for an O/W and a W/O microemulsion are shown in Table X. The ratio, g surfactant/g solubilized or emulsified oil or water is in the range of 2 to 20 for micellar solutions and 0.01 to 0.1 for emulsions. Microemulsions have intermediate values: The ratios for the formulations in Table X are near unity. In industrial formulations,

Table X—Microemulsion Formulations

Compound	Function	Content in microemulsions, % O/W	Content in microemulsions, % W/O
Sodium lauryl sulfate	Surfactant	13	10
1-Pentanol	Cosurfactant	8	25
Xylene	Oil	8	50
Water		71	15

the ratios are closer to 0.1 to reduce costs. Microemulsions are used in such diverse applications as floor polish and agricultural pesticide formulations and in tertiary petroleum recovery. The use of O/W microemulsions as aqueous vehicles for oil-soluble drugs to be administered by the percutaneous, oral or parenteral route is being investigated.

Colloidal Dispersions

Historical Background of Colloids

The term *colloid*, derived from the Greek word for glue, was applied *ca* 1850 by the British chemist Thomas Graham to polypeptides such as albumin and gelatin, to vegetable gums such as acacia, starch and dextrin, and to inorganic compounds such as gelatinous metal hydroxides and Prussian blue (ferric ferrocyanide). These compounds did not crystallize, and diffused very slowly when dissolved or dispersed in water. They could be separated from ordinary solutes such as salts and sugar, called "crystalloids," as the latter diffused through the fine pores of dialysis membranes made from animal gut which retained the "colloids." "Crystalloids" crystallized readily from solution.[21,22]

Von Weimarn was the first to identify colloidality as a state of subdivision of matter rather than as a category of substances. Many of Graham's "colloids," especially proteins, have been crystallized. Moreover, von Weimarn was able to prepare all "crystalloids" investigated in the colloidal state. Colloidal dispersions by the condensation method resulted from high relative supersaturation, which produced a large number of small nuclei.[21-23,28] For instance, clear, transparent solidified jellies were prepared by cooling aqueous solutions of $CaCl_2$, $Ba(SCN)_2$ and $Al_2(SO_4)_3$, and aqueous-alcoholic solutions of NaCl, KCl, NH_4Cl, KSCN, NaBr and NH_4NO_3 which were nearly saturated at room temperature.[28]

Colloid chemistry became a science in its own right around 1906, when Wolfgang Ostwald wrote the booklet "The World of the Neglected Dimensions." In it, he focused on colloidal systems as a state of matter that has disperse phases intermediate in size between small molecules or ions in solution and large, visible particles in suspension. Ostwald became the first editor of the journal *Kolloid-Zeitschrift* in 1907. The studies of colloidal systems and surface or interfacial phenomena are intimately related. The properties of colloidal dispersions are largely governed by the nature of the surface of their particles. The division of the American Chemical Society specializing in colloidal systems and interfaces is called the "Division of Colloid and Surface Chemistry," while the pertinent session of the Gordon Research Conferences is called "Chemistry at Interfaces."

Colloid and surface chemistry deals with an unusually wide variety of industrial and biological systems. A few examples are catalysts, lubricants, adhesives, latexes for paints, rubbers and plastics, soaps and detergents, clays, packaging films, cigarette smoke, liquid crystals, cell membranes, mucous secretions and aqueous humors.

Definitions and Classifications

Colloidal Systems and Interfaces

Colloidal dispersions consist of at least two discrete phases, namely, one or more disperse, dispersed or internal phases and a continuous or external phase called the *dispersion medium* or *vehicle*. What distinguishes colloidal dispersions from solutions and coarse dispersions is the particle size of the disperse phase. Systems in the colloidal state contain one or more substances that have at least one dimension in the range of 10 to 100 Å (1 Angstrom unit = 10^{-8} cm = 10^{-10} m) or 1–10 nm (1 nanometer = 10^{-9} m) at the lower end, and a few micrometers (μm) at the upper end (1 μm = 10^4 Å = 10^{-6} m). Thus blood, cell membranes, the thinner nerve fibers, milk, rubber latex, fog and beer foam are colloidal systems. Some types of materials, such as many emulsions, and oral suspensions of most organic drugs, are coarser than true colloidal systems but exhibit similar behavior. Even though serum albumin, acacia and povidone form true or molecular solutions in water, the size of the individual solute molecules places such solutions in the colloidal range (particle size > 10 Å).[21-27]

The following features distinguish colloidal dispersions from coarse suspensions. Disperse particles in the colloidal range are usually too fine to be visible in a light microscope, because at least one dimension measures 1 μm or less. They are often visible in the ultramicroscope and always in the electron microscope. Coarse suspended particles are frequently visible to the naked eye and always in the light microscope. Colloidal particles, as opposed to coarse particles, pass through ordinary filter paper but are retained by dialysis or ultrafiltration membranes. Because of their small size, colloidal dispersions undergo little or no sedimentation or creaming: Brownian motion maintains the disperse particles in suspension (see below).

Except for high polymers, most soluble substances can be prepared either as low-molecular-weight solutions, or as colloidal dispersions or coarse suspensions depending on the choice of the dispersion medium and the dispersion technique.[26,28]

Because of the small size of colloidal particles, appreciable fractions of their atoms, ions or molecules are located in the boundary layer between a particle and air (surface) or between a particle and a liquid or solid (interface). The ions in the surface of a sodium chloride crystal and the water molecules in the surface of a rain drop are subjected to unbalanced forces of attraction, whereas the ions or molecules in the interior of the materials are surrounded by similar ions or molecules on all sides, with balanced force fields. Thus a surface free energy component is added to the total free energy of colloidal particles, which becomes relatively more important as the particles become smaller, ie, as greater fractions of their ions, atoms or molecules are located in their surface or interfacial region. Hence the solubility of very fine solid particles and the vapor pressure of very small liquid droplets are larger than the corresponding values of coarse particles and large drops of the same materials, respectively.

Specific Surface Area—Decreasing particle size increases the surface-to-volume ratio, which is expressed as the specific surface area A_{sp}, namely, the area A (cm^2) per unit volume V (1 cm^3) or per unit mass M (1 gram). For a sphere, $A = 4\pi r^2$ and $V = 4/3\,\pi r^3$. If the density, d, of the material is expressed in g/cm^3, the specific surface area is

$$A_{sp} = \frac{A}{V} = \frac{4\pi r^2}{4/3\pi r^3} = \frac{3}{r}\ cm^2/cm^3 = \frac{3}{r}\ cm^{-1}$$

or

$$A_{sp} = \frac{A}{M} = \frac{A}{Vd} = \frac{4\pi r^2}{4/3\pi r^3 d} = \frac{3}{rd}\ cm^2/g$$

Table XI—Effect of Comminution on Specific Surface Area of a Volume of $4\pi/3$ cm^3, Divided into Uniform Spheres of Radius R

Number of spheres	R	A_{sp} cm^2/cm^3
1	1 cm	3
10^3	0.1 cm = 1 mm	3×10
10^6	0.1 mm	3×10^2
10^9	0.01 mm = 10 μm	3×10^3
10^{12}	1 μm	3×10^4
10^{15}	0.1 μm	3×10^5
10^{18}	0.01 μm	3×10^6
10^{21}	10 Å = 1 nm	3×10^7
10^{23}	1 Å	3×10^8

Shaded region corresponds to colloidal particle-size range.

Table XI illustrates the effect of comminution on the specific surface area of $4\ \pi/3$ cm^3 of a material consisting initially of one sphere of 1 cm radius. As the material is broken up into an increasingly larger number of smaller and smaller spheres, its specific surface area increases commensurately.

The solid adsorbents activated charcoal and kaolin have specific surface areas of about 6×10^6 cm^2/g and 10^4 cm^2/g, respectively. One gram of activated charcoal, because of its extensive porosity and internal voids, has an area equal to ⅙ acre.

In conclusion, colloidal systems by definition are those polyphasic systems where at least one dimension of the disperse phase measures between 10 or 100 Å and a few micrometers. The term "colloidal" designates a state of matter characterized by submicroscopic dimensions rather than certain substances. Any dispersed substance with the proper dimension or dimensions is in the colloidal state.

Physical States of Disperse and Continuous Phases

A useful classification of colloidal systems (systems in the colloidal particle size range) is based on the state of matter of the disperse phase and the dispersion medium, ie, whether they are solid, liquid or gaseous.[25,27] Table XII summarizes the various combinations and lists examples. A *sol* is the colloidal dispersion of a solid in a liquid or gaseous medium. Prefixes designate the dispersion medium, such as hydrosol, alcosol, aerosol for water, alcohol and air, respectively. Sols are fluid. If the solid particles form bridged structures possessing some mechanical strength, the system is called a gel (hydrogel, alcogel, aerogel).

Interaction Between Disperse Phase and Dispersion Medium

A second useful classification of colloidal dispersions, originated by Ostwald, is based on the affinity or interaction between the disperse phase and the dispersion medium.[2,3,8] It refers mostly to solid-in-liquid dispersions. According to this classification, colloidal dispersions are divided into the two broad categories of lyophilic and lyophobic. Some soluble, low-molecular-weight substances have molecules with both tendencies, forming a third category called association colloids.

Lyophilic Dispersions—Where there is considerable attraction between the disperse phase and the liquid vehicle, ie, extensive solvation, the system is said to be *lyophilic* (solvent-loving). If the dispersion medium is water, the system is said to be *hydrophilic*. Such solids as bentonite, starch, gelatin, acacia and povidone swell, disperse or dissolve spontaneously in water.

Hydrophilic colloidal dispersions can be subdivided further as follows:

True solutions, formed by water-soluble polymers (acacia and povidone).

Gelled solutions, gels or jellies if the polymers are present at high concentrations and/or at temperatures where their water solubility is low. Examples of such hydrogels are relatively concentrated solutions of gelatin and starch, which set to gels on cooling, or of methylcellulose, which gel on heating.

Particulate dispersions, where the solids do not form molecular solutions but remain as discrete though minute particles. Bentonite and microcrystalline cellulose form such hydrosols.

Lipophilic or oleophilic substances have pronounced affinity for oils. Oils are nonpolar liquids consisting mainly of hydrocarbons, with few polar groups and low dielectric constants. Examples are mineral oil, benzene, carbon tetrachloride, vegetable oils (cottonseed or peanut oil) and essential oils (lemon or peppermint oil). Substances which form *oleophilic* colloidal dispersions include polymers like polystyrene and unvulcanized or gum rubber, which dissolve molecularly in benzene, magnesium or aluminum stearate or which dissolve or disperse in cottonseed oil, and activated charcoal, which forms sols or particulate dispersions in all oils.

Because of the high affinity or attraction between the dispersion medium and the disperse phase, lyophilic dispersions form spontaneously when the liquid vehicle is brought into contact with the solid phase. They are thermodynamically stable and reversible, ie, they are easily reconstituted even after the dispersion medium has been removed from the solid phase.[22,24-27]

Table XII—Classification of Colloidal Dispersions According to State of Matter

Disperse Phase	Dispersion Medium (Vehicle)		
	Solid	Liquid	Gas
Solid	Zinc oxide paste (zinc oxide + starch in petrolatum). Toothpaste (dicalcium phosphate or calcium carbonate with sodium carboxymethylcellulose binder). Pigmented plastics (titanium dioxide in polyethylene).	Sols: Bentonite Magma NF. Trisulfapyrimidines Oral Suspension USP. Magnesia and Alumina Oral Suspension USP. Tetracycline Oral Suspension USP.	Solid aerosols: Smoke, dust. Epinephrine Bitartrate Inhalation Aerosol USP. Isoproterenol Sulfate Inhalation Aerosol.
Liquid	Absorption bases (aqueous medium in Hydrophilic Petrolatum USP). Emulsion bases (oil in Hydrophilic Ointment USP). Butter.	Emulsions: Mineral Oil Emulsion USP. Soybean oil in water emulsion for IV feeding. Milk. Mayonnaise.	Liquid aerosols: Mist, fog. Nasal relief sprays (naphazoline hydrochloride solution). Betamethasone Valerate Topical Aerosol USP. Povidone-Iodine Topical Aerosol.
Gas	Solid foams (foamed plastics and rubbers). Pumice.	Foams. Carbonated beverages. Effervescent salts in water.	No colloidal dispersions.

Lyophobic Dispersions—When there is little attraction between the disperse phase and the dispersion medium, the dispersion is said to be *lyophobic* (solvent-hating). *Hydrophobic* dispersions consist of particles that are not hydrated, so that water molecules interact with or attract one another in preference to solvating the particles. They include aqueous dispersions of oleophilic materials such as polystyrene or gum rubber (latex), steroids and other organic lipophilic drugs, paraffin wax, magnesium stearate, and of cottonseed or soybean oil (emulsion). While lipophilic materials are generally hydrophobic, materials like sulfur, silver chloride and gold form hydrophobic dispersions without being lipophilic. Water-in-oil emulsions are lyophobic dispersions in lipophilic vehicles.

Because of the lack of attraction between the disperse and the continuous phase, lyophobic dispersions are intrinsically unstable and irreversible. Their large surface free energy is not lowered by solvation. The dispersion process does not take place spontaneously, and once the dispersion medium has been separated from the disperse phase, the dispersion is not easily reconstituted. The dividing line between hydrophilic and hydrophobic dispersions is not very sharp. For instance, gelatinous hydroxides of polyvalent metals such as $Al(OH)_3$ and $Mg(OH)_2$, and clays such as bentonite and kaolin, possess some characteristics of both.[22,24,27]

Association Colloids—Organic compounds which contain large hydrophobic moieties together with strongly hydrophilic groups in the same molecule are said to be amphiphilic. While the individual molecules are generally too small to bring their solutions into the colloidal size range, they tend to associate in aqueous or oil solutions into micelles (see above). Because micelles are large enough to qualify as colloidal particles, such compounds are called association colloids.

Lyophobic Dispersions

Most of the discussion of lyophobic dispersions deals with hydrophobic dispersions or hydrosols (hydrophobic solids or liquids dispersed in aqueous media) because water is the most widely used vehicle. They comprise aqueous dispersions of insoluble organic and inorganic compounds which usually have low degrees of hydration. Organic compounds which are preponderantly hydrocarbon in nature and possess few hydrophilic or polar groups are insoluble in water and hydrophobic.

Hydrophobic dispersions are intrinsically unstable. The most stable state of such systems contains the disperse phase coalesced into large crystals or drops, so that the specific surface area and surface free energy are reduced to a minimum. Therefore, mechanical, chemical or electrical energy must be supplied to the system to break up the disperse phase into small particles, providing for the increase in surface free energy resulting from the parallel increase in specific surface area. Furthermore, special means must be found to stabilize hydrophobic dispersions, preventing the otherwise spontaneous coalescence or coagulation of the disperse phase after it has been finely dispersed.

Preparation and Purification of Lyophobic Dispersions

Colloidal dispersions are intermediate in size between true solutions and coarse suspensions. They can be prepared by aggregation of small molecules or ions until particles of colloidal dimensions result (condensation methods), or by reducing coarse particles to colloidal dimensions through comminution or peptization (dispersion methods).

Dispersion Methods—The first method, *mechanical disintegration* of solids and liquids into small particles and their dispersion in a fluid vehicle, is frequently carried out by input of mechanical energy via shear or attrition. Equipment such as colloid and ball mills, micronizers and, for emulsions, homogenizers is described in Chapters 83 and 88 and in Ref 29. Dry grinding with inert, water-soluble diluting agents also produces colloidal dispersions. Sulfur hydrosols may be prepared by triturating the powder with urea or lactose followed by shaking with water.

Ultrasonic generators provide exceptionally high concentrations of energy. Successful dispersion of solids by means of ultrasonic waves can only be achieved with comparatively soft materials such as many organic compounds, sulfur, talcum, and graphite. Where fine emulsions are mandatory, such as soybean oil-in-water emulsions used for intravenous feeding, emulsification by ultrasound waves is the method of choice.[29] The formation of aerosols is described in Chapter 92.

It should be reiterated that hydrosols of hydrophobic substances are intrinsically unstable. While mechanical disintegration may break up the disperse phase into colloidal particles, the resultant dispersions tend towards separation of that phase. Recrystallization, coagulation or coalescence causes the disperse particles to become progressively coarser and fewer, ultimately resulting in the separation of a macroscopic phase. To avoid this, stabilizing agents must be added during or shortly after the dispersion process (see below). For instance, lecithin may be used to stabilize soybean oil emulsions.

Peptization is a second method for preparing colloidal dispersions. The term, coined by Graham, is defined as the breaking up of aggregates or secondary particles into smaller aggregates or into primary particles in the colloidal size range. Particles which are not formed of smaller ones are called "primary." Peptization is synonymous with *deflocculation*. It can be brought about by the removal of flocculating agents, usually electrolytes, or by the addition of deflocculating or peptizing agents, usually surfactants, water-soluble polymers or ions which are adsorbed at the particle surface.[24,27]

The mechanisms of the following examples are explained in subsequent sections. When powdered activated charcoal is added to water with stirring, the aggregated grains are broken up only incompletely and the resultant suspension is gray and translucent. The addition of 0.1% or less of sodium lauryl sulfate or octoxynol disintegrates the grains into finely dispersed particles forming a deep black and opaque dispersion. Ferric or aluminum hydroxide freshly precipitated with ammonia can be peptized with small amounts of acids which reduce the pH below the isoelectric points of the hydroxides (see below). Even washing the gelatinous precipitate of $Al(OH)_3$ with water tends to peptize it. In quantitative analysis, the precipitate is therefore washed with dilute solutions of ammonium salts that act as flocculating agents, rather than with water.

Condensation Methods—The preparation of sulfur hydrosols is employed to illustrate condensation or aggregation methods. Sulfur is insoluble in water but somewhat soluble in alcohol. When an alcoholic solution of sulfur is mixed with water, a bluish white colloidal dispersion results. In the absence of added stabilizing agents, the particles tend to agglomerate and precipitate on standing. This technique of dissolving the material in a water-miscible solvent such as alcohol or acetone and producing a hydrosol by precipitation with water is applicable to many organic compounds, and has been used to prepare hydrosols of natural resins like mastic, of stearic acid and of polymers (the so-called pseudolatexes).

For sulfur, another less common physical method is to introduce a current of sulfur vapor into water. Condensation produces colloidal particles. Alternatively, the very fine powder produced by condensing sulfur vapor on cold

solid surfaces (sublimed sulfur or flowers of sulfur) can be dispersed in water by addition of a suitable surfactant to produce a hydrosol.

Chemical methods include the reaction between hydrogen sulfide and sulfur dioxide, eg, by bubbling H_2S into an aqueous SO_2 solution:

$$2\ H_2S + SO_2 \rightarrow 3\ S + 2\ H_2O$$

The same reaction occurs when aqueous solutions containing sodium sulfide and sulfite are acidified with an excess of sulfuric or hydrochloric acid. Another reaction is the decomposition of sodium thiosulfate by sulfuric acid, using either very dilute or very concentrated solutions to obtain colloidally dispersed sulfur:

$$H_2SO_4 + 3\ Na_2S_2O_3 \rightarrow 4\ S + 3\ Na_2SO_4 + H_2O$$

Both reactions also produce pentathionic acid, $H_2S_5O_6$, as a by-product. The preferential adsorption of the pentathionate anion at the surface of the sulfur particles confers a negative electric charge on the particles, stabilizing the sol (see below).[22,26,27] When powdered sulfur is boiled with a slurry of lime, it dissolves with the formation of calcium pentasulfide and thiosulfate. Subsequent acidification produces the colloidal "milk of sulfur," which on washing and drying yields Precipitated Sulfur USP (see Chapter 82).

Sols of ferric, aluminum, chromic, stannic and titanium hydroxides or hydrous oxides are produced by hydrolysis of the corresponding chlorides or nitrates:

$$AlCl_3 + 3\ H_2O \rightleftharpoons Al(OH)_3 + 3\ HCl$$

Hydrolysis is promoted by boiling the solution and/or by adding a base to neutralize the acid formed.

Double decompositions producing insoluble salts can lead to colloidal dispersions. Examples are silver chloride and nickel sulfide:

$$NaCl + AgNO_3 \rightarrow AgCl + NaNO_3$$

$$(NH_4)_2S + NiCl_2 \rightarrow NiS + 2\ NH_4Cl$$

Compare also the preparation of White Lotion, which contains precipitated zinc sulfide and sulfur (Chapter 63). Reducing salts of gold, silver, copper, mercury, platinum, rhodium and palladium with formaldehyde, hydrazine, hydroxylamine, hydroquinone or stannous chloride produces hydrosols of the metals. These are strongly colored, eg, red or blue.[21,22,27]

Radioactive Colloids—Colloidal dispersions containing radioactive isotopes find increasing diagnostic and therapeutic application in nuclear medicine. Radioactive colloids that accumulate in tumors and/or lesions or emboli, indicating their location and size, may be used as diagnostic aids. Radioactive colloids with a particle size of about 300 Å, injected intravenously, locate mainly in the reticuloendothelial systems of liver, spleen and other organs and are used in scintillation imaging. The radiation emitted by the colloids is made visible by stationary or scanning devices which show the location, size and shape of the organ being investigated, as well as any tumors within. Radiocolloids are useful in anticancer radiation therapy because of their low solubility, radiation characteristics, and their ability to accumulate and remain located in certain target organs or tumors.[30]

Colloidal gold Au 198 is made by reducing a solution of gold (^{198}Au) chloride either by treatment with ascorbic acid or by heating with an alkaline glucose solution. Gelatin is added as a protective colloid (see below). The particle size ranges from 50 to 500 Å with a mean of 300 Å. The color of the sol is cherry-red in transmitted light. Violet or blue sols have excessively large particle sizes and should be discarded. Colloidal gold is used as a diagnostic and therapeutic aid (see Chapter 33). The half-life of ^{198}Au is 2.7 days.

Technetium 99m sulfur colloid is prepared by reducing sodium pertechnetate ^{99m}Tc with sodium thiosulfate. The product, a mixture of technetium sulfide and sulfur in the colloidal particle size range, is stabilized with gelatin. It is used chiefly in liver, spleen and bone scanning. Its half-life is 6.0 hour.

Microspheres of gelatin or human serum albumin can be prepared in fairly narrow particle-size ranges from 100–200 Å through 45–55 μm. A variety of β- and γ-emitting radionuclides such as ^{131}I, ^{99m}Tc, ^{113m}In or ^{51}Cr can be incorporated to label the microspheres. Such products have been used to scan heart, brain, urogenital and gastrointestinal tracts, liver, and in pulmonary perfusion and inhalation studies.[30]

Refer to Chapters 32 and 33 for an in-depth discussion of radioisotopes.

Organic compounds that are weak bases, such as alkaloids, are usually much more soluble at lower pH values where they are ionized than at higher pH values where they exist as the free base. Increasing the pH of their aqueous solutions well above their pKa may cause precipitation of the free base. Organic compounds which are weak acids, such as barbiturates, are usually much more soluble at higher pH values where they are ionized than at lower pH values where they are in the un-ionized acid form. Lowering the pH of their solutions well below their pKa may cause precipitation of the un-ionized acid. Depending on the supersaturation of the un-ionized acids or bases and on the presence of stabilizing agents, the resultant dispersions may be in the colloidal range.

Kinetics of Particle Formation—When the solubility of a compound in water is exceeded, its solution becomes supersaturated and the compound may precipitate or crystallize. The rate of precipitation, the particle size (whether colloidal or coarse), and the particle size uniformity or distribution (whether a narrow distribution and nearly monodisperse or homodisperse particles, or a broad distribution and polydisperse or heterodisperse particles) depend on two successive and largely independent processes, nucleation and growth of nuclei.

When a solution of a salt or of sucrose is supercooled, or when a chemical reaction produces a salt in a concentration exceeding its solubility product, separation of the excess solid from the supersaturated solution is far from instantaneous. Clusters of ions or molecules called nuclei must exceed a critical size before they become stable and capable of growing into colloidal size crystals. These embryonic particles have much more surface for a given weight of material than large and stable crystals, resulting in higher surface free energy and greater solubility.

Whether *nucleation* takes place depends on the *relative supersaturation*. If C is the actual concentration of the solute before crystallization has set in, and C_s is its solubility limit, $C - C_s$ is the supersaturation and $(C - C_s)/C_s$ is the relative supersaturation. Von Weimarn recognized that the rate or velocity of nucleation (number of nuclei formed per liter per second) is proportional to the relative supersaturation. Nucleation seldom occurs at relative supersaturations below 3. The foregoing statement refers to homogeneous nucleation, where the nuclei are clusters of the same chemical composition as the crystallizing phase. If the solution contains solid impurities, such as dust particles in suspension, these may act as nuclei or centers of crystallization (heterogeneous nucleation).

Once nuclei have formed, the second process, *crystallization*, begins. Nuclei grow by accretion of ions or molecules from solution forming colloidal or coarser particles until the supersaturation is relieved, ie, until $C = C_s$. The rate of

crystallization or growth of nuclei is proportional to the supersaturation. The appropriate equation,

$$\frac{dm}{dt} = \frac{A_{sp}D}{\delta}(C - C_s)$$

is similar to the Noyes-Whitney equation governing the dissolution of particles (see Chapter 31) except that $C < C_s$ for the latter process, making dm/dt negative. In both equations, m is the mass of material crystallizing out in time t, D is the diffusion coefficient of the molecules or ions of the solute, δ is the length of the diffusion path or the thickness of the liquid layer adhering to the growing particles, and A_{sp} is their specific surface area. The presence of dissolved impurities may affect the rate of crystallization and even change the crystal habit, provided that these impurities are surface-active and become adsorbed on the nuclei or growing crystals.[22,23,25-28] For instance, 0.005% polysorbate 80 or octoxynol 9 significantly retard the growth of methylprednisolone crystals in aqueous media. Gelatin or povidone, at concentrations <0.10%, retard the crystal growth of sulfathiazole in water.

Von Weimarn found that the particle size of the crystals depends strongly on the concentration of the precipitating substance. At a very low concentration and slight relative supersaturation, diffusion is quite slow because the concentration gradient is very small. Sufficient nuclei will usually form to relieve the slight supersaturation locally. Crystal growth is limited by the small amount of excess dissolved material available to each particle. Hence, the particles cannot grow beyond colloidal dimensions. This condition is represented by points A, D and G of the schematic plot of von Weimarn (Fig 19-20). At intermediate concentrations, the extent of nucleation is somewhat greater but much more material is available for crystal growth. Coarse crystals rather than colloidal particles result (points B, E or H).

At high concentrations, nuclei appear so quickly and in such large numbers that supersaturation is relieved almost immediately, before appreciable diffusion occurs. The high viscosity of the medium also slows down diffusion of excess dissolved ions or molecules, retarding crystal growth without substantially affecting the rate of nucleation. A large number of very small particles results which, because of their proximity, tend to link, producing a translucent gel (points C and F). On subsequent dilution with water, such gels usually yield colloidal dispersions.

Thus, colloidal systems are usually produced at very low and high supersaturations. Intermediate values of supersaturation tend to produce coarse crystals. Low solubility is a necessary condition for producing colloidal dispersions. If the solubility of the precipitate is increased, for instance by heating the dispersion, a new family of curves will result, similar in shape to ABC, DEF, and GHI of Fig 19-20, but displaced upwards (towards larger particle sizes) and to the right (towards higher concentrations).[25-28]

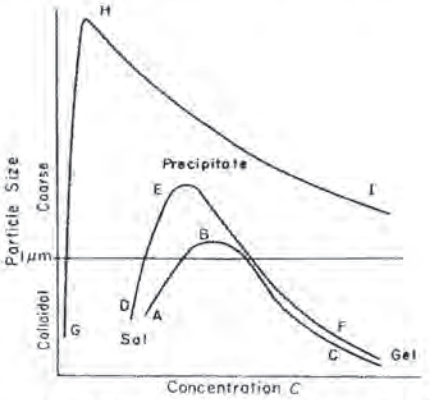


Fig 19-20. Effect of the concentration of the precipitating material and of aging on particle size.[26] Curves ABC, DEF and GHI correspond to increasing aging. Both axes are on a logarithmic scale.

Condensation methods generally produce polydisperse sols because nucleation continues while established nuclei grow. The particles in the resultant dispersion grew from nuclei formed at different times and had different growth periods.

A useful technique for preparing monodispersed sols in the colloidal range by precipitation consists in forming all the nuclei in a single, brief burst: When, in the course of the precipitation process, the rate of homogeneous nucleation becomes appreciable, a brief period of nucleation relieves the supersaturation partially to such an extent that no new nuclei form subsequently. By controlling the precipitation process, it is rendered so slow that the supersaturation remains too small for further nucleation. Therefore, the nuclei formed in the initial burst grow uniformly by diffusion of the precipitating material as the precipitation process proceeds slowly. Throughout the rest of the precipitation, the supersaturation never again reaches sufficiently high values for forming new nuclei. It is relieved by continuous growth of the existing nuclei.[23,25,31]

Controlled hydrolysis of salts of di- and trivalent cations in aqueous solution at elevated temperatures has been used to produce colloidal dispersions of metal (hydrous) oxides of uniform size and shape, in a variety of well-defined shapes (eg, sphere, lath, cube, disc, hexagonal). Complexation of the cations, concentration and temperature control the rate of hydrolysis and, hence, the chemical composition, crystallinity, shape and size of the dispersed phase.[32]

A feature of Fig 19-20 is that aging increases the particle size. Curves ABC, DEF and GHI correspond to increasing times after mixing the reagents. Typical ages are 10–30 min, several hours, and weeks or years, respectively. This gradual increase in particle size of crystals in their mother liquor is a recrystallization process called *Ostwald ripening*. Very small particles have a higher solubility than large particles of the same substance owing to their greater specific surface area and higher surface free energy. In a saturated solution containing precipitated particles of the solute in a wide range of particle sizes, the very smallest particles dissolve spontaneously and the material deposits onto the large particles. The growth of the large crystals at the expense of the very small ones occurs because this process lowers the free energy of the dispersion. As mentioned above, the most stable system is the suspension of a few coarse crystals, whereas the colloidal dispersion of a great many fine particles of the same substance is intrinsically less stable.

The spontaneous coarsening of colloidal dispersions on aging is accelerated by a relatively high solubility of the precipitate and can be retarded by lowering the solubility or by adding traces of surface-active compounds which are adsorbed at the particle surface. For instance, barium sulfate precipitated by mixing concentrated solutions of sodium sulfate and barium chloride is largely in the colloidal range and passes through filter paper. The colloidal particles gradually grow in size by Ostwald ripening, forming large crystals which can be removed quantitatively by filtration. Heating the aqueous dispersion speeds up this recrystallization by increasing the solubility of barium sulfate in water. The addition of ethyl alcohol lowers the solubility, retarding Ostwald ripening so that the dispersion remains in the colloidal state for years.

Mathematically the effect of particle size on solubility is expressed as

$$S = S_\infty \exp\left(\frac{2\gamma M}{r\rho RT}\right) \qquad (34)$$

Table XIII—Effects of Particle Size on Solubility

r (μm)	S
0.01	$7S_\infty$
0.10	$1.12S_\infty$
1.0	$1.01S_\infty$
10	$1.001S_\infty$

$M = 500$; $\gamma = 30$ ergs/cm^2; $\rho = 1$

where S is the solubility of a spherical crystal of radius r, S_∞ is the solubility of an infinitely large crystal ($r = \infty$), M is the molecular weight, ρ is the density, γ is the crystal/solvent interfacial tension, R is the gas constant and T is the absolute temperature. Only approximations can be obtained with this equation because the particles are not spheres, and γ values are different for different crystal faces. Table XIII shows the magnitude of particle size effects on the solubility for reasonable values of M, γ and ρ. It is evident that with particles in the colloidal range, ie, $r \geq 1$ μm, S values become appreciably greater than that for a coarse crystal, hence the tendency for very fine particles to dissolve and for coarse crystals to grow at the expense of the former. This difference in solubility explains why difficulty is encountered in preparing and stabilizing suspensions of very fine particles of certain substances.

Two techniques are used to increase the solubility of very slightly soluble drugs and, hence, their rate of dissolution *in vivo*. Many organic compounds exist in various polymorphic modifications. For instance, corticosterone, testosterone, sulfaguanidine and pentobarbital each have four polymorphic forms, with different melting points and crystal structures. The three metastable polymorphs have higher solubilities than the stable form. Solvates of solid drugs, eg, hydrates, have different crystalline structures and either higher or lower solubilities than the anhydrous forms. Theophylline monohydrate is less soluble than the anhydrous form while succinylsulfathiazole is less soluble than its solvate with 1-pentanol. Milling and grinding organic crystals may produce significant proportions of amorphous or strained crystalline material, which has higher solubility than the original crystalline material.[33]

Another process by which particles in colloidal dispersions grow in size is by agglomeration of individual particles into aggregates. This process, called coagulation, is discussed below.

Purification of Hydrosols by Dialysis and Ultrafiltration

Many hydrosols contain low molecular-weight, water-soluble impurities. Inorganic dispersions often contain salts formed by the reaction producing the disperse phase. Salts are especially objectionable in the case of hydrophobic dispersions because they tend to coagulate such dispersions. Protein solutions often contain salts added as part of the separation procedure. The blood of patients with renal insufficiency contains excessive concentrations of urea and other low-molecular-weight metabolites and salts. These dissolved impurities of small molecular size are removed from the colloidal dispersions by means of membranes with pore openings smaller than the colloidal particles.

Membranes—Conventional filter papers are permeable to colloidal particles as well as to small solute molecules. Among the early membranes capable of retaining colloidal particles but permeable to small solute molecules were pig's bladder and parchment. Most membranes in current use consist of cellulose, cellulose nitrate prepared from collodion, cellulose acetate or synthetic polymers, and are available in a variety of shapes, gauges, and pore sizes. *Gel cellophane* is most widely used. It consists of sheets or tubes of cellulose made by extruding cellulose xanthate solutions (viscose) through slit or annular dies into a sodium bisulfate/sulfuric acid bath which decomposes the xanthate, precipitating the regenerated cellulose in a highly swollen or gel state. If the cellulose film were permitted to dry after purification and washing with water, it would crystallize and shrink excessively, losing most of its extensive micropore structure and turning somewhat brittle. The film is therefore impregnated with glycerin before drying. Glycerin remains in the film rather than evaporating like water. It reduces the shrinkage and blocks crystallization. This action prevents the collapse of the porous gel structure and plasticizes the film, keeping it flexible. A typical dialysis tube made from sausage casing swells to about twice its thickness in water and has an average pore diameter of 34 Å. While the pore structure of cellophane films used in dialysis and ultrafiltration causes retention of colloidal particles but permits the passage of small solute molecules, osmotic membranes are only permeable to water and retain small solute molecules as well as colloidal particles.

Dialysis—The colloidal dispersion is placed inside a sac made of sausage casing dipping in water. The small solute molecules diffuse out into the water while the colloidal material remains trapped inside because of its size. The rate of dialysis is increased by increasing the area of the membrane, by stirring, and by maintaining a high concentration gradient across the membrane. For the latter purpose, the water is replenished continuously or at least frequently. A membrane configuration which provides a particularly extensive transfer area for a given volume of dispersion is the hollow fiber. A typical fiber measures 175 μm inside diameter and 225 μm outside diameter. The dispersion to be dialyzed is circulated inside a bundle of parallel fibers while water is circulated outside the fibers throughout the bundle. Dialysis of the diffusing species takes place across the thin fiber wall. Dialysis is used in the laboratory to purify sols and to study binding of drugs by proteins, as well as in some manufacturing processes.

Electrodialysis—If the low-molecular-weight impurities to be removed are electrolytes, the dialysis can be speeded up by applying an electric potential to the sol which produces electrolysis. An electrodialyzer (Fig 19-21) is divided into three compartments by two dialysis membranes supported by screens. The two outer compartments, in which the two electrodes are placed, are filled with water while the sol is placed into the center compartment. Under the influence of the applied potential, the anions migrate from the sol into the anode (right) compartment while the cations migrate into the cathode compartment. Low-molecular-weight nonelectrolyte solutes diffuse into either compartment.

Colloidal particles are usually charged and therefore tend to migrate towards the membrane sealing off the compartment with the electrode of opposite charge. The combination of electrophoresis (see below) and gravitational sedimentation produces the accumulation of negatively charged sol particles shown in Fig 19-21. Hence the supernatant

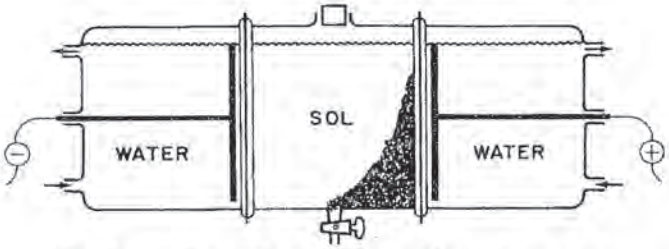


Fig 19-21. Electrodialyzer showing electrodecantation.

liquid can be changed by decantation. This process, which may be used to speed up electrodialysis, is called *electrodecantation.*[21,25]

Ultrafiltration—When a sol is placed in a compartment closed by a dialysis membrane and pressure is applied, the liquid and the small solute molecules are forced through the membrane while the colloidal particles are retained. This process, called ultrafiltration, is based on a sieving mechanism in which all components smaller than the pore size of the filter membrane pass through it. The pressure difference required to push the dispersion medium through the ultrafilter is provided by gas pressure applied on the sol side or by suction on the filtrate side. The membrane is usually supported on a fine wire screen.[24-27]

As ultrafiltrate is being removed, the sol becomes more concentrated because a constant amount of disperse particles is confined to a decreasing volume of liquid. Some dissolved small molecules or ions are left in the sol together with the residual water. To avoid the increase in concentration of the colloidal particles and remove the dissolved impurities completely, the ultrafiltrate squeezed from the sol is replenished continuously or intermittently with an equal volume of water. During ultrafiltration, solids tend to accumulate on and near the membrane. To prevent this buildup and maintain uniform composition throughout the sol, it is stirred.

Bundles of hollow fibers are used for ultrafiltration in the laboratory and on large scale. To withstand higher pressures, the wall thickness of the fibers used in ultrafiltration is usually greater than that of fibers used exclusively for dialysis. When hollow fibers are fouled by excessive accumulation of solids on the inner wall, they are cleaned by backflushing with water or ultrafiltrate.

Hemodialysis—The blood of uremic patients is dialyzed periodically in "artificial kidney" dialyzers to remove urea, creatinine, uric acid, phosphate and other metabolites, and excess sodium and potassium chloride. The dialyzing fluid contains sodium, potassium, calcium, chloride and acetate ions (the latter are converted in the body to bicarbonate), dextrose and other constituents in the same concentration as normal plasma. Since it contains no urea, creatinine, uric acid, phosphate nor any of the other metabolites normally eliminated by the kidneys, these compounds diffuse from the patient's blood into the dialyzing fluid until their concentration is the same in blood and fluid. Sodium and potassium chloride diffuse from blood to fluid because of their higher initial concentration in the blood, and continue to diffuse until the concentration is equalized. The volume of dialyzing fluid is much greater than that of blood. The great disparity in volume and the replenishment of dialyzate with fresh fluid ensure that the metabolites and the excess of electrolytes are removed almost completely from the blood. Hemodialysis is also employed in acute poisoning cases.

Plasma proteins and blood cells cannot pass through the dialysis membrane because of their size. Edema resulting from water retention can be relieved by ultrafiltration through the application of a slight pressure on the blood side or a partial vacuum on the fluid side.

The three geometries used to circulate the blood and the dialyzing fluid in a countercurrent fashion are a coil of flattened cellulose tubing wound concentrically with a supporting mesh screen around a core, a stack of flat cellulose sheets separated by ridged or grooved plates, and hollow fibers. The regenerated cellulose used in the former two is precipitated from a cuprammonium solution. The hollow cellulose acetate fibers have an outside diameter of about 270 μm and a wall thickness of 30 μm.[34] The advantage of hollow fibers is their compactness. A bundle of 10,000 fibers 18 cm long has a surface area of 1.4 m^2.

Particle Shape, Optical, and Transport Properties of Lyophobic Dispersions

Hydrophobic materials handled by pharmacists in aqueous dispersion range from metallic conductors to inorganic precipitates to organic solids and liquids which are electric insulators. Despite the great diversity of the hydrophobic disperse phase, their hydrosols have certain common characteristics.

Particle Shape and Particle Size Distribution—Both of these properties depend on the chemical and physical nature of the disperse phase and on the method employed to prepare the dispersion. Primary particles exist in a great variety of shapes. Their aggregation produces an even greater variety of shapes and structures. Precipitation and mechanical comminution generally produce randomly shaped particles unless the precipitating solids possess pronounced crystallization habits or the solids being ground possess strongly developed cleavage planes. Precipitated aluminum hydroxide gels and micronized particles of sulfonamides and other organic powders have typical irregular random shapes. An exception is bismuth subnitrate. Even though its particles are precipitated by hydrolyzing bismuth nitrate solutions with sodium carbonate, its particles are lath-shaped. Precipitated silver chloride particles have a cubic habit which is apparent under the electron microscope. Lamellar or plate-like solids in which the molecular cohesion between layers is much weaker than within layers frequently preserve their lamellar shape during mechanical comminution, because milling and micronization break up stacks of thin plates in addition to fragmenting plates in the lateral dimensions. Examples are graphite, mica and kaolin. Figure 19-22 shows a Georgia crude clay as mined. Processing yields the refined, fine-particle kaolinite of Fig 19-23. Similarly, macroscopic asbestos and cellulose fibers consist of bundles of microscopic and submicroscopic fibrils. Mechanical comminution or beating splits these bundles into the component fibrils of very small diameters as well as cutting them shorter.

Microcrystalline cellulose is a fibrous thickening agent and tablet additive made by selective hydrolysis of cellulose.

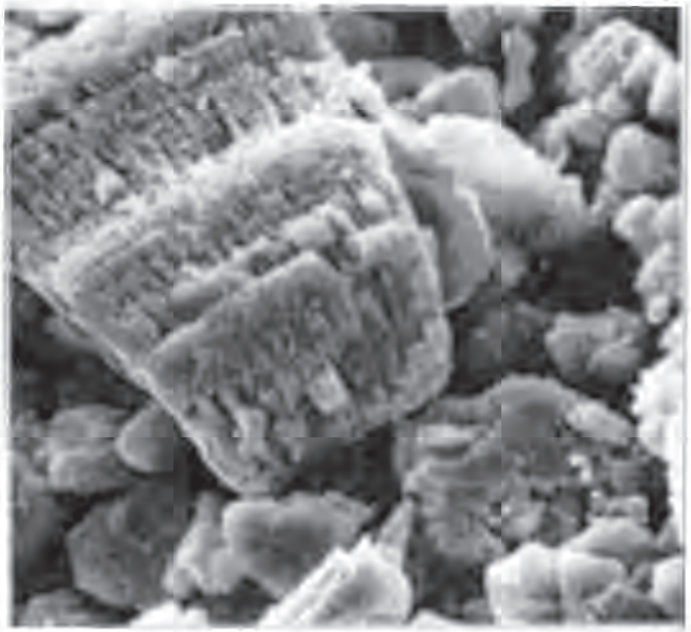


Fig 19-22. Scanning electron micrograph of a crude kaolin clay as mined. Processing yields the fine particle material of Fig 19-23 (courtesy, John L Brown, Engineering Experiment Station, Georgia Institute of Technology).

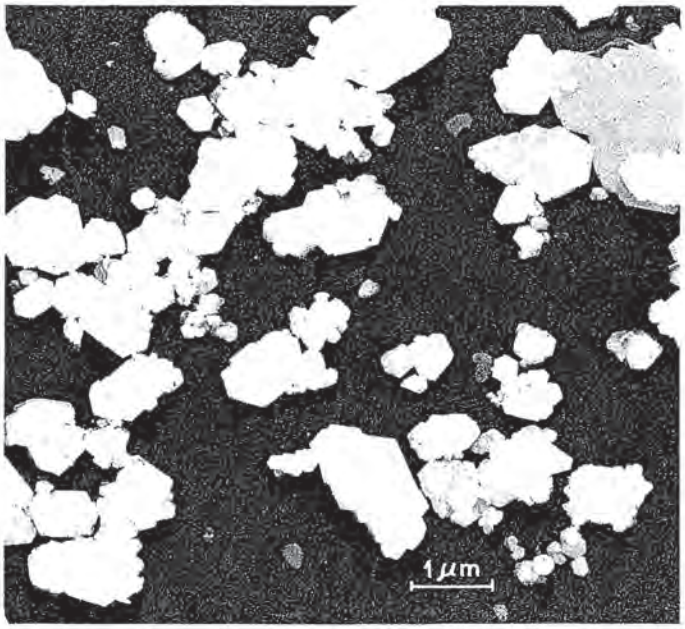


Fig 19-23. Transmission electron micrograph of a well crystallized, fine-particle kaolin. Note hexagonal shape of the clay platelets (courtesy, John L Brown, Engineering Experiment Station, Georgia Institute of Technology).

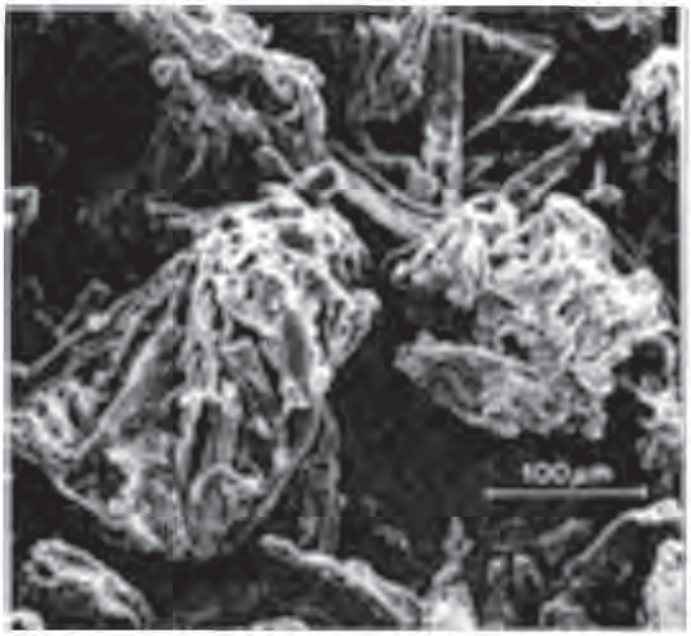


Fig 19-24. Scanning electron micrograph of Avicel PH-102 tableting grade microcrystalline cellulose. The aggregates of fiber bundles are porous and compressible (courtesy, FMC Corporation; Avicel is a registered trademark of FMC Corporation).

Native cellulose consists of crystalline regions where the polymer chains are well aligned and in registry, with maximum interchain attraction by secondary valence forces, called crystallites, and of more disordered regions having lower density and reduced interchain attraction and crystallinity, the so-called "amorphous" regions. During treatment with dilute mineral acid, the acid penetrates the amorphous regions relatively fast and hydrolyzes the polymer chains into water-soluble fragments. If the acid is washed out before it penetrates the crystalline regions appreciably, the crystallites remain intact. Wet milling and spray-drying the aqueous suspension produces spongy and porous aggregates of rod-shaped or fibrillar bundles shown in Fig 19-24. These aggregates, averaging 100 μm in size, were embrittled by the acid treatment and lost the elasticity of the native cellulose. They are well compressible and capable of undergoing plastic deformation, a property important in tableting. Their porosity permits the aggregates to absorb liquid ingredients while still remaining a free-flowing powder, thus preventing these liquids from reducing the flowability of the granulation or direct-compression mass during tableting. The swelling of the cellulosic particles in water speeds up the disintegration of the ingested tablets.

Additional shear breaks up the aggregated bundles into the individual, needle- or rod-shaped cellulose crystallites shown in Fig 19-25. The latter, which average 0.3 μm in length and 0.02 μm in width, are of colloidal dimensions. These primary particles act as suspending agents in water, producing thixotropic structured vehicles. At concentrations above 10%, eg 14 or 15%, the cellulose microcrystals gel water to ointment consistency by swelling and producing a continuous network of rods extending throughout the entire vehicle. Attraction between the elongated particles is presumably due to flocculation in the secondary minimum (see below). Treatment of the microcrystalline mass with sodium carboxymethylcellulose facilitates its disintegration into the primary needle-shaped particles and enhances their thickening action.

While in the special cases of certain clays and cellulose, comminution produces lamellar and fibrillar particles, respectively, as a rule regular particle shapes are produced by

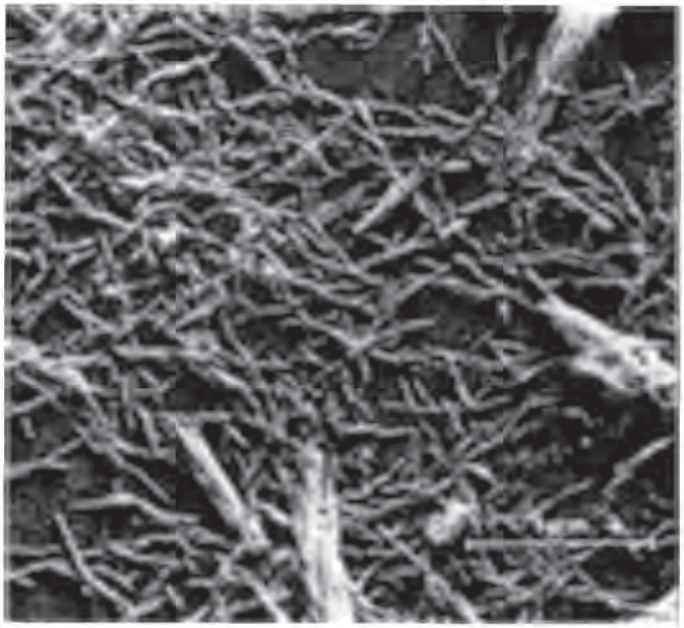


Fig 19-25. Transmission electron micrograph of Avicel RC-591 thickening grade microcrystalline cellulose. The needles are individual cellulose crystallites; some are aggregated into bundles (courtesy, FMC Corporation; Avicel is a registered trademark of FMC Corporation).

condensation rather than by disintegration methods. *Colloidal silicon dioxide* is called fumed or pyrogenic silica because it is manufactured by high-temperature, vapor-phase hydrolysis of silicon tetrachloride in an oxy-hydrogen flame, ie, a flame produced by burning hydrogen in a stream of oxygen. The resultant white powder consists of submicroscopic spherical particles of rather uniform size (narrow particle size distribution). Different grades are produced by different reaction conditions. Relatively large, single

spherical particles are shown in Fig 19-26. Their average diameter is 50 nm (500 Å), corresponding to the comparatively small specific surface area of 50 m^2/g. Smaller spherical particles have correspondingly larger specific surface areas; the grade with the smallest average diameter, 5 nm, has a specific surface area of 380 m^2/g. During the manufacturing process, the finer-grade particles tend to sinter or grow together into chain-like aggregates resembling pearl necklaces or streptococci (see Fig 19-27).

Since fumed silica is amorphous, its inhaled dust causes no silicosis. The spheres of colloidal silicon dioxide are nonporous. While the density of the spherical particles is 2.13 g/cm^3, the bulk density of their powder is a mere 0.05 g/cm^3; the powder is extremely light. This results in two pharmaceutical and cosmetic applications for colloidal silicon dioxide. It is used to increase the fluffiness or bulk volume of powders. Even more than microcrystalline cellulose, the high porosity of silica enables it to absorb a variety of liquids from fluid fragrances to viscous tars, transforming them into free-flowing powders that can be incorporated into tablets or capsules. The porosity in colloidal silicon dioxide is due entirely to the enormous void space between the particles, which themselves are solid.

When these ultrafine particles are incorporated at levels as low as 0.1 to 0.5% into a powder consisting of coarse particles or granules, they coat the surface of the latter and act as tiny ball bearings and spacers, improving the flowability of the powder and eliminating caking. This action is important in tableting. Moreover, colloidal silicon dioxide improves tablet disintegration.

The surface of the particles contains siloxane (Si—O—Si) and silanol (Si—OH) groups. When colloidal silicon dioxide powder is dispersed in nonpolar liquids, the particles tend to adhere to one another by hydrogen bonds between their surface groups. With finer grades of colloidal silicon dioxide, the spherical particles are linked together into short chain-like aggregates as shown in Fig 19-27, thus agglomerating into loose three-dimensional networks which increase the viscosity of the liquid vehicles very effectively at levels as low as a few percent. These hydrogen-bonded structures are torn apart by stirring but rebuilt while at rest, conferring thixotropy to the thickened liquids.

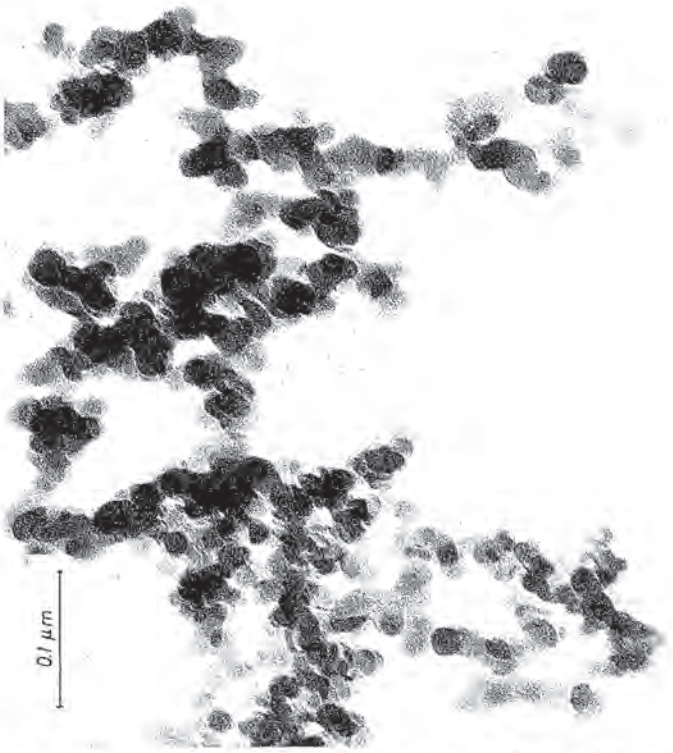


Fig 19-27. Transmission electron micrograph of Aerosil 130, ground and dusted on. The spheres are fused together into chain-like aggregates (courtesy, Degussa AG of Hanau, West Germany; Aerosil is a registered trademark of Degussa). The suffix 130 gives the specific surface area in m^2/g.

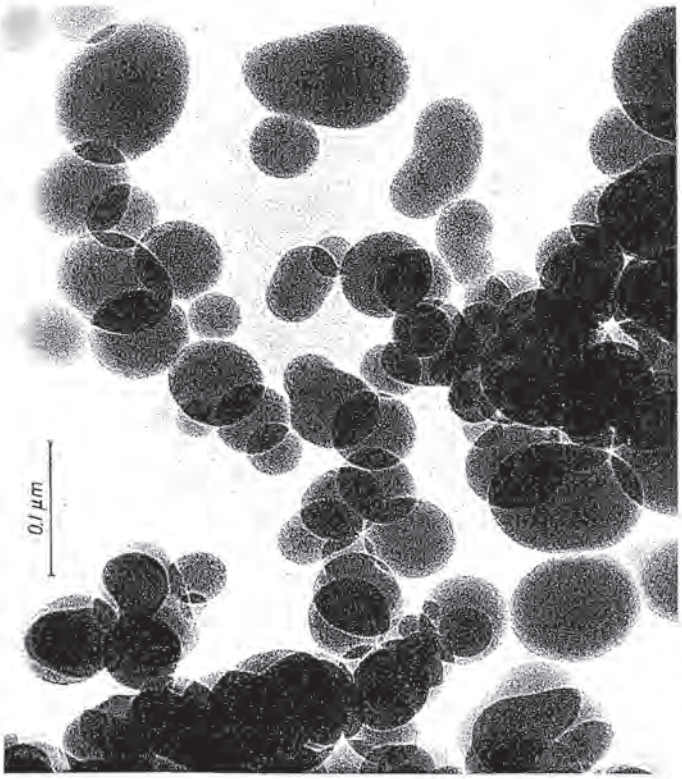


Fig 19-26. Transmission electron micrograph of Aerosil OX 50, ground and dusted on. The spheres are translucent to the electron beam, causing overlapping portions to be darker owing to increased thickness (courtesy, Degussa AG of Hanau, West Germany; Aerosil is a registered trademark of Degussa). The suffix 50 indicates the specific surface area in m^2/g.

The grades which consist of relatively large and unattached spherical particles, such as those of Fig 19-26, are less efficient thickening agents as they lack the high specific surface area and the asymmetry of the finer grades, which consist of short chains of fused spherical particles. In the latter category is Aerosil 200, the grade most widely used as a pharmaceutical adjuvant, whose primary spheres, which are extensively sintered together, have an average diameter of 12 nm. At levels of 8 to 10%, it thickens liquids of low polarity such as vegetable and mineral oils to the consistency of ointments, imparting considerable yield values to them. The consistency of ointments thickened with colloidal silicon dioxide is not appreciably reduced at higher temperatures. Incorporation of colloidal silicon dioxide into ointments and pastes, such as those of zinc oxide, also reduces the syneresis or *bleeding* of the liquid vehicles.

Hydrogen-bonding liquids like alcohols and water solvate the silica spheres, reducing the hydrogen bonding between particles. These solvents are gelled at silica levels of 12–18% or higher.

Latexes of polymers are aqueous dispersions prepared by emulsion polymerization. Their particles are spherical because polymerization of solubilized liquid monomer takes

place inside spherical surfactant micelles which swell because additional monomer keeps diffusing into the micelles. Examples include latex-based paints. Some *clays* grow as plate-like particles possessing straight edges and hexagonal angles, eg bentonite and kaolin (see Fig 19-23). Other clays have lath-shaped (nontronite) or needle-shaped particles (attapulgite).

Emulsification produces spherical droplets to minimize the oil-water interfacial area. Cooling the emulsion below the melting point of the disperse phase freezes it in the spherical shape. For instance, paraffin can be emulsified in 80° water; cooling to room temperature produces a hydrosol with spherical particles.

Sols of viruses and globular proteins, which are hydrophilic, contain compact particles possessing definite geometric shapes. Poliomyelitis virus is spherical, tobacco mosaic virus is rod-shaped, while serum albumin and the serum globulins are prolate ellipsoids of revolution (football-shaped).

Dispersion methods produce sols with wide particle size distributions. Condensation methods *may* produce essentially monodisperse sols provided specialized techniques are employed. Monodisperse polystyrene latexes are available for calibration of electron micrographs (see Fig 19-23). Biologic hydrophilic polymers, such as nucleic acids and proteins, form largely monodisperse particles, as do more highly organized structures such as lipoproteins and viruses.

Light-Scattering by Colloidal Particles—The optical properties of a medium are determined by its refractive index. When the refractive index is uniform throughout, light will pass the medium undeflected. Whenever there are discrete variations in the refractive index caused by the presence of particles or by small-scale density fluctuations, part of the light will be scattered in all directions. An optical property characteristic of colloidal systems, called the *Tyndall beam*, is familiar to everyone in the case of aerosols. When a narrow beam of sunlight is admitted through a small hole into a darkened room, the presence of the minute dust particles suspended in air is revealed by bright flashing points.

A beam of light striking a particle polarizes the atoms and molecules of that particle, inducing dipoles which act as secondary sources and reemit weak light of the same wavelength as the incident light. This phenomenon is called *light-scattering*. The scattered radiation propagates in all directions away from the particle. In a bright room, the light scattered by the dust particles is too weak to be noticeable.

Colloidal particles suspended in a liquid also scatter light. When an intense, narrowly defined beam of light is passed through a suspension, its path becomes visible because of the scattering of light by the particles in the beam. This Tyndall beam becomes most visible when viewed against a dark background in a direction perpendicular to the incident beam. The magnitude of the turbidity or opalescence depends on the nature, size and concentration of the particles. When clear mineral oil is dispersed in an equal volume of a clear aqueous surfactant solution, the resultant emulsion is milky white and opaque due to light scattering. Microemulsions, where the emulsified droplets are about 40 nm (400 Å) in diameter, ie, much smaller than the wavelength of visible light, are transparent and clear to the naked eye.

The *dark-field microscope* or *ultramicroscope*, which permits observation of particles much smaller than the wavelength of light, was the only means of detecting submicroscopic particles before the advent of electron microscopy. A special cardioid condenser produces a hollow cylinder of light and converges it into a hollow cone focused on the sample. The sample is at the apex of the cone, where the light intensity is high. After passing through the sample, the cone of light diverges and passes outside of the microscope objective. A homogeneous sample thus gives a dark field. A similar effect can be produced with a regular Abbe condenser outfitted with a central stop and a strong light source. Colloidal particles scatter light in all directions. Some of the scattered light enters the objective and shows up the particles as bright spots. Thus, even particles smaller than the wavelength of light can be detected, provided their refractive index differs sufficiently from that of the medium. Dissolved polymer molecules and highly solvated gel particles do not scatter enough light to become visible. Asymmetric particles like flat bentonite platelets give flashing effects as they rotate in Brownian motion, because they scatter more light with their basal plane perpendicular to the light beam than edgewise. Brownian motion, sedimentation, electrophoretic mobility, and the progress of flocculation can be studied with the dark-field microscope. Polydispersity can be estimated qualitatively because larger particles scatter more light and appear brighter. The resolving power of the ultramicroscope is no greater than that of the ordinary light microscope. Particles closer together than 0.2 μm appear as a single blur.

Turbidity may be used to measure the concentration of dispersed particles in two ways. In *turbidimetry*, a spectrophotometer or photoelectric colorimeter is used to measure the intensity of the light transmitted in the incident direction. Turbidity, τ, is defined by an equation analogous to Beer's law for the absorption of light (see Chapter 30),[24,25,27] namely

$$\tau = \frac{1}{l} \ln \frac{I_0}{I_t}$$

where I_0 and I_t are the intensities of the incident and transmitted light beams, and l is the length of the dispersion through which the light passes.

If the dispersion is less turbid, the intensity of light scattered at 90° to the incident beam is measured with a *nephelometer*. Both methods require careful standardization with suspensions containing known amounts of particles similar to those to be measured. The concentration of colloidal dispersions of inorganic and organic compounds and of bacterial suspensions can thus be measured by their turbidity.

The turbidity or Tyndall effect of hydrophilic colloidal systems like aqueous solutions of gums, proteins and other polymers is far weaker than that of lyophobic dispersions. These solutions appear clear to the naked eye. Their turbidity can be measured with a photoelectric cell/photomultiplier tube and serves to determine the molecular weight of the solute.

The theory of light scattering was developed in detail by Lord Rayleigh. For white nonabsorbing nonconductors or dielectrics like sulfur and insoluble organic compounds, the equation obtained for spherical particles whose radius is small compared to the wavelength of light λ is[24-27]

$$I_s = I_0 \frac{4\pi^2 n_0^2 (n_1 - n_0)^2}{\lambda^4 d^2 c} (1 + \cos^2 \theta)$$

I_0 is the intensity of the unpolarized incident light; I_s is the intensity of light scattered in a direction making an angle θ with the incident beam and measured at a distance d. The scattered light is largely polarized. The concentration c is expressed as the number of particles per unit volume. The refractive indices n_1 and n_0 refer to the dispersion and the solvent, respectively.

Since the intensity of scattered light is inversely proportional to the fourth power of the wavelength, blue light ($\lambda \cong$ 450 nm or 4500 Å) is scattered much more strongly than red light ($\lambda \cong$ 650 nm or 6500 Å). With incident white light, colloidal dispersions of colorless particles appear blue when

viewed in scattered light, ie, in lateral directions such as 90° to the incident beam. Loss of the blue rays due to preferential scattering leaves the transmitted light yellow or red. Preferential scattering of blue radiation sideways accounts for the blue color of the sky, sea, cigarette smoke, and diluted milk and for the yellow-red color of the rising and setting sun viewed head-on.

The particles in pharmaceutical suspensions, emulsions and lotions are generally larger than the wavelength of light λ. When the particle size exceeds $\lambda/20$, destructive interference between light scattered by different portions of the same particle lowers the intensity of scattered light and changes its angular dependence. Rayleigh's theory was extended to large and to strongly absorbing and conducting particles by Mie and to nonspherical particles by Gans.[21,22,24-27] By using appropriate precautions in experimental techniques and in interpretation, it is possible to determine an average particle size and even the particle size distribution of colloidal dispersions and coarser suspensions by means of turbidity measurements.

Diffusion and Sedimentation—The molecules of a gas or liquid are engaged in a perpetual, random thermal motion which causes them to collide with one another and with the container wall billions of times per second. Each collision changes the direction and the velocity of the molecules involved. Dissolved molecules and suspended colloidal particles are continuously and randomly buffeted by the molecules of the suspending medium. This random bombardment imparts to solutes and particles an equally unceasing and erratic movement called *Brownian motion*, after the botanist Robert Brown who first observed it under the microscope with an aqueous pollen suspension. The Brownian motion of colloidal particles mirrors on a magnified scale the random movement of the molecules of the liquid or gaseous suspending medium, and represents a three-dimensional random walk.

Solute molecules and suspended colloidal particles undergo rotational and translational Brownian movement. For the latter, Einstein derived the equation

$$\bar{x} = \sqrt{2Dt}$$

where $\bar{x}$ is the mean displacement in the x-direction in time t and D is the *diffusion coefficient*. Einstein also showed that for spherical particles of radius r under conditions specified in Chapter 20 for the validity of Stokes' law and Einstein's law of viscosity

$$D = \frac{RT}{6\pi\eta rN}$$

where R is the gas constant, T the absolute temperature, N Avogadro's number, and η the viscosity of the suspending medium.

The diffusion coefficient is a measure of the mobility of a dissolved molecule or suspended particle in a liquid medium. Representative values at room temperature, in cm^2/sec, are 4.7×10^{-6} for sucrose and 6.1×10^{-7} for serum albumin in water. With a diffusion coefficient of 1×10^{-7} cm^2/sec, Brownian motion causes a particle to move by an average distance of 1 cm in one direction in 58 days, by 1 mm in 14 hr, and by 1 μm in 0.05 sec. Smaller molecules diffuse faster in a given medium. Assuming spherical shape, the radius of a serum albumin molecule is 35 Å and that of a sucrose molecule 4.4 Å. The ratio of the radii of the two molecules 35/4.4 = 7.9, is nearly identical with the inverse ratio of their diffusion coefficients in water, $4.7 \times 10^{-6}/6.1 \times 10^{-7} = 7.7$, in agreement with the above equation. Diffusion coefficients of steroids and other molecules of similar size dissolved in absorption bases based on petrolatum are generally in the 10^{-10} to 10^{-8} cm^2/sec range. Steroids have only slightly higher molecular weights than sucrose. Their much smaller diffusion coefficients are due to the much higher viscosity of the vehicle.

Dynamic light-scattering or photon-correlation spectroscopy is based on the fact that the light scattered by particles in Brownian motion undergoes a minute shift in wavelength by the usual Doppler effect. The shift is so small that it can be detected only by laser light beams, which are strictly monochromatic and very intense. The wavelength shift, which shows up as line broadening, is used to determine the diffusion coefficient of the particles,[23,26] which in turn yields their radius according to the equation above.

Brownian motion and convection currents maintain dissolved molecules and small colloidal particles in suspension indefinitely. As the particle size and r increase, the Brownian motion decreases; $\bar{x}$ is proportional to $r^{-1/2}$. Provided that the density of the particle d_P and of the liquid vehicle d_L are sufficiently different, larger particles have a greater tendency to settle out when $d_P > d_L$ or to rise to the top of the suspension when $d_P < d_L$ than smaller particles of the same material.

The rate of *sedimentation* is expressed by the Stokes' equation (Eq 35), which can be rewritten as

$$h = \frac{2(d_P - d_L)r^2gt}{9\eta}$$

where h is the height through which a spherical particle settles in time t. The rate of sedimentation is proportional to r^2. Thus, with increasing particle size, the Brownian motion diminishes while the tendency to sediment increases. The two become equal for a critical radius when the distance h through which the particle settles equals the mean displacement $\bar{x}$ due to Brownian motion in the same time interval t.[35] In most pharmaceutical suspensions, sedimentation prevails. Intravenous vegetable oil emulsions do not tend to cream because the mean droplet size, *ca* 0.5 μm, is smaller than the critical radius.

Passive diffusion caused by a concentration gradient and carried out through Brownian motion is important in the release of drugs from topical preparations (see Chapter 87) and in the gastrointestinal absorption of drugs (see Chapter 35).

Viscosity—Most lyophobic dispersions have viscosities not much greater than that of the liquid vehicle. This holds true even at comparatively high volume fractions of the disperse phase unless the particles form continuous network aggregates throughout the vehicle, in which case yield values are observed. Most O/W and W/O emulsions have specific viscosities not much greater than those predicted by Einstein's modified law of viscosity (see Eq 11 of Chapter 20 and text). For instance, emulsions containing 40% v/v of the internal phase generally have viscosities only three to five times higher than that of the continuous phase. By contrast, the apparent viscosities of lyophilic dispersions, especially of polymer solutions, are several orders of magnitude greater than the viscosity of the solvent or vehicle even at concentrations of only a few percent solids. Lyophilic dispersions are also generally much more pseudoplastic or shear-thinning than lyophobic dispersions (see Chapter 20).

Electric Properties and Stability of Lyophobic Dispersions

Difference between Lyophilic and Lyophobic Dispersions—*Lyophilic* or solvent-loving solids are called hydrophilic if the solvent is water. Owing to the presence of high concentrations of hydrophilic groups, they dissolve or disperse spontaneously in water as far as is possible without breaking covalent bonds. Among hydrophilic groups are ionized ones which dissociate into highly hydrated ions like carboxylate, sulfonate or alkylammonium ions, and organic

functional groups like hydroxyl, carbonyl, amino, and imino which bind water through hydrogen bonding.

The free energy of dissolution or dispersion, ΔG_s, of hydrophilic solids includes a large negative (exothermic) heat or enthalpy of solvation, ΔH_s, and a large increase in entropy, ΔS_s. Since $\Delta G_s = \Delta H_s - T\Delta S_s$, ΔG_s has a large negative value: the dissolution of hydrophilic macromolecules and the dispersion of hydrophilic particulate solids in water occur spontaneously (see Chapter 16), overcoming the parallel increases in surface area and surface free energy. Dissolution and dispersion take place so that water can come into contact and interact with the hydrophilic groups of the solids (enthalpy of solvation), and to increase the number of available configurations of the macromolecules and particles (entropy increase).

The van der Waals energies of attraction between dissolved macromolecules or dispersed hydrophilic solid particles are smaller than ΔG_s and are, therefore, insufficient to cause separation of a solid polymer phase or agglomeration through flocculation or coagulation of the dispersed particles. Furthermore, the hydration layer surrounding dissolved macromolecules and dispersed particles forms a barrier preventing their close approach.

Hydrophobic solids and liquids such as organic compounds consisting largely of hydrocarbon portions with few if any hydrophilic functional groups, like cholesterol and other steroids, and some nonionized inorganic substances like sulfur, are hydrated slightly or not at all. Hence they do not disperse or dissolve spontaneously in water: ΔG_s is positive because of a positive (endothermic) ΔH_s term, making the reverse process (agglomeration) the spontaneous one. Aqueous dispersions of such hydrophobic solids or liquids can be prepared by physical means which supply the appropriate energy to the system (see above). They are unstable, however. The van der Waals attractive forces between the particles cause them to aggregate, since the solvation forces which promote dispersal in water are weak. If aqueous dispersions of hydrophobic solids are to resist reaggregation (coagulation and flocculation), they must be stabilized. Stabilizing factors include electric charges at the particle surface (due to dissociation of ionogenic groups of the solid or pertaining to adsorbed ions such as ionic surfactants) and the presence of adsorbed macromolecules or nonionic surfactants. These stabilizing factors do not alter the intrinsic thermodynamic instability of lyophobic dispersions; ΔG_s is still positive so that the reverse process of phase separation or aggregation is energetically favored over dispersal. They establish kinetic barriers which delay the aggregation processes almost indefinitely; the dispersed particles cannot come together close enough for the van der Waals attractive forces to produce coagulation.[24,26,27] These stabilization mechanisms are discussed below.

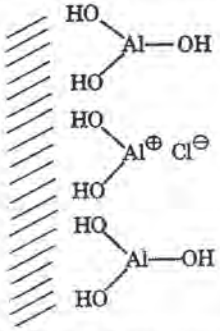
The reductions in surface area and surface free energy accompanying flocculation or coagulation are small because irregular solid particles, being rigid, touch only at a few points upon aggregation. The loose initial contacts may grow with time by sintering or recrystallization. Sintering consists of the "fusion" of primary particles into larger primary particles which propagates from initial small areas of contact. This recrystallization process is spontaneous because it decreases the specific surface area of the disperse solid and the surface free energy of the dispersion. Sintering is analogous to Ostwald ripening, the recrystallization process of transferring solid from colloidal to coarse particles discussed above. Low solubility and the presence of adsorbed surface-active substances retard both processes.

Origin of Electric Charges—Particles can acquire charges from several sources. In *proteins*, one end group of the polypeptide chain and aspartic and glutamic acid units contribute carboxylic acid groups, which are ionized into carboxylate ions in neutral to alkaline media. The other chain end group and lysine units contribute amino groups, arginine units contribute guanidine groups, and histidine units contribute imidazole groups. The nitrogen atoms of these groups become protonated in neutral to acid media. For electroneutrality, these cationic groups require anions, such as Cl^- if hydrochloric acid was used to make the medium acid and to supply the protons. The neutralizing ions, called counterions, dissociate from the ionogenic basic functional groups and can be replaced by other ions of like charge: they are not an integral part of the protein particle but are located in its immediate vicinity. The alkylammonium, guanidinium and imidazolium ions, which are attached to the protein molecule by covalent bonds, confer a positive charge to it. In neutral and alkaline media, Na^+, K^+, Ca^{2+} and Mg^{2+} are among the counterions neutralizing the negative charges of the carboxylate groups. The latter are covalently attached to and constitute an integral part of the protein particle, conferring a negative charge to it.

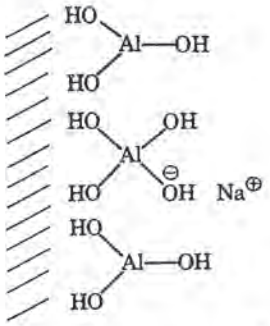
At an intermediate pH value, which ranges from 4.5 to 7 for the various proteins, the carboxylate anions and the alkylammonium, guanidinium, and imidazolium cations neutralize each other exactly. There is no need for counterions since the ionized functional groups which are an integral part of the protein molecule are in exact balance. At this pH value, called the *isoelectric point*, the protein particle or molecule is neutral; its electric charge is neither negative nor positive, but zero.[22,24,27]

Many other organic polymers contain ionic groups and are, therefore, called *polyelectrolytes* (polymeric electrolytes or salts). Natural polysaccharides of vegetable origin such as acacia, tragacanth, alginic acid and pectin contain carboxylic acid groups, which are ionized in neutral to alkaline media. Agar and carrageenan as well as the animal polysaccharides heparin and chondroitin sulfate, contain sulfuric acid hemiester groups, which are strongly acidic and ionize even in acid media. Cellulosic polyelectrolytes include *sodium carboxymethylcellulose*, while synthetic carboxylated polymers include *carbomer*, a copolymer of acrylic acid.

Aluminum hydroxide, $Al(OH)_3$, is dissolved by acids and alkalis forming aluminum ions, Al^{3+}, and aluminate ions, $[Al(OH)_4]^-$, respectively. In neutral or weakly acid media, at acid concentrations too low to cause dissolution, an aluminum hydroxide particle has some positive charges attributable to incompletely neutralized positive Al^{3+} valences. The portion of the surface of an aluminum hydroxide particle represented schematically below has one such positive charge neutralized by a Cl^- counterion:



In weakly alkaline media, at base concentrations too low to transform the aluminum hydroxide particles completely into aluminate and dissolve them, they bear some negative charges due to the presence of a few aluminate groups. The portion of the particle surface represented schematically below has one such negative group neutralized by a Na^+ counterion:



At a pH of 8.5 to 9.1,[36,37] there are neither $[Al(OH)_2]^+$ nor $[Al(OH)_4]^-$ ions in the particle surface but only neutral $Al(OH)_3$ molecules. The particles have zero charge and therefore need no counterions for charge neutralization. This pH is the isoelectric point. In the case of inorganic particulate compounds such as aluminum hydroxide, it is also called zero point of charge.

Bentonite clay is a lamellar aluminum silicate. Each lattice layer consists of a sheet of hydrated alumina sandwiched between two silica sheets. Isomorphous replacement of Al^{3+} by Mg^{2+} or of Si^{4+} by Al^{3+} confers net negative charges to the thin clay lamellas in the form of cation-exchange sites resembling silicate ions built into the lattice. The counterions producing electroneutrality are usually Na^+ (sodium bentonite) or Ca^{2+} (calcium bentonite). The zero point of charge is probably close to that of quartz, silica gel and other silicates, namely, at a pH of about 1.5 to 2.

Silver iodide sols can be prepared by the reaction

$$AgNO_3 + NaI \rightarrow AgI(s) + NaNO_3$$

In the bulk of the silver iodide particles, there is a 1:1 stoichiometric ratio of Ag^+ to I^- ions. If the reaction is carried out with an excess silver nitrate, there will be more Ag^+ than I^- ions in the surface of the particles. The particles will thus be positively charged and the counterions surrounding them will be NO_3^-. If the reaction is carried out using an exact stoichiometric 1:1 ratio of silver nitrate to sodium iodide or with an excess sodium iodide, the surface of the particles will contain an excess I^- over Ag^+ ions.[24,25,27] The particles will be negatively charged, and Na^+ will be the counterions surrounding the particles and neutralizing their charges.

An additional mechanism through which particles acquire electric charges is by the adsorption of ions,[25-27] including ionic surfactants.

Electric Double Layers—The surface layer of a silver iodide particle prepared with an excess of sodium iodide contains more I^- than Ag^+ ions, whereas its bulk contains the two ions in exactly equimolar proportion. The aqueous solution in which this particle is suspended contains relatively high concentrations of Na^+ and NO_3^-, a lower concentration of I^-, and traces of H^+, OH^- and Ag^+.

The negatively charged particle surface attracts positive ions from the solution and repels negative ions: the solution in the vicinity of the surface contains a much higher concentration of Na^+, which are the counterions, and a much lower concentration of NO_3^- ions than the bulk of the solution. A number of Na^+ ions equal to the number of excess I^- ions in the surface (ie, the number of I^- ions in the surface layer minus the number of Ag^+ ions in the surface layer) and equivalent to the net negative surface charge of a particle are pulled towards its surface. These counterions tend to stick to the surface, approaching it as closely as their hydration spheres permit (Helmholtz double layer), but the thermal agitation of the water molecules tends to disperse them throughout the solution. As a result, the layer of counterions surrounding the particle is spread out. The Na^+ concentration is highest in the immediate vicinity of the negative surface, where they form a compact layer called the Stern layer, and decreases with distance from the surface, throughout a diffuse layer called the Gouy-Chapman layer: the sharply defined negatively charged surface is surrounded by a cloud of Na^+ counterions required for electroneutrality. The combination of the two layers of oppositely charged ions constitutes an electric double layer. It is illus-

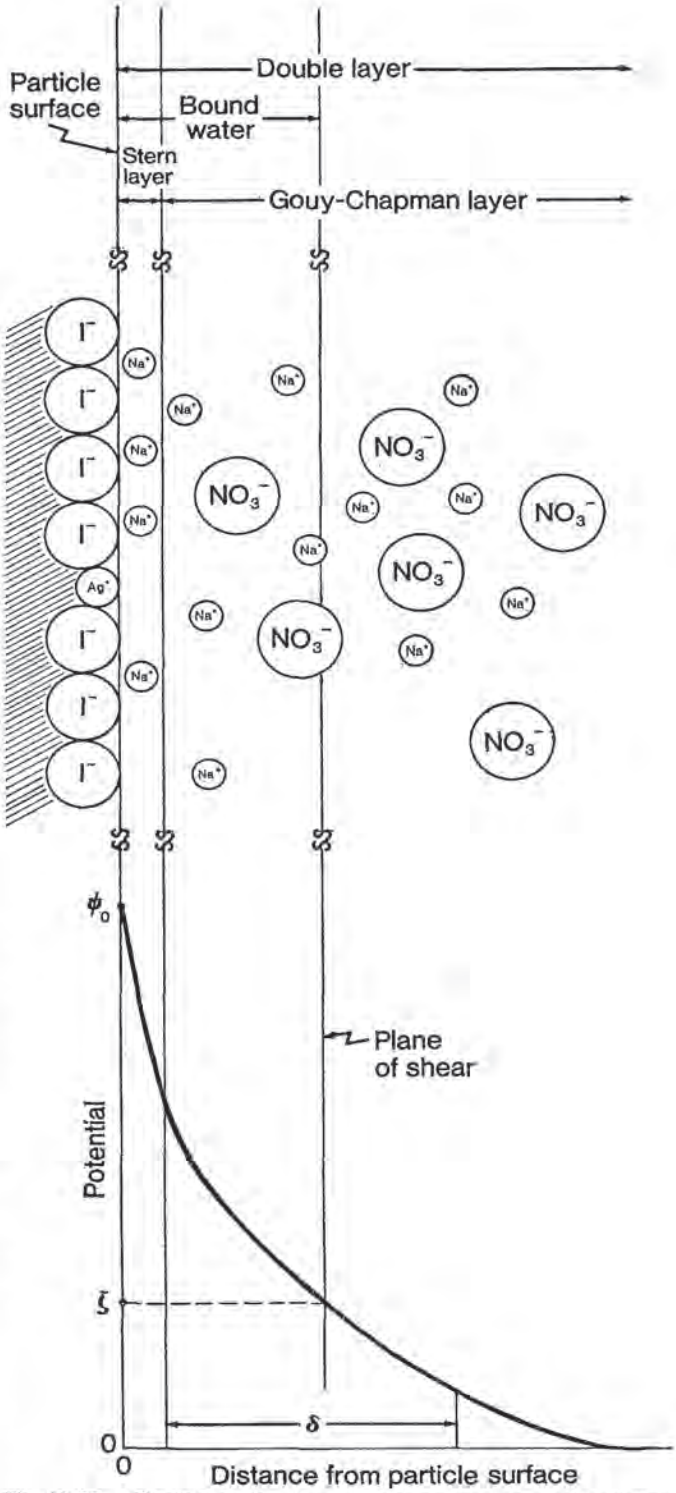


Fig 19-28. Electric double layer at the surface of a silver iodide particle (upper part) and the corresponding potentials (lower part). The distance from the particle surface, plotted on the horizontal axis, refers to both the upper and lower parts.

trated in the top part of Fig 19-28. The horizontal axis represents the distance from the particle surface in both the top and bottom parts.

The electric potential of a plane is equal to the work against electrostatic forces required to bring a unit electric charge from infinity (in this case, from the bulk of the solution) to that plane. If the plane is the surface of the particle, the potential is called surface or ψ_0 potential, which measures the total potential of the double layer. This is the thermodynamic potential which operates in galvanic cells. On moving away from the particle surface towards the bulk solution in the direction of the horizontal axis, the potential drops rapidly across the Stern layer because the Na^+ ions in the immediate vicinity of the surface screen Na^+ ions farther removed, in the diffuse part of the double layer, from the effect of the negative surface charge. The decrease in potential across the Gouy-Chapman layer is more gradual. The diffuse double layer gradually comes to an end as the composition approaches that of the bulk liquid where the anion concentration equals the cation concentration, and the potential approaches zero asymptotically. In view of the indefinite end point, the thickness δ of the diffuse double layer is arbitrarily assigned the value of the distance over which the potential at the boundary between the Stern and Gouy-Chapman layers drops to $1/e = 0.37$ of its value.[24-27] The thickness of double layers usually ranges from 10 to 1000 Å. It decreases as the concentration of electrolytes in solution increases, more rapidly for counterions of higher valence. The value of δ is approximately equal to the reciprocal of the Debye-Hückel theory parameter, κ.

Of practical importance, because it can be measured experimentally, is the electrokinetic or ζ (zeta) potential. In aqueous dispersion, even relatively hydrophobic inorganic particles and organic particles containing polar functional groups are surrounded by a layer of water of hydration attached to them by ion-dipole and dipole-dipole interaction. When a particle moves, this shell of bound water and all ions located inside it move along with the particle. Conversely, if water or a solution flows through a fixed bed of these solid particles, the hydration layer surrounding each particle remains stationary and attached to it. The electric potential at the plane of shear or slip separating the bound water from the free water is the ζ potential. It does not include the Stern layer and only that part of the Gouy-Chapman layer which lies outside the hydration shell. The various potentials are shown on the bottom part of Fig 19-28.

Stabilization by Electrostatic Repulsion—When two uncharged hydrophobic particles are in close proximity, they attract each other by van der Waals secondary valences, mainly by London dispersion forces. For individual atoms and molecules, these forces decrease with the seventh power of the distance between them. In the case of two particles, every atom of one attracts every atom of the other particle. Because the attractive forces are nearly additive, they decay much less rapidly with the interparticle distance as a result of this summation, approximately with the second or third power. Since energies of attraction are equal to force x distance, they decrease approximately with the first or second power of the distance. Therefore, whenever two particles approach each other closely, the attractive forces take over and cause them to adhere. Coagulation occurs as the primary particles aggregate into increasingly larger secondary particles or flocs.

If the dispersion consists of two kinds of particles with positive and negative charges, respectively, the electrostatic attraction between oppositely charged particles is superimposed on the attraction by van der Waals forces, and coagulation is accelerated. If the dispersion contains only one kind, as is customary, all particles have surface charges of the same sign and density. In that case, electrostatic repulsion tends to prevent the particles from approaching closely enough to come within effective range of each other's van der Waals attractive forces, thus stabilizing the dispersion against interparticle attachments or coagulation. The electrostatic repulsive energy has a range of the order of δ.

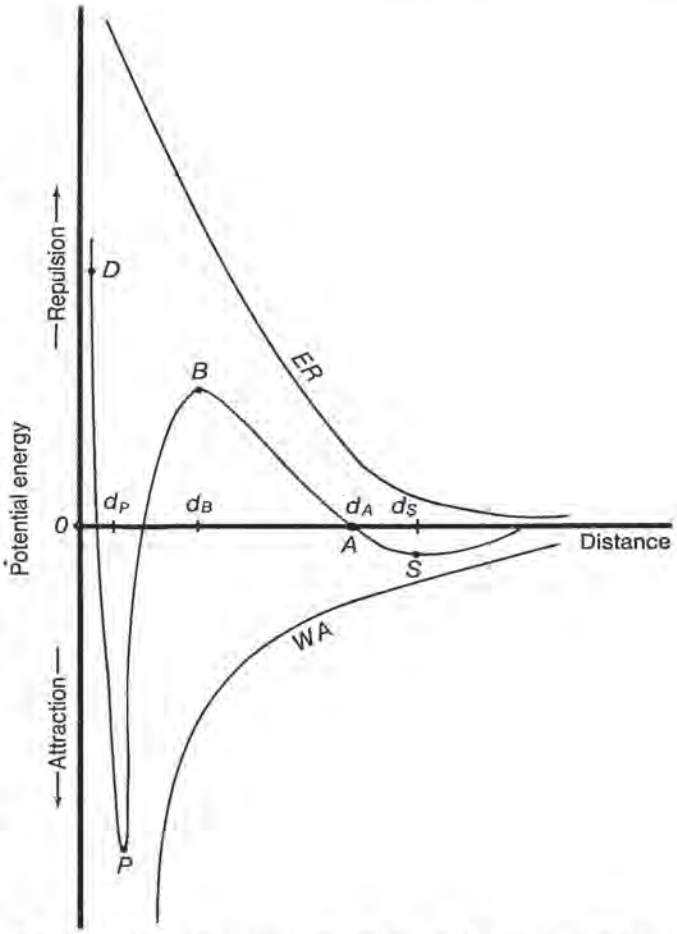


Fig 19-29. Curves representing the van der Waals energy of attraction (*WA*), the energy of electrostatic repulsion (*ER*), and the net energy of interaction (*DPBAS*) between two identical charged particles, as a function of the interparticle distance.

A quantitative theory of the interaction between lyophobic disperse particles was worked out independently by Derjaguin and Landau in the USSR and by Verwey and Overbeek in the Netherlands in the early 1940s.[21,24-27,38] Detailed calculations are also found in Chapter 21 of RPS-17. The so-called DLVO theory predicts and explains many but not all experimental data. Its refinement to account for discrepancies is still continuing.

The DLVO theory is summarized in Fig 19-29, where curve *WA* represents the van der Waals attractive energy which decreases approximately with the second power of the interparticle distance, and curve *ER* represents the electrostatic repulsive energy which decreases exponentially with distance. Because of the combination of these two opposing effects, attraction predominates at small and large distances whereas repulsion may predominate at intermediate distances. Negative energy values indicate attraction, and positive values repulsion. The resultant curve *DPBA*, obtained by algebraic addition of curves *WA* and *ER*, gives the total, net energy of interaction between two particles.

The interparticle attraction depends mainly on the chemical nature and particle size of the material to be dispersed. Once these have been selected, the attractive energy is fixed

and cannot readily be altered. The electrostatic repulsion depends on ψ_0 or the density of the surface charge and on the thickness of the double layer, both of which govern the magnitude of the ζ potential. Thus, stability correlates to some extent with this potential.[24] The ζ potential can be adjusted within wide limits by additives, especially ionic surfactants, water-miscible solvents, and electrolytes (see below). If the absolute value of the ζ potential is small, the resultant potential energy is negative and van der Waals attraction predominates over electrostatic repulsion at all distances. Such sols coagulate rapidly.

The two identical particles whose interaction is depicted in Fig 19-29 have a large (positive or negative) ζ potential resulting in an appreciable positive or repulsive potential energy at intermediate distances. They are on a collision course because of Brownian motion, convection currents, sedimentation, or because the dispersion is being stirred.

As the two particles approach each other, the two atmospheres of counterions surrounding them begin to interpenetrate or overlap at point A corresponding to the distance d_A. This produces a net repulsive (positive) energy because of the work involved in distorting the diffuse double layers and in pushing water molecules and counterions aside, which increases if the particles approach further. If the particles continue to approach each other, even after most of the intervening solution of the counterions between them has been displaced, the repulsion between their surface charges increases the net potential energy of interaction to its maximum positive value at B. If the height of the potential energy barrier B exceeds the kinetic energy of the approaching particles, they will not come any closer than the distance d_B but move away from each other. A net positive potential energy of about 25 kT units usually suffices to keep them apart, rendering the dispersion permanently stable; k is the Boltzmann constant and T is the absolute temperature. At $T = 298°K$, this corresponds to 1×10^{-12} erg. The kinetic energy of a particle is of the order of kT.

On the other hand, if their kinetic energy exceeds the potential energy barrier B, the particles continue to approach each other past d_B, where the van der Waals attraction becomes increasingly more important compared to the electrostatic repulsion. Therefore, the net potential energy of interaction decreases to zero and then becomes negative, pulling the particles still closer together. When the particles touch, at a distance d_P, the net energy has acquired the large negative value P. This deep minimum in potential energy corresponds to a very stable situation in which the particles adhere. Since it is unlikely that enough kinetic energy can be supplied to the particles or that their ζ potential can be increased sufficiently to cause them to climb out of the potential energy well P, they are attached permanently to each other. When most or all of the primary particles agglomerate into secondary particles by such a process, the sol coagulates.

Any closer approach of two particles, than the touching distance d_P, is met with a very rapid rise in potential energy along PD because the solid particles would interpenetrate each other, causing atomic orbitals to overlap (Born repulsion).

Coagulation of Hydrophobic Dispersions—The height of the potential energy barrier and the range over which the electrostatic repulsion is effective (or the thickness of the double layer) determine the stability of hydrophobic dispersions. Both factors are reduced by the addition of electrolytes. The transition between a coagulating and a stable sol is gradual and depends on the time of observation. By using standard conditions, however, it is possible to classify a sol as either coagulated or coagulating, or as stable or fully dispersed.

To determine the value of the coagulating concentration of a given electrolyte for a given sol, a series of test tubes is filled with equal portions of the sol. Identical volumes of solutions of the electrolyte, of increasing concentration, are added with vigorous stirring. After some time at rest (eg, 2 hours), the mixtures are agitated again. After an additional, shorter rest period (eg, ½ hour), they are inspected for signs of coagulation. The tubes can be classified into two groups, one showing no signs of coagulation and the other showing at least some signs, eg, visible flocs. Alternatively, they can be classified into one group showing complete coagulation and the other containing at least some deflocculated colloid left in the supernatant. In either case, the separation between the two classes is quite sharp. The intermediate agitation breaks the weakest interparticle bonds and brings small particles in contact with larger ones, thus increasing the sharpness of separation between coagulation and stability. After repeating the experiment with a narrower range of electrolyte concentrations, the coagulation value c_{CV} of the electrolyte, ie, the lowest concentration at which it coagulates the sol, is established with good reproducibility.[24,25,27]

Typical c_{CV} data for a silver iodide sol prepared with an excess of iodide are listed in Table XIV. The following conclusions can be drawn from the left half of Table XIV:

1. The c_{CV} does not depend on the valence of the anion, since nitrate and sulfate of the same metal have nearly identical values.
2. The differences among the c_{CV}s of cations with the same valence are relatively minor. However, there is a slight but significant trend of decreasing c_{CV} with increasing atomic number in the alkali and in the alkaline earth metal groups. Arranging these cations in the order of decreasing c_{CV} produces the *Hofmeister* or *lyotropic series*. It governs many other colloidal phenomena, including the effect of salts on the temperature of gelation and the swelling of aqueous gels and on the viscosity of hydrosols, the salting out of hydrophilic colloids, the cation exchange on ion-exchange resins, and the permeability of membranes toward salts. The series is also observed in many phenomena involving only small atoms or ions and true solutions, including the ionization potential and electronegativity of metals, the heats of hydration of cations, the size of the hydrated cations, the viscosity, surface tension and infrared spectra of salt solutions, and the solubility of gases therein. For monovalent cations, the lyotropic series is

$$Li^+ > Na^+ > K^+ > NH_4^+ > Rb^+ > Cs^+$$

A similar lyotropic series exists for anions.[21,22,24-26]

The lithium ion has a higher c_{CV} than the cesium ion because it is more extensively hydrated, so that Li^+ (aq), including the hydration shell, is larger than Cs^+ (aq). Owing to its smaller size, the hydrated cesium ion can approach the negative particle surface more closely than the hydrat-

Table XIV—Coagulation Values for Negative Silver Iodide Sol[a]

Electrolyte	c_{CV}, mM/L	Electrolyte	c_{CV}, mM/L
$LiNO_3$	165	$AgNO_3$	0.01
$NaNO_3$	140	½ $(C_{12}H_{25}NH_3)_2SO_4$	0.7
½ Na_2SO_4	141	Strychnine nitrate	1.7
KNO_3	136	½ Morphine sulfate	2.5
½ K_2SO_4	138		
$RbNO_3$	126		
Mean	141		
$Mg(NO_3)_2$	2.60	Quinine sulfate	0.7
$MgSO_4$	2.57		
$Ca(NO_3)_2$	2.40		
$Sr(NO_3)_2$	2.38		
$Ba(NO_3)_2$	2.26		
$Zn(NO_3)_2$	2.50		
$Pb(NO_3)_2$	2.43		
Mean	2.45		
$Al(NO_3)_3$	0.067		
$La(NO_3)_3$	0.069		
$Ce(NO_3)_3$	0.069		
Mean	0.068		

[a] From Ref 21 and unpublished data.

ed lithium ion. Moreover, because of its greater electron cloud, the Cs^+ ion is more polarizable than the Li^+ ion. Therefore, it is more strongly adsorbed in the Stern layer, which makes it a more effective coagulating agent.

3. The coagulation values depend primarily on the valence of the counterions, decreasing by one to two orders of magnitude for each increase of one in their valence (Schulze-Hardy rule). According to the DLVO theory, the coagulation values vary inversely with the sixth power of the valence of the counterions. For mono-, di- and trivalent counterions, they should be in the ratio

$$\frac{1}{1^6} : \frac{1}{2^6} : \frac{1}{3^6} \text{ or } 100 : 1.6 : 0.14$$

The mean c_{CV}'s of Table XIV are 141 : 2.45 : 0.068, or 100 : 1.7 : 0.05, in satisfactory agreement with the DLVO theory.

The following conclusion can be drawn from the right half of Table XIV:

4. The cations on the right side of Table XIV constitute obvious exceptions to the preceding. Ag^+ is the potential-determining counterion. *Potential-determining ions* are those whose concentration determines the surface potential. When silver nitrate is added to the negative silver iodide dispersion, some of its silver ions are incorporated into the negatively charged surface of the particles and lower the magnitude of their charge by reducing the excess of I^- ions in the surface. Thus, silver salts are exceptionally effective coagulating agents because they reduce the magnitude of the ψ_0 as well as of the ζ potential. Indifferent salts, which reduce only the latter, require much higher salt concentrations for comparable reductions in the ζ potential. The other potential-determining ion of silver iodide is I^-. Alkali iodides have higher c_{CV}'s than 141 millimole/liter because they supply iodide ions which enter the surface layer of the silver iodide particles and increase its excess of I^- over Ag^+ ions, thereby making ψ_0 more negative. Bromide and chloride ions act similarly but less effectively.

The principal potential-determining ion for proteins is H^+; those for aluminum hydroxide are OH^- (and hence H^+) and Al^{3+}, but also Fe^{3+} and Cr^{3+} which form mixed hydroxides with Al^{3+}.

5. The cationic surfactant in Table XIV and the alkaloidal salts, which also behave as such, constitute the second exception to the Schulze-Hardy rule. Surface-active compounds contain hydrophilic and hydrophobic moieties in the same molecule, the latter being hydrocarbon portions which by themselves are water-insoluble. Their dual nature causes these compounds to accumulate in interfaces. Dodecylammonium and alkaloidal cations displace inorganic monovalent cations from the Stern layer of a negatively charged silver iodide particle because they are attracted to it not only by electrostatic forces like sodium ions but also by van der Waals forces between their hydrocarbon moieties (dodecyl chains in the case of the dodecylammonium ions) and the solid. Because they are strongly adsorbed from solution onto the surface and do not tend to dissociate from it, surface-active cations are very effective in reducing the ζ potential of the negative silver iodide particles, ie, they have lower c_{CV} than purely inorganic cations of the same valence.

6. Anionic surfactants like those containing lauryl sulfate ions also have a tendency to be adsorbed at solid-liquid interfaces. However, because of electrostatic repulsion between the negatively charged surface of silver iodide particles whose surface layer contains an excess iodide ions and the surface-active anions, adsorption usually does not occur below the critical micelle concentration (see below). If such adsorption does occur, it increases the density of negative charges in the particle surface, raising the c_{CV} of anionic surfactants above that corresponding to their valence.

Ionic solids with surface layers containing the ionic species in near proper stoichiometric balance, and most water-insoluble organic compounds have relatively low surface charge densities. They adsorb ionic surfactants of like charge from solution even at low concentrations, which increases their surface charge densities and the magnitude of their ζ potentials, stabilizing their aqueous dispersions.

The addition of water-miscible solvents such as alcohol, glycerin, propylene glycol or polyethylene glycols to aqueous dispersions lowers the dielectric constant of the medium. This reduces the thickness of the double layer and, therefore, the range over which electrostatic repulsion is effective, and lowers the size of the potential energy barrier. Addition of solvents to aqueous dispersions tends to coagulate them. At concentrations too low to cause coagulation by themselves, solvents make the dispersions more sensitive to coagulation by added electrolytes, ie, they lower the c_{CV}.

Progressive addition of the salt of a counterion of high valence reduces the ζ potential of colloidal particles gradually to zero. Eventually, the sign of the ζ potential may be inverted and its magnitude may increase again, but in the opposite direction. The ψ_0 and ζ potentials of aqueous sulfamerazine suspensions are negative above their isoelectric points; those of bismuth subnitrate are positive. As discussed on page 297, the addition of Al^{3+} to the former and of PO_4^{3-} to the latter in large enough amounts inverts the sign of their ζ potentials; their ψ_0 potentials remain unchanged. Surface-active ions of opposite charge may also produce such charge inversion.

The superposition of the van der Waals attractive energy with its long-range effectiveness and the electrostatic repulsive energy with its intermediate-range effectiveness frequently produces a shallow minimum (designated S in Fig 19-29) in the resultant energy-distance curve at interparticle distances d_S several times greater than δ. If this minimum in potential energy is small compared to kT, Brownian motion prevents aggregation. For large particles such as those of many pharmaceutical suspensions and for particles which are large in one or two dimensions (rods and plates), the *secondary minimum* may be deep enough to trap them at distances d_S from each other. This requires a depth of several kT units. Such fairly long-range and weak attraction produces loose aggregates or flocs which can be dispersed by agitation or by removal or reduction in the concentration of flocculating electrolytes.[21,25–27,38] This reversible aggregation process involving the secondary minimum is called *flocculation*. By contrast, aggregation in the deep primary minimum P, called *coagulation*, is irreversible.

Stabilization by Adsorbed Surfactants—As discussed above, surfactants tend to accumulate at interfaces because of their amphiphilic nature. This process is an *oriented physical adsorption*. Surfactant molecules arrange themselves at the interface between water and an organic solid or liquid of low polarity in such a way that the hydrocarbon chain is in contact with the surface of the solid particle or sticks inside the oil droplet while the polar headgroup is oriented towards the water phase. This orientation removes the hydrophobic hydrocarbon chain from the bulk of the water, where it is unwelcome because it interferes with the hydrogen bonding among the water molecules, while leaving the polar headgroup in contact with water so that it can be hydrated.

Figure 19-30*A* shows schematically that at low surfactant concentration and low surface coverage, the hydrocarbon chains of the adsorbed surfactant molecules lie flat against the solid surface. At higher surfactant concentrations, the surfactant molecules are adsorbed in the upright position to permit the adsorption of more surfactant per unit surface area. Figure 19-30*B* shows a nearly close-packed monolayer of adsorbed surfactant molecules. The terminal methyl groups of their hydrocarbon tails are in contact with the hydrophobic surface and the hydrocarbon tails are in lateral contact with each other. London dispersion forces promote attraction between both types of adjoining groups. The polar headgroups protrude into the water and are hydrated.

The adsorption of ionic surfactants increases the charge density and the ζ potential of the disperse particles. These two parameters are low for organic substances lacking ionic or strongly polar groups. The increase in electrostatic repulsion among the nonpolar organic particles due to adsorption of surface-active ions stabilizes the dispersion against coagulation. This "charge stabilization" is described by the DLVO theory.

Most water-soluble nonionic surfactants are polyoxyethylated (see above): Each molecule consists of a hydrophobic hydrocarbon chain combined with a hydrophilic polyethylene glycol chain, eg $CH_3(CH_2)_{15}(OCH_2CH_2)_{10}OH$. Hydration of the 10 ether groups and of the terminal hydroxyl

group renders the surfactant molecule water-soluble. It adsorbs at the interface between a hydrophobic solid and water, with the hydrocarbon moiety adhering to the solid surface and the polyethylene glycol moiety protruding into the water, where it is hydrated. The particle surface is thus surrounded by a thin layer of hydrated polyethylene glycol chains. This hydrophilic shell forms a steric barrier which prevents close contact between particles and, hence, coagulation ("steric stabilization"). Nonionic surfactants also reduce the sensitivity of hydrophobic dispersions toward coagulation by salts, ie, they increase the coagulation values.[39]

In a flocculated dispersion, groups of several particles are agglomerated into flocs. Frequently, the particles of a floc are in physical contact. When a surfactant is added to a flocculated sol, the dissolved surfactant molecules become adsorbed at the surface of the particles. Surfactant molecules tend to pry apart flocs by wedging themselves between the particles at their areas of contact. This action opens up for surfactant adsorption additional surface area that was previously blocked by adhesion of another solid surface. The breaking up of flocs or secondary particles is defined above as deflocculation or peptization.

Ophthalmic suspensions should be deflocculated because the large particle size of flocs causes eye irritation. Parenteral suspensions should be deflocculated to prevent flocs from blocking capillary blood vessels and hypodermic syringes, and to reduce tissue irritation. Deflocculated suspensions tend to cake, however, ie, the sediment formed by gravitational settling is compact and may be hard to disperse by shaking. Caking in oral suspensions is prevented by controlled flocculation as discussed below.

Stabilization by Adsorbed Polymers—Water-soluble polymers are adsorbed at the interface between water and a hydrophobic solid if they have some hydrophobic groups that limit their water solubility and render them amphiphilic and, hence, surface-active. Such polymers also tend to accumulate at the air-water interface and lower the surface tension of the aqueous phase. A high concentration of ionic groups in polyelectrolytes tends to eliminate surface activity and the tendency to adsorb at interfaces, because the polymer is excessively water-soluble. An example is *sodium carboxymethylcellulose*. *Polyvinyl alcohol* is very water-soluble due to the high concentration of hydroxyl groups and does not adsorb extensively at interfaces. Polyvinyl alcohol is manufactured by the hydrolysis of polyvinyl acetate, which is water-insoluble. Incomplete hydrolysis of, say, only 85% of the acetyl groups produces a copolymer which is water-soluble but surface-active as well. Other surface-active polymers include methylcellulose, hydroxypropyl cellulose, high-molecular-weight polyethylene glycols (polyethylene oxides), and proteins. The surface activity of proteins is due to the presence of hydrophobic groups in the side chains at concentrations too low to cause insolubility in water. Proteins are denatured upon adsorption at air-water and solid-water interfaces.

The long, chain-like polymer molecules are adsorbed from solution onto solid surfaces in the form of loops projecting into the aqueous phase, as shown in Fig 19-31*A*, rather than lying flat against the solid substrate. Only a small portion of the chain segments of an adsorbed macromolecule is actually in contact with and adheres directly to the surface. Because of its great length, however, there are enough of such areas of contact to anchor the adsorbed macromolecule firmly onto the solid. Figure 19-30 is drawn on a much more expanded scale than Fig 19-31.

The sol particles are surrounded by a layer consisting of the adsorbed polymer chains, the water of hydration associated with them, and water trapped mechanically inside the chain loops. This sheath is an integral part of the particle surface. The layers of adsorbed polymer prevent the particles from approaching each other closely enough for the interparticle attraction by London dispersion forces to produce coagulation. These forces are effective only over very small interparticle distances of less than twice the thickness of the adsorbed polymer layer.

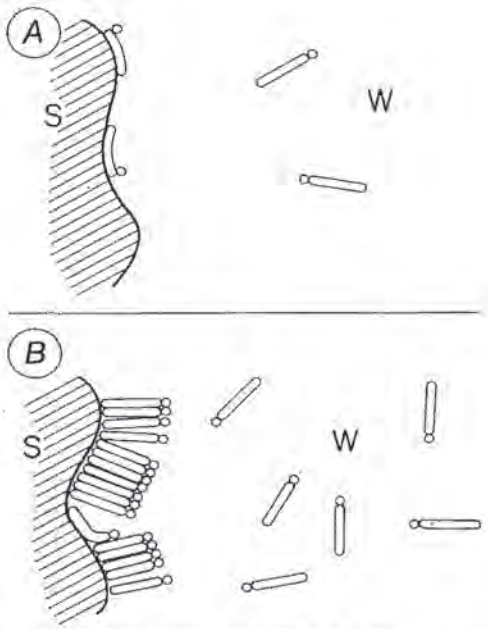


Fig 19-30. Schematic representation of the physical adsorption of surfactant molecules at a hydrophobic solid (S)/water (W) interface. Cylindrical portions and spheres represent hydrocarbon chains and polar headgroups of the surfactant molecules, respectively. (*A*) low surfactant concentration/low surface coverage; (*B*) near critical micelle concentration/surface coverage near saturation.

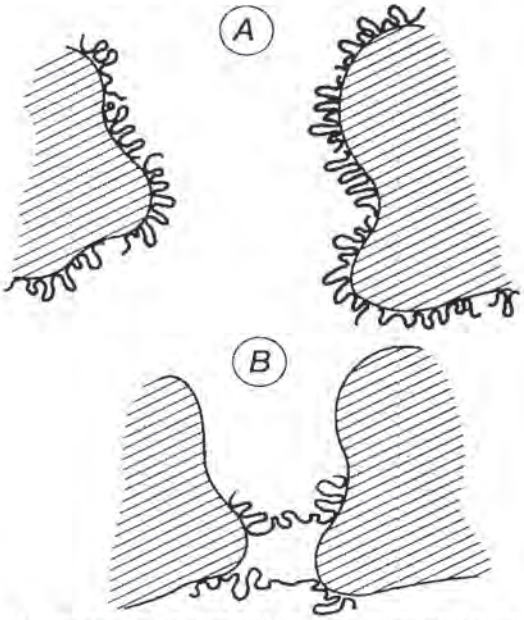


Fig 19-31. Protective action (*A*) and sensitization (*B*) of sols of hydrophobic particles by adsorbed polymer chains.

The mechanisms of *steric stabilization* by which adsorbed nonionic macromolecules prevent coagulation of hydrophobic sols (*protective action*) are also operative in the stabilization of sols by nonionic surfactants. The difference between adsorbed nonionic surfactants and adsorbed polymers

is that the hydrophilic polyethylene glycol moieties of the adsorbed surfactant molecules protruding into water resemble the chain ends of the adsorbed macromolecules rather than their looped segments. The following protective mechanisms are operative:

1. The layer of adsorbed polymer and enmeshed water surrounding the particles forms a *mechanical* or *steric barrier* between them that prevents the close interparticle approach necessary for coagulation. At dense surface coverage, these layers are somewhat elastic. They may be dented by a collision between two particles but tend to spring back.
2. When two particles approach so closely that their adsorbed polymer layers overlap, the chain loops of the two opposing layers compress and mix with or interpenetrate each other. The resulting restriction to the freedom of motion of the chain segments in the overlap region produces a negative entropy change which tends to make the free energy change for the reduction in interparticle distance required for coagulation positive. The reverse process of disentanglement of the two opposing adsorbed polymer layers resulting from separation of the particles occurs because it is energetically more favorable. The particles are thus prevented from coagulation by *entropic repulsion* through the mechanism of *entropic stabilization* of the sol. This mechanism predominates when the concentration of polymer in the adsorbed layer is low.
3. As the polymer layers adsorbed on two approaching particles overlap and compress or interpenetrate each other, more polymer segments become crowded into a given volume of the aqueous region between the particles. The increased polymer concentration in the overlap region causes a local increase in osmotic pressure, which is relieved by an influx of water. This influx to dilute the polymer loops pushes the two particles apart, preventing coagulation.
4. If the adsorbed polymer has some ionic groups, stabilization by electrostatic repulsion or charge stabilization described above is added to the three steric stabilization mechanisms to prevent a close interparticle approach and, hence, coagulation.
5. The adsorption of water-soluble polymers changes the nature of the surface of the hydrophobic particles to hydrophilic, resulting in an increased resistance of the sol to coagulation by salts.[40]

The water-soluble polymers whose adsorption stabilizes hydrophobic sols and protects them against coagulation are called *protective colloids*. *Gelatin* and *serum albumin* are the preferred protective colloids for stabilizing parenteral suspensions because of their biocompatibility. These two polymers, as well as casein (milk protein), dextrin (partially hydrolyzed starch) and vegetable gums like acacia and tragacanth are metabolized in the human body. Cellulose derivatives and most synthetic protective colloids such as *povidone* are not biotransformed. Because of this and because of their large molecular size, polymers pertaining to the last two categories are not absorbed but excreted intact when they are administered in an oral dosage form.

A semiquantitative assessment of the stabilizing efficiency of protective colloids is the *gold number*, developed by Zsigmondy. It is the largest number of milligrams of a protective colloid which, when added to 10 mL of a special standardized gold sol, just fails to prevent the change in color from red to blue on addition of 1 mL of 10% NaCl solution. The gold sol contains 0.0058% gold with a particle size of about 250 Å. Coagulation by sodium chloride causes the color change. Representative gold numbers are 0.005 to 0.01 for gelatin, 0.01 for casein, 0.02 to 0.5 for egg albumin, 0.15 to 0.5 for acacia, and 1 to 7 for dextrin.[22,27] Gelatin is a more effective protective colloid than acacia or dextrin because the presence of some hydrophobic side groups makes it more surface active and causes more extensive adsorption from solution. Other protective numbers are based on different hydrophobic disperse solids, eg, silver, Prussian blue, sulfur, ferric oxide. The ranking of different protective colloids depends somewhat on the substrate. When formulating a disperse dosage form, one should measure the protective action on the actual solid hydrophobic phase to be dispersed as a sol.

Sensitization is the opposite of protective action, namely, a decrease in the stability of hydrophobic sols. It is brought about by some protective colloids, at concentrations well below those at which they exert a protective action. A protective colloid may, at very low concentrations, flocculate a sol in the absence of added salts and/or lower the coagulation values of the sol.

In the case of nonionic polymers or of polyelectrolytes with charges of the same sign as the sol, flocculation is the result of the bridging mechanism illustrated in Fig 19-31*B*. At very low polymer concentrations, there are not nearly enough polymer molecules present to cover each sol particle completely. Since the particle surfaces are largely bare, a single macromolecule may be adsorbed on two particles, bridging the gap between them and pulling them close together. Flocs of several particles are formed when one particle is bridged or connected to two or more other particles by two or more polymer molecules adsorbed jointly on two or possibly even three particles. Such flocculation usually occurs over a narrow range and at very low values of polymer concentrations. At higher concentrations, when enough polymer is available to cover the surface of all particles completely, bridging is unlikely to occur and the adsorbed polymer stabilizes or peptizes the sol.[23,40]

The nonionic Polymer A of Fig 19-32 stabilizes the sol at all concentrations. Neither sensitization by bridging nor by charge neutralization is observed. The reason that Polymer A lowers the positive ζ potential of the sol slightly is that increasing amounts of adsorbed polymer chains gradually shift the plane of shear outward, away from the positively charged surface. If Polymer A was a cationic polyelectrolyte, the ζ potential–protective colloid concentration plot would gradually rise with increasing polymer adsorption rather than drop.

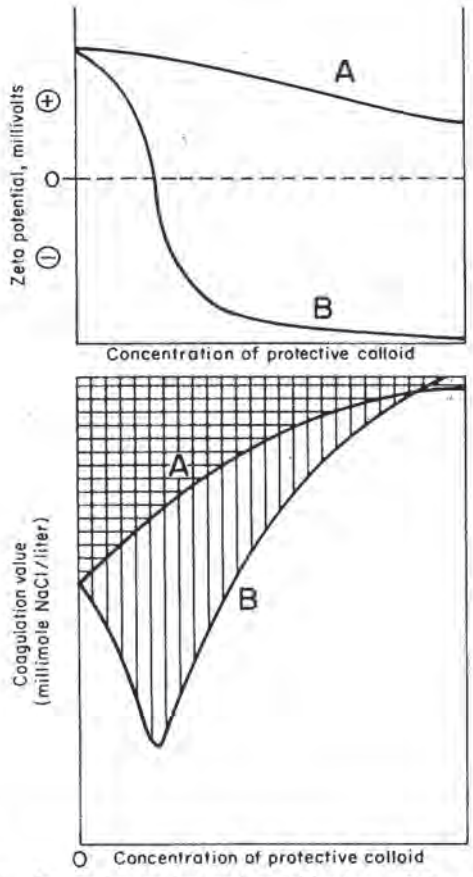


Fig 19-32. Protective action and sensitization: Polymer A exerts protective action at all concentrations, while Polymer B sensitizes at low concentrations and stabilizes at high concentrations. Horizontal and vertical hatching indicates region of flocculation for a sol treated with various concentrations of Polymers A and B, respectively. Clear region underneath indicates sol is deflocculated.

If the polymer has ionic groups of charge opposite to the charge of the sol particles, limited adsorption neutralizes the charge of the particles, reducing their ζ potential to near zero. With stabilization by electrostatic repulsion thus inoperative, and steric stabilization ineffective because of low surface coverage with adsorbed polymer, the sol either coagulates by itself or is coagulated by very small amounts of sodium chloride. At higher polymer concentrations and more extensive adsorption, charge reversal of the particles to the sign of the charge of the polyelectrolyte reactivates charge stabilization and adds steric stabilization, increasing the coagulation value of the sol well above the initial value before polymer addition.

For example, a partly hydrolyzed polyacrylamide with about 20% of ammonium acrylate repeating units is an anionic polyelectrolyte. At the ppm level, the polymer flocculates aluminum hydroxide sols at a pH of 6 to 7, where the sols are positively charged and the polyelectrolyte is fully ionized. At a polymer concentration of 1:10,000, the sol becomes negatively charged because extensive polymer adsorption introduces an excess of $-COO^-$ groups over $\equiv Al^+$ ions into the particle surface. Steric stabilization plus electrostatic repulsion make the sol more stable against flocculation by salts than it was before the polyacrylamide addition.

Polymer B in Fig 19-32 illustrates this example. The curve in the lower plot indicates sensitization, with the coagulation value of sodium chloride lowered by as much as 60%. Zeta potential measurements can distinguish between sensitization by bridging and by charge neutralization. The charge reversal caused by adsorption of Polymer B shown in the upper plot pinpoints charge neutralization as the cause of sensitization. If Polymer B had a ζ potential–polymer concentration plot similar to Polymer A, sensitization would be ascribed to bridging.

Even water-soluble polymers which are too thoroughly hydrophilic to be adsorbed by hydrophobic sol particles can stabilize those sols. Their thickening action slows down Brownian motion and sedimentation, giving the particles less opportunity to come into contact and hence retarding flocculation.

Electrokinetic Phenomena—When a dc electric field is applied to a dispersion, the particles move towards the electrode of charge opposite to that of their surface. The counterions located inside their hydration shell are dragged along while the counterions in the diffuse double layer outside the plane of slip, in the free or mobile solvent, move toward the other electrode. This phenomenon is called *electrophoresis*. If the charged surface is immobile, as is the case with a packed bed of particles or a tube filled with water, application of an electric field causes the counterions in the free water to move towards the opposite electrode, dragging solvent with them. This flow of liquid is called *electroosmosis*, and the pressure produced by it, *electroosmotic pressure*. Conversely, if the liquid is made to flow past charged surfaces by applying hydrostatic pressure, the displacement of the counterions in the free water produces a potential difference between the two ends of the tube or bed called *streaming potential*.

The three phenomena depend on the relative motion of a charged surface and of the diffuse double layer outside the plane of slip surrounding that surface. The major part of the diffuse double layer is within the free solvent and can, therefore, move along the surface.[24–27,41] All three electrokinetic phenomena measure the identical ζ potential, which is the potential at the plane of slip.

The particles of pharmaceutical suspensions and emulsions are visible in the microscope or ultramicroscope, as are bacteria, erythrocytes and other isolated cells, latex particles, and many contaminant particles in pharmaceutical solutions. Their ζ potential is conveniently measured by *microelectrophoresis*. A potential difference E applied between two electrodes dipping into the dispersion and separated by a distance d produces the potential gradient or field strength E/d, expressed in v/cm. From the average velocity v of the particles, measured with the eyepiece micrometer of a microscope and a stopwatch, the ζ potential is calculated by the Smoluchowski equation

$$\zeta = \left(\frac{4\pi\eta}{D}\right)\left(\frac{v}{E/d}\right) = \left(\frac{4\pi\eta}{D}\right)\mu$$

The electrophoretic mobility $u = v/(E/d)$ is the velocity in a potential gradient of 1 v/cm. Particle size and shape do not affect the ζ potential according to the above equation. However, if the particle radius is comparable to δ or smaller (in which case the particles cannot be detected in a microscope), the factor 4 is replaced by 6. The viscosity η and the dielectric constant D refer to the aqueous medium in the double layer and cannot be measured directly.[42] Using the values for water at 25°, expressing the velocity in μm/sec and the electrophoretic mobility in (μm/sec)/(volts/cm), and converting into the appropriate units reduces the Smoluchowski equation to $\zeta = 12.9\,u$, with ζ given in millivolts (mV). If the particle surface has appreciable conductance, the ζ potential calculated by this equation may be low.[25,41,42] Dispersions of hydrophobic particles with ζ potentials below 20–30 mV are frequently unstable and tend to coagulate. On the other hand, values as high as ±180 mV have been reported for the ζ potential.[21,24,41]

The chief experimental precautions in microelectrophoresis measurements are:

1. Electroosmosis causes liquid to flow along the walls of the cell containing the dispersion. This in turn produces a return flow in the center of the cell. The microscope must be focused on the stationary boundary between the two liquid layers flowing in opposite directions in order to measure the true velocity of the particles.
2. Only in very dilute dispersions is it possible to follow the motion of single particles in the microscope field and to measure their velocity. Since the ζ potential depends largely on the nature, ionic strength, and pH of the suspending medium, dispersions should be diluted not with water but with solutions of composition identical to their continuous phase, eg, with their own serum separated by ultrafiltration or centrifugation. The Zeta-Meter is a commercial microelectrophoresis apparatus of easy, fast and reproducible operation.

When the particles cannot be observed individually with a microscope or ultramicroscope, other electrophoresis methods are employed.[24,27,41,43,44] In *moving boundary electrophoresis*, the movement of the boundary formed between a sol or solution and the pure dispersion medium in an electric field is studied. If the disperse phase is colorless, the boundary is located by the refractive index gradient (Tiselius apparatus, used frequently with protein solutions). If several species of particles or solutes with different mobilities are present, each will form a boundary moving with a characteristic velocity. Unlike microelectrophoresis, this method permits the identification of different colloidal components in a mixture, the measurement of the electrophoretic mobility of each, and an estimation of the relative amounts present.

Zone electrophoresis theoretically permits the complete separation of all electrophoretically different components, requires much smaller samples than moving boundary electrophoresis, and can be performed in simpler and less expensive equipment. The method avoids convection by supporting the solution in an inert and porous solid like filter paper, cellulose acetate membrane, agar, starch or polyacrylamide gels cut into strips, or disks or columns of polyacrylamide gel.

A strip of filter paper or gel is saturated with a conducting buffer solution and a few microliters of the solution being analyzed is deposited as a spot or narrow band. A potential difference is applied between the ends of the strip which are

in contact with the electrode compartments. The spot or band spreads and unfolds as each component migrates towards one or the other electrode at a rate determined primarily by its electrophoretic mobility. Evaporation of water due to the heating effect of the electric current may be minimized by immersing the strip in a cooling liquid or sandwiching it between impervious solid sheets. After a sufficient time has elapsed to afford good separation, the strip is removed and dried. The position of the spots or bands corresponding to the individual components is detected by color reactions or radioactive counting.

Zone electrophoresis is applied mainly in analysis and for small-scale preparative separations. It does not permit mobility measurements. Because several samples can be analyzed simultaneously (in parallel strips or gel columns), because only minute amounts of sample are needed, and because the equipment is simple and easy to operate, zone electrophoresis is widely used to study the proteins in blood serum, erythrocytes, lymph and cerebrospinal fluid, saliva, gastric and pancreatic juices and bile.

Immunodiffusion combined with electrophoresis is called *immunoelectrophoresis*.[43,45] The proteins in a fluid, including the antigens, are first separated by gel electrophoresis. A longitudinal trench is then cut along one or both sides of the gel strip near the edge in the direction of the electrophoresis axis. The trench is filled with the antibody solution. On standing, antibody and antigen proteins diffuse in all directions, including toward each other. Precipitation occurs along an elliptical arc (precipitin band) wherever an antigen meets its specific antibody. The precipitin bands are either visible directly or may be developed by staining. Since diseases frequently produce abnormal electrophoretic patterns in body fluids, zone electrophoresis and immunoelectrophoresis are convenient and powerful diagnostic techniques.

Isoelectric focusing[44,46] uses electrophoresis to separate proteins according to their isoelectric points. At pH values equal to their isoelectric points, proteins do not migrate in an electric field because their net charge is zero. In a liquid column on which a pH gradient is imposed, different species arrange themselves so that the protein with the highest isoelectric point will be located nearest to the cathode, which is immersed in the solution of a strong base. The protein with the lowest isoelectric point will be located nearest to the anode, which is immersed in the solution of a strong acid. The other proteins settle into intermediate positions, where the pH values are intermediate and equal to their isoelectric points.

Hydrophilic Dispersions

Most liquid disperse systems of pharmaceutical interest are aqueous. Therefore, most lyophilic colloidal systems discussed below consist of hydrophilic solids dissolved or dispersed in water. Most of the products mentioned below are official in the USP or NF, where more detailed descriptions may be found, also elsewhere in this text.

Hydrophilic colloids can be divided into particulate and soluble materials. The latter are water-soluble linear or branched polymers dissolved molecularly in water. Their aqueous solutions are classified as colloidal dispersions because the individual molecules are in the colloidal particle size range, exceeding 50 or 100 Å. Particulate or corpuscular hydrophilic colloidal dispersions are formed by solids which swell and are peptized in water but whose primary particles do not dissolve or break down into individual molecules or ions. One subdivision of particulate hydrophilic colloids is comprised of dispersions of cross-linked polymers whose linear, uncross-linked analogues are water-soluble.

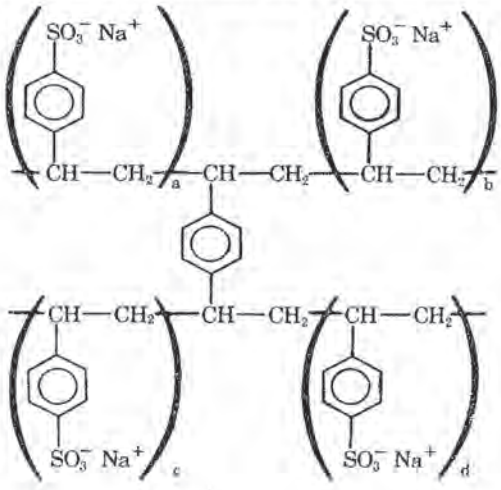
Particulate Hydrophilic Dispersions

The disperse phase of these sols consists of solids which in water swell and break up spontaneously into particles of colloidal dimensions. The disperse particles have high specific surface areas and are, therefore, extensively hydrated. They have characteristic shapes. If the attraction between individual particles is strong, the dispersions have yield values at relatively low solids content.

Bentonite is an aluminum silicate crystallizing in a layer structure (see above), with individual lamellas 9.4 Å thick. Their top and bottom surfaces are sheets of oxygen ions from silica plus an occasional sodium ion neutralizing a silicate ion-exchange site. The clay particles consist of stacks of these lamellas. Water penetrates inside the stacks between lamellas to hydrate the oxygen ions, causing extensive swelling. Bentonite particles in bentonite magma consist of single lamellas and packets of a few lamellas with intercalated water. The specific surface area amounts to several hundred square meters per gram. *Kaolin* also has a layer structure, but does not swell in water because water does not intercalate between individual lattice layers. Kaolin plates dispersed in water are, therefore, much thicker than those of bentonite, *ca* 0.04 to 0.2 μm. In kaolin, hydrated alumina lattice planes alternate with silica planes. Thus, one of the two external surfaces of a kaolin plate consists of a sheet of oxygen ions from silica, the other is a sheet of hydroxide ions from hydrated alumina. Both surfaces are well hydrated. Magnesium aluminum silicate (*Veegum*) is a clay similar to bentonite but contains magnesium; it is white whereas bentonite is gray.

Additional hydrophilic particles producing colloidal dispersions in water are listed below. *Colloidal silicon dioxide* consists of roughly spherical particles covered with siloxane and silanol groups (pages 280–281). *Titanium dioxide* is a white pigment with excellent covering power due to its high refractive index. *Microcrystalline cellulose* (page 279) is hydrophilic because of the hydroxyl and ether groups in the surface of the cellulose crystals. Gelatinous precipitates of hydrophilic compounds such as *aluminum hydroxide gel*, *aluminum phosphate gel*, and *magnesium hydroxide* consist of coarse flocs produced by agglomeration of the colloidal particles formed in the initial stage of the precipitation. They possess large internal surface areas, which is one of the reasons why the first two are used as substrates for adsorbed vaccines and toxoids.

Cross-linked Polymers—The polymers discussed below are polyelectrolytes, ie, they contain ionic groups and would be soluble in water in the absence of cross-linking. For instance, *sodium polystyrene sulfonate* is a copolymer of about 92% styrene and 8% divinylbenzene, which is sulfonated and neutralized to produce the cation-exchange resin



Chains a–b and c–d are water-soluble linear polymer chains. They are cross-linked or bound together via a phenylene group as shown. There are many such cross-links tieing every chain to two or more other chains, so that every atom in a grain of ion-exchange resin is bound to every other atom by primary, covalent bonds. The grains swell in water until the cross-links are strained but do not dissolve, because this would involve the rupture of primary valence bonds. Swelling renders the ion-exchange sites in the interior of a grain accessible to the gastrointestinal fluids. Partial exchange of Na^+ by K^+ followed by excretion of the used resin in the feces reduces hyperkalemia resulting from acute renal failure. Partial replacement of Na^+ by H^+ could reduce acidosis.

Cholestyramine resin is an anion-exchange resin containing the same backbone of cross-linked polystyrene, but substituted with $—CH_2—N^+(CH_3)_3Cl^-$ instead of sodium sulfonate. Part of the chloride anions is exchanged or replaced by bile salt anions, which are thus eliminated in the feces bound to the resin grains rather than reabsorbed. *Colestipol hydrochloride* is another orally administered anion-exchange resin used to increase the fecal excretion of bile salts. It is an extensively cross-linked, insoluble but permeable copolymer made from diethylenetriamine, tetraethylenepentamine, and epichlorohydrin. Strong cation- and anion-exchange resins are used as sustained-release vehicles for basic and acid drugs, respectively (see Chapter 91).

Polycarbophil is a copolymer of acrylic acid cross-linked with a small amount of divinyl glycol. The weakly acidic carboxyl groups are not ionized in the strongly acid environment of the stomach but only in the more nearly neutral intestines. Therefore, swelling by osmotic influx of water occurs mostly in the intestines, where imbibition of water decreases the fluidity of stools associated with diarrhea. Among natural polymers, tragacanth consists of $\frac{1}{3}$ of a water-soluble fraction, tragacanthin, and $\frac{2}{3}$ of a gel fraction called bassorin which swells in water but does not dissolve. Starch consists of $\frac{1}{6}$ of a fraction, soluble in hot water, called amylose. The remainder, amylopectin, merely absorbs water and swells. It owes its insolubility to extensive branching rather than cross-linking.

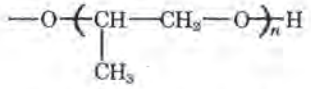
Soluble Polymers as Lyophilic Colloids

Most hydrophilic colloidal systems used in dosage forms are molecular solutions of water soluble, high molecular weight polymers. The polymers are either linear or slightly branched but not cross-linked.

Classifications—According to their origin, water-soluble polymers are divided into three classes. *Natural polymers* include polysaccharides (acacia, agar, heparin sodium, pectin, sodium alginate, tragacanth, xanthan gum) and polypeptides (casein, gelatin, protamine sulfate). Of these, agar and gelatin are only soluble in hot water.

Cellulose derivatives are produced by chemical modification of cellulose obtained from wood pulp or cotton to produce soluble polymers. *Cellulose* is an insoluble, linear polymer of glucose repeat units in the ring or pyranose form joined by β-1,4 glucosidic linkages. Each glucose repeat unit (except for the two terminal ones) contains a primary hydroxyl group on the No 6 carbon and two secondary hydroxyls on No 2 and 3 carbons. The primary hydroxyl is more reactive. Chemical modification of cellulose consists in reactions or substitutions of the hydroxyl groups. The extent of such reactions is expressed as *degree of substitution* (DS), namely, the number of substituted hydroxyl groups per glucose residue. The highest value is DS = 3.0. Fractional values are the rule because the DS is averaged over a multitude of glucose residues. A DS value of 0.6 indicates that some glucose repeat units are unsubstituted while others have one or even two substituents.

Soluble cellulose derivatives are listed below. The DS values correspond to the pharmaceutical grades. The groups shown are the replacements for the hydrogen atoms of the cellulosic hydroxyls. Official derivatives are *methylcellulose* (DS = 1.65–1.93), $—O—CH_3$ and *sodium carboxymethylcellulose* (DS = 0.60–1.00), $—O—CH_2—COO^-Na^+$. *Hydroxyethyl cellulose* (DS ≅ 1.0), $—O\text{-}(CH_2CH_2—O\text{-})_nH$ and *hydroxypropyl cellulose* (DS ≅ 2.5) are manufactured



by the addition of ethylene oxide and propylene oxide, respectively, to alkali-treated cellulose. The value of n is about 2.0 for the former and not much greater than 1.0 for the latter. *Hydroxypropyl methylcellulose* is prepared by reacting alkali-treated cellulose first with methyl chloride to introduce methoxy groups (DS = 1.1–1.8) and then with propylene oxide to introduce propylene glycol ether groups (DS = 0.1–0.3). In general, the introduction of hydroxypropyl groups into cellulose reduces the water solubility somewhat while promoting the solubility in polar organic solvents like short-chain alcohols, glycols and some ethers.

The molecular weight of native cellulose is so high that soluble derivatives of approximately the same degree of polymerization would dissolve too slowly, and their solutions would be excessively viscous even at concentrations of 1% and less. Controlled degradation is used to break the cellulose chains into shorter segments, reducing the viscosity of the solutions of the corresponding soluble derivatives. Commercial grades of a given cellulose derivative such as sodium carboxymethylcellulose come in various molecular weights or viscosity grades as well as with various degrees of substitution, offering the pharmacist a wide selection.

Official cellulose derivatives which are insoluble in water but soluble in some organic solvents include *ethylcellulose* (DS = 2.2–2.7), $—O—C_2H_5$; *cellulose acetate phthalate* (DS = 1.70 for acetyl and 0.77 for phthalyl); and *pyroxylin* or cellulose nitrate (DS ≅ 2), $—O—NO_2$. *Collodion*, a 4.0% w/v solution of pyroxylin in a mixture of 75% (v/v) ether and 25% (v/v) ethyl alcohol, constitutes a lyophilic colloidal system.

The third class, water soluble *synthetic polymers*, consists mostly of vinyl derivatives including *polyvinyl alcohol*, *povidone* or polyvinylpyrrolidone, and *carbomer* (*Carbopol*), a copolymer of acrylic acid. High molecular weight polyethylene glycols are also called *polyethylene oxides*.

A second classification of hydrophilic polymers is based on their charge. *Nonionic* or uncharged polymers include methylcellulose, hydroxyethyl and hydroxypropyl cellulose, ethylcellulose, pyroxylin, polyethylene oxide, polyvinyl alcohol and povidone. *Anionic* or negatively charged *polyelectrolytes* include the following carboxylated polymers: acacia, alginic acid, pectin, tragacanth, xanthan gum and carbomer at pH values leading to ionization of the carboxyl groups; sodium alginate and sodium carboxymethylcellulose; also polypeptides at pH values above their isoelectric points, eg, sodium caseinate. A stronger acid group is sulfuric acid, which exists as a monoester in agar and heparin and as a monoamide in heparin. *Cationic* or positively charged *polyelectrolytes* are rare. Examples are polypeptides at pH values below their isoelectric points. Protamines are strongly basic due to a high arginine content, with isoelectric points around pH 12, eg protamine sulfate.

Gel Formation—As described in Chapter 20 and illustrated in Fig 20-7*A*, the flexible chains of dissolved polymers interpenetrate and are entangled because of the constant Brownian motion of their segments. The chains writhe and forever change their conformations. Each chain is encased in a sheath of solvent molecules that solvate its functional groups. In the case of aqueous solutions, water molecules

are hydrogen-bonded to the hydroxyl groups of polyvinyl alcohol, hydroxyl groups and ether links of polysaccharides, ether links of polyethylene oxide or polyethylene glycol, amide groups of polypeptides and povidone, and carboxylate groups of anionic polyelectrolytes. The envelope of water of hydration prevents chains segments in close proximity from touching and attracting one another by interchain hydrogen bonds and van der Waals forces as they do in the solid state. The slippage of solvated chains past one another when the solution flows is lubricated by the free solvent between their solvation sheaths.

Factors that lower the hydration of dissolved macromolecules reduce or thin out the sheath of hydration separating adjacent chains. When the hydration is low, contiguous chains tend to attract one another by secondary valence forces including hydrogen bonds and van der Waals forces. Hydrophobic bonding makes an important contribution to interchain attraction between polypeptide chains even in solution. Van der Waals forces and hydrogen bonds thus establish weak and reversible cross-links between chains at their points of contact or entanglement, bringing about phase separation or precipitation.

Most water-soluble polymers have higher solubilities in hot than in cold water and tend to precipitate on cooling, as the sheaths of hydration surrounding adjacent chains become too sparse to prevent interchain attraction. Dilute solutions separate into a solvent phase practically free of polymer and a viscous liquid phase containing practically all of the polymer but still a large excess of solvent. This process is called *simple coacervation* and the polymer-rich liquid phase a *coacervate*.[21,47] If the polymer solution is concentrated enough and/or the temperature low enough, cooling causes the formation of a continuous network of precipitating chains attached to one another through weak cross-links consisting of interchain hydrogen bonds and van der Waals forces at the points of mutual contact. Segments of regularly sequenced polymer chains even associate laterally into crystalline bundles or crystallites. Irregular chain structures as found in random copolymers, randomly substituted cellulose ethers and esters, and highly branched polymers like acacia prevent crystallization during precipitation from solution. Chain entanglements provide the sole temporary cross-links in those cases. The network of associated polymer chains immobilizes the solvent and causes the solution to set to a gel. Gelatinous precipitates or highly swollen flocs may separate when cooling more dilute polymer solutions.

Besides the chemical nature of polymer and solvent, the three most important factors causing phase separation, precipitation and gelation of polymer solutions are temperature, concentration and molecular weight. Lower temperatures, higher concentrations and higher molecular weights promote gelation and produce stronger gels.

For a typical *gelatin*, 10% solutions acquire yield values and begin to gel at about 25°, 20% solutions at about 30° and 30% solutions at about 32°. The *gelation* is reversible: the gels liquefy when heated above these temperatures. Gelation is rarely observed above 34° regardless of concentration, so that gelatin solutions do not gel at 37°. Conversely, gelatin will dissolve readily in water at body temperature. The gelation temperature or gel point of gelatin is highest at the isoelectric point, where the attachment between adjacent chains by coulombic attraction or ionic bonds between carboxylate ions and alkylammonium, guanidinium or imidazolium groups is most extensive. Since the carboxyl groups are not ionized at gastric pH, interchain ionic bonds are practically nonexistent, and interchain attraction is limited to hydrogen bonds and van der Waals forces. The gelation temperature or the melting point of gelatin gels depends more strongly on temperature and concentration than on pH.[48,49] The combination of an acid pH considerably below the isoelectric point and a temperature of 37° completely prevents the gelation of gelatin solutions. Conversely, these two conditions promote rapid dissolution of gelatin capsules in the stomach. Agar and pectic acid solutions set to gels at only a few percent of solids.

Unlike most water-soluble polymers, methylcellulose, hydroxypropyl cellulose and polyethylene oxide are more soluble in cold than in hot water. Their solutions therefore tend to gel on heating (*thermal gelation*).

When dissolving powdered polymers in water, temporary gel formation often slows the process down considerably. As water diffuses into loose clumps of powder, their exterior frequently turns to a cohesive gel of solvated particles encasing dry powder. Such blobs of gel dissolve very slowly because of their high viscosity and the low diffusion coefficient of the macromolecules. Especially for large-scale dissolution, it is helpful to disperse the polymer powder in water before it can agglomerate into lumps of gel. In order to permit dispersion to precede hydration and to prevent temporary gel formation, the polymer powders are dispersed in water at temperatures where the solubility of the polymer is lowest. Most polymer powders, such as sodium carboxymethylcellulose, are dispersed with high shear in *cold* water before the particles can hydrate and swell to sticky gel grains agglomerating into lumps. Once the powder is well dispersed, the solution is heated with moderate shear to about 60° for fastest dissolution. Because methylcellulose hydrates most slowly in hot water, the powder is dispersed with high shear in 1/5 to 1/3 of the required amount of water heated to 80 to 90°. Once the powder is finely dispersed, the rest of the water is added cold or even as ice, and moderate stirring causes prompt dissolution. For maximum clarity, fullest hydration and highest viscosity, the solution should be cooled to 0 to 10° for about an hour.

The following are two alternative methods for preventing the formation of gelatinous lumps upon addition of water. The powder is prewetted with a water-miscible organic solvent such as ethyl alcohol or propylene glycol that does not swell the polymer, in the proportion of from three to five parts solvent to each part of polymer. If other nonpolymeric powdered adjuvants are to be incorporated into the solution, these are dry-blended with the polymer powder. The latter should comprise 1/4 or less of the blend for best results.

A pharmaceutical application of *gelation* in a nonaqueous medium is the manufacture of *Plastibase* or *Jelene* (*Squibb*), which consists of 5% of a low-molecular-weight polyethylene and 95% of mineral oil. The polymer is soluble in mineral oil above 90°, which is close to its melting point. When the solution is cooled below 90°, the polymer precipitates and causes gelation. The mineral oil is immobilized in the network of entangled, and adhering, insoluble polyethylene chains which probably even associate into small crystalline regions. Unlike petrolatum, this gel can be heated to about 60° without substantial loss in consistency.

Large increases in the concentration of polymer solutions may lead to precipitation and gelation. One way of effectively increasing the concentration of aqueous polymer solutions is to add inorganic salts. The salts will bind part of the water of the polymer solution in order to become hydrated. Competition for water of hydration dehydrates the polymer molecules and precipitates them, causing gelation. This phenomenon is called *salting out*. Because of its high solubility in water, ammonium sulfate is often used by biochemists to precipitate and separate proteins from dilute solution. To the pharmacist, salting out usually represents an undesirable problem. It is reversible, however, and subsequent addition of water redissolves the precipitated polymers and liquefies their gels. Salting out may cause the polymer to separate as a concentrated and viscous liquid solution or simple coacervate rather than as a solid gel.

The effectiveness of electrolytes to salt out, precipitate or gel hydrophilic colloidal systems depends on how extensively the electrolytes are hydrated. The *Hofmeister* or *lyotropic series* arranges ions in the order of increasing hydration and increasing effectiveness in salting out hydrophilic colloids. The series, for monovalent cations, is

$$Cs^+ < Rb^+ < NH_4^+ < K^+ < Na^+ < Li^+$$

and for divalent cations,

$$Ba^{2+} < Sr^{2+} < Ca^{2+} < Mg^{2+}$$

This series also arranges the cations in the order of decreasing coagulating power or increasing coagulation values for negative hydrophobic sols (see Table XIV) and of increasing ease of their displacement from cation exchange resins: K^+ displaces Na^+ and Li^+. For anions, the lyotropic series in the order of decreasing coagulating power and decreasing effectiveness in salting out is

$$F^- > \text{citrate}^{3-} > HPO_4^{2-} > \text{tartrate}^{2-} > SO_4^{2-} > \text{acetate}^- > Cl^- > NO_3^- > ClO_3^- > Br^- > ClO_4^- > I^- > CNS^-$$

Iodides and thiocyanates and to a lesser extent bromides and nitrates actually tend to increase the solubility of polymers in water, salting them in.[21,22,24-26] These large polarizable anions destructure water, reducing the extent of hydrogen bonding among water molecules and thereby making more of the hydrogen-bonding capacity of water available to the solute. Most salts except nitrates, bromides, perchlorates, iodides and thiocyanates raise the temperature of precipitation or gelation of most hydrophilic colloidal solutions or their gel melting points. Exceptions among hydrophilic colloids are methylcellulose, hydroxypropyl cellulose and polyethylene oxide whose gelation temperatures or gel points and gel melting points are lowered by salting out.

Hydrophobic aqueous dispersions are coagulated by electrolytes at 0.0001–0.1 *M* concentrations (see Table XIV). Moreover, the coagulation is irreversible, ie, removal of the coagulating salt does not allow the coagulum to be redispersed, because the hydrophobic sols are intrinsically unstable. By contrast, most hydrophilic sols require electrolyte concentrations of 1 *M* or higher for precipitation. Their precipitation or gelation can be reversed, and the polymer redissolved by removing the salt through dialysis or by adding more water. Hydrophilic colloids disperse or dissolve spontaneously in water, and their sols are intrinsically stable.

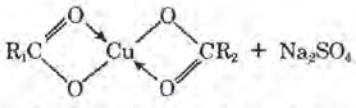
Most of the hydrophilic and water-soluble polymers mentioned above are only slightly soluble or insoluble in alcohol. Addition of alcohol to their aqueous solutions may cause precipitation or gelation because alcohol is a nonsolvent or precipitant, lowering the dielectric constant of the medium, and it tends to dehydrate the hydrophilic solute. Alcohol lowers the concentrations at which electrolytes salt out hydrophilic colloids. Phase separation through the addition of alcohol to an aqueous polymer solution may cause coacervation, ie, the separation of a concentrated viscous liquid phase, rather than precipitation or formation of a gel. Sucrose also competes for water of hydration with hydrophilic colloids, and may cause phase separation. However, most hydrophilic sols tolerate substantially higher concentrations of sucrose than of electrolytes or alcohol. Lower viscosity grades of a given polymer are usually more resistant to electrolytes, alcohol and sucrose than grades of higher viscosity and higher molecular weights.

Whenever hydrophilic colloidal dispersions undergo irreversible precipitation or gelation, chemical reactions are involved. Neither dilution with water nor heating nor attempts to remove the gelling or precipitating agent by washing or dialysis will liquefy those gels or redissolve the gelatinous precipitates formed at lower polymer concentrations. Carboxyl groups are not ionized in strongly acid media. If a polymer owes its solubility to the ionization of these weakly acid groups, reducing the pH of its solution below 3 may lead to precipitation or gelation. This is observed with such carboxylated polymers as many gums, sodium carboxymethylcellulose and carbomer. Hydrogen carboxymethylcellulose swells and disperses but does not dissolve in water. Neutralization to higher pH values returns the carboxyl groups to their ionized state and reverses the gelation or precipitation.

Only the sodium, potassium, ammonium and triethanolammonium salts of carboxylated polymers are well soluble in water. In the case of carboxymethylcellulose, salts with heavy metal cations (silver, copper, mercury, lead) and trivalent cations (aluminum, chromic, ferric) are practically insoluble. Salts with divalent cations, especially of the alkaline earth metals, have borderline solubilities. Generally, higher degrees of substitution tend to increase the tolerance of the carboxymethylcellulose to salts.

Precipitation or gelation occur due to metathesis when inorganic salts of heavy or trivalent cations are mixed with alkali metal salts of carboxylated polymers in solution. For instance, if a soluble copper salt is added to a solution of sodium carboxymethylcellulose, the double decomposition can be written schematically as

$$R_1COO^-Na^+ + R_2COO^-Na^+ + CuSO_4 \longrightarrow$$



$+ Na_2SO_4$

R_1 and R_2 represent two carboxymethylcellulose chains which are cross-linked by a chelated copper ion. Dissociation of the cupric carboxylate complex is negligible.

Particle Phenomena and Coarse Dispersions

The Dispersion Step

The pharmaceutical formulator is concerned primarily with producing a smooth, uniform, easily flowing (pouring or spreading) suspension or emulsion in which dispersion of particles can be effected with minimum expenditure of energy.

In preparing suspensions, particle–particle attractive forces need to be overcome by the high shearing action of such devices as the colloid mill, or by use of surface-active agents. The latter greatly facilitate wetting of lyophobic powders and assist in the removal of surface air that shearing alone may not remove; thus the clumping tendency of the particles is reduced. Moreover, lowering of the surface free energy by the adsorption of these agents directly reduces the thermodynamic driving force opposing dispersion of the particles.

In emulsification shear rates are frequently necessary for dispersion of the internal phase into fine droplets. The shear forces are opposed by forces operating to resist distortion and subsequent breakup of the droplets. Again surface-active agents help greatly by lowering interfacial ten-

sion, which is the primary reversible component resisting droplet distortion. Surface-active agents also may play an important role in determining whether an oil-in-water or a water-in-oil emulsion preferentially survives the shearing action.

Once the process of dispersion begins there develops simultaneously a tendency for the system to revert to an energetically more stable state, manifested by flocculation, coalescence, sedimentation, crystal growth, and caking phenomena. If these physical changes are not inhibited or controlled, successful dispersions will not be achieved or will be lost during shelf life.

Settling and Its Control

In order to control the settling of dispersed material in suspension, the pharmacist must be aware of those physical factors that will affect the rate of sedimentation of particles under ideal and nonideal conditions. He must also be aware of the various coefficients used to express the amount of flocculation in the system and the effect flocculation will have on the structure and volume of the sediment.

Sedimentation Rate

The rate at which particles in a suspension sediment is related to their size and density and the viscosity of the suspension medium. Brownian movement may exert a significant effect, as will the absence or presence of flocculation in the system.

Stokes' Law—The velocity of sedimentation of a uniform collection of spherical particles is governed by Stokes' law, expressed as follows:

$$v = \frac{2r^2(\rho_1 - \rho_2)g}{9\eta} \qquad (35)$$

where v is the terminal velocity in cm/sec, r is the radius of the particles in cm, ρ_1 and ρ_2 are the densities (g/cm^3) of the dispersed phase and the dispersion medium, respectively, g is the acceleration due to gravity (980.7 cm/sec^2) and η is the Newtonian viscosity of the dispersion medium in poises (g/cm sec). Stokes' law holds only if the downward motion of the particles is not sufficiently rapid to cause turbulence. Micelles and small phospholipid vesicles do not settle unless they are subjected to centrifugation.

While conditions in a pharmaceutical suspension are not in strict accord with those laid down for Stokes' law, Eq 35, provides those factors that can be expected to influence the rate of settling. Thus, sedimentation velocity will be reduced by decreasing the particle size, provided the particles are kept in a deflocculated state. The rate of sedimentation will be an inverse function of the viscosity of the dispersion medium. However, too high a viscosity is undesirable, especially if the suspending medium is Newtonian rather than shear-thinning (see Chapter 20), since it then becomes difficult to redisperse material which has settled. It also may be inconvenient to remove a viscous suspension from its container. When the size of particles undergoing sedimentation is reduced to approximately 2 μm, random Brownian movement is observed and the rate of sedimentation departs markedly from the theoretical predictions of Stokes' law. The actual size at which Brownian movement becomes significant depends on the density of the particle as well as the viscosity of the dispersion medium.

Flocculation and Deflocculation—Zeta potential ψ_z is a measurable indication of the potential existing at the surface of a particle. When ψ_z is relatively high (25 mV or more), the repulsive forces between two particles exceed the attractive London forces. Accordingly, the particles are dispersed and are said to be *deflocculated*. Even when brought close together by random motion or agitation, deflocculated particles resist collision due to their high surface potential.

The addition of a preferentially adsorbed ion whose charge is opposite in sign to that on the particle leads to a progressive lowering of ψ_z. At some concentration of the added ion the electrical forces of repulsion are lowered sufficiently that the forces of attraction predominate. Under these conditions the particles may approach each other more closely and form loose aggregates, termed flocs. Such a system is said to be *flocculated*.

Some workers restrict the term *flocculation* to the aggregation brought about by chemical bridging; aggregation involving a reduction of repulsive potential at the double layer is referred to as *coagulation*. Other workers regard flocculation as aggregation in the secondary minimum of the potential energy curve of two interacting particles and coagulation as aggregation in the primary minimum. In the present chapter the term *flocculation* is used for all aggregation processes, irrespective of mechanism.

The continued addition of the flocculating agent can reverse the above process, if the zeta potential increases sufficiently in the opposite direction. Thus, the adsorption of anions onto positively charged deflocculated particles in suspension will lead to flocculation. The addition of more anions can eventually generate a net negative charge on the particles. When this has achieved the required magnitude, deflocculation may occur again. The only difference from the starting system is that the net charge on the particles in their deflocculated state is negative rather than positive.

Table XV—Relative Properties of Flocculated and Deflocculated Particles in Suspension

Deflocculated	Flocculated
1. Particles exist in suspension as separate entities.	Particles form loose aggregates.
2. Rate of sedimentation is slow, since each particle settles separately and particle size is minimal.	Rate of sedimentation is high, since particles settle as a floc, which is a collection of particles.
3. A sediment is formed slowly.	A sediment is formed rapidly.
4. The sediment eventually becomes very closely packed, due to weight of upper layers of sedimenting material. Repulsive forces between particles are overcome and a hard cake is formed which is difficult, if not impossible, to redisperse.	The sediment is loosely packed and possesses a scaffold-like structure. Particles do not bond tightly to each other and a hard, dense cake does not form. The sediment is easy to redisperse, so as to reform the original suspension.
5. The suspension has a pleasing appearance, since the suspended material remains suspended for a relatively long time. The supernatant also remains cloudy, even when settling is apparent.	The suspension is somewhat unsightly, due to rapid sedimentation and the presence of an obvious, clear supernatant region. This can be minimized if the volume of sediment is made large. Ideally, volume of sediment should encompass the volume of the suspension.

Some of the major differences between suspensions of flocculated and deflocculated particles are presented in Table XV.

Effect of Flocculation—In a deflocculated system containing a distribution of particle sizes, the larger particles naturally settle faster than the smaller particles. The very small particles remain suspended for a considerable length of time, with the result that no distinct boundary is formed between the supernatant and the sediment. Even when a sediment becomes discernible, the supernatant remains cloudy.

When the same system is flocculated (in a manner to be discussed later), two effects are immediately apparent. First, the flocs tend to fall together so that a distinct boundary between the sediment and the supernatant is readily observed; second, the supernatant is clear, showing that the very fine particles have been incorporated into the flocs. The initial rate of settling in flocculated systems is determined by the size of the flocs and the porosity of the aggregated mass. Under these circumstances it is perhaps better to use the term *subsidence*, rather than sedimentation.

Quantitative Expressions of Sedimentation and Flocculation

Frequently, the pharmacist needs to assess a formulation in terms of the amount of flocculation in the suspension and to compare this with that found in other formulations. The two parameters commonly used for this purpose are outlined below.

Sedimentation Volume—The *sedimentation volume*, F, is the ratio of the equilibrium volume of the sediment, V_u, to the total volume of the suspension, V_0. Thus,

$$F = V_u/V_0 \tag{36}$$

As the volume of suspension which appears occupied by the sediment increases, the value of F, which normally ranges from nearly 0 to 1, increases. In the system where $F = 0.75$, for example, 75% of the total volume in the container is apparently occupied by the loose, porous flocs forming the sediment. This is illustrated in Fig 19-33. When $F = 1$, no sediment is apparent even though the system is flocculated. This is the ideal suspension for, under these conditions, no sedimentation will occur. Caking also will be absent. Furthermore, the suspension is esthetically pleasing, there being no visible, clear supernatant.

Degree of Flocculation—A better parameter for comparing flocculated systems is the *degree of flocculation*, β, which relates the sedimentation volume of the flocculated suspension, F, to the sedimentation volume of the suspension when deflocculated, F_∞. It is expressed as

$$\beta = F/F_\infty \tag{37}$$

The degree of flocculation is, therefore, an expression of the increased sediment volume resulting from flocculation.

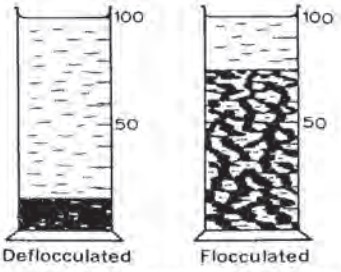


Fig 19-33. Sedimentation parameters of suspensions. Deflocculated suspension: $F_\infty = 0.15$. Flocculated suspension: $F = 0.75$; $\beta = 5.0$.

If, for example, β has a value of 5.0 (Fig 19-33), this means that the volume of sediment in the flocculated system is five times that in the deflocculated state. If a second flocculated formulation results in a value for β of say 6.5, this latter suspension obviously is preferred, if the aim is to produce as flocculated a product as possible. As the degree of flocculation in the system decreases, β approaches unity, the theoretical minimum value.

Suspensions and their Formulation

A pharmaceutical suspension may be defined as a coarse dispersion containing finely divided insoluble material suspended in a liquid medium. Suspension dosage forms are given by the oral route, injected intramusculary or subcutaneously, applied to the skin in topical preparations, and used ophthalmically in the eye. They are an important class of dosage form. Since some products are occasionally prepared in a dry form, to be placed in suspension at the time of dispensing by the addition of an appropriate vehicle, this definition is extended to include these products.

There are certain criteria that a well-formulated suspension should meet. The dispersed particles should be of such a size that they do not settle rapidly in the container. However, in the event that sedimentation occurs, the sediment must not form a hard cake. Rather, it must be capable of redispersion with a minimum effort on the part of the patient. Additionally, the product should be easy to pour, pleasant to take, and resistant to microbial attack.

The three major problem areas associated with suspensions are (1) adequate dispersion of the particles in the vehicle, (2) settling of the dispersed particles, and (3) caking of these particles in the sediment so as to resist redispersion. Much of the following discussion will deal with the factors that influence these processes and the ways in which they can be minimized.

The formulation of a suspension possessing optimal physical stability depends on whether the particles in suspension are to be flocculated or to remain deflocculated. One approach involves use of a structured vehicle to keep deflocculated particles in suspension; a second depends on controlled flocculation as a means of preventing cake formation. A

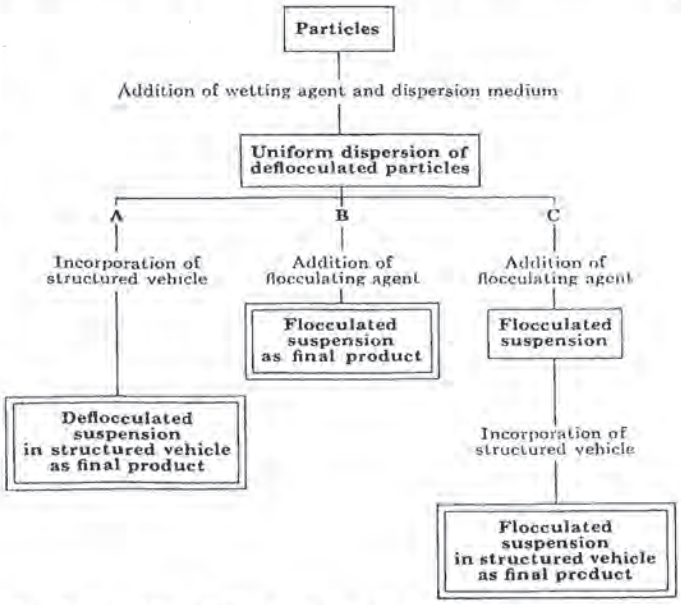


Fig 19-34. Alternative approaches to the formulation of suspensions.

third, a combination of the two previous methods, results in a product with optimum stability. The various schemes are illustrated in Fig 19-34.

Dispersion of Particles—The dispersion step has been discussed earlier in this chapter. Surface-active agents commonly are used as wetting agents; maximum efficiency is obtained when the HLB value lies within the range of 7 to 9. A concentrated solution of the wetting agent in the vehicle may be used to prepare a slurry of the powder; this is diluted with the required amount of vehicle. Alcohol and glycerin may be used sometimes in the initial stages to disperse the particles, thereby allowing the vehicle to penetrate the powder mass.

Only the minimum amount of wetting agent should be used, compatible with producing an adequate dispersion of the particles. Excessive amounts may lead to foaming or impart an undesirable taste or odor to the product. Invariably, as a result of wetting, the dispersed particles in the vehicle are deflocculated.

Structured Vehicles—Structured vehicles are generally aqueous solutions of polymeric materials, such as the hydrocolloids, which are usually negatively charged in aqueous solution. Typical examples are methylcellulose, carboxymethylcellulose, bentonite, and Carbopol. The concentration employed will depend on the consistency desired for the suspension which, in turn, will relate to the size and density of the suspended particles. They function as viscosity-imparting suspending agents and, as such, reduce the rate of sedimentation of dispersed particles.

The rheological properties of suspending agents are considered elsewhere (Chapter 20). Ideally, these form pseudoplastic or plastic systems which undergo shear-thinning. Some degree of thixotropy is also desirable. Non-Newtonian materials of this type are preferred over Newtonian systems because, if the particles eventually settle to the bottom of the container, their redispersion is facilitated by the vehicle thinning when shaken. When the shaking is discontinued, the vehicle regains its original consistency and the redispersed particles are held suspended. This process of redispersion, facilitated by a shear-thinning vehicle, presupposes that the deflocculated particles have not yet formed a cake. If sedimentation and packing have proceeded to the point where considerable caking has occurred, redispersion is virtually impossible.

Controlled Flocculation—When using this approach (see Fig 19-34, B and C), the formulator takes the deflocculated, wetted dispersion of particles and attempts to bring about flocculation by the addition of a flocculating agent; most commonly, these are either electrolytes, polymers, or surfactants. The aim is to *control* flocculation by adding that amount of flocculating agent which results in the maximum sedimentation volume.

Electrolytes are probably the most widely used flocculating agents. They act by reducing the electrical forces of repulsion between particles, thereby allowing the particles to form the loose flocs so characteristic of a flocculated suspension. Since the ability of particles to come together and form a floc depends on their surface charge, zeta potential measurements on the suspension, as an electrolyte is added, provide valuable information as to the extent of flocculation in the system.

This principle is illustrated by reference to the following example, taken from the work of Haines and Martin.[50] Particles of sulfamerazine in water bear a negative charge. The serial addition of a suitable electrolyte, such as aluminum chloride, causes a progressive reduction in the zeta potential of the particles. This is due to the preferential adsorption of the trivalent aluminum cation. Eventually, the zeta potential will reach zero and then become positive as the addition of $AlCl_3$ is continued.

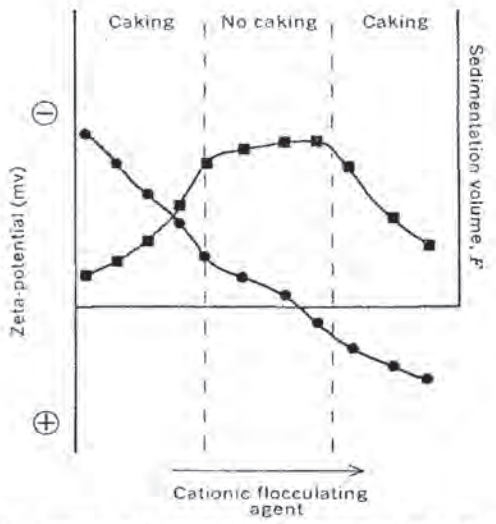


Fig 19-35. Typical relationship between caking, zeta potential and sedimentation volume, as a positively charged flocculating agent is added to a suspension of negatively charged particles. ●: zeta potential; ■: sedimentation volume.

If sedimentation studies are run simultaneously on suspensions containing the same range of $AlCl_3$ concentrations, a relationship is observed (Fig 19-35) between the sedimentation volume, F, the presence or absence of caking, and the zeta potential of the particles. In order to obtain a flocculated, noncaking suspension with the maximum sedimentation volume, the zeta potential must be controlled so as to lie within a certain range (generally less than 25 mV). This is achieved by the judicious use of an electrolyte.

A comparable situation is observed when a negative ion such as PO_4^{3-} is added to a suspension of positively charged particles such as bismuth subnitrate. Ionic and nonionic surfactants and lyophilic polymers also have been used to flocculate particles in suspension. Polymers, which act by forming a "bridge" between particles, may be the most efficient additives for inducing flocculation. Thus, it has been shown that the sedimentation volume is higher in suspensions flocculated with an anionic heteropolysaccharide than when electrolytes were used.

Work by Matthews and Rhodes,[51-53] involving both experimental and theoretical studies, has confirmed the formulation principles proposed by Martin and Haines. The suspensions used by Matthews and Rhodes contained 2.5% w/v of griseofulvin as a fine powder together with the anionic surfactant sodium dioxyethylated dodecyl sulfate (10^{-3} molar) as a wetting agent. Increasing concentrations of aluminum chloride were added and the sedimentation height (equivalent to the sedimentation volume, see page 295) and the zeta potential recorded. Flocculation occurred when a concentration of 10^{-3} molar aluminum chloride was reached. At this point the zeta potential had fallen from −46.4 mV to −17.0 mV. Further reduction of the zeta potential, to −4.5 mV by use of 10^{-2} molar aluminum chloride did not increase sedimentation height, in agreement with the principles shown in Fig 19-35.

Matthews and Rhodes then went on to show, by computer analysis, that the DLVO theory (see page 285) predicted the results obtained, namely, that the griseofulvin suspensions under investigation would remain deflocculated when the concentration of aluminum chloride was 10^{-4} molar or less. Only at concentrations in the range of 10^{-3} to 10^{-2} molar aluminum chloride did the theoretical plots show deep primary minima, indicative of flocculation. These occurred at a distance of separation between particles of approximately

50 Å, and led Matthews and Rhodes to conclude that coagulation had taken place in the primary minimum.

Schneider, *et al*[54] have published details of a laboratory investigation (suitable for undergraduates) that combines calculations based on the DLVO theory carried out with an interactive computer program with actual sedimentation experiments performed on simple systems.

Flocculation in Structured Vehicles—The ideal formulation for a suspension would seem to be when flocculated particles are supported in a structured vehicle.

As shown in Fig 19-34 (under C), the process involves dispersion of the particles and their subsequent flocculation. Finally, a lyophilic polymer is added to form the structured vehicle. In developing the formulation, care must be taken to ensure the absence of any incompatibility between the flocculating agent and the polymer used for the structured vehicle. A limitation is that virtually all the structured vehicles in common use are hydrophilic colloids and carry a negative charge. This means that an incompatibility arises if the charge on the particles is originally negative. Flocculation in this instance requires the addition of a positively charged flocculating agent or ion; in the presence of such a material, the negatively charged suspending agent may coagulate and lose its suspendability. This situation does not arise with particles that bear a positive charge, as the negative flocculating agent which the formulator must employ is compatible with the similarly charged suspending agent.

Chemical Stability of Suspensions—Particles that are completely insoluble in a liquid vehicle are unlikely to undergo most chemical reactions leading to degradation. However, most drugs in suspension have a finite solubility, even though this may be of the order of fractions of a microgram per mL. As a result, the material in solution may be susceptible to degradation. However, Tingstad and coworkers[55] developed a simplified method for determining the stability of drugs in suspension. The approach is based on the assumptions that (1) degradation takes place only in the solution and is first order, (2) the effect of temperature on drug solubility and reaction rate conforms with classical theory, and (3) dissolution is not rate-limiting on degradation.

Preparation of Suspensions—The small-scale preparation of suspensions may be readily undertaken by the practicing pharmacist with the minimum of equipment. The initial dispersion of the particles is best carried out by trituration in a mortar, the wetting agent being added in small increments to the powder. Once the particles have been wetted adequately, the slurry may be transferred to the final container. The next step depends on whether the deflocculated particles are to be suspended in a structured vehicle, flocculated, or flocculated and then suspended. Regardless of which of the alternative procedures outlined in Fig 19-34 is employed, the various manipulations can be carried out easily in the bottle, especially if an aqueous solution of the suspending agent has been prepared beforehand.

For a detailed discussion of the methods used in the large-scale production of suspensions, see the relevant section in Chapter 82.

Emulsions in Pharmacy

An emulsion is a dispersed system containing at least two immiscible liquid phases. The majority of conventional emulsions in pharmaceutical use have dispersed particles ranging in diameter from 0.1 to 100 μm. As with suspensions, emulsions are thermodynamically unstable as a result of the excess free energy associated with the surface of the droplets. The dispersed droplets, therefore, strive to come together and reduce the surface area. In addition to this flocculation effect, also observed with suspensions, the dispersed particles can coalesce, or fuse, and this can result in the eventual destruction of the emulsion. In order to minimize this effect a third component, the *emulsifying agent*, is added to the system to improve its stability. The choice of emulsifying agent is critical to the preparation of an emulsion possessing optimum stability. The efficiency of present-day emulsifiers permits the preparation of emulsions which are stable for many months and even years, even though they are thermodynamically unstable.

Emulsions are widely used in pharmacy and medicine, and emulsified materials can possess advantages not observed when formulated in other dosage forms. Thus, certain medicinal agents having an objectionable taste have been made more palatable for oral administration when formulated in an emulsion. The principles of emulsification have been applied extensively in the formulation of dermatological creams and lotions. Intravenous emulsions of contrast media have been developed to assist the physician in undertaking X-ray examinations of the body organs while exposing the patient to the minimum of radiation. Considerable attention has been directed towards the use of sterile, stable intravenous emulsions containing fat, carbohydrate, and vitamins all in one preparation. Such products are administered to patients unable to assimilate these vital materials by the normal oral route.

Emulsions offer potential in the design of systems capable of giving controlled rates of drug release and of affording protection to drugs susceptible to oxidation or hydrolysis. There is still a need for well-characterized dermatological products with reproducible properties, regardless of whether these products are antibacterial, sustained-release, protective, or emollient lotions, creams or ointments. The principle of emulsification is involved in an increasing number of aerosol products.

The pharmacist must be familiar with the types of emulsions and the properties and theories underlying their preparation and stability; such is the purpose of the remainder of this chapter. Microemulsions, which can be regarded as isotropic, swollen micellar systems are discussed in Chapter 83.

Emulsion Type and Means of Detection

A stable emulsion must contain at least three components; namely, the dispersed phase, the dispersion medium, and the emulsifying agent. Invariably, one of the two immiscible liquids is aqueous while the second is an oil. Whether the aqueous or the oil phase becomes the dispersed phase depends primarily on the emulsifying agent used and the relative amounts of the two liquid phases. Hence, an emulsion in which the oil is dispersed as droplets throughout the aqueous phase is termed an oil-in-water, O/W, emulsion. When water is the dispersed phase and an oil the dispersion medium, the emulsion is of the water-in-oil, W/O, type. Most pharmaceutical emulsions designed for oral administration are of the O/W type; emulsified lotions and creams are either O/W or W/O, depending on their use. Butter and salad creams are W/O emulsions.

Recently, so-called *multiple* emulsions have been developed with a view to delaying the release of an active ingredient. In these types of emulsions three phases are present, ie, the emulsion has the form W/O/W or O/W/O. In these

"emulsions within emulsions," any drug present in the innermost phase must now cross two phase boundaries to reach the external, continuous, phase.

It is important for the pharmacist to know the type of emulsion he has prepared or is dealing with, since this can affect its properties and performance. Unfortunately, the several methods available can give incorrect results, and so the type of emulsion determined by one method should always be confirmed by means of a second method.

Dilution Test—This method depends on the fact that an O/W emulsion can be diluted with water and a W/O emulsion with oil. When oil is added to an O/W emulsion or water to a W/O emulsion, the additive is not incorporated into the emulsion and separation is apparent. The test is greatly improved if the addition of the water or oil is observed microscopically.

Conductivity Test—An emulsion in which the continuous phase is aqueous can be expected to possess a much higher conductivity than an emulsion in which the continuous phase is an oil. Accordingly, it frequently happens that when a pair of electrodes, connected to a lamp and an electrical source, are dipped into an O/W emulsion, the lamp lights due to passage of a current between the two electrodes. If the lamp does not light, it is assumed that the system is W/O.

Dye-Solubility Test—The knowledge that a water-soluble dye will dissolve in the aqueous phase of an emulsion while an oil-soluble dye will be taken up by the oil phase provides a third means of determining emulsion type. Thus, if microscopic examination shows that a water-soluble dye has been taken up by the continuous phase, we are dealing with an O/W emulsion. If the dye has not stained the continuous phase, the test is repeated using a small amount of an oil-soluble dye. Coloring of the continuous phase confirms that the emulsion is of the W/O type.

Formation and Breakdown of Dispersed Liquid Droplets

An emulsion exists as the result of two competing processes, namely, the dispersion of one liquid throughout another as droplets, and the combination of these droplets to reform the initial bulk liquids. The first process increases the free energy of the system, while the second works to reduce the free energy. Accordingly, the second process is spontaneous and continues until breakdown is complete; ie, the bulk phases are reformed.

It is of little use to form a well-dispersed emulsion if it quickly breaks down. Similarly, unless adequate attention is given to achieving an optimum dispersion during preparation, the stability of an emulsion system may be compromised from the start. Dispersion is brought about by well-designed and well-operated machinery, capable of producing droplets in a relatively short period of time. Such equipment is discussed in Chapter 83. The reversal back to the bulk phases is minimized by utilizing those parameters which influence the stability of the emulsion once it is formed.

Dispersion Process To Form Droplets—Consider two immiscible liquid phases in a test tube. In order to disperse one liquid as droplets within the other, the interface between the two liquids must be disturbed and expanded to a sufficient degree so that "fingers" or threads of one liquid pass into the second liquid, and *vice versa*. These threads are unstable, and become varicosed or beaded. The beads separate and become spherical, as illustrated in Fig 19-36. Depending on the agitation or the shear rate used, larger droplets are also deformed to give small threads, which in turn produce smaller drops.

The time of agitation is important. Thus, the mean size of droplets decreases rapidly in the first few seconds of agitation. The limiting size range is generally reached within 1 to 5 minutes, and results from the number of droplets coalescing being equivalent to the number of new droplets being formed. It is uneconomical to continue agitation any further.

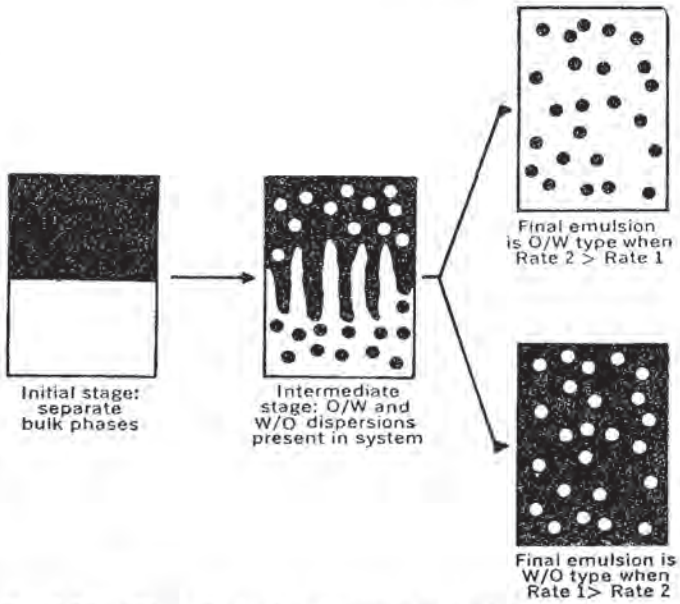


Fig 19-36. Effect of rate of coalescence on emulsion type. Rate 1: O/W coalescence rate; Rate 2: W/O coalescence rate. ●: oil; O: water. For an explanation of Rates 1 and 2, refer to the discussion of Davies on page 304.

The liquids may be agitated or sheared by several means. Shaking is commonly employed, especially when the components are of low viscosity. Intermittent shaking is frequently more efficient than continual shaking, possibly because the short time interval between shakes allows the thread which is forced across the interface time to break down into drops which are then isolated in the opposite phase. Continuous, rapid agitation tends to hinder this breakdown to form drops. A mortar and pestle is employed frequently in the extemporaneous preparation of emulsions. It is not a very efficient technique and is not used on a large scale. Improved dispersions are achieved by the use of high-speed mixers, blenders, colloid mills and homogenizers. Ultrasonic techniques also have been employed and are described in Chapter 83.

The phenomenon of spontaneous emulsification, as the name implies, occurs without any external agitation. There is, however, an internal agitation arising from certain physicochemical processes that affect the interface between the two bulk liquids. For a description of this process, see Davies and Rideal in the *Bibliography*.

Coalescence of Droplets—Coalescence is a process distinct from flocculation (aggregation), which commonly precedes it. While flocculation is the clumping together of particles, coalescence is the fusing of the agglomerates into a larger drop, or drops. Coalescence is usually rapid when two immiscible liquids are shaken together, since there is no large energy barrier to prevent fusion of drops and reformation of the original bulk phases. When an emulsifying agent is added to the system, flocculation still may occur but coalescence is reduced to an extent depending on the efficacy of the emulsifying agent to form a stable, coherent interfacial film. It is therefore possible to prepare emulsions that are flocculated, yet which do not coalesce. In addition to the interfacial film around the droplets acting as a mechanical

barrier, the drops also are prevented from coalescing by the presence of a thin layer of continuous phase between particles clumped together.

Davies[56] showed the importance of coalescence rates in determining emulsion type; this work is discussed in more detail on page 304.

Emulsifying Agent

The process of coalescence can be reduced to insignificant levels by the addition of a third component—the emulsifying agent or emulsifier. The choice of emulsifying agent is frequently critical in developing a successful emulsion, and the pharmacist should be aware of

The desirable properties of emulsifying agents.
How different emulsifiers act to optimize emulsion stability.
How the type and physical properties of the emulsion can be affected by the emulsifying agent.

Desirable Properties

Some of the desirable properties of an emulsifying agent are that it should

1. Be surface-active and reduce surface tension to below 10 dynes/cm.
2. Be adsorbed quickly around the dispersed drops as a condensed, nonadherent film which will prevent coalescence.
3. Impart to the droplets an adequate electrical potential so that mutual repulsion occurs.
4. Increase the viscosity of the emulsion.
5. Be effective in a reasonably low concentration.

Not all emulsifying agents possess these properties to the same degree; in fact, not every good emulsifier necessarily possesses all these properties. Further, there is no one "ideal" emulsifying agent because the desirable properties of an emulsifier depend, in part, on the properties of the two immiscible phases in the particular system under consideration.

Interfacial Tension—Lowering of interfacial tension is one way in which the increased surface free energy associated with the formation of droplets, and hence surface area, in an emulsion can be reduced (Eq 29). Assuming the droplets to be spherical, it can be shown that

$$\Delta F = \frac{6\gamma V}{d} \tag{38}$$

where V is the volume of dispersed phase in mL and d is the mean diameter of the particles. In order to disperse 100 mL of oil as 1-μm (10^{-4}-cm) droplets in water when $\gamma_{O/W} = 50$ dynes/cm, requires an energy input of

$$\Delta F = \frac{6 \times 50 \times 100}{1 \times 10^{-4}} = 30 \times 10^7 \text{ ergs}$$

$$= 30 \text{ joules or } 30/4.184 = 7.2 \text{ cal}$$

In the above example the addition of an emulsifier that will reduce γ from 50 to 5 dynes/cm will reduce the surface free energy from 7.2 to around 0.7 cal. Likewise, if the interfacial tension is reduced to 0.5 dyne/cm, a common occurrence, the original surface free energy is reduced a hundredfold. Such a reduction can help to maintain the surface area generated during the dispersion process.

Film Formation—The major requirement of a potential emulsifying agent is that it readily form a film around each droplet of dispersed material. The main purpose of this film—which can be a monolayer, a multilayer, or a collection of small particles adsorbed at the interface—is to form a barrier which prevents the coalescence of droplets that come into contact with one another. For the film to be an efficient barrier, it should possess some degree of surface elasticity and should not thin out and rupture when sandwiched between two droplets. If broken, the film should have the capacity to reform rapidly.

Electrical Potential—The origin of an electrical potential at the surface of a droplet has been discussed earlier in the chapter. Insofar as emulsions are concerned, the presence of a well-developed charge on the droplet surface is significant in promoting stability by causing repulsion between approaching drops. This potential is likely to be greater when an ionized emulsifying agent is employed.

Concentration of Emulsifier—The main objective of an emulsifying agent is to form a condensed film around the droplets of the dispersed phase. An inadequate concentration will do little to prevent coalescence. Increasing the emulsifier concentration above an optimum level achieves little in terms of increased stability. In practice the aim is to use the minimum amount consistent with producing a satisfactory emulsion.

It frequently helps to have some idea of the amount of emulsifier required to form a condensed film, one molecule thick, around each droplet. Suppose we wish to emulsify 50 g of an oil, density = 1.0, in 50 g of water. The desired particle diameter is 1 μm. Thus,

Particle diameter = 1 μm = 1×10^{-4} cm

$$\text{Volume of particle} = \frac{\pi d^3}{6} = 0.524 \times 10^{-12} \text{ cm}^3$$

$$\text{Total number of particles in 50 g} = \frac{50}{0.524 \times 10^{-12}} = 95.5 \times 10^{12}$$

Surface area of each particle = $\pi d^2 = 3.142 \times 10^{-8}$ cm^2

$$\text{Total surface area} = 3.142 \times 10^{-8} \times 95.5 \times 10^{12} = 300 \times 10^4 \text{ cm}^2$$

If the area each molecule occupies at the oil/water interface is 30 Å^2 (30×10^{-16} cm^2), we require

$$\frac{300 \times 10^4}{30 \times 10^{16}} = 1 \times 10^{21} \text{ molecules}$$

A typical emulsifying agent might have a molecular weight of 1000. Thus, the required weight is

$$\frac{1000 \times 10^{21}}{6.023 \times 10^{23}} = 1.66 \text{ g}$$

To emulsify 10 g of oil would require 0.33 g of the emulsifying agent, etc. While the approach is an oversimplification of the problem, it does at least allow the formulator to make a reasonable estimate of the required concentration of emulsifier.

Emulsion Rheology—The emulsifying agent and other components of an emulsion can affect the rheologic behavior of an emulsion in several ways and these are summarized in Table XVI. It should be borne in mind that the droplets of the internal phase are deformable under shear and that the adsorbed layer of emulsifier affects the interactions between adjacent droplets and also between a droplet and the continuous phase.

The means by which the rheological behavior of emulsions can be controlled have been discussed by Rogers.[58]

Mechanism of Action

Emulsifying agents may be classified in accordance with the type of film they form at the interface between the two phases.

Monomolecular Films—Those surface-active agents which are capable of stabilizing an emulsion do so by form-

Table XVI—Factors Influencing Emulsion Viscosity[57]

1. Internal phase
   a. Volume concentration (ϕ); hydrodynamic interaction between globules; flocculation, leading to formation of globule aggregates.
   b. Viscosity (η_1); deformation of globules in shear.
   c. Globule size, and size distribution, technique used to prepare emulsion; interfacial tension between the two liquid phases: globule behavior in shear; interaction with continuous phase; globule interaction.
   d. Chemical constitution.
2. Continuous phase
   a. Viscosity (η_0), and other rheological properties.
   b. Chemical constitution, polarity, pH; potential energy of interaction between globules.
   c. Electrolyte concentration if polar medium.
3. Emulsifying agent
   a. Chemical constitution; potential energy of interaction between globules.
   b. Concentration, and solubility in internal and continuous phases; emulsion type; emulsion inversion; solubilization of liquid phases in micelles.
   c. Thickness of film adsorbed around globules, and its rheological properties, deformation of globules in shear; fluid circulation within globules.
   d. Electroviscous effect.
4. Additional stabilizing agents
   Pigments, hydrocolloids, hydrous oxides; effect on rheologic properties of liquid phases, and interfacial boundary region.

ing a monolayer of adsorbed molecules or ions at the oil/water interface (Fig 19-37). In accordance with Gibbs' law (Eq 29) the presence of an interfacial excess necessitates a reduction in interfacial tension. This results in a more stable emulsion because of a proportional reduction in the surface free energy. Of itself, this reduction is probably not the main factor promoting stability. More significant is the fact that the droplets are surrounded now by a coherent monolayer which prevents coalescence between approaching droplets. If the emulsifier forming the monolayer is ionized, the presence of strongly charged and mutually repelling droplets increases the stability of the system. With unionized, nonionic surface-active agents, the particles may still carry a charge; this arises from adsorption of a specific ion or ions from solution.

Multimolecular Films—Hydrated lyophilic colloids form multimolecular films around droplets of dispersed oil (Fig 19-37). The use of these agents has declined in recent years because of the large number of synthetic surface-active agents available which possess well-marked emulsifying properties. While these hydrophilic colloids are adsorbed at an interface (and can be regarded therefore as "surface-active"), they do not cause an appreciable lowering in surface tension. Rather, their efficiency depends on their ability to form strong, coherent multimolecular films. These act as a coating around the droplets and render them highly resistant to coalescence, even in the absence of a well-developed surface potential. Furthermore, any hydrocolloid not adsorbed at the interface increases the viscosity of the continuous aqueous phase; this enhances emulsion stability.

Solid Particle Films—Small solid particles that are wetted to some degree by both aqueous and nonaqueous liquid phases act as emulsifying agents. If the particles are too hydrophilic, they remain in the aqueous phase; if too hydrophobic, they are dispersed completely in the oil phase. A second requirement is that the particles are small in relation to the droplets of the dispersed phase (Fig 19-37).

Chemical Types

Emulsifying agents may also be classified in terms of their chemical structure; there is some correlation between this

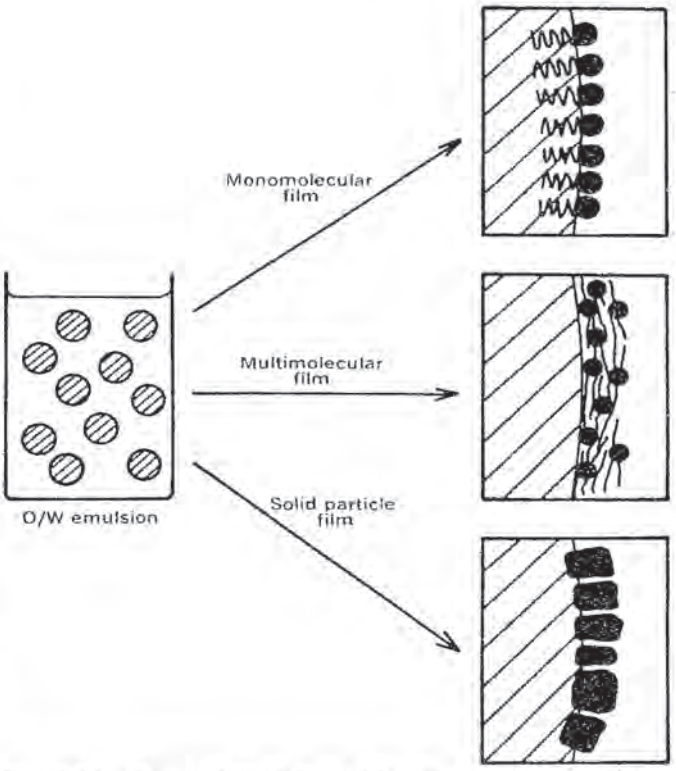


Fig 19-37. Types of films formed by emulsifying agents at the oil/water interface. Orientations are shown for O/W emulsions. ▨: oil; □: water.

classification and that based on the mechanism of action. For example, the majority of emulsifiers forming monomolecular films are synthetic, organic materials. Most of the emulsifiers that form multimolecular films are obtained from natural sources and are organic. A third group is composed of solid particles, invariably inorganic, that form films composed of finely divided solid particles.

Accordingly, the classification adopted divides emulsifying agents into *synthetic*, *natural*, and *finely dispersed solids* (Table XVII). A fourth group, the *auxiliary materials* (Table XVIII), are weak emulsifiers. The agents listed are designed to illustrate the various types available; they are not meant to be exhaustive.

Synthetic Emulsifying Agents—This group of surface-active agents which act as emulsifiers may be subdivided into anionic, cationic, and nonionic, depending on the charge possessed by the surfactant.

Anionics—In this subgroup the surfactant ion bears a negative charge. The potassium, sodium, and ammonium salts of lauric and oleic acid are soluble in water and are good O/W emulsifying agents. They do, however, have a disagreeable taste and are irritating to the gastrointestinal tract; this limits them to emulsions prepared for external use. Potassium laurate, a typical example, has the structure

$$CH_3(CH_2)_{10}COO^- \quad K^+$$

Solutions of alkali soaps have a high pH; they start to precipitate out of solution below pH 10 because the unionized fatty acid is now formed, and this has a low aqueous solubility. Further, the free fatty acid is ineffective as an emulsifier and so emulsions formed from alkali soaps are not stable at pH values less than about 10.

The calcium, magnesium and aluminum salts of fatty acids, often termed the metallic soaps, are water insoluble and result in W/O emulsions.

Table XVII—Classification of Emulsifying Agents

Type	Type of film	Examples
Synthetic (surface-active agents)	Monomolecular	*Anionic:* Soaps Potassium laurate Triethanolamine stearate Sulfates Sodium lauryl sulfate Alkyl polyoxyethylene sulfates Sulfonates Dioctyl sodium sulfosuccinate *Cationic:* Quaternary ammonium compounds Cetyltrimethylammonium bromide Lauryldimethylbenzylammonium chloride *Nonionic:* Polyoxyethylene fatty alcohol ethers Sorbitan fatty acid esters Polyoxyethylene sorbitan fatty acid esters
Natural	Multimolecular	*Hydrophilic colloids:* Acacia Gelatin
	Monomolecular	Lecithin Cholesterol
Finely divided solids	Solid particle	*Colloidal clays:* Bentonite Veegum *Metallic hydroxides:* Magnesium hydroxide

Table XVIII—Auxiliary Emulsifying Agents[55]

Product	Source and composition	Principal use
Bentonite	Colloidal hydrated aluminum silicate	Hydrophilic thickening agent and stabilizer for O/W and W/O lotions and creams
Cetyl alcohol	Chiefly $C_{16}H_{33}OH$	Lipophilic thickening agent and stabilizer for O/W lotions and ointments
Glyceryl monostearate	$C_{17}H_{35}COOCH_2CHOHCH_2OH$	Lipophilic thickening agent and stabilizer for O/W lotions and ointments
Methylcellulose	Series of methyl esters of cellulose	Hydrophilic thickening agent and stabilizer for O/W emulsions; weak O/W emulsifier
Sodium alginate	The sodium salt of alginic acid, a purified carbohydrate extracted from giant kelp	Hydrophilic thickening agent and stabilizer for O/W emulsions
Sodium carboxymethylcellulose	Sodium salt of the carboxymethyl esters of cellulose	Hydrophilic thickening agent and stabilizer for O/W emulsions
Stearic acid	A mixture of solid acids from fats, chiefly stearic and palmitic	Lipophilic thickening agent and stabilizer for O/W lotions and ointments. Forms a true emulsifier when reacted with an alkali
Stearyl alcohol	Chiefly $C_{18}H_{37}OH$	Lipophilic thickening agent and stabilizer for O/W lotions and ointments
Veegum	Colloidal magnesium aluminum silicate	Hydrophilic thickening agent and stabilizer for O/W lotions and creams

Another class of soaps are salts formed from a fatty acid and an organic amine such as triethanolamine. While these O/W emulsifiers are also limited to external preparations, their alkalinity is considerably less than that of the alkali soaps and they are active as emulsifiers down to around pH 8. These agents are less irritating than the alkali soaps.

Sulfated alcohols are neutralized sulfuric acid esters of such fatty alcohols as lauryl and cetyl alcohol. These compounds are an important group of pharmaceutical surfactants. They are used chiefly as wetting agents, although they do have some value as emulsifiers, particularly, when used in conjunction with an auxiliary agent. A frequently used compound is sodium lauryl sulfate.

$$CH_3(CH_2)_{10}CH_2OSO_3^-\ \ Na^+$$

Sulfonates are a class of compounds in which the sulfur atom is connected directly to the carbon atom, giving the general formula

$$CH_3(CH_2)_nCH_2SO_3^-\ \ Na^+$$

Sulfonates have a higher tolerance to calcium ions and do not hydrolyze as readily as the sulfates. A widely used surfactant of this type is dioctyl sodium sulfosuccinate.

Cationics—The surface activity in this group resides in the positively charged cation. These compounds have marked bactericidal properties. This makes them desirable in emulsified anti-infective products such as skin lotions and creams. The pH of an emulsion prepared with a cationic emulsifier lies in the pH 4–6 range. Since this includes the normal pH of the skin, cationic emulsifiers are advantageous in this regard also.

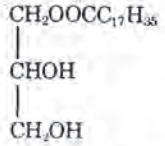
Cationic agents are weak emulsifiers and are generally formulated with a stabilizing or auxiliary emulsifying agent such as cetostearyl alcohol. The only group of cationic agents used extensively as emulsifying agents are the quaternary ammonium compounds. An example is cetyltrimethylammonium bromide.

$$CH_3(CH_2)_{14}CH_2N^+(CH_3)_3\ \ Br^-$$

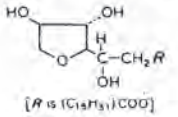
Cationic emulsifiers should not be used in the same formulation with anionic emulsifiers as they will interact. While the incompatibility may not be immediately apparent as a precipitate, virtually all of the desired antibacterial activity will generally have been lost.

Nonionics—These undissociated surfactants find widespread use as emulsifying agents when they possess the proper balance of hydrophilic and lipophilic groups within the molecule. Their popularity is based on the fact that, unlike the anionic and cationic types, nonionic emulsifiers are not susceptible to pH changes and the presence of electrolytes. The number of nonionic agents available is legion; the most frequently used are the glyceryl esters, polyoxyethylene glycol esters and ethers, and the sorbitan fatty acid esters and their polyoxyethylene derivatives.

A glyceryl ester, such as glyceryl monostearate, is too lipophilic to serve as a good emulsifier; it is widely used as an auxiliary agent (Table XVIII) and has the structure

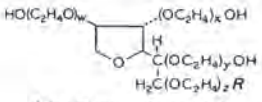


Sorbitan fatty acid esters, such as sorbitan monopalmitate



[*R* is $(C_{15}H_{31})COO$]

are nonionic oil-soluble emulsifiers that promote W/O emulsions. The polyoxyethylene sorbitan fatty acid esters, such as polyoxyethylene sorbitan monopalmitate, are hydrophilic water-soluble derivatives that favor O/W emulsions.



[Sum of *w*, *x*, *y* and *z* is 20; *R* is $(C_{15}H_{31})COO$]

Polyoxyethylene glycol esters, such as the monostearate, $C_{17}H_{35}COO(CH_2OCH_2)_nH$, also are used widely.

Very frequently, the best results are obtained from blends of nonionic emulsifiers. Thus, an O/W emulsifier customarily will be used in an emulsion with a W/O emulsifier. When blended properly, the nonionics produce fine-textured stable emulsions.

Natural Emulsifying Agents—Of the numerous emulsifying agents derived from natural (ie, plant and animal) sources, consideration will be given only to acacia, gelatin, lecithin, and cholesterol. Many other natural materials are only sufficiently active to function as auxiliary emulsifying agents or stabilizers.

Acacia is a carbohydrate gum that is soluble in water and forms O/W emulsions. Emulsions prepared with acacia are stable over a wide pH range. Because it is a carbohydrate it is necessary to preserve acacia emulsions against microbial attack by the use of a suitable preservative. The gum can be precipitated from aqueous solution by the addition of high concentrations of electrolytes or solvents less polar than water, such as alcohol.

Gelatin, a protein, has been used for many years as an emulsifying agent. Gelatin can have two isoelectric points, depending on the method of preparation. So-called Type A gelatin, derived from an acid-treated precursor, has an isoelectric point of between pH 7 and 9. Type B gelatin, obtained from an alkali-treated precursor, has an isoelectric point of approximately pH 5. Type A gelatin acts best as an emulsifier around pH 3, where it is positively charged; on the other hand, Type B gelatin is best used around pH 8, where it is negatively charged. The question as to whether the gelatin is positively or negatively charged is fundamental to the stability of the emulsion when other charged emulsifying agents are present. In order to avoid an incompatibility, all emulsifying agents should carry the same sign. Thus, if gums (such as tragacanth, acacia or agar) which are negatively charged are to be used with gelatin, Type B material should be used at an alkaline pH. Under these conditions the gelatin is similarly negatively charged.

Lecithin is a phospholipid which, because of its strongly hydrophilic nature, produces O/W emulsions. It is liable to microbial attack and tends to darken on storage.

Cholesterol is a major constituent of wool alcohols, obtained by the saponification and fractionation of wool fat. It is cholesterol that gives wool fat its capacity to absorb water and form a W/O emulsion.

Finely Dispersed Solids—This group of emulsifiers forms particulate films around the dispersed droplets and produces emulsions which, while coarse-grained, have considerable physical stability. It appears possible that any solid can act as an emulsifying agent of this type, provided it is reduced to a sufficiently fine powder. In practice the group of compounds used most frequently are the colloidal clays.

Several colloidal clays find application in pharmaceutical emulsions; the most frequently used are bentonite, a colloidal aluminum silicate, and Veegum (*Vanderbilt*), a colloidal magnesium aluminum silicate.

Bentonite is a white to gray, odorless, and tasteless powder that swells in the presence of water to form a translucent suspension with a pH of about 9. Depending on the sequence of mixing it is possible to prepare both O/W and W/O emulsions. When an O/W emulsion is desired, the bentonite is first dispersed in water and allowed to hydrate so as to form a magma. The oil phase is then added gradually with constant trituration. Since the aqueous phase is always in excess, the O/W emulsion type is favored. To prepare a W/O emulsion, the bentonite is first dispersed in oil; the water is then added gradually.

While Veegum is used as a solid particle emulsifying agent, it is employed most extensively as a stabilizer in cosmetic lotions and creams. Concentrations of less than 1% Veegum will stabilize an emulsion containing anionic or nonionic emulsifying agents.

Auxiliary Emulsifying Agents—Included under this heading are those compounds which are normally incapable themselves of forming stable emulsions. Their main value lies in their ability to function as thickening agents and thereby help stabilize the emulsion. Agents in common use are listed in Table XVIII.

Emulsifying Agents and Emulsion Type

For a molecule, ion, colloid, or particle to be active as an emulsifying agent, it must have some affinity for the interface between the dispersed phase and the dispersion medium. With the mono- and multilayer films the emulsifier is in solution and, therefore, must be soluble to some extent in one or both of the phases. At the same time it must not be overly soluble in either phase, otherwise it will remain in the bulk of that phase and not be adsorbed at the interface. This balanced affinity for the two phases also must be evident with finely divided solid particles used as emulsifying agents. If their affinity, as evidenced by the degree to which they are wetted, is either predominantly hydrophilic or hydrophobic, they will not function as effective wetting agents.

The great majority of the work on the relation between

Table XIX—Approximate HLB Values for a Number of Emulsifying Agents

Generic or chemical name	HLB
Sorbitan trioleate	1.8
Sorbitan tristearate	2.1
Propylene glycol monostearate	3.4
Sorbitan sesquioleate	3.7
Glycerol monostearate (non self-emulsifying)	3.8
Sorbitan monooleate	4.3
Propylene glycol monolaurate	4.5
Sorbitan monostearate	4.7
Glyceryl monostearate (self-emulsifying)	5.5
Sorbitan monopalmitate	6.7
Sorbitan monolaurate	8.6
Polyoxyethylene-4-lauryl ether	9.5
Polyethylene glycol 400 monostearate	11.6
Polyoxyethylene-4-sorbitan monolaurate	13.3
Polyoxyethylene-20-sorbitan monooleate	15.0
Polyoxyethylene-20-sorbitan monopalmitate	15.6
Polyoxyethylene-20-sorbitan monolaurate	16.7
Polyoxyethylene-40-stearate	16.9
Sodium oleate	18.0
Sodium lauryl sulfate	40.0

emulsifier and emulsion type has been concerned with surface-active agents that form interfacial monolayers. The present discussion, therefore, will concentrate on this class of agents.

Hydrophile–Lipophile Balance—As the emulsifier becomes more hydrophilic, its solubility in water increases and the formation of an O/W emulsion is favored. Conversely, W/O emulsions are favored with the more lipophilic emulsifiers. This led to the concept that the type of emulsion is related to the balance between hydrophilic and lipophilic solution tendencies of the surface-active emulsifying agent.

Griffin[59] developed a scale based on the balance between these two opposing tendencies. This so-called *HLB scale* is a numerical scale, extending from 1 to approximately 50. The more hydrophilic surfactants have high HLB numbers (in excess of 10), while surfactants with HLB numbers from 1 to 10 are considered to be lipophilic. Surfactants with a proper balance in their hydrophilic and lipophilic affinities are effective emulsifying agents since they concentrate at the oil/water interface. The relationship between HLB values and the application of the surface-active agent is shown in Table XV. Some commonly used emulsifiers and their HLB numbers are listed in Table XIX. The utility of the HLB system in rationalizing the choice of emulsifying agents when formulating an emulsion will be discussed in a later section.

Rate of Coalescence and Emulsion Type—Davies[56] indicated that the type of emulsion produced in systems prepared by shaking is controlled by the relative coalescence rates of oil droplets dispersed in the oil. Thus, when a mixture of oil and water is shaken together with an emulsifying agent, a multiple dispersion is produced initially which contains oil dispersed in water and water dispersed in oil (Fig 19-36). The type of the final emulsion which results depends on whether the water or the oil droplets coalesce more rapidly. If the O/W coalescence rate (Rate 1) is much greater than W/O coalescence rate (Rate 2), a W/O emulsion is formed since the dispersed water droplets are more stable than the dispersed oil droplets. Conversely, if Rate 2 is significantly faster than Rate 1, the final emulsion is an O/W dispersion because the oil droplets are more stable.

According to Davies, the rate at which oil globules coalesce when dispersed in water is given by the expression

$$\text{Rate 1} = C_1 e^{-W_1/RT} \qquad (39)$$

The term C_1 is a collision factor which is directly proportional to the phase volume of the oil relative to the water, and is an inverse function of the viscosity of the continuous phase (water). W_1 defines an energy barrier made up of several contributing factors that must be overcome before coalescence can take place. First, it depends on the electrical potential of the dispersed oil droplets, since this affects repulsion. Second, with an O/W emulsion, the hydrated layer surrounding the polar portion of emulsifying agent must be broken down before coalescence can occur. This hydrated layer is probably around 10 Å thick with a consistency of butter. Finally, the total energy barrier depends on the fraction of the interface covered by the emulsifying agent.

Equation 40 describes the rate of coalescence of water globules dispersed in oil, namely

$$\text{Rate 2} = C_2 e^{-W_2/RT} \qquad (40)$$

Here, the collision factor C_2 is a function of the water/oil phase volume ratio divided by the viscosity of the oil phase. The energy barrier W_2 is, as before, related to the fraction of the interface covered by the surface-active agent. Another contributing factor is the number of $—CH_2—$ groups in the emulsifying agent; the longer the alkyl chain of the emulsifier, the greater the gap that has to be bridged if one water droplet is to combine with a second drop.

Davies[56] showed that the HLB concept is related to the distribution characteristics of the emulsifying agent between the two immiscible phases. An emulsifier with an HLB of less than 7 will be preferentially soluble in the oil phase and will favor formation of a W/O emulsion. Surfactants with an HLB value in excess of 7 will be distributed in favor of the aqueous phase and will promote O/W emulsions.

Preparation of Emulsions

Several factors must be taken into account in the successful preparation and formulation of emulsified products. Usually, the type of emulsion (ie, O/W or W/O) is specified; if not, it probably will be implied from the anticipated use of the product. The formulator's attention is focused primarily on the selection of the emulsifying agent, or agents, necessary to achieve a satisfactory product. No incompatibilities should occur between the various emulsifiers and the several components commonly present in pharmaceutical emulsions. Finally, the product should be prepared in such a way as not to prejudice the formulation.

Selection of Emulsifying Agents

The selection of the emulsifying agent, or agents, is of prime importance in the successful formulation of an emulsion. In addition to its emulsifying properties, the pharmacist must ensure that the material chosen is nontoxic and that the taste, odor, and chemical stability are compatible with the product. Thus, an emulsifying agent which is entirely suitable for inclusion in a skin cream may be unacceptable in the formulation of an oral preparation due to its potential toxicity. This consideration is most important when formulating intravenous emulsions.

The HLB System—With the increasing number of available emulsifiers, particularly the nonionics, the selection of emulsifiers for a product was essentially a trial-and-error procedure. Fortunately, the work of Griffin[59,60] provided a logical means of selecting emulsifying agents. Griffin's method, based on the balance between the hydrophilic and lipophilic portions of the emulsifying agent, is now widely used and has come to be known as the *HLB system*. It is used most in the rational selection of combinations of non-

Table XX—Relationship between HLB Range and Surfactant Application

HLB range	Use
0–3	Antifoaming agents
4–6	W/O emulsifying agents
7–9	Wetting agents
8–18	O/W emulsifying agents
13–15	Detergents
10–18	Solubilizing agents

Table XXI—Required HLB Values for Some Common Emulsion Ingredients

Substance	W/O	O/W
Acid, stearic	...	17
Alcohol, cetyl	...	13
Lanolin, anhydrous	8	15
Oil, cottonseed	...	7.5
mineral oil, light	4	10–12
mineral oil, heavy	4	10.5
Wax, beeswax	5	10–16
microcrystalline	...	9.5
paraffin	...	9

ionic emulsifiers, and we shall limit our discussion accordingly.

As shown in Table XX, if an O/W emulsion is required, the formulator should use emulsifiers with an HLB in the range of 8–18. Emulsifiers with HLB values in the range of 4–6 are given consideration when a W/O emulsion is desired. Some typical examples are given in Table XIX.

Another factor is the presence or absence of any polarity in the material being emulsified, since this will affect the polarity required in the emulsifier. Again, as a result of extensive experimentation, Griffin evolved a series of "required HLB" values; ie, the HLB value required by a particular material if it is to be emulsified effectively. Some values for oils and related materials are contained in Table XXI. Naturally, the required HLB value differs depending on whether the final emulsion is O/W or W/O.

Fundamental to the utility of the HLB concept is the fact that the HLB values are algebraically additive. Thus, by using a low HLB surfactant with one having a high HLB it is possible to prepare blends having HLB values intermediate between those of the two individual emulsifiers. Naturally, one should not use emulsifiers that are incompatible. The following formula should serve as an example.

O/W Emulsion

Liquid petrolatum (Required HLB 10.5)	50 g
Emulsifying agents	5 g
Sorbitan monooleate (HLB 4.3)	
Polyoxyethylene 20 sorbitan monoleate (HLB 15.0)	
Water, qs	100 g

By simple algebra it can be shown that 4.5 parts by weight of sorbitan monooleate blended with 6.2 parts by weight of polyoxyethylene 20 sorbitan monooleate will result in a mixed emulsifying agent having the required HLB of 10.5. Since the formula calls for 5 g, the required weights are 2.1 g and 2.9 g, respectively. The oil-soluble sorbitan monooleate is dissolved in the oil and heated to 75°; the water-soluble polyoxyethylene 20 sorbitan monooleate is added to the aqueous phase which is heated to 70°. At this point the oil phase is mixed with the aqueous phase and the whole stirred continuously until cool.

The formulator is not restricted to these two agents to produce a blend with an HLB of 10.5. Table XXII shows

Table XXII—Nonionic Blends having HLB Values of 10.5

Surfactant blend	HLB	Required amounts (%) to give HLB = 10.5
Sorbitan tristearate	2.1	34.4
Polyoxethylene 20 sorbitan monostearate	14.9	65.6
Sorbitan monopalmitate	6.7	57.3
Polyoxyethylene 20 sorbitan monopalmitate	15.6	42.7
Sorbitan sesquioleate	3.7	48.5
Polyoxyethylene lauryl ether	16.9	51.5

the various proportions required, using other pairs of emulsifying agents, to form a blend of HLB 10.5. When carrying out preliminary investigations with a particular material to be emulsified, it is advisable to try several pairs of emulsifying agents. Based on an evaluation of the emulsions produced, it becomes possible to choose the best combination.

Occasionally, the required HLB of the oil may not be known, in which case it becomes necessary to determine this parameter. Various blends are prepared to give a wide range of HLB mixtures and emulsions are prepared in a standardized manner. The HLB of the blend used to emulsify the best product, selected on the basis of physical stability, is taken to be the required HLB of the oil. The experiment should be repeated using another combination of emulsifiers to confirm the value of the required HLB of the oil to within, say, ±1 HLB unit.

There are methods for finding the HLB value of a new surface-active agent. Griffin[60] developed simple equations which can be used to obtain an estimate with certain compounds. It has been shown that the ability of a compound to spread at a surface is related to its HLB. In another approach a linear relation between HLB and the logarithm of the dielectric constant for a number of nonionic surfactants has been observed. An interesting approach has been developed by Davies[56] and is related to his studies on the relative rates of coalescence of O/W and W/O emulsions (page 304). According to Davies, hydrophilic groups on the surfactant molecule make a positive contribution to the HLB number, whereas lipophilic groups exert a negative effect. Davies calculated these contributions and termed them HLB Group Numbers (Table XXIII). Provided the molecular structure of the surfactant is known, one simply adds the various group numbers in accordance with the following formula:

Table XXIII—HLB Group Numbers[61]

	Group number
Hydrophilic groups	
$-SO_4^-Na^+$	38.7
$-COO^-K^+$	21.1
$-COO^-Na^+$	19.1
N (tertiary amine)	9.4
Ester (sorbitan ring)	6.8
Ester (free)	2.4
—COOH	2.1
Hydroxyl (free)	1.9
—O—	1.3
Hydroxyl (sorbitan ring)	0.5
Lipophilic groups	
—CH—	
$-CH_2-$	
CH_3-	−0.475
=CH—	
Derived groups	
$-(CH_2-CH_2-O)-$	+0.33
$-(CH_2-CH_2-CH_2-O)-$	−0.15

$$HLB = \Sigma(\text{hydrophilic group numbers}) - m(\text{group number}/\text{—}CH_2\text{— group}) + 7$$

where m is the number of —CH_2— groups present in the surfactant. Poor agreement is found between the HLB values calculated by the use of group numbers and the HLB values obtained using the simple equations developed by Griffin. However, the student should realise that the absolute HLB values *per se* are of limited significance. The utility of the HLB approach (using values calculated by either Griffin's or Davies' equations) is to (i) provide the formulator with an idea of the relative balance of hydrophilicity and lipophilicity in a particular surfactant, and (ii) relate that surfactant's emulsifying and solubilizing properties to other surfactants. The formulator still needs to confirm experimentally that a particular formulation will produce a stable emulsion.

Later, Davies and Rideal[61] attempted to relate HLB to the C_{water}/C_{oil} partition coefficient and found good agreement for a series of sorbitan surfactants. Schott[62] showed, however, that the method does not apply to polyoxyethylated octylphenol surfactants. Schott concluded that "so far, the search for a universal correlation between HLB and another property of the surfactant which could be determined more readily than HLB has not been successful."

The HLB system gives no information as to the *amount* of emulsifier required. Having once determined the correct blend, the formulator must prepare another series of emulsions, all at the same HLB, but containing increasing concentrations of the emulsifier blend. Usually, the minimum concentration giving the desired degree of physical stability is chosen.

Mixed Emulsifying Agents—Emulsifying agents are frequently used in combination since a better emulsion usually is obtained. This enhancement may be due to several reasons, one or more of which may be operative in any one system. Thus, the use of a blend or mixture of emulsifiers may (1) produce the required hydrophile–lipophile balance in the emulsifier, (2) enhance the stability and cohesiveness of the interfacial film, and (3) affect the consistency and feel of the product.

The first point has been considered in detail in the previous discussion of the HLB system.

With regard to the second point, Schulman and Cockbain in 1940 showed that combinations of certain amphiphiles formed stable films at the air/water interface. It was postulated that the complex formed by these two materials (one, oil-soluble; the other, water-soluble) at the air/water interface was also present at the O/W interface. This interfacial complex was held to be responsible for the improved stability. For example, sodium cetyl sulfate, a moderately good O/W emulsifier, and elaidyl alcohol or cholesterol, both stabilizers for W/O emulsions, show evidence of an interaction at the air/water interface. Furthermore, an O/W emulsion prepared with sodium cetyl sulfate and elaidyl alcohol is much more stable than an emulsion prepared with sodium cetyl sulfate alone.

Elaidyl alcohol is the *trans* isomer. When oleyl alcohol, the *cis* isomer, is used with sodium cetyl sulfate, there is no evidence of complex formation at the air/water interface. Significantly, this combination does not produce a stable O/W emulsion either. Such a finding strongly suggests that a high degree of molecular alignment is necessary at the O/W interface to form a stable emulsion.

Finally, some materials are added primarily to increase the consistency of the emulsion. This may be done to increase stability or improve emolliency and feel. Examples include cetyl alcohol, stearic acid and beeswax.

When using combinations of emulsifiers, care must be taken to ensure their compatibility, as charged emulsifying agents of opposite sign are likely to interact and coagulate when mixed.

Small-Scale Preparation

Mortar and Pestle—This approach invariably is used only for those emulsions that are stabilized by the presence of a multimolecular film (eg, acacia, tragacanth, agar, chondrus) at the interface. There are two basic methods for preparing emulsions with the mortar and pestle. These are the *Wet Gum* (or so-called *English*) *Method* and the *Dry Gum* (or so-called *Continental*) *Method.*

The Wet Gum Method—In this method the emulsifying agent is placed in the mortar and dispersed in water to form a mucilage. The oil is added in small amounts with continuous trituration, each portion of the oil being emulsified before adding the next increment. Acacia is the most frequently used emulsifying agent when preparing emulsions with the mortar and pestle. When emulsifying a fixed oil, the optimum ratio of oil : water : acacia to prepare the initial emulsion is 4 : 2 : 1. Thus, the preparation of 60 mL of a 40% cod liver oil emulsion requires the following:

Cod liver oil	24 g
Acacia	6 g
Water, qs	60 mL

The acacia mucilage is formed by adding 12 mL of water to the 6 g of acacia in the mortar and triturating. The 24 g of oil is added in increments of 1–2 g and dispersed. The product at this stage is known as the *primary emulsion*, or *nucleus*. The primary emulsion should be triturated for at least 5 min, after which sufficient water is added to produce a final volume of 60 mL.

The Dry Gum Method—In this method, preferred by most pharmacists, the gum is added to the oil, rather than the water as with the wet gum method. Again, the approach is to prepare a primary emulsion from which the final product can be obtained by dilution with the continuous phase. If the emulsifier is acacia and a fixed oil is to be emulsified, the ratio of oil : water : gum is again 4 : 2 : 1.

Provided dispersion of the acacia in the oil is adequate, the dry gum method can almost be guaranteed to produce an acceptable emulsion. Because there is no incremental addition of one of the components, the preparation of an emulsion by this method is rapid.

With both methods the oil : water : gum ratio may vary, depending on the type of oil to be emulsified and the emulsifying agent used. The usual ratios for tragacanth and acacia are shown in Table XXIV.

The preparation of emulsions by both the wet and dry gum methods can be carried out in a bottle rather than a mortar and pestle.

Other Methods—An increasing number of emulsions are being formulated with synthetic emulsifying agents, especially of the nonionic type. The components in such a for-

Table XXIV—Usual Ratios of Oil, Water and Gum Used to Produce Emulsions

System	Acacia	Tragacanth
Fixed oils (excluding liquid petrolatum and linseed oil)	4	40
Water	2	20
Gum	1	1
Volatile oils, plus liquid petrolatum and linseed oil	2–3	20–30
Water	2	20
Gum	1	1

mulation are separated into those that are oil-soluble and those that are water-soluble. These are dissolved in their respective solvents by heating to about 70 to 75°. When solution is complete, the two phases are mixed and the product is stirred until cool. This method, which requires nothing more than two beakers, a thermometer and a source of heat, is necessarily used in the preparation of emulsions containing waxes and other high-melting-point materials that must be melted before they can be dispersed in the emulsion. The relatively simple methodology involved in the use of synthetic surfactant-type emulsifiers is one factor which has led to their widespread use in emulsion preparation. This, in turn, has led to a decline in the use of the natural emulsifying agents.

With hand homogenizers an initial rough emulsion is formed by trituration in a mortar or shaking in a bottle. The rough emulsion is then passed several times through the homogenizer. A reduction in particle size is achieved as the material is forced through a narrow aperture under pressure. A satisfactory product invariably results from the use of a hand homogenizer and overcomes any deficiencies in technique. Should the homogenizer fail to produce an adequate product, the formulation, rather than the technique, should be suspected.

For a discussion of the techniques and equipment used in the large-scale manufacture of emulsions, see Chapter 83.

Stability of Emulsions

There are several criteria which must be met in a well-formulated emulsion. Probably the most important and most readily apparent requirement is that the emulsion possess adequate physical stability; without this, any emulsion soon will revert back to two separate bulk phases. In addition, if the emulsified product is to have some antimicrobial activity (eg, a medicated lotion), care must be taken to ensure that the formulation possesses the required degree of activity. Frequently, a compound exhibits a lower antimicrobial activity in an emulsion than, say, in a solution. Generally, this is because of partitioning effects between the oil and water phases, which cause a lowering of the "effective" concentration of the active agent. Partitioning has also to be taken into account when considering preservatives to prevent microbiological spoilage of emulsions. Finally, the chemical stability of the various components of the emulsion should receive some attention, since such materials may be more prone to degradation in the emulsified state than when they exist as a bulk phase.

In the present discussion, detailed consideration will be limited to the question of physical stability. Reviews of this topic have been published by Garrett[63] and Kitchener and Mussellwhite.[64] For information on the effect that emulsification can have on the biologic activity and chemical stability of materials in emulsions, see Wedderburn,[65] Burt[66] and Swarbrick.[67]

The theories of emulsion stability have been discussed by Eccleston[68] in an attempt to understand the situation in both a simple O/W emulsion and complex commercial systems.

The three major phenomena associated with physical stability are

1. The upward or downward movement of dispersed droplets relative to the continuous phase, termed *creaming* or *sedimentation*, respectively.
2. The aggregation and possible coalescence of the dispersed droplets to reform the separate, bulk phases.
3. Inversion, in which an O/W emulsion inverts to become a W/O emulsion, and *vice versa*.

Creaming and Sedimentation—Creaming is the upward movement of dispersed droplets relative to the continuous phase, while sedimentation, the reverse process, is the downward movement of particles. In any emulsion one process or the other takes place, depending on the densities of the disperse and continuous phases. This is undesirable in a pharmaceutical product where homogeneity is essential for the administration of the correct and uniform dose. Furthermore, creaming, or sedimentation, brings the particles closer together and may facilitate the more serious problem of coalescence.

The rate at which a spherical droplet or particle sediments in a liquid is governed by Stokes' law (Eq 35). While other equations have been developed for bulk systems, Stokes' equation is still useful since it points out the factors that influence the rate of sedimentation or creaming. These are the diameter of the suspended droplets, the viscosity of the suspending medium, and the difference in densities between the dispersed phase and the dispersion medium.

Usually, only the use of the first two factors is feasible in affecting creaming or sedimentation. Reduction of particle size contributes greatly toward overcoming or minimizing creaming, since the rate of movement is a square-root function of the particle diameter. There are, however, technical difficulties in reducing the diameter of droplets to below about 0.1 μm. The most frequently used approach is to raise the viscosity of the continuous phase, although this can be done only to the extent that the emulsion still can be removed readily from its container and spread or administered conveniently.

Aggregation and Coalescence—Even though creaming and sedimentation are undesirable, they do not necessarily result in the breakdown of the emulsion, since the dispersed droplets retain their individuality. Furthermore, the droplets can be redispersed with mild agitation. More serious to the stability of an emulsion are the processes of aggregation and coalescence. In aggregation (flocculation) the dispersed droplets come together but do not fuse. Coalescence, the complete fusion of droplets, leads to a decrease in the number of droplets and the ultimate separation of the two immiscible phases. Aggregation precedes coalescence in emulsions; however, coalescence does not necessarily follow from aggregation. Aggregation is, to some extent, reversible. While not as serious as coalescence, it will accelerate creaming or sedimentation, since the aggregate behaves as a single drop.

While aggregation is related to the electrical potential on the droplets, coalescence depends on the structural properties of the interfacial film. In an emulsion stabilized with surfactant-type emulsifiers forming monomolecular films, coalescence is opposed by the elasticity and cohesiveness of the films sandwiched between the two droplets. In spite of the fact that two droplets may be touching, they will not fuse until the interposed films thin out and eventually rupture. Multilayer and solid-particle films confer on the emulsion a high degree of resistance to coalescence, due to their mechanical strength.

Particle-size analysis can reveal the tendency of an emulsion to aggregate and coalesce long before any visible signs of instability are apparent. The methods available have been reviewed by Groves and Freshwater.[69]

Inversion—An emulsion is said to invert when it changes from an O/W to a W/O emulsion, or *vice versa*. Inversion sometimes can be brought about by the addition of an electrolyte or by changing the phase–volume ratio. For example, an O/W emulsion having sodium stearate as the emulsifier can be inverted by the addition of calcium chloride, because the calcium stearate formed is a lipophilic emulsifier and favors the formation of a W/O product.

Inversion often can be seen when an emulsion, prepared by heating and mixing the two phases, is being cooled. This takes place presumably because of the temperature-depen-

dent changes in the solubilities of the emulsifying agents. The phase inversion temperature, or PIT, of nonionic surfactants has been shown by Shinoda, *et al*[70] to be influenced by the HLB number of the surfactant. The higher the PIT value, the greater the resistance to inversion.

Apart from work on PIT values, little quantitative work has been carried out on the process of inversion; nevertheless, it would appear that the effect can be minimized by using the proper emulsifying agent in an adequate concentration. Wherever possible, the volume of the dispersed phase should not exceed 50% of the total volume of the emulsion.

Bioavailability from Coarse Dispersions

In recent years, considerable interest has focused on the ability of a dosage form to release drug following administration to the patient. Both the rate and extent of release are important. Ideally, the extent of release should approach 100%, while the rate of release should reflect the desired properties of the dosage form. For example, with products designed to have a rapid onset of activity, the release of drug should be immediate. With a long-acting product, the release should take place over several hours, or days, depending on the type of product used. The rate and extent of drug release should be reproducible from batch to batch of the product, and should not change during shelf life.

The principles on which biopharmaceutics is based are dealt with in some detail in Chapters 35 to 37. While most published work in this area has been concerned with the bioavailability of solid dosage forms administered by the oral route, the rate and extent of release from both suspensions and emulsions is important and so will be considered in some detail.

Bioavailability from Suspensions—Suspensions of a drug may be expected to demonstrate improved bioavailability compared to the same drug formulated as a tablet or capsule. This is because the suspension already contains discrete drug particles, whereas tablet dosage forms must invariably undergo disintegration in order to maximize the necessary dissolution process. Frequently, antacid suspensions are perceived as being more rapid in action and therefore more effective than an equivalent dose in the form of tablets. Bates, *et al*[71] observed that a suspension of salicylamide was more rapidly bioavailable, at least during the first hour following administration, than two different tablet forms of the drug; these workers were also able to demonstrate a correlation between the initial *in vitro* dissolution rates for the several dosage forms studied and the initial rates of *in vivo* absorption. A similar argument can be developed for hard gelatin capsules, where the shell must rupture or dissolve before drug particles are released and can begin the dissolution process. Such was observed by Antal, *et al*[72] in a study of the bioavailability of several doxycycline products, including a suspension and hard gelatin capsules. Sansom, *et al*[73] found mean plasma phenytoin levels higher after the administration of a suspension than when an equivalent dose was given as either tablets or capsules. It was suggested that this might have been due to the suspension having a smaller particle size.

In common with other products in which the drug is present in the form of solid particles, the rate of dissolution and thus potentially the bioavailability of the drug in a suspension can be affected by such factors as particle size and shape, surface characteristics, and polymorphism. Strum, *et al*[74] conducted a comparative bioavailability study involving two commercial brands of sulfamethiazole suspension (Product A and Product B). Following administration of the products to 12 normal subjects and taking blood samples at predetermined times over a period of 10 hr, the workers found no statistically significant difference in the extent of drug absorption from the two suspensions. The absorption rate, however, differed, and from *in vitro* studies it was concluded that product A dissolved faster than product B and that the former contained more particles of smaller size than the latter, differences that may be responsible for the more rapid dissolution of particles in product A. Product A also provided higher serum levels in *in vivo* tests half an hour after administration. The results showed that the rate of absorption of sulfamethiazole from a suspension depended on the rate of dissolution of the suspended particles, which in turn was related to particle size. Previous studies[75,76] have shown the need to determine the dissolution rate of suspensions in order to gain information as to the bioavailability of drugs from this type of dosage form.

The viscosity of the vehicle used to suspend the particles has been found to have an effect on the rate of absorption of nitrofurantoin but not the total bioavailability. Thus Soci and Parrott were able to maintain a clinically acceptable urinary nitrofurantoin concentration for an additional two hours by increasing the viscosity of the vehicle.[77]

Bioavailability from Emulsions—There are indications that improved bioavailability may result when a poorly absorbed drug is formulated as an orally administered emulsion. However, little study appears to have been made in direct comparison of emulsions and other dosage forms such as suspensions, tablets, and capsules; thus it is not possible to draw unequivocal conclusions as to advantages of emulsions. If a drug with low aqueous solubility can be formulated so as to be in solution in the oil phase of an emulsion, its bioavailability may be enhanced. It must be recognized, however, that the drug in such a system has several barriers to pass before it arrives at the mucosal surface of the gastrointestinal tract. For example, with an oil-in-water emulsion, the drug must diffuse through the oil globule and then pass across the oil/water interface. This may be a difficult process, depending on the characteristics of the interfacial film formed by the emulsifying agent. In spite of this potential drawback, Wagner, *et al*[78] found that indoxole, a nonsteroidal anti-inflammatory agent, was significantly more bioavailable in an oil-in-water emulsion than in either a suspension or a hard gelatin capsule. Bates and Sequeira[79] found significant increases in maximum plasma levels and total bioavailability of micronized griseofulvin when formulated in a corn oil/water emulsion. In this case, however, the enhanced effect was not due to emulsification of the drug in the oil phase *per se* but more probably because of the linoleic and oleic acids present having a specifical effect on gastrointestinal motility.

References

1. Semat H: *Fundamentals of Physics*, 3rd ed, Holt-Rinehart-Winston, New York, 1957.
2. Michaels AS: *J Phys Chem 65:* 1730, 1961.
3. Zisman WA: *Adv Chem Ser 43:* 1, 1964.
4. Titoff Z: *Z Phys Chem 74:* 641, 1910.
5. Lowell S: *Introduction to Power Surface Area*, Wiley-Interscience, New York, 1979.
6. Osipow LI: *Surface Chemistry: Theory and Industrial Applications*, Reinhold, New York, 1962.
7. Langmuir I: *J Am Chem Soc 39:* 1848, 1917.
8. Giles CH: In EH Lucassen-Reynders, ed, *Anionic Surfactants*, Marcel Dekker, New York, 1981, Ch 4.
9. Weiser HB: *A Textbook of Colloid Chemistry*, Elsevier, New York, 1949.
10. Ter-Minassian-Saraga L: *Adv Chem Ser 43:* 232, 1964.
11. Schott H, Martin AN. In Dittert LW, ed, *American Pharmacy*, 7th ed, Lippincott, Philadelphia, Chap 6, 1974.

12. Shinoda K, Nakagawa T, Tamamushi BI, Isemura T: *Colloidal Surfactants*, Academic, New York, Chap 2, 1963.
13. Sjoblom L. In Shinoda K, ed, *Solvent Properties of Surfactant Solutions*, Marcel Dekker, New York, Chap 5, 1967.
14. Prince, LM: *Microemulsions—Theory and Practice*, Academic, New York 1977.
15. Shinoda K, Friberg S: *Adv Colloid Interface Sci 4:* 281, 1975.
16. Friberg SE, Venable RV in Becher P, ed: *Encyclopedia of Emulsion Technology*, vol 1, Marcel Dekker, Chapt 4, New York, 1983.
17. Overbeek JThG: *Disc Faraday Soc 65:* 7, 1978.
18. Davis SS. In Bundgaard H, Hansen AB, Kofod H, eds: In *Optimization of Drug Delivery*, Alfred Benzon Symposium 17, Munksgaard, Copenhagen, 1982.
19. Fendler JH, Fendler EJ: *Catalysis in Micellar and Macromolecular Systems*, Academic, New York, 1975.
20. Mackay RA: *Adv Colloid Interface Sci 15*, 131, 1981.
21. Kruyt HR: *Colloid Science*, vols I and II, Elsevier, Houston, 1952 and 1949.
22. Alexander AE, Johnson P: *Colloid Science*, Oxford University Press, Oxford, 1949.
23. Ross S, Morrison ID: *Colloidal Systems and Interfaces*, Wiley, New York, 1988.
24. Mysels KJ: *Introduction to Colloid Chemistry*, Wiley-Interscience, New York, 1959.
25. Shaw DJ: *Introduction to Colloid and Surface Chemistry*, 3rd ed, Butterworths, London, 1980.
26. Vold RD, Vold MJ: *Colloid and Interface Chemistry*, Addison-Wesley, Reading, MA., 1983.
27. Hiemenz PC: *Principles of Colloid and Surface Chemistry*, Marcel Dekker, New York, 1986.
28. von Weimarn PP. In Alexander J, ed: *Colloid Chemistry*, vol I, Chemical Catalog Co (Reinhold), New York, 1926. See also *Chem Rev 2:* 217, 1926.
29. Lachman L *et al:* *Theory and Practice of Industrial Pharmacy*, 3rd ed, Lea & Febiger, Philadelphia, 1986.
30. Tubis M, Wolf W, eds: *Radiopharmacy*, Wiley-Interscience, New York, 1976.
31. LaMer VK, Dinegar RH: *J Am Chem Soc 72:* 4847, 1950.
32. Matijevic E: *Acc Chem Res 14:* 22, 1981 and *Ann Rev Mater Sci 15:* 483, 1985.
33. Florence AT, Attwood D: *Physicochemical Principles of Pharmacy*, Chapman & Hall, New York, 1982.
34. Gutch CF, Stoner MH: *Review of Hemodialysis*, Mosby, St. Louis, 1975.
35. Schott H, Martin AN. In Dittert LW, ed: *American Pharmacy*, 7th ed, Lippincott, Philadelphia, 1974.
36. Parks GA: *Chem Rev 65:* 177, 1965.
37. Schott H: *J Pharm Sci 66:* 1548, 1977.
38. Sonntag H, Strenge K: *Coagulation and Stability of Disperse Systems*, Halstead, New York, 1972.
39. Hough DB, Thompson L. In Schick MJ, ed: *Nonionic Surfactants-Physical Chemistry*, 2nd ed, Marcel Dekker, Chapt 11, New York, 1987.
40. Vincent B: *Adv Colloid Interface Sci 4:* 193, 1974.
41. Hunter RJ: *Zeta Potential in Colloid Science*, Academic, New York, 1981.
42. Davies JT, Rideal EK: *Interfacial Phenomena*, 2nd ed, Academic, New York, 1963.
43. Bier M, ed: *Electrophoresis*, vols I and II, Academic, New York, 1959 and 1967.
44. Shaw DJ: *Electrophoresis*, Academic, New York, 1969.
45. Cawley LP: *Electrophoresis and Immunoelectrophoresis*, Little-Brown, Boston, 1969.
46. Catsimpoolas N, ed: *Isoelectric Focusing and Isotachophoresis, Ann NY Acad Sci 209:* June 15, 1973.
47. Morawetz H: *Macromolecules in Solution*, 2nd ed, Wiley-Interscience, New York, 1975.
48. Veis A: *The Macromolecular Chemistry of Gelatin*, Academic, New York, 1964.
49. Ward AG, Courts A, eds: *The Science and Technology of Gelatin*, Academic, Chapt 6, New York, 1977.
50. Haines BA, Martin A: *J Pharm Sci 50:* 228, 753, 756, 1961.
51. Matthews BA, Rhodes CT: *J Pharm Pharmacol 20* Suppl: 204S, 1968.
52. Matthews BA, Rhodes CT: *J Pharm Sci 57:* 569, 1968.
53. *Ibid 59:* 521, 1970.
54. Schneider W, *et al:* *Am J Pharm Ed 42:* 280, 1978.
55. Tingstad J *et al:* *J Pharm Sci 62:* 1361, 1973.
56. Davies JT: *Proc Intern Congr Surface Activity*, 2nd, London, 426, 1957.
57. Sherman P: In *Emulsion Science*, Chap 4, Academic, New York, 1968.
58. Rogers JA: *Cosmet Toiletries 93:* 49, July, 1978.
59. Griffin WC: *J Soc Cos Chem 1:* 311, 1949.
60. Griffin WC: *J Soc Cos Chem 5:* 249, 1954.
61. Davies JT, Rideal EK: *Interfacial Phenomena*, Chap 8, Academic, New York, 1961. Davies JT: *Proc Intern Congr Surface Activity*, 2nd, London, 426, 1957.
62. Schott J: *J Pharm Sci 60:* 649, 1971.
63. Garrett ER: *J Pharm Sci 54:* 1557, 1965.
64. Kitchener JA, Mussellwhite PR. In *Emulsion Science*, Academic, New York, Chap 2, 1968.
65. Wedderburn DL. In *Advances in Pharmaceutical Sciences*, vol 1, Academic, London, 195, 1964.
66. Burt BW: *J Soc Cosm Chem 16:* 465, 1965.
67. Swarbrick J: *Ibid 19:* 187, 1968.
68. Eccleston GM: *Cosmet Toiletries*: 101, 73, Nov 1986.
69. Groves MJ, Freshwater DC: *J Pharm Sci 57:* 1273, 1968.
70. Shinoda K, Kunieda H: In *Encyclopedia of Emulsion Technology*, Chap 5, Marcel Dekker, New York, 1983.
71. Bates TR *et al:* *J Pharm Sci 58:* 1468, 1969.
72. Antal EJ *et al:* *Ibid 64:* 2015, 1975.
73. Sansom LN *et al:* *Med J Aust* 1975(2): 593.
74. Strum JD *et al:* *J Pharm Sci 67:* 1659, 1978.
75. Bates TR *et al:* *Ibid 62:* 2057, 1973.
76. Howard SA *et al:* *Ibid 66:* 557, 1977.
77. Soci MM, Parrott EL: *Ibid 69:* 403, 1980.
78. Wagner JG *et al:* *Clin Pharmacol Ther 7:* 610, 1966.
79. Bates TR, Sequeira JA: *J Pharm Sci 64:* 793, 1975.

Bibliography

Interfacial Phenomena

Adamson AW: *Physical Chemistry of Surfaces*, 4th ed, Interscience, New York, 1982.

Davis JT, Rideal EK: *Interfacial Phenomena*, 2nd ed, Academic, New York, 1963.

Hiemenz, PC: *Principles of Colloid and Surface Chemistry*, 2nd ed, Marcel Dekker, New York, 1986.

Shaw DJ: *Introduction to Colloid and Surface Chemistry*, Butterworths, London, 1980.

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Davies JT, Rideal EK: *Interfacial Phenomena*, Academic, New York, 1963.

Osipow LI: *Surface Chemistry*, Reinhold, New York, 1962.

Hiemenz PC: *Principles of Colloidal and Surface Chemistry*, Marcel Dekker, New York, 2nd ed, 1986.

Matijevic E, ed: *Surface and Colloid Science*, vols 1–4, Wiley, New York, 1971.

Cadle RD: *Particle Size*, Reinhold, New York, 1965.

Parfitt G: *Dispersion of Powders in Liquids*, Applied Science, 1973.

Adamson AW: *Physical Chemistry of Surfaces*, 4th ed, Wiley-Interscience, New York, 1980.

Fowkes FM, ed: *Hydrophobic Surfaces*, Academic, New York, 1969.

Sherman P: *Rheology of Emulsions*, Macmillan, New York, 1963.

Becher P: *Emulsions: Theory and Practice*, 2nd ed, Reinhold, New York, 1965.

Vold RD, Vold MJ, *Colloid and Interface Chemistry*, Addison-Wesley, Reading, Mass, 1983.

Becher P: *Encyclopedia of Emulsion Technology*, Vols 1 to 3, Marcel Dekker, New York, 1983–1988.

CHAPTER 83

Solutions, Emulsions, Suspensions and Extracts

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The dosage forms described in this chapter may be prepared by dissolving the active ingredient(s) in an aqueous or nonaqueous solvent, by suspending the drug (if it is insoluble in pharmaceutically or therapeutically acceptable solvents) in an appropriate medium or by incorporating the medicinal agent into one of the two phases of an oil and water system. Such solutions, suspensions and emulsions are further defined in subsequent paragraphs but some, with similar properties, are considered elsewhere. These dosage forms are useful for a number of reasons. They can be formulated for different routes of administration: oral use, introduction into body cavities or applied externally. The dose easily can be adjusted by dilution, and the oral liquid form readily can be administered to children or people unable to swallow tablets or capsules. Extracts eliminate the need to isolate the drug in pure form, allow several ingredients to be administered from a single source (eg, pancreatic extract) and permit the preliminary study of drugs from natural sources. Occasionally, solutions of drugs such as potassium chloride are used to minimize adverse effects in the gastrointestinal tract.

The preparation of these dosage forms involves several considerations on the part of the pharmacist: purpose of the drug, internal or external use, concentration of the drug, selection of the liquid vehicle, physical and chemical stability of the drug, preservation of the preparation and use of appropriate excipients such as buffers, solubilizers, suspending agents, emulsifying agents, viscosity controlling agents, colors and flavors. The theory of many of these preparations is discussed in earlier chapters in Part 2, *Pharmaceutics*. Because of the complexity of some manufactured products, compounding may be carried out with the aid of linear programming models in order to obtain the optimal product. The appropriate chapters (see the index) should be consulted for information on the preparation and characteristics of those liquid preparations that are intended for ophthalmic or parenteral use.

Much has been written during the past decade about the biopharmaceutical properties of, in particular, the solid dosage forms. In assessing the bioavailability of drugs in tablets and capsules, many researchers first have studied the absorption of drugs administered in solution. Since drugs are absorbed in their dissolved state, frequently it is found that the absorption rate of oral dosage forms decreases in the following order: aqueous solution > aqueous suspension > tablet or capsule. The bioavailability of a medicament, for oral ingestion and absorption, should be such that eventually all of the drug is absorbed as it passes through the gastrointestinal tract, regardless of the dosage form. There are a number of reasons for formulating drugs in forms in which the drug is not in the molecular state. These are: improved stability, improved taste, low water solubility, palatability and ease of administration. It becomes apparent, then, that each dosage form will have advantages and disadvantages.

The pharmacist handles liquid preparations in one of three ways. He may dispense the product in its original container, buy the product in bulk and repackage it at the time a prescription is presented by the patient or compound the solution, suspension or emulsion in the dispensary. Compounding may involve nothing more than mixing marketed products in the manner indicated on the prescription or, in specific instances, may require the incorporation of active ingredients in a logical and pharmaceutically acceptable manner into the aqueous or nonaqueous solvents which will form the bulk of the product.

The pharmacist, in the first instance, depends on the pharmaceutical manufacturer to produce a product that is effective, elegant and stable when stored under reasonably adverse conditions. Most manufacturers attempt to guarantee efficacy by evaluating their products in a scientifically acceptable manner but, in some instances, such efficacy is relative. For example, cough mixtures marketed by two different manufacturers may contain the same active ingredients and it becomes difficult to assess the relative merits of the two products. In such instances the commercial advantage gained by one over the other may be based on product elegance. Thus, color, odor, taste, pourability and homogeneity are important pharmaceutical properties.

The stability of the active ingredient in the final product is of prime concern to the formulator. In general, drug substances are less stable in aqueous media than in the solid dosage form and it is important, therefore, to properly buffer, stabilize or preserve, in particular those solutions, suspensions and emulsions that contain water. Certain simple chemical reactions can occur in these products. These may involve an ingredient-ingredient interaction (which implies a poor formulation), a container-product interaction (which may alter product pH and thus, for pH-sensitive ingredients, be responsible for the subsequent formation of precipitates) or a direct reaction with water (ie, hydrolysis). The stability of pharmaceutical products is discussed in Chapter 81.

The more complicated reactions usually involve oxygen. Vitamins, essential oils and almost all fats and oils can be oxidized. Formulators usually use the word *autoxidation* when the ingredient(s) in the product react with oxygen but without drastic external interference. Such reactions first must be initiated by heat, light (including ultraviolet radiant energy), peroxides or other labile compounds or heavy metals such as copper or iron. This initiation step results in the formation of a free radical (R*) which then reacts with oxygen.

$$R^* + O_2 \rightarrow RO_2^* \text{ (peroxy radical)}$$

$$RO_2^* + RH \rightarrow ROOH + R^*$$

The free radical thus is regenerated and reacts with more oxygen. This propagation step is followed by the termination reactions.

$$RO_2^* + RO_2^* \rightarrow \text{inactive product}$$

$$RO_2^* + R^* \rightarrow \text{inactive product}$$

$$R^* + R^* \rightarrow \text{inactive product}$$

The effect of trace metals can be minimized by using citric acid or EDTA (ie, sequestering agents). Antioxidants, on the other hand, may retard or delay oxidation by reacting with the free radicals formed in the product. Examples of antioxidants are the propyl, octyl and dodecyl esters of gallic acid, butylated hydroxyanisole (BHA) and the tocopherols or vitamin E. For a more detailed approach to the prevention of oxidative deterioration in pharmaceuticals, the papers by Ostendorf[1] and Chalmers,[2] should be consulted. A description of many antioxidants is given in Chapter 66.

The problem of drug stability has been well-defined by pharmaceutical scientists but during the past few years a secondary and, in some respects, more serious problem has confronted the manufacturer of liquid preparations. Such pharmaceutically diverse products as baby lotions and milk of magnesia have been recalled from the market because of microbial contamination. In a survey of retail packages of liquid antacid preparations containing magnesium hydroxide, it was found that 30.5% of the finished bottles were contaminated with *Pseudomonas aeruginosa*. The aerobic plate count ranged from less than 100 to 9,300,000 organisms/g. Other examples could be cited but the range of microorganisms which can contaminate the liquid preparation includes the *Salmonella* sp, *E coli*, certain *Pseudomonas* sp, including *P aeruginosa*, and *Staphylococcus aureus*. Bruch[3] describes the types of microorganisms found in various products and attempts to evaluate the hazards associated with the use of nonsterile pharmaceuticals. Coates[4] in a series of papers describes various interactions which must be considered when preservatives are selected.

The USP recommends that certain classes of products be tested routinely for microbial contamination, eg, natural plant, animal and some mineral products, for freedom from *Salmonella* sp; oral solutions and suspensions, for freedom from *E coli*; articles applied topically, for freedom from *P aeruginosa* and *S aureus* and articles for rectal, urethral or vaginal administration, for total microbial count.

Products may become contaminated for a number of reasons.

The raw materials used in the manufacture of solutions, suspensions and emulsions are excellent growth media for bacteria. Water, in particular, must be handled with care but substances such as gums, dispersing agents, surfactants, sugars and flavors can be the carriers of bacteria which ultimately contaminate the product.

Equipment. Bacteria grow well in the nooks and crevices of pharmaceutical equipment (and in the simple equipment used in the dispensary). Such equipment should be cleaned thoroughly prior to use.

Environment and personnel can contribute to product contamination. Hands and hair are the most important carriers of contaminants. General cleanliness thus is vital. Head coverings must be used by those involved in the manufacturing process and face masks should be used by those individuals suffering from colds, coughs, hay fever and other allergic manifestations.

Packaging should be selected so that it will not contaminate the product and also will protect it from the environment.

The factors cited above relate to good manufacturing practice. However, the formulator can add a preservative to the product and decrease the probability of product contamination. If the product contains water, it almost is mandatory to include a preservative in the formulation. It must be stressed that this in no way replaces good in-plant control but merely provides further assurance that the product will retain its pharmaceutically acceptable characteristics until it is used by the patient.

The major criteria that should be considered in selecting a preservative: it should be effective against a wide spectrum of microorganisms, stable for its shelf life, nontoxic, nonsensitizing, compatible with the ingredients in the dosage form and relatively free of taste and odor.

Preservatives may be used alone or in combination to prevent the growth of microorganisms. Ethanol is a highly effective preservative. It is used at the 15% level in acidic media and at the 18% level in neutral or slightly alkaline media. Isopropyl alcohol is a fairly effective agent but it can be used only in topical preparations. Propylene glycol, a dihydric alcohol, has germicidal activity similar to that of ethanol. It normally is used in a 10% concentration.

A 0.5% solution of phenol is a good preservative but it is toxic, has its own characteristic odor and reacts chemically with many of the drugs and adjuvants which are incorporated into liquid preparations.

The use of hexachlorophene, a germicidal agent which is effective mainly against gram-positive organisms, is restricted to those preparations which are intended for external use only. Several years ago, an incorrectly formulated baby powder (which was found to contain 6.5% hexachlorophene) was responsible for the deaths of 30 French infants. Because of this and other evidence it can be used as a preservative only if its concentration in the final product is 0.1% or less. However, certain liquid preparations (eg, Hexachlorophene Liquid Soap USP-0.25%) are available.

Organic mercury compounds are powerful biostatic agents. Their activity may be reduced in the presence of anionic emulsifying or suspending agents. They are not suitable for oral consumption but are used at the 0.005% concentration level in ophthalmic, nasal and topical preparations.

Benzoic acid is effective only at pH 4 or less. Its solubility in certain aqueous preparations is poor and, in those instances, sodium benzoate may be used. Sorbic acid has a broad range of antimycotic activity but its antibacterial properties are more limited. It is effective only at a pH of less than 5.

Quaternary ammonium surface-active agents, eg, benzalkonium chloride, exhibit an objectionable taste and have been reported to be incompatible with a number of anionic substances. In concentrations of 1:5000 to 1:20,000 they are used in ophthalmic preparations.

3-Phenylpropan-1-ol (hydrocinnamyl alcohol) is claimed to be more effective than 2-phenylethanol and benzyl alcohol in inhibiting the growth of *P aeruginosa*, and it has been suggested that this substance may be a suitable preservative for oral suspensions and mixtures.

The methyl and propyl esters of *p*-hydroxybenzoic acid (the parabens) are used widely in the pharmaceutical industry. They are effective over a wide pH range (from about 3 to 9) and are employed up to about the 0.2% concentration level. The two esters often are used in combination in the same preparation. This achieves a higher total concentration and the mixture is active against a wide range of organisms. The hydroxybenzoates are effective against most organisms; however, their activity may be reduced in the presence of nonionic surface-active agents because of binding.

It now should be obvious that when the pharmacist dispenses or compounds the various liquid preparations he assumes responsibility, with the manufacturer, for the maintenance of product stability. The USP includes a section on stability considerations in dispensing, which should be studied in detail. Certain points are self-evident. Stock should be rotated and replaced if expiration dates on the label so indicate. Products should be stored in the manner indicated in the compendium; eg, in a cool place or a tight, light-resistant container. Further, products should be checked for evidence of instability. With respect to solutions, elixirs, and syrups, color change, precipitation and evidence of microbial or chemical gas formation are major signs of instability. Emulsions may cream but if they break (ie, there is a

separation of an oil phase) the product is considered to be unstable. Sedimentation and caking are primary indications of instability in suspensions. The presence of large particles may mean that excessive crystal growth has occurred.

The USP states that repackaging is inadvisable. However, if the product must be repackaged, care and the container specified by the compendium must be used. For example, a plastic container should never be used if a light-resistant container is specified. If a product is diluted, or where two products are mixed, the pharmacist should use his knowledge to guard against incompatibility and instability. Oral antibiotic preparations constituted into liquid form should never be mixed with other products. Since the chemical stability of extemporaneously prepared liquid preparations often is unknown, their use should be minimized and every care taken to insure that product characteristics will not change during the time it must be used by the patient.

Because of the number of excipients and additives in these preparations, it is recommended that all the ingredients be listed on the container to reduce the risks which confront hypersensitive patients when these products are administered.

Solutions

Aqueous Solutions

A solution is a homogeneous mixture that is prepared by dissolving a solid, liquid or gas in another liquid and represents a group of preparations in which the molecules of the solute or dissolved substance are dispersed among those of the solvent. Solutions also may be classified on the basis of physical or chemical properties, method of preparation, use, physical state, number of ingredients and particle size. The narrower definition herein limits the solvent to water and excludes those preparations that are sweet and/or viscid in character. This section includes, therefore, those pharmaceutical forms that are designated as *Water, Aromatic Waters, Aqueous Acids, Solutions, Douches, Enemas, Gargles, Mouthwashes, Juices, Nasal Solutions, Otic Solutions* and *Irrigation Solutions.*

Water

The major ingredient in most of the dosage forms described herein is water. It is used both as a vehicle and as a solvent for the desired flavoring or medicinal ingredients. Its tastelessness, freedom from irritating qualities and lack of pharmacological activity make it ideal for such purposes. There is, however, a tendency to assume that its purity is constant and that it can be stored, handled and used with a minimum of care. While it is true that municipal supplies must comply with Environmental Protection Agency (EPA) regulations (or comparable regulations in other countries), drinking water *must* be repurified before it can be used in pharmaceuticals. For further information on water, see Chapter 21.

Five of the six solvent waters described in the USP are used in the preparation of parenterals, irrigations or inhalations. *Purified water* must be used for all other pharmaceutical operations and, as needed, in all USP tests and assays. It must meet rigid specifications for chemical purity. Such water may be prepared by distillation, by use of ion-exchange resins or by reverse osmosis.

A wide variety of commercially available stills are used to produce distilled water. The end use of the product dictates the size of the still and extent of pretreatment of the drinking water introduced into the system. A description of stills is provided in Chapter 84. Such water may be sterile provided the condenser is sterile, but to be called sterile it must be subjected to a satisfactory sterilization process. However, it has been shown that *P aeruginosa* (and other microorganisms) can grow in the distilled water produced in hospitals. The implications of this are obvious. Sterile water may be sterile at the time of production but may lose this characteristic if it is stored improperly. Hickman *et al*,[5] by regrouping the components of conventional distillation equipment, have described a method for the continuous supply of sterile, ultrapure water. Quality-control procedures for monitoring the microbiological quality of water should be performed in the pharmaceutical manufacturer's production facilities.

The major impurities in water are calcium, iron, magnesium, manganese, silica and sodium. The cations usually are combined with the bicarbonate, sulfate or chloride anions. "Hard" waters are those that contain calcium and magnesium cations. Bicarbonates are the major impurity in "alkaline" waters.

Ion-exchange (deionization, demineralization) processes will remove most of the major impurities in water efficiently and economically. A cation exchanger, H_2R, first converts bicarbonates, sulfates and chlorides to their respective acids.

$$\left.\begin{matrix}CaSO_4\\MgSO_4\\Na_2SO_4\end{matrix}\right| + H_2R \rightarrow \left|\begin{matrix}Ca\\Mg\\Na_2\end{matrix}\right| R + H_2SO_4$$

$$\left.\begin{matrix}Ca(HCO_3)_2\\Mg(HCO_3)_2\\2NaHCO_3\end{matrix}\right| + H_2R \rightarrow \left|\begin{matrix}Ca\\Mg\\Na_2\end{matrix}\right| R + 2H_2CO_3$$

Carbonic acid decomposes to carbon dioxide (which is removed by aeration in the decarbonator) and water.

The anion exchanger may contain either a weakly basic or a strongly basic anion resin. These adsorb sulfuric, hydrochloric and nitric acids. Chemical reactions may involve complete adsorption or an exchange with some other anion.

$$H_2SO_4 + A \rightarrow A \cdot H_2SO_4$$

If the resin contains a hydroxyl radical, water is formed during the purification process.

$$H_2SO_4 + 2AOH \rightarrow A_2SO_4 + 2H_2O$$

Weakly dissociated carbonic and silicic acids can be removed only by strongly basic anion resins.

$$H_2SiO_3 + 2AOH \rightarrow A_2SiO_2 + 2H_2O$$

Unit capacity varies with the nature of the installation, but it is possible to process as much as 15,000 gal of water/min.

Deionization processes do not necessarily produce *Purified Water* which will comply with EPA requirements for drinking water. Resin columns retain phosphates and organic debris. Either alone or in combination, these substances can act as growth media for microorganisms. Observations have shown that deionized water containing 90 organisms/mL contained, after 24-hour storage, 10^6

organisms/mL. Columns can be cleaned partially of pseudomonads by recharging, but a 0.25% solution of formaldehyde will destroy most bacteria. The column must be washed thoroughly and checked for the absence of aldehyde (with a Schiffs Reagent) before it can be used to generate deionized water.

Ultraviolet radiant energy (240–280 nm), heat or filtration can be used to limit the growth, kill or remove microorganisms in water. The latter method employs membrane filters and can be used to remove bacteria from heat-labile materials as described under membrane filters in Chapter 78.

The phenomenon of osmosis involves the passage of water from a dilute solution across a semipermeable membrane to a more concentrated solution. Flow of water can be stopped by applying pressure, equal to the osmotic pressure, to the concentrated solution. The flow of water can be reversed by applying a pressure, greater than the osmotic pressure. The process of reverse osmosis utilizes the latter principle; by applying pressure, greater than the osmotic pressure, to the concentrated solution, eg, tap water, pure water may be obtained (see *Reverse Osmosis* in Chapter 77).

Cellulose acetate is used in the manufacture of semipermeable membranes for purifying water by reverse osmosis. This polymer has functional groups that can hydrogen-bond to water or other substances such as alcohol. The water molecules which enter the polymer are transported from one bonding site to the next under pressure. Because of the thin layer of pure water strongly adsorbed at the surface of the membrane, salts, to a large extent, are repelled from the surface, the higher-valent ions being repelled to a greater extent, thus causing a separation of ions from the water. Organic molecules are rejected on the basis of a sieve mechanism related to their size and shape. Small organic molecules, with a molecular weight smaller than approximately 200, will pass through the membrane material. Since there are few organic molecules with a molecular weight of less than 200 in the municipal water supply, reverse osmosis usually is sufficient for the removal of organic material. The pore sizes of the selectively permeable reverse-osmosis membranes are between 5 and 100 Å. Viruses and bacteria larger than 100 Å are rejected if no imperfections exist in the membrane. The membranes may and do develop openings which permit the passage of microorganisms. Because of the semistatic conditions, bacteria can grow both upstream and downstream of the membrane. Improvements in membranes are being made continually in type and manufacturing process such as the use of polyamide materials. It is expected that the preparation of water with negligible or no bacteria present will be achieved by this process.

The selection of water-treatment equipment depends upon the quality of water to be tested, the quality of water required and the specific pharmaceutical purpose of the water. Frequently, two or more methods are used to produce the water desired, for example, filtration and distillation, or filtration, reverse osmosis and ion exchange.

Aromatic Waters

Aromatic waters, known also as medicated waters, are clear, saturated aqueous solutions of volatile oils or other aromatic or volatile substances. Their odors and tastes are similar to those of the drugs or volatile substances from which they are prepared, and the preparations should be free from empyreumatic (smoke-like) and other foreign odors. They are used principally as flavored or perfumed vehicles. The volatile substances from which they are to be made should be of pharmacopeial quality or, in the case of nonofficial preparations, of the best quality if the finest flavors are to be obtained.

Aromatic waters may be prepared by one of two official processes.

Distillation—Different authorities give different directions for preparing aromatic waters by distillation. For fresh drugs the proportions range from 1 part of drug to 2 of distillate, to 2 parts of drug to 1 of distillate. For dried drugs such as cinnamon, anise, dill, caraway and fennel the proportion is 1 part of drug to 10 of distillate. For dried leaf drugs such as peppermint the proportion is 3 parts of drug to 10 of distillate. The drug should be contused or coarsely ground and combined with a sufficient quantity of *Purified Water*. Most of the water then is distilled; care should be taken to avoid charring or scorching the substances to prevent the formation of empyreumatic odors. On completion of the distillation, any excess oil in the distillate is removed and, if necessary, the clear-water portion is filtered.

Solution—Aromatic waters may be prepared by shaking repeatedly 2 g or (2 mL if a liquid) of the volatile substance with 1000 mL of purified water for 15 min. The mixture is set aside for 12 hr, filtered through wetted filter paper and made to volume (1000 mL) by adding purified water through the filter. Peppermint Water USP can be prepared by either of the two official methods.

Alternately aromatic waters also may be prepared by incorporating thoroughly the volatile oil with 15 g of talc, or with a sufficient quantity of purified siliceous earth or pulped filter paper. Purified water (1000 mL) is added and the mixture is agitated for 10 min. The water then is filtered (and, if necessary, refiltered) and its volume adjusted to 1000 mL by passing purified water through the filter.

This is the process most frequently employed since the water can be prepared promptly, only 10 minutes of agitation being required. The use of talc, purified siliceous earth or pulped filter paper greatly increases the surface of the volatile substance, insuring more rapid saturation of the water. These dispersing substances also form an efficient filter bed which produces a clear solution. They also are unreactive.

Other methods have been suggested for preparing aromatic waters based on the use of soluble concentrates or on incorporation of solubilizing agents such as polysorbate 20 (Tween 20, *Atlas*). However, such preparations are susceptible to mold growth and, in concentrations higher than 2%, impart an objectionable oily taste.

Concentrated waters (eg, peppermint, dill, cinnamon, caraway and anise) may be prepared as follows:

Dissolve 20 mL of the volatile oil in 600 mL of 90% ethanol. Add sufficient purified water in successive small portions to produce 1000 mL. Shake vigorously after each addition. Add 50 g of sterilized purified talc, shake occasionally for several hours and filter.

If anise concentrate is being prepared, the volume of ethanol must be increased to 700 mL.

The aromatic water is prepared by diluting the concentrate with 39 times its volume of water. In general, these methods yield aromatic waters that are slightly inferior in quality to those prepared by distillation or solution.

The chemical composition of many of the volatile oils used in preparing pharmaceuticals and cosmetics now is known. Similarly, many synthetic aromatic substances have a characteristic odor; eg, geranyl phenyl acetate has a honey odor. Such substances, either alone or in combination, can be used in nonofficial preparations and, by combining them in definite proportions, it is possible to produce substitutes for the officially recognized oil. Imitation Otto of Rose (which contains phenylethyl alcohol, rhodinol, citronellol and other ingredients) is an example of the types of substitutes which are now available. Additional information regarding the appropriate preparation of aromatic waters is provided in RPS-17, Chapter 84.

Incompatibilities—The principal difficulty experienced in compounding prescriptions containing aromatic waters is due to a "salting out" action of certain ingredients, such as very soluble salts, on the volatile principle of the aromatic water. A replacement of part of the aromatic water with purified water is permissible when no other function is being

served than that of a vehicle. Otherwise, a dilution of the product, with a suitable increase in dosage, is indicated.

Preservation—Aromatic waters will deteriorate with time and should, therefore, be made in small quantities and protected from intense light, excessive heat and stored in airtight, light-resistant containers. Deterioration may be due to volatilization, decomposition or mold growth and will produce solutions that are cloudy and have lost all traces of their agreeable odor. Distilled water usually is contaminated with mold-producing organisms. *Recently* distilled and boiled water should, therefore, be used in the preparation of medicated waters. No preservative should be added to medicated waters. If they become cloudy or otherwise deteriorate, they should be discarded.

Aqueous Acids

The official inorganic acids and certain organic acids, although of minor significance as therapeutic agents, are of great importance in chemical and pharmaceutical manufacturing. This is especially true of acetic, hydrochloric and nitric acids.

Percentage Strengths—Many of the more important inorganic acids are available commercially in the form of concentrated aqueous solutions. The percentage strength varies from one acid to another and depends on the solubility and stability of the solute in water and on the manufacturing process. Thus, the official Hydrochloric Acid contains from 36.5 to 38% by weight of HCl, whereas Nitric Acid contains from 69 to 71% by weight of HNO_3.

Because the strengths of these concentrated acids are stated in terms of % by weight, it is essential that specific gravities also be provided if one is to be able to calculate conveniently the amount of absolute acid contained in a unit volume of the solution as purchased. The mathematical relationship involved is given by the equation $M = V \times S \times F$, where M is the mass in g of absolute acid contained in V mL of solution having a specific gravity S and a fractional percentage strength F. As an example, Hydrochloric Acid containing 36.93% by weight of HCl has a specific gravity of 1.1875. Therefore, the amount of absolute HCl supplied by 100 mL of this solution is given by:

$$M = 100 \times 1.1875 \times 0.3693 = 43.85 \text{ g HCl}$$

Incompatibilities—Although many of the reactions characteristic of acids offer opportunities for incompatibilities, only a few are of sufficient importance to require more than casual mention. Acids and acid salts decompose carbonates with liberation of carbon dioxide and, in a closed container, sufficient pressure may be developed to produce an explosion. Inorganic acids react with salts of organic acids to produce the free organic acid and a salt of the inorganic acid. If insoluble, the organic acid will be precipitated. Thus, salicylic acid and benzoic acid are precipitated from solutions of salicylates and benzoates. Boric acid likewise is precipitated from concentrated solutions of borates. By a similar reaction, certain soluble organic compounds are converted into an insoluble form. Phenobarbital sodium, for example, is converted into phenobarbital which will precipitate in aqueous solution.

The ability of acids to combine with alkaloids and other organic compounds containing a basic nitrogen atom is used in preparing soluble salts of these substances.

It should be borne in mind that certain solutions, syrups, elixirs and other pharmaceutical preparations, may contain free acid, which causes these preparations to exhibit the incompatibilities characteristic of the acid.

Acids also possess the incompatibilities of the anions which they contain and, in the case of organic acids, these are frequently of prime importance. These are discussed under the specific anions.

Diluted Acids—The diluted acids in the USP are aqueous solutions of acids, of a suitable strength (usually 10% *w/v* but Diluted Acetic Acid is 6% *w/v*) for internal administration or for the manufacture of other preparations.

The strengths of the official undiluted acids are expressed as percentages *w/w*, whereas the strengths of the official diluted acids are expressed as percent *w/v*. It, therefore, becomes necessary to consider the specific gravities of the concentrated acids when calculating the volume required to make a given quantity of diluted acid. The following equation will give the number of mL required to make 1000 mL of diluted acid:

$$\frac{\text{Strength of diluted acid} \times 1000}{\text{Strength of undiluted acid} \times \text{sp gr of undiluted acid}}$$

Thus, if one wishes to make 1000 mL of Diluted Hydrochloric Acid USP using Hydrochloric Acid which assays 37.5% HCl (sp gr 1.18), the amount required is

$$\frac{10 \times 1000}{37.5 \times 1.18} = 226 \text{ mL}$$

Diluted Hydrochloric Acid USP is used in the treatment of achlorhydria. However, it may irritate the mucous membrane of the mouth and attack the enamel of the teeth. The usual dose is 5 mL, well-diluted with water. In the treatment of achlorhydria no attempt is made to administer more than a relief-producing dose. The normal pH of the gastric juice is 0.9 to 1.5 and, in order to attain this level, particularly in severe cases of gastric malfunction, somewhat larger doses of the acid would be required.

Solutions

A solution is a liquid preparation that contains one or more soluble chemical substances dissolved in water. The solute usually is nonvolatile. Solutions are used for the specific therapeutic effect of the solute, either internally or externally. Although the emphasis here is on the aqueous solution, certain preparations of this type (syrups, infusions and decoctions) have distinctive characteristics and, therefore, are described later in the chapter.

Solvents, solubility and general methods for the incorporation of a solute in a solvent are discussed in Chapter 16. Solutions are usually bottled automatically with equipment of the type shown in Fig 83-1.

Preparation—A specific method of preparation is given in the compendia for most solutions. These procedures fall into three main categories.

Simple Solutions—Solutions of this type are prepared by dissolving the solute in a suitable solvent. The solvent may contain other ingredients which stabilize or solubilize the active ingredient. Calcium Hydroxide Topical Solution (Lime Water), Sodium Phosphates Oral Solution and Strong Iodine Solution are examples.

Calcium Hydroxide Topical Solution contains, in each 100 mL, not less than 140 mg of $Ca(OH)_2$. The solution is prepared by agitating vigorously 3 g of calcium hydroxide with 1000 mL of cool, purified water. Excess calcium hydroxide is allowed to settle out and the clear, supernatant liquid dispensed.

An increase in solvent temperature usually implies an increase in solute solubility. This rule does not apply, however, to the solubility of calcium hydroxide in water, which decreases with increasing temperature. The official solution is prepared at 25°.

Solutions containing hydroxides react with the carbon dioxide in the atmosphere.

$$OH^- + CO_2 \rightarrow HCO_3^-$$

$$OH^- + HCO_3^- \rightarrow CO_3^{2-} + H_2O$$

$$Ca^{2+} + CO_3^{2-} \rightarrow CaCO_3$$

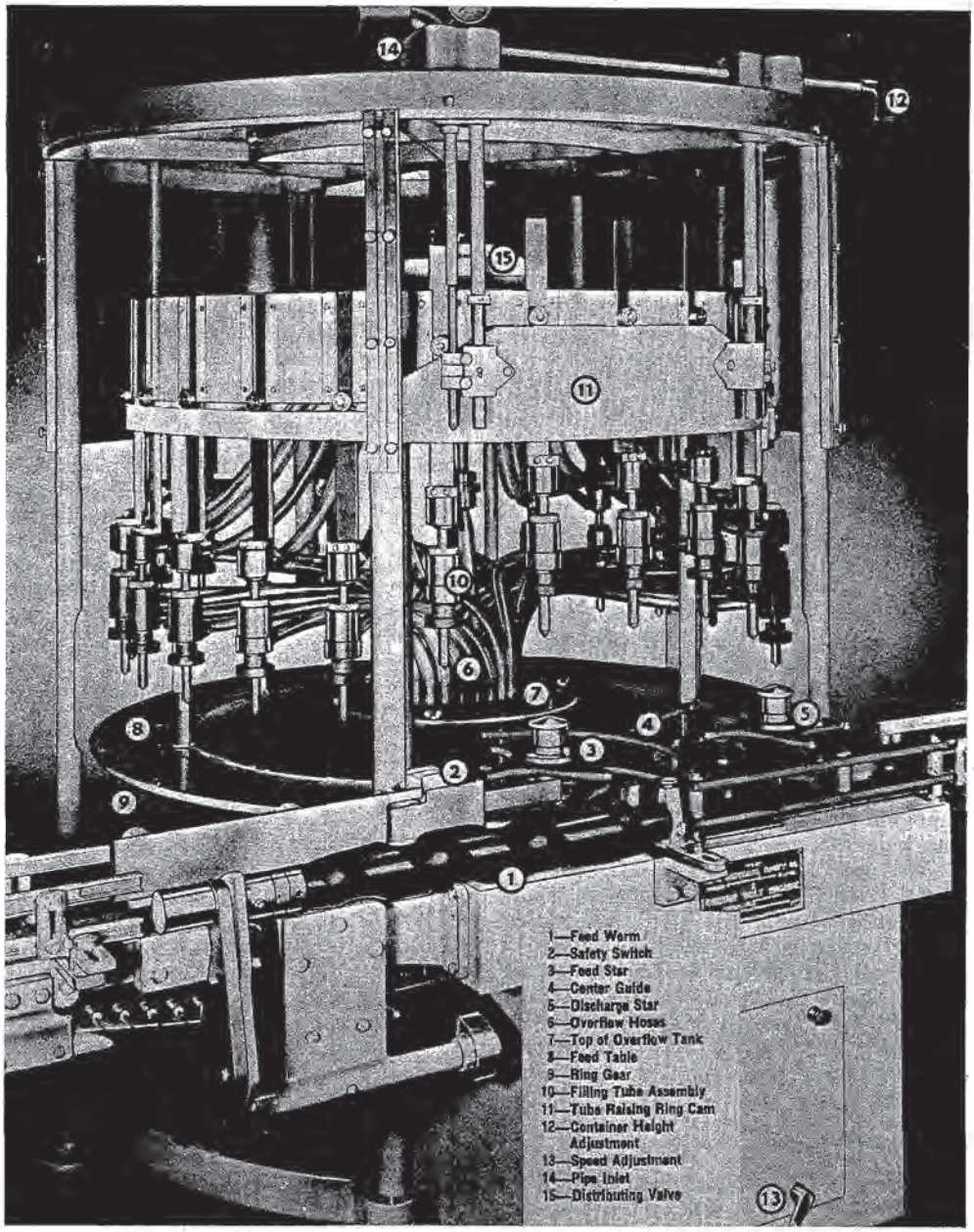


Fig 83-1. A rotary gravity bottle filler (courtesy, US Bottlers).

Calcium Hydroxide Topical Solution, therefore, should be preserved in well-filled, tight containers, at a temperature not exceeding 25°.

Strong Iodine Solution contains, in each 100 mL, 4.5–5.5 g of iodine, and 9.5–10.5 g of potassium iodide. It is prepared by dissolving 50 g of iodine in 100 mL of purified water containing 100 g of potassium iodide. Sufficient purified water then is added to make 1000 mL of solution.

One g of iodine dissolves in 2950 mL of water. However, solutions of iodides dissolve large quantities of iodine. Strong Iodine Solution is, therefore, a solution of polyiodides in excess iodide.

$$I^- + nI_2 \rightarrow I^-_{(2n+1)}$$

Doubly charged anions may be found also

$$2I^- + nI_2 \rightarrow I^{2-}_{(2n+2)}$$

Strong Iodine Solution is classified as an antigoitrogenic. The usual dose is 0.3 mL, 3 times a day.

Several antibiotics (eg, cloxacillin sodium, nafcillin sodium and vancomycin), because they are relatively unstable in aqueous solution, are prepared by manufacturers as dry powders or granules in combination with suitable buffers, colors, diluents, dispersants, flavors and/or preservatives. These preparations, Cloxacillin Sodium for Oral Solution, Nafcillin for Oral Solution and Vancomycin for Oral Solution meet the requirements of the USP. Upon dispensing to the patient, the pharmacist adds the appropriate amount of water. The products are stable for up to 14 days when refrigerated. This period usually provides sufficient time for the patient to complete the administration of all the medication.

Solution by Chemical Reaction—These solutions are prepared by reacting two or more solutes with each other in a suitable solvent. An example is Aluminum Subacetate Topical Solution.

Aluminum sulfate (145 g) is dissolved in 600 mL of cold water. The solution is filtered, and precipitated calcium carbonate (70 g) is added, in several portions, with constant stirring. Acetic acid (160 mL) is added slowly and the mixture set aside for 24 hr. The product is filtered and the magma on the Büchner filter washed with cold water until the total filtrate measures 1000 mL.

The solution contains pentaquohydroxo- and tetraquodihydroxoaluminum (III) acetates and sulfates dissolved in an aqueous medium saturated with calcium sulfate. The solution contains a small amount of acetic acid. It is stabilized by the addition of not more than 0.9% boric acid.

The reactions involved in the preparation of the solution are given below. The hexaquo aluminum cations first are converted to the nonirritating $[Al(H_2O)_5(OH)]^{2+}$ and $[Al(H_2O)_4(OH)_2]^+$ cations.

$$[Al(H_2O)_6]^{3+} + CO_3^{2-} \rightarrow [Al(H_2O)_5(OH)]^{2+} + HCO_3^-$$

$$[Al(H_2O)_6]^{3+} + HCO_3^- \rightarrow [Al(H_2O)_5(OH)]^{2+} + H_2O + CO_2$$

As the concentration of the hexaquo cations decreases, secondary reactions involving carbonate and bicarbonate occur.

$$[Al(H_2O)_5(OH)]^{2+}\ CO_3^{2-} \rightarrow [Al(H_2O)_4(OH)_2]^+ + HCO_3^-$$

$$[Al(H_2O)_5(OH)]^{2+} + HCO_3^- \rightarrow [Al(H_2O)_4(OH)_2]^+ + H_2CO_3$$

The pH of the solution now favors the precipitation of dissolved calcium ions as the insoluble sulfate. Acetic acid now is added. The bicarbonate which is formed in the final stages of the procedure is removed as carbon dioxide.

Aluminum Subacetate Topical Solution is used in the preparation of Aluminum Acetate Topical Solution (Burow's Solution). The latter solution contains 15 mL of glacial acetic acid, 545 mL of Aluminum Subacetate Topical Solution and sufficient water to make 1000 mL. It is defined as a solution of aluminum acetate in approximately 5%, by weight, of acetic acid in water. It is stabilized by the addition of not more than 0.6% boric acid.

Solution by Extraction—Drugs or pharmaceutical necessities of vegetable or animal origin often are extracted with water or with water containing other substances. Preparations of this type may be classified as solutions but, more often, are classified as extracts.

Douches

A douche is an aqueous solution directed against a part or into a cavity of the body. It functions as a cleansing or antiseptic agent. An *eye douche*, used to remove foreign particles and discharges from the eyes, is directed gently at an oblique angle and allowed to run from the inner to the outer corner of the eye. *Pharyngeal douches* are used to prepare the interior of the throat for an operation and cleanse it in suppurative conditions. Similarly, there are *nasal douches* and *vaginal douches*. Douches usually are directed to the appropriate body part by using bulb syringes (Chapter 104).

Douches most frequently are dispensed in the form of a powder with directions for dissolving in a specified quantity of water (usually warm). However, tablets for preparing solutions are available (eg, Dobell's Solution Tablets) or the solution may be prepared by the pharmacist. If powders or tablets are supplied, they must be free from insoluble material, in order to produce a clear solution. Tablets are produced by the usual processes (see Chapter 89) but any lubricants or diluents used must be readily soluble in water. Boric acid may be used as a lubricant and sodium chloride normally is used as a diluent. Tablets deteriorate on exposure to moist air and should be stored in airtight containers.

Preparations of this type may contain alum, zinc sulfate, boric acid, phenol or sodium borate. The ingredients in one douche are alum (4 g), zinc sulfate (4 g), liquefied phenol (5 mL), glycerin (125 mL) and water (qs to make 1000 mL of solution). Sodium borate (borax, sodium tetraborate) is used in the preparation of Compound Sodium Borate Solution NF XI (Dobell's Solution). Its aqueous solution is alkaline to litmus paper. In the presence of water, sodium metaborate, boric acid and sodium hydroxide are formed.

$$Na_2B_4O_7 + 3H_2O \rightarrow 2NaBO_2 + 2H_3BO_3$$

$$NaBO_2 + 2H_2O \rightarrow NaOH + H_3BO_3$$

The official solution contains sodium borate, sodium bicarbonate, liquefied phenol and glycerin. The reaction between boric acid and glycerin is given in the section on *Mouthwashes*. See also the section on *Honeys* for a discussion on the toxic manifestations associated with the topical application of boric acid and borax.

Douches are not official as a class of preparations but several substances in the compendia frequently are employed as such in weak solutions, eg, benzalkonium chloride is used in various douches and Compound Sodium Borate Solution is used as a nasal or pharyngeal douche. A sodium bicarbonate vaginal douche has been used to improve the postcoital test.

Vaginal douches are used for cleansing the vagina and hygienic purposes. Liquid concentrates or powders, which may be prepared in bulk or as single-use packages, should be diluted or dissolved in the appropriate amount of warm water prior to use. The ingredients used in vaginal douches include antimicrobial agents such as benzalkonium chloride, the parabens or chlorothymol, anesthetics or antipruritics such as phenol or menthol. Astringents such as zinc sulfate or potassium alum, surface-active agents such as sodium lauryl sulfate and chemicals to alter the pH such as sodium bicarbonate or citric acid also are used.

Enemas

These preparations are rectal injections employed to evacuate the bowel (evacuation enemas), influence the general system by absorption (retention enemas) or to affect locally the seat of disease. They may possess anthelmintic, nutritive, sedative or stimulating properties, or they may contain radiopaque substances for roentgenographic examination of the lower bowel. Some official retention enemas are those of aminophylline, hydrocortisone and methylprednisolone acetate. Since they are to be retained in the intestine, they should not be used in larger quantities than 150 mL for an adult. Usually, the volume is considerably smaller, such as a few mL. *Microenema* is a term used to describe these small-volume preparations. Vehicles for retention microenemas have been formulated with small quantities of ethanol and propylene glycol, and no significant difference in irritation, as compared with water, was found. A number of drugs such as valproic acid, indomethacin and metronidazole have been formulated as microenemas for the purpose of absorption. The absorption of large molecular weight drugs, such as insulin, is under current investigation.

Starch enema may be used either by itself or as a vehicle for other forms of medication. A thin paste is made by triturating 30 g of powdered starch with 200 mL of cold water. Sufficient boiling water is added to make 1000 mL of enema. The preparation then is reheated to obtain a transparent liquid.

Sodium chloride, sodium bicarbonate, sodium monohydrogen phosphate and sodium dihydrogen phosphate are used in enemas to evacuate the bowel. These substances may be used alone, in combination with each other or in combination with irritants such as soap. Enema of Soap BPC 1963 is prepared by dissolving 50 g of soft soap in sufficient purified water to make 1000 mL of enema. Fleet Enema, a commercially available enema containing 16 g of sodium acid phosphate and 6 g of sodium phosphate in 100 mL, is marketed as a single-dose disposable unit. Evacuation enemas usually are given at body temperature in quantities of 1 to 2 pt injected slowly with a syringe.

Sulfasalazine rectal enema has been administered for the treatment of ulcerative colitis and may be prepared by dispersing the tablets (1-g strength) in 250 mL water. Barium sulfate enema contains 120 g of barium sulfate, 100 mL of acacia mucilage and sufficient starch enema to make 500 mL.

Gargles

Gargles are aqueous solutions used for treating the pharynx and nasopharynx by forcing air from the lungs through

the gargle which is held in the throat. Many gargles must be diluted with water prior to use. Although mouthwashes are considered as a separate class of pharmaceuticals, many are used as gargles, either as is, or diluted with water.

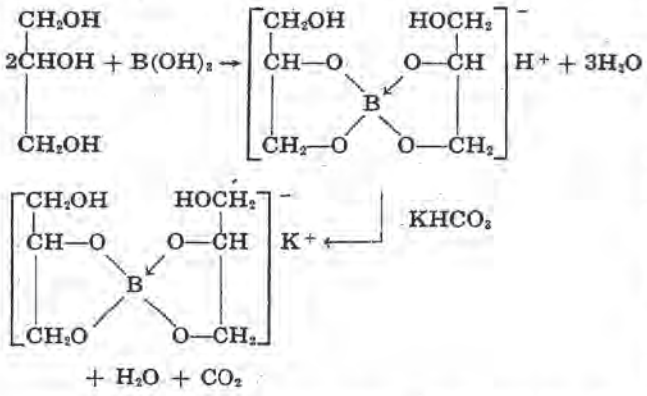
Potassium Chlorate and Phenol Gargle is official in the PC. It contains potassium chlorate, 30 g, patent blue V (Color Index No 42051) commercial food grade (0.01 g), liquified phenol (15 mL) and water for preparations qs to 1000 mL. It should be diluted with 10 volumes of warm water before use. The product should be labeled so that it cannot be mistaken for preparations intended for internal administration.

A flavored solution containing 7.5% povidone-iodine and 35% alcohol (*Isodine*) is available commercially as a mouthwash or gargle after suitable dilution.

Mouthwashes

A mouthwash is an aqueous solution which is most often used for its deodorant, refreshing or antiseptic effect or for control of plaque. It may contain alcohol, glycerin, synthetic sweeteners and surface-active, flavoring and coloring agents. Commercial preparations contain such local antiinfective agents as hexetidine and cetylpyridinium chloride. They may be either acidic or basic in reaction and, in some instances, may be effective in reducing bacterial concentrations and odors in the mouth for short periods of time.

The products of commerce (eg, Cepacol, Listerine, Micrin or Scope) vary widely in composition. Compound Sodium Borate Solution NF XI (Dobell's Solution) is used as an antiseptic mouthwash and gargle. Antiseptic Solution and Mouthwash are described in NF XII. The latter wash contains sodium borate, glycerin and potassium bicarbonate. The reactions which take place when these substances are dissolved in water are given below.



Compound Sodium Chloride Mouthwash, and Zinc Sulphate and Zinc Chloride Mouthwash are described in the BPC. The former wash contains sodium chloride, sodium bicarbonate, concentrated peppermint emulsion and double-strength chloroform water.

Mouthwashes may be used for a number of purposes: for example, cetylpyridinum chloride and dibucaine hydrochloric mouthwashes provide satisfactory relief of pain in patients with ulcerative lesions of the mouth, mouthwashes or creams containing carbenoxolone are highly effective dosage forms for the treatment of orofacial herpes simplex infections, and undetected oral cancer has been recognized using toluidine blue in the form of a mouth rinse.

Juices

A juice is prepared from fresh ripe fruit, is aqueous in character and is used in making syrups which are employed as vehicles. The freshly expressed juice is preserved with benzoic acid and allowed to stand at room temperature for several days, until the pectins which naturally are present are destroyed by enzymatic action, as indicated by the filtered juice yielding a clear solution with alcohol. Pectins, if allowed to remain, would cause precipitation in the final syrup.

Cherry Juice is described in the current USP and Raspberry Juice in USP XVIII. Concentrated Raspberry Juice PC is prepared from the clarified juice of raspberries. Pectinase is stirred into pulped raspberries and the mixture allowed to stand for 12 hours. The pulp is pressed, the juice clarified and sufficient sucrose added to adjust the weight at 20° to 1.050 to 1.060 g per mL. The juice then is concentrated to one-sixth of its original volume. Sufficient sulfurous acid or sodium metabisulfite is added as a preservative.

Artificial flavors now have replaced many of the natural fruit juices. Although they lack the flavor of the natural juice, they are more stable and easier to incorporate into the final pharmaceutical form.

Recent information on cranberry juice indicates that it may be effective in controlling some urinary tract infections and urolithiosis.

Nasal Solutions

Nasal solutions are usually aqueous solutions designed to be administered to the nasal passages in drops or sprays. While many of the drugs are administered for their local sympathomimetic effect such as Ephedrine Sulfate or Naphazoline Hydrochloride Nasal Solution USP, to reduce nasal congestion, a few other official preparations, Lypressin Nasal Solution USP and Oxytocin Nasal Solution USP, are administered in spray form for their systemic effect for the treatment of diabetes insipidus and *milk letdown* prior to breast feeding, respectively. The current route of administration of peptides and proteins is limited to parenteral injection because of inactivation within the gastrointestinal tract. As a result, there is considerable research on intranasal delivery of these drugs such as analogs of enkephalins or luteinizing hormone releasing hormone and insulin.

Nasal solutions are prepared so that they are similar in many respects to nasal secretions, so that normal ciliary action is maintained. Thus, the aqueous nasal solutions usually are isotonic and slightly buffered to maintain a pH of 5.5 to 6.5. In addition, antimicrobial preservatives, similar to those used in ophthalmic preparations, and appropriate drug stabilizers, if required, are included in the formulation.

Commercial nasal preparations, in addition to the drugs listed above also include antibiotics, antihistamines and drugs for asthma prophylaxis.

A formula for Ephedrine Nasal Drops PC is

Ephedrine hydrochloride	**0.5 g**
Chlorobutanol	**0.5 g**
Sodium Chloride	**0.5 g**
Water for preparations	**to 100 mL**

Current studies indicate that nasal sprays are deposited mainly in the atrium and cleared slowly into the pharynx with the patient in an upright position. Drops spread more extensively than the spray and three drops cover most of the walls of the nasal cavity, with the patient in a supine position and head tilted back and turned left and right. It is suggested that drop delivery, with appropriate movement by the patient, leads to extensive coverage of the walls of the nasal cavity.

Otic Solutions

These solutions occasionally are referred to as aural preparations. Other otic preparations often include formula-

tions such as suspensions and ointments for topical application in the ear.

The main classes of drugs used for topical administration to the ear include analgesics, eg, benzocaine; antibiotics, eg, neomycin; and anti-inflammatory agents, eg, cortisone. The USP preparations include Antipyrine and Benzocaine Otic Solution. The Neomycin and Polymyxin B Sulfates and Hydrocortisone Otic Solutions contain appropriate buffers and dispersants usually in an aqueous solution. These preparations include the main types of solvents used, namely glycerin or water. The viscous glycerin vehicle permits the drug to remain in the ear for a long time. Anhydrous glycerin, being hygroscopic, tends to remove moisture from surrounding tissues, thus reducing swelling. Viscous liquids like glycerin or propylene glycol either are used alone or in combination with a surfactant to aid in the removal of cerumen (ear wax).

In order to provide sufficient time for aqueous preparations to act, it is necessary for the patient to remain on his side for a few minutes so the drops do not run out of the ear. Otic preparations are dispensed in a container which permits the administration of drops.

Irrigation Solutions

These solutions are used to wash or bathe surgical incisions, wounds or body tissues. Because they come in contact with exposed tissue, they must meet stringent requirements for Injections of the USP such as sterility, particulate matter and the requirements of the Pyrogen Test. These products are prepared by dissolving the active ingredient in Water for Injection. They are packaged in single-dose containers, preferably Type I or Type II glass, or suitable plastic containers, and then sterilized. See Chapter 78 for sterilization procedures. A number of irrigations are described in the USP: Acetic Acid Irrigation for bladder irrigation, Aminoacetic Acid Irrigation for urethral surgery and Sodium Chloride Irrigation for washing wounds. Other drugs such as amphotericin B also may be formulated as irrigations.

Sweet or Other Viscid Aqueous Solutions

Solutions which are sweet or viscid include syrups, honeys, mucilages and jellies. All of these are viscous liquids or semisolids. The basic sweet or viscid substances giving body to these preparations are sugars, polyols or polysaccharides (gums).

Syrups

Syrups are concentrated solutions of sugar such as sucrose in water or other aqueous liquid. When Purified Water alone is used in making the solution of sucrose, the preparation is known as *Syrup*, or *simple syrup*. In addition to sucrose, certain other polyols, such as glycerin or sorbitol, may be added to retard crystallization of sucrose or to increase the solubility of added ingredients. Alcohol often is included as a preservative and also as a solvent for flavors; further resistance to microbial attack can be enhanced by incorporating antimicrobial agents. When the aqueous preparation contains some added-medicinal substance, the syrup is called a *medicated syrup*. A *flavored* syrup is one which usually is not medicated, but which contains various aromatic or pleasantly flavored substances and is intended to be used as a vehicle or flavor for prescriptions.

Flavored syrups offer unusual opportunities as vehicles in extemporaneous compounding and are accepted readily by both children and adults. Because they contain no, or very little, alcohol they are vehicles of choice for many of the drugs that are prescribed by pediatricians. Their lack of alcohol makes them superior solvents for water-soluble substances. However, sucrose-based medicines continuously administered to children apparently cause an increase in dental caries and gingivitis; consequently, alternate formulations of the drug either unsweetened or sweetened with noncariogenic substances should be considered. A knowledge of the sugar content of liquid medicines is useful for patients who are on a restricted calorie intake; a list has been prepared by Bergen.[6]

Syrups possess remarkable masking properties for bitter or saline drugs. Glycyrrhiza syrup has been recommended for disguising the salty taste of bromides, iodides and chlorides. This has been attributed to its colloidal character and its double sweetness—the immediate sweetness of the sugar and the lingering sweetness of the glycyrrhizin. This syrup is also of value in masking bitterness in preparations containing the B complex vitamins. Acacia Syrup USP, because of its colloidal character, is of particular value as a vehicle for masking the disagreeable taste of many medicaments. Raspberry Syrup PC is one of the most efficient flavoring agents and is especially useful in masking the taste of bitter drugs. Many factors, however, enter into the choice of a suitable flavoring agent. Literature reports are often contradictory and there appears to be no substitute for the taste panel. The literature on this subject has been reviewed by Meer,[7] and this reference and Chapter 66 should be consulted for further information on the flavoring of pharmaceuticals and the preparation of a number of official syrups. A series of papers by Schumacher deals with improving the palatability of bulk-compounded products using flavoring and sweetening agents.[8]

In manufacturing syrups the sucrose must be selected carefully and a purified water, free from foreign substances, and clean vessels and containers must be used. The operation must be conducted with care to avoid contamination, if the products are to be stable.

It is important that the concentration of sucrose approach but not quite reach the saturation point. In dilute solutions sucrose provides an excellent nutrient for molds, yeasts and other microorganisms. In concentrations of 65% by weight or more, the solution will retard the growth of such microorganisms. However, a saturated solution may lead to crystallization of a part of the sucrose under conditions of changing temperature.

When heat is used in the preparation of syrups, there is almost certain to be an inversion of a slight portion of the sucrose. Sucrose solutions are dextrorotary but, as hydrolysis proceeds, the optical rotation decreases and becomes negative when the reaction is complete. This reaction is termed *inversion* because *invert sugar* (dextrose plus levulose) is formed. The speed of inversion is increased greatly by the presence of acids; the hydrogen ion acts as a catalyst in this hydrolytic reaction. Invert sugar is more readily fermentable than sucrose and tends to be darker in color. Nevertheless, its two reducing sugars are of value in retarding the oxidation of other substances.

Invert Syrup is described in the PC. It is prepared by hydrolyzing sucrose with hydrochloric acid and neutralizing the solution with calcium or sodium carbonate. The sucrose in the 66.7% *w/w* solution must be at least 95% inverted. The monograph states that invert syrup, when mixed in suitable proportions with syrup, prevents the deposition of crystals of sucrose under most conditions of storage.

The levulose formed during inversion is sweeter than su-

crose and, therefore, the resulting syrup is sweeter than the original syrup. The relative sweetness of levulose, sucrose and dextrose is in the ratio of 173:100:74. Thus, invert sugar is $1/100\ (173 + 74)^{1/2} = 1.23$ times as sweet as sucrose. The levulose formed during the hydrolysis also is responsible for the darkening of syrup. It is sensitive to heat and darkens readily, particularly in solution. When syrup or sucrose is overheated, it caramelizes. See *Caramel* (page 1290). Occasionally, it is appropriate to use a sugar-free liquid preparation; a list of these has been published.[9]

Preparation—Syrups are prepared in various ways, the choice of the proper method depending on the physical and chemical characteristics of the substances entering into the preparation.

Solution with Heat—This is the usual method of making syrups when the valuable constituent is neither volatile nor injured by heat, and when it is desirable to make the syrup rapidly. The sucrose usually is added to the purified water or aqueous solution and heated until solution is effected, then strained and sufficient purified water added to make the desired weight or volume. If the syrup is made from an infusion, a decoction or an aqueous solution containing organic matter, such as sap from maple trees, it usually is proper to heat the syrup to the boiling point to coagulate albuminous matter; subsequently, this is separated by straining. If the albumin or other impurities were permitted to remain in the syrup, fermentation probably would be induced in warm weather. Saccharometers are very useful in making syrups by the hot process in cases where the proper specific gravity of the finished syrup is known. They may be floated in the syrup while boiling, and thus the exact degree of concentration determined without waiting to cool the syrup and having to heat it again to concentrate it further. When taking a reading of the specific gravity of the hot syrup, allowance must be made for the variation from the official temperature (specific gravities in the USP are taken at 25°).

Excessive heating of syrups at the boiling temperature is undesirable since more or less inversion of the sucrose occurs with an increased tendency to ferment. Syrups cannot be sterilized in an autoclave without some caramelization. This is indicated by a yellowish or brownish color resulting from the formation of caramel by the action of heat upon sucrose.

The formula and procedure given for Acacia Syrup (page 1301) illustrates this method of preparation.

Agitation without Heat—This process is used in those cases where heat would cause the loss of valuable, volatile constituents. In making quantities up to 2000 mL the sucrose should be added to the aqueous solution in a bottle of about twice the size required for the syrup. This permits active agitation and rapid solution. Stoppering the bottle is important, as it prevents contamination and loss during the process. The bottle should be allowed to lie on its side when not being agitated. Glass-lined tanks with mechanical agitators, especially adapted to dissolving of sucrose, are used for making syrups in large quantities.

This method and that previously described are used for the preparation of a wide variety of preparations that are popularly described as syrups. Most cough syrups, for example, contain sucrose and one or more active ingredients. However, the exact composition of such products is not given on the label. Furthermore, some of these products are listed in the USP but no directions are given for their preparation. For example, Guaifenesin Syrup USP (glyceryl guaiacolate syrup) is official but the only known ingredients are guaifenesin (glyceryl guaiacolate) and ethanol (not less than 3% or more than 4%).

The PC, on the other hand, gives a method for the preparation of Codeine Phosphate Syrup. This contains codeine phosphate (5 g), water for preparations (15 mL), chloroform spirit (25 mL) and sufficient syrup to make 1000 mL. It can be used for the relief of cough. Another syrup for this purpose is Codeine Linctus PC. This is really a medicated syrup which possesses demulcent, expectorant or sedative properties. Unlike the syrup, it is colored and flavored. The formula for Codeine Linctus PC is:

Codeine Phosphate	3 g
Compound Tartrazine Solution	10 mL
Benzoic Acid Solution	20 mL
Chloroform Spirit	20 mL
Water for Preparations	20 mL
Lemon Syrup	200 mL
Syrup	to 1000 mL

Dissolve the codeine phosphate in the water, add 500 mL of the syrup and mix. Add the other ingredients and sufficient syrup to produce 1000 mL.

For pediatric use, 200 mL of this linctus is diluted with sufficient syrup to make 1000 mL. If sugar is contraindicated in the diet, Diabetic Codeine Linctus can be used:

Codeine Phosphate	3 g
Citric Acid monohydrate	5 g
Lemon Spirit	1 mL
Compound Tartrazine Solution	10 mL
Benzoic Acid Solution	20 mL
Chloroform Spirit	20 mL
Water for Preparations	20 mL
Sorbitol Solution	to 1000 mL

Dissolve the codeine phosphate and the citric acid in the water, add 750 mL of the sorbitol solution and mix. Add the other ingredients and sufficient sorbitol solution to produce 1000 mL.

Sorbitol Solution is the sweetening agent and contains 70% *w/w* of total solids, consisting mainly of D-sorbitol. It has about half the sweetening power of syrup. In the US the FDA has banned the use of chloroform in medicines and cosmetics because of reported carcinogenicity in animals.

Basic formulations can be varied easily to produce the highly advertised articles of commerce. The prescription-only drug (eg, codeine phosphate or methadone) must, of course, be omitted from the formulation but, in certain countries, such as Canada, a decreased quantity of codeine phosphate is permitted in an OTC cough syrup. In addition to the ingredients cited or listed in the official compendia (eg, tolu, squill or ipecacuanha), many cough syrups contain an antihistamine.

Many other active ingredients (eg, ephedrine sulfate, dicyclomine hydrochloride, chloral hydrate or chlorpromazine hydrochloride) are marketed as syrups. Like cough syrups, these preparations are flavored, colored and recommended in those instances where the patient cannot swallow the solid dosage form.

Addition of a Medicating Liquid to Syrup—This method is resorted to in those cases in which fluidextracts, tinctures or other liquids are added to syrup to medicate it. Syrups made in this way usually develop precipitates since alcohol is often an ingredient of the liquids thus used, and the resinous and oily substances dissolved by the alcohol precipitate when mixed with the syrup, producing unsightly preparations. A modification of this process, frequently adopted, consists of mixing the fluidextract or tincture with the water, allowing the mixture to stand to permit the separation of insoluble constituents, filtering and then dissolving the sucrose in the filtrate. It is obvious that this procedure is not permissible when the precipitated ingredients are the valuable medicinal agents.

The formula and procedure given for Aromatic Eriodictyon Syrup USP (page 1301) illustrate this method of preparation.

Percolation—In this procedure, purified water, or an aqueous solution, is permitted to pass slowly through a bed of crystalline sucrose, thus dissolving it and forming a syrup. A cotton pledget is placed in the neck of the percolator and the water or aqueous solution added. By means of a suitable stopcock the flow is regulated so that drops appear in rapid succession. If necessary, a portion of the liquid is recycled through the percolator to dissolve all the sucrose. Finally, sufficient purified water is passed through the cotton to make the required volume.

To be successful in using this process, care in several particulars must be exercised: (1) the percolator used should be cylindrical or semicylindrical and cone-shaped as it nears the lower orifice; (2) a coarse granular sugar must be used, otherwise it will coalesce into a compact mass, which the liquid cannot permeate; (3) the purified cotton must be introduced with care.

If pressed in too tightly, the cotton will stop the process effectually; if inserted too loosely, the liquid will pass through the cotton rapidly and the filtrate will be weak and turbid (from imperfect filtration); it should be inserted completely within the neck of the percolator, since a protruding end, inside the percolator, up through the sucrose, will permit the last portions of water to pass out at the lower orifice without dissolving all the sucrose. For specific directions see *Syrups* (page 1301). The process of percolation is applied on a commercial scale for the making of official syrups as well as those for confectionary use.

Percolation is the preferred method for the preparation of Syrup USP (page 1301). The sucrose, in this instance, is placed in the percolator. However, a slightly modified approach must be used if a drug of vegetable origin is to be incorporated into the syrup. For example, wild cherry bark is first percolated with water; the collection vessel contains sucrose (800 g) and glycerol (50 mL). When the total volume is 1000 mL, the percolate is agitated to produce Wild Cherry Syrup PC.

Reconstitution—In order to improve stability and minimize microbial contamination, dry syrup formulations can be prepared and Purified Water USP added just prior to dispensing or use. Powder mixtures, wholly granulated products and partially granulated products have been investigated for this purpose by Ryder.[10]

The powder mixture preparation requires less equipment and energy to prepare. Chemical stability problems are minimal, since no heat or solvents are used in the process and a low moisture content can be obtained in the final product; unfortunately, powder mixtures are prone to homogeneity problems. In the case of the wholly granulated product all the ingredients are included in the granulation stage. The drug may be incorporated into the dry product before granulation or dissolved or suspended in the granulating fluid. After formation, the granules are dried and then screened to break down oversize particles. The advan-

tages of granulated over powder mixtures include better appearance, better flow, fewer segregation problems and less dust during processing. Partially granulated mixtures are used to gain some of the advantages of granulation without the disadvantages. Usually the drug, and other fine particles, are included at the granulation stage, perhaps with some diluents to improve flow and reduce segregation and dust. Materials selected for mixing with the dried granules would include thermolabile excipients, such as flavors, and free flowing materials, such as sugars.

Preservation—Syrups should be made in quantities which can be consumed within a few months, except in those cases where special facilities can be employed for their perservation; a low temperature is the best method. The USP indicates that syrups should not be exposed to excessive heat. Concentration without super-saturation is also a condition favorable to preservation. The USP states that syrups may contain preservatives to prevent bacterial and mold growth such as glycerin, methylparaben, benzoic acid and sodium benzoate, particularly when the concentration of sucrose in the syrup is low. Combinations of alkyl esters of *p*-hydroxybenzoic acid are effective inhibitors of yeasts which have been implicated in the contamination of commercial syrups. Any attempt to restore syrups spoiled through fermentation by heating them and "working them over" is reprehensible.

The official syrups should be preserved in well-dried bottles, preferably those which have been sterilized. These bottles should not hold more than is likely to be required during 4 to 6 weeks and should be filled completely, stoppered carefully and stored in a cool, dark place.

Syrups Prepared from Juices

Blackberry, pineapple and strawberry syrups may be prepared by following the directions in Raspberry Syrup PC. One volume of the concentrated raspberry juice is diluted with 11 volumes of syrup. Black Current Syrup PC is prepared in a similar manner but also can be prepared from black currants, with certain modifications. The pectin in the juice is destroyed with pectinase. The syrup is prepared from 700 g of sucrose and 560 mL of clarified juice and is preserved with sulfurous acid or sodium metabisulfite. The addition of a dye is permitted, provided it complies with the pertinent government regulations. Cherry Syrup USP is prepared from cherry juice by the addition of alcohol, sucrose and water (page 1301).

Honeys

Honeys are thick liquid preparations somewhat allied to the syrups, differing in that honey, instead of syrup, is used as a base. They are unimportant as a class of preparations today but at one time, before sugar was available and honey was the most common sweetening agent, they were used widely. PC lists two preparations containing honey. The first, Oxymel, or "acid honey," is a mixture of acetic acid (150 mL), purified water (150 mL) and honey (sufficient to produce 1000 mL of product). Squill Oxymel contains squill, water, acetic acid and honey and is prepared by a maceration process.

One nonofficial preparation contains borax (10.5 g), glycerin (5.25 g) and sufficient honey to make 1000 g. It has been indicated that this type of product can cause serious boric acid intoxication in babies. It should not be used in pharmaceutical practice. Thick and thin sugar pastes containing Caster sugar (very fine granular sugar), icing sugar (additive-free), polyethylene glycol 400 and hydrogen peroxide (in a final concentration of 0.15%) have been prepared and shown to be beneficial in the process of wound healing.

Mucilages

The official mucilages are thick, viscid, adhesive liquids, produced by dispersing gum in water, or by extracting the mucilaginous principles from vegetable substances with water. The mucilages all are prone to decomposition, showing appreciable decrease in viscosity on storage; they should never be made in quantities larger than can be used immediately, unless a preservative is added. Acacia Mucilage NF XII contains benzoic acid and Tragacanth Mucilage BPC (1973) contains alcohol and chloroform water. Chloroform in manufactured products for internal use is banned in some countries.

Acacia Mucilage may be prepared by placing 350 g of acacia in a graduated bottle, washing the drug with cold purified water, allowing it to drain and adding enough warm purified water, in which 2 g of benzoic acid has been dissolved, to make the product measure 1000 mL. The bottle then is stoppered, placed on its side, rotated occasionally and the product strained when the acacia has dissolved.

Tragacanth Mucilage BPC (1973) is prepared by mixing 12.5 g of tragacanth with 25 mL alcohol (90%) in a dry bottle and then quickly adding sufficient chloroform water to 1000 mL and shaking vigorously. The alcohol is used to disperse the gum to prevent agglomeration on addition of the water.

Mucilages are used primarily to aid in suspending insoluble subtances in liquids; their colloidal character and viscosity help prevent immediate sedimentation. Examples include sulfur in lotions, resin in mixtures and oils in emulsions. Both tragacanth and acacia either are partially or completely insoluble in alcohol. Tragacanth is precipitated from solution by alcohol, but acacia, on the other hand, is soluble in diluted alcoholic solutions. A 60% solution of acacia may be prepared with 20% alcohol and a 4% solution of acacia may be prepared even with 50% alcohol.

The viscosity of tragacanth mucilage is reduced by acid, alkali or sodium chloride, particularly if the mucilage is heated. It shows maximum viscosity at pH 5. Acacia is hydrolyzed by dilute mineral acids to arabinose, galactose, aldobionic and galacturonic acids. Its viscosity is low but is maintained over a wide pH range.

Recent research on mucilages includes the preparation of mucilage from plantain and the identification of its sugars, the preparation and suspending properties of cocoa gum, the preparation of glycerin ointments using flaxseed mucilage and the consideration of various gums and mucilages obtained from several Indian plants for pharmaceutical purposes.

Several synthetic mucilage-like substances such as *polyvinyl alcohol*, *methylcellulose*, *carboxymethylcellulose* and related substances, as described in Chapter 66, are used as mucilage substitutes, emulsifying and suspending agents. Methylcellulose (page 1306) is used widely as a bulk laxative since it absorbs water and swells to a hydrogel in the intestine, in much the same manner as *psyllium* or *karaya gum*. Methylcellulose Oral Solution is a flavored solution of the agent. It may be prepared by adding slowly the methylcellulose to about one-third the amount of boiling water, with stirring, until it is thoroughly wetted. Cold water then should be added and the wetted material allowed to dissolve while stirring. The viscosity of the solution will depend upon the concentration and the specifications of the methylcellulose. The synthetic gums are nonglycogenetic and may be used in the preparation of diabetic syrups. Several formulas for such syrups, based on sodium carboxymethylcellulose, have been proposed.

Uniformly smooth mucilages sometimes are difficult to prepare due to the uneven wetting of the gums. In general, it is best to use fine gum particles and disperse them with good agitation in a little 95% alcohol or in cold water (except for methylcellulose). The appropriate amount of water then can be added with constant stirring. A review of the chemistry and properties of acacia and other gums has been prepared.[11]

Jellies

Jellies are a class of gels in which the structural coherent matrix contains a high portion of liquid, usually water. They are similar to mucilages, in that they may be prepared from similar gums, but they differ from the latter in having a jelly-like consistency. A whole gum of the best quality, rather than a powdered gum, is desirable in order to obtain a clear preparation of uniform consistency. Tragacanth is the gum used in the preparation of Ephedrine Sulfate Jelly NF XII. While the specific thickening agent in the USP jellies is not indicated, reference usually is made in the monograph to a water-soluble viscous base. These preparations also may be formulated with water from acacia, chondrus, gelatin, carboxymethylcellulose and similar substances.

Jellies are used as lubricants for surgical gloves, catheters and rectal thermometers. Lidocaine Hydrochloride Jelly USP is used as a topical anesthetic. Therapeutic vaginal jellies are available and certain jelly-like preparations are used for contraceptive purposes, which often contain surface-active agents to enhance the spermatocidal properties of the jelly. Aromatics, such as methyl salicylate and eucalyptol, often are added to give the preparation a desirable odor.

Jellies are prone to microbial contamination and therefore contain preservatives, eg, methyl *p*-hydroxybenzoate is used as a preservative in a base for medicated jellies. This base contains sodium alginate, glycerin, calcium gluconate and water. The calcium ions cause a cross-linking with sodium alginate to form a gel of firmer consistency. A discussion of gels is provided later in the chapter.

Nonaqueous Solutions

It is difficult to evaluate fairly the importance of nonaqueous solvents in pharmaceutical processes. That they are important in the manufacture of pharmaceuticals is an understatment. However, pharmaceutical preparations, and, in particular, those intended for internal use, rarely contain more than minor quantities of the organic solvents that are common to the manufacturing or analytical operation. For example, industry uses large quantities of chloroform in some operations but the solvent is of only minor importance with respect to the final product. One mL of chloroform dissolves in about 200 mL of water and the solution so formed finds some use as a vehicle (see the section on *Aromatic Waters*). Chloroform has been an ingredient in a number of cough syrups in the past but it has been banned in the US by the FDA in manufactured products intended for internal use. Solvents such as acetone, benzene and petroleum ether must not be ingredients in preparations intended for internal use.

Products of commerce may contain solvents such as ethanol, glycerin, propylene glycol, certain oils and liquid paraffin. Preparations intended for external use may contain ethanol, methanol, isopropyl alcohol, polyethylene glycols, various ethers and certain esters. A good example of preparations of this type are the rubefacient rubbing alcohols. Rubbing Alcohol must be manufactured in accordance with the requirements of the Bureau of Alcohol, Tobacco and Firearms, US Treasury Dept, using Formula 23-H denatured alcohol. This mixture contains 8 parts by volume of acetone, 1.5 parts by volume of methyl isobutyl ketone and 100 parts by volume of ethanol. Besides the alcohol in the Rubbing Alcohol, the final product must contain water, sucrose octaacetate or denatonium benzoate and may contain color additives, perfume oils and a suitable stabilizer. The alcohol content, by volume, is not less than 68.5% and not more than 71.5%. The isopropyl alcohol content in Isopropyl Rubbing Alcohol can vary from 68.0% to 72.0% and the finished product may contain color additives, perfume oils and suitable stabilizers.

Although the lines between aqueous and nonaqueous preparations tend to blur in those cases where the solvent is water-soluble, it is possible to categorize a number of products as nonaqueous. This section is, therefore, devoted to groups of nonaqueous solutions; the alcoholic or hydroalcoholic solutions (eg, elixirs and spirits), ethereal solutions (eg, collodions), glycerin solutions (eg, glycerins), oleaginous solutions (eg, liniments, oleovitamins and toothache drops), inhalations and inhalants.

Although this list is self-limiting, a wide variety of solvents are used in various pharmaceutical preparations. Solvents such as glycerol formal, dimethylacetamide and glycerol dimethylketal have been recommended for many products produced by the industry. However, the toxicity of many of these solvents is not well-established and, for this reason, careful clinical studies should be carried out on the formulated product before it is released to the marketplace.

It is essential that the toxicity of solvents be tested appropriately and approved in order to avoid problems: for example, the tragic loss of life which occurred during 1937 when diethylene glycol was used in an elixir of sulfanilamide. The result of this tragedy was the 1938 Federal Food, Drug and Cosmetic Act, which required that products be tested for both safety and effectiveness.

Collodions

Collodions are liquid preparations containing pyroxylin (a nitrocellulose) in a mixture of ethyl ether and ethanol. They are applied to the skin by means of a soft brush or other suitable applicator and, when the ether and ethanol have evaporated, leave a film of pyroxylin on the surface. The official medicated collodion, Salicylic Acid Collodion USP, contains 10% *w/v* of salicylic acid in Flexible Collodion USP and is used as a keratolytic agent in the treatment of corns and warts. Collodion USP and Flexible Collodion USP are water-repellent protectives for minor cuts and scratches. Collodion is made flexible by the addition of castor oil and camphor. Collodion has been used to reduce or eliminate the side effects of fluorouracil treatment of solar keratoses. Vehicles other than flexible collodion, such as a polyacrylic base, have been used to incorporate salicylic acid for the treatment of warts with less irritation.

Elixirs

Elixirs are clear, pleasantly flavored, sweetened hydroalcoholic liquids intended for oral use. They are used as flavors and vehicles such as Aromatic Elixir (page 1302) for drug substances and, when such substances are incorporated into the specified solvents, they are classified as medicated elixirs, eg, Dexamethasone Elixir USP and Phenobarbital Elixir USP. The main ingredients in elixirs are ethanol and water but glycerin, sorbitol, propylene glycol, flavoring agents, preservatives and syrups often are used in the preparation of the final product.

The distinction between some of the medicated syrups and elixirs is not always clear. For example, Ephedrine Sulfate Syrup USP contains between 20 and 40 mL of alcohol in 1000 mL of product. Ephedrine Elixir PC contains syrup and 100 mL of ethanol in the same final volume. Definitions are, therefore, inconsistent and, in some in-

stances, not too important with respect to the naming of the articles of commerce. The exact composition must, however, be known if the presence or absence of an ingredient (eg, sucrose) is of therapeutic significance or when an additional ingredient must be incorporated in the product.

Elixirs contain ethyl alcohol. However, the alcoholic content will vary greatly, from elixirs containing only a small quantity to those that contain a considerable portion as a necessary aid to solubility. For example, Aromatic Elixir USP contains 21 to 23% of alcohol; Compound Benzaldehyde Elixir, on the other hand, contains 3 to 5%.

Elixirs also may contain glycerin and syrup. These may be added to increase the solubility of the medicinal agent or for sweetening purposes. Some elixirs contain propylene glycol. Claims have been made for this solvent as a satisfactory substitute for both glycerin and alcohol. Sumner,[12] in his paper on terpin hydrate preparations, summarized the advantages and disadvantages of this solvent and suggested several formulations with therapeutic characteristics superior to those of the elixir described in NF XIII.

One usual dose of the elixir (5 mL) contains 85 mg of terpin hydrate. This substance is used in bronchitis in doses of 125 to 300 mg as an expectorant. Therefore, the elixir is ineffective for the treatment of bronchitis. However, it is used as a vehicle for the drugs in many commercially available cough syrups. These may contain dextromethorphan hydrobromide codeine phosphate, chlorpheniramine maleate, pyrilamine maleate, ammonium chloride, creosote and a wide variety of other drugs with expectorant and antitussive properties.

One of the four formulations described in Sumner's paper is given below:

Terpin Hydrate	6.0 g
Orange Oil	0.1 mL
Benzaldehyde	0.005 mL
Sorbitol Solution USP	10.0 mL
Propylene Glycol	40.0 mL
Alcohol	43.0 mL
Purified Water, a sufficient quantity, to make	100.0 mL

Dissolve the terpin hydrate in the propylene glycol and sorbitol solution which have been heated to 50°. Add the oil and the benzaldehyde to the alcohol and mix with the terpin hydrate solution at 25°. Add sufficient purified water to make the product measure 100 mL.

The elixir contains 300 mg of terpin hydrate/5 mL, a minimal quantity of alcohol and flavoring agents which adequately mask the taste of propylene glycol.

Although alcohol is an excellent solvent for some drugs, it does accentuate the saline taste of bromides and similar salts. It often is desirable, therefore, to substitute some other solvent that is more effective in masking such tastes for part of the alcohol in the formula. In general, if taste is a consideration, the formulator is more prone to use a syrup rather than a hydroalcoholic vehicle.

An elixir may contain water- and alcohol-soluble ingredients. If such is the case, the following procedure is indicated:

Dissolve the water-soluble ingredients in part of the water. Add and solubilize the sucrose in the aqueous solution. Prepare an alcoholic solution containing the other ingredients. Add the aqueous phase to the alcoholic solution, filter and make to volume with water.

Sucrose increases viscosity and decreases the solubilizing properties of water and so must be added after primary solution has been effected. A high alcoholic content is maintained during preparation by adding the aqueous phase to the alcoholic solution. Elixirs always should be brilliantly clear. They may be strained or filtered and, if necessary, subjected to the clarifying action of purified talc or siliceous earth.

One of the former official elixirs, Iso-Alcoholic Elixir NF XV (page 1328), actually is a combination of two solutions, one containing 8 to 10% ethanol and the other containing 73 to 78%. It is used as a vehicle for various medicaments that require solvents of different alcoholic strengths. For example, the alcoholic strength of the elixir to be used with a single liquid galenical is approximately the same as that of the galenical. When different alcoholic strengths are employed in the same prescription, the elixir to be used is the one that produces the best solution. This is usually the average of the alcoholic strengths of the several ingredients. For nonextractive substances, the lowest alcoholic strength of elixir that will produce a clear solution should be selected.

The formula for High-Alcoholic Elixir is:

Compound Orange Spirit	4 mL
Saccharin	3 g
Glycerin	200 mL
Alcohol, a sufficient quantity, to make	1000 mL

This elixir, and many other liquid preparations intended for internal use (eg, the diabetic syrups thickened with sodium carboxymethylcellulose or similar substances) contain saccharin. During the past few years, scientists have studied the toxic effects of this sweetening agent and of the cyclamates. The cyclamate studies showed that the sweetener could produce cancer in animals and, as a result, this substance was removed from a wide variety of products. Similar studies have been carried out on saccharin.

Cyclamates and saccharin have been banned in some countries as ingredients in manufactured products. Much reserch has been done to find a safe synthetic substitute for sucrose. As a result, aspartame (methyl *N*(-L-α-aspartyl)-L-phenylalaninate), which is about 200 times sweeter than sucrose, is being used now in many commercial preparations as the sweetening agent. It is sparingly soluble in water and is most stable at a pH of 4.3. This compound likely will be used in a number of pharmaceutical formulations in the future.[13]

Incompatibilities—Since elixirs contain alcohol, incompatibilities of this solvent are an important consideration during formulation. Alcohol precipitates tragacanth, acacia and agar from aqueous solutions. Similarly, it will precipitate many inorganic salts from similar solutions. The implication here is that such substances should be absent from the aqueous phase or present in such concentrations that there is no danger of precipitation on standing.

If an aqeous solution is added to an elixir, a partial precipitation of ingredients may occur. This is due to the reduced alcoholic content of the final preparation. Usually, however, the alcoholic content of the mixture is not sufficiently decreased to cause separation. As vehicles for tinctures and fluidextracts, the elixirs generally cause a separation of extractive matter from these products due to a reduction of the alcoholic content.

Many of the incompatibilities between elixirs, and the substances combined with them, are due to the chemical characteristics of the elixir *per se*, or of the ingredients in the final preparation. Thus, certain elixirs are acid in reaction while others may be alkaline and will, therefore, behave accordingly.

Glycerins

Glycerins or glycerites are solutions or mixtures of medicinal substances in not less than 50% by weight of glycerin. Most of the glycerins are extremely viscous and some are of a jelly-like consistency. Few of them are used extensively.

Glycerin is a valuable pharmaceutical solvent forming permanent and concentrated solutions not otherwise obtainable. Some of these solutions are used in their original form as medicinal agents while others are used to prepare aqueous and alcoholic dilutions of substances which are not readily soluble in water or alcohol. Antipyrine and Benzocaine Otic Solution USP was discussed previously under *Otic Solutions*. One of the glycerins, Phenol Glycerin PC is diluted with glycerin to form the pharmaceutical preparation, Phenol Ear-Drops PC.

Phenol Glycerin PC

Phenol	**160 g**
Glycerin	**840 g**

Dissolve the phenol in the glycerin.

Phenol Ear-Drops PC

Phenol Glycerin	**40 mL**
Glycerin, a sufficient quantity, to make	**100 mL**

Water must not be added to this preparation. It reacts with the phenol to produce a preparation which is caustic and, consequently, damaging to the area of application. This product no longer is recommended because of the possibility of necrosis and perforation of the tympanic membrane. As noted under *Otic Solutions*, glycerin alone is used to aid in the removal of cerumen.

Sodium Bicarbonate Ear-Drops PC may be used if wax is to be removed from the ear. This preparation contains sodium bicarbonate (5 g), glycerin (30 mL) and purified water (a sufficient quantity to make 100 mL). A glycerin base was chosen as the optimum solvent for an otic preparation in a study involving the stability and antimicrobial activity of kanamycin sulfate otic drops.

Starch Glycerin, an emollient, contains starch (100 g), benzoic acid (2 g), purified water (200 mL) and glycerin (700 mL).

Glycerins are hygroscopic and should be stored in tightly closed containers.

Inhalations and Inhalants

Inhalations

These preparations are so used or designed that the drug is carried into the respiratory tree of the patient. The vapor or mist reaches the affected area and gives prompt relief from the symptoms of bronchial and nasal congestion. The USP defines Inhalations in the following way:

> Inhalations are drugs or solutions of drugs administered by the nasal or oral respiratory route for local or systemic effect. Examples in this Pharmacopeia are Epinephrine Inhalation and Isoproterenol Hydrochloride Inhalation. Nebulizers are suitable for the administration of inhalation solutions only if they give droplets sufficiently fine and uniform in size so that the mist reaches the bronchioles.
>
> Another group of products, also known as inhalations, and sometimes called insufflations, consists of finely powdered or liquid drugs that are carried into the respiratory passages by the use of special delivery systems, such as pharmaceutical aerosols, that hold a solution or suspension of the drug in a liquefied gas propellant (see Aerosols). When released through a suitable valve and oral adapter, a metered dose of the inhalation is propelled into the respiratory tract of the patient. Powders also may be administered by mechanical devices that require a manually produced pressure or a deep inspiration by the patient, eg, *Cromolyn Sodium*.
>
> Solutions may be nebulized by use of inert gases. Nebulized solutions may be breathed directly from the nebulizer, or the nebulizer may be attached to a plastic face mask, tent or intermittent positive-pressure breathing (IPPB) machine.

As stated in the USP, particle size is of major importance in the administration of this type of preparation. The various mechanical devices that are used in conjunction with inhalations are described in some detail in Chapter 104. It has been reported that the optimum particle size for penetration into the pulmonary cavity is of the order of 0.5 to 7 μm. Fine mists are produced by pressurized aerosols and hence possess basic advantages over the older nebulizers; in addition, metered aerosols deliver more uniform doses. See Chapter 92.

The term *Inhalation* is used commonly by the layman to represent preparations intended to be vaporized with the aid of heat, usually steam, and inhaled. Benzoin Inhalation PC contains benzoin, storax and alcohol. The vapors from a preparation containing 1 teaspoonful of the tincture and 1 qt of boiling water may be inhaled. The device known as a *vaporizer* is used with a number of commercially available preparations of this type.

Epinephrine Inhalation and Isoproterenol Hydrochloride Inhalation are described in the USP.

Inhalants

The USP defines inhalants as follows:

> A special class of inhalations termed "inhalants" consists of drugs or combinations of drugs that, by virtue of their high vapor pressure, can be carried by an air current into the nasal passage where they exert their effect. The container from which the inhalant is administered is known as an inhaler.

Propylhexedrine Inhalant and Tuaminoheptane Inhalant consist of cylindrical rolls of suitable fibrous material impregnated with propylhexedrine or tuaminoheptane (as carbonate), usually aromatized, and contained in a suitable inhaler. Propylhexedrine is the active ingredient in the widely used Benzedrex Inhaler. Both of these drugs are vasoconstrictors used to relieve nasal congestion. Inhalers which come in contact with the mouth or nasal passages become contaminated by bacteria, thus, they should be restricted to personal use.

Another inhalant is Amyl Nitrite USP which is very flammable and should not be used where it may be ignited. It is packaged in sealed glass vials in a protective gauze. Upon breaking the vial, the gauze absorbs the drug which is then inhaled for the treatment of anginal pain. See page 843.

Liniments

Liniments are solutions or mixtures of various substances in oil, alcoholic solutions of soap or emulsions. They are intended for external application and should be so labeled. They are rubbed onto the affected area and, because of this, were once called *embrocations*. Dental liniments, which are no longer official, are solutions of active substances and are rubbed into the gums. Most dentists question their usefulness and, consequently, this type of preparation is relatively unimportant as a pharmaceutical form.

Liniments usually are applied with friction and rubbing of the skin, the oil or soap base providing for ease of application and massage. Alcoholic liniments are used generally for their rubefacient, counterirritant, mildly astringent and penetrating effects. Such liniments penetrate the skin more readily than do those with an oil base. The oily liniments, therefore, are milder in their action but are more useful when massage is required. Depending on their ingredients, such liniments may function solely as protective coatings. Liniments should not be applied to skin that is bruised or broken.

Many of the marketed "white" liniments are based on the formulation below or variations thereof.

White Liniment PC

Ammonium Chloride	**12.5 g**
Dilute Ammonia Solution	**45 mL**
Oleic Acid	**85 mL**

Turpentine Oil	250	mL
Water for Preparations	625	mL

Mix the oleic acid with the turpentine oil. Add the dilute ammonia solution mixed with 45 mL of previously warmed water and shake. Dissolve the ammonium chloride in the remainder of the water, add to the emulsion and mix.

Other liniments contain antipruritics, astringents, emollients or analgesics and are classified on the basis of their active ingredient. An example is:

Compound Calamine Application PC
(Compound Calamine Liniment)

Calamine	100 g
Zinc Oxide	50 g
Wool Fat	25 g
Zinc Stearate	25 g
Yellow Soft Paraffin	250 g
Liquid Paraffin	550 g

The powders are triturated to a smooth paste with some of the liquid paraffin (Liquid Petrolatum). The wool fat, zinc stearate and yellow soft paraffin (Petrolatum) are melted, mixed with some of the liquid paraffin, the mixture incorporated with the triturated powders and the rest of the liquid paraffin added with mixing.

Dermatologists prescribe products of this type but only those containing the rubefacients are advertised extensively and used by consumers for treating minor muscular aches and pains.

Because of the confusion of camphorated oil (camphor liniment) with castor oil, which has resulted in ingestion and, perhaps, to poisoning, camphorated oil has been banned from the market. It is essential that these applications be marked clearly for external use only. (Camphorated Oil presently is classified as a new drug by the FDA.)

Oleovitamins

Oleovitamins are fish-liver oils diluted with edible vegetable oil or solutions of the indicated vitamins or vitamin concentrates (usually vitamin A and D) in fish-liver oil. The definition is broad enough to include a wide variety of marketed products.

Oleovitamin A and D is official; vitamin D may be present as ergocalciferol or cholecalciferol obtained by the activation of ergosterol or 7-dehydrocholesterol or may be obtained from natural sources. Synthetic vitamin A, or a concentrate, may be used to prepare oleovitamin A. The starting material for the concentrate is a fish-liver oil, the active ingredient being isolated by molecular distillation or by a saponification and extraction procedure. The latter procedure is described in detail in the monograph for Concentrated Vitamin A Solution PC.

These vitamins are unstable in the presence of rancid oils and, therefore, these preparations and, in particular, Oleovitamin A, should be stored in small, tight containers, preferably under vacuum or under an atmosphere of an inert gas, protected from light.

Spirits

Spirits, popularly known as essences, are alcoholic or hydroalcoholic solutions of volatile substances. Like the aromatic waters, the active ingredient in the spirit may be a solid, liquid or gas. The genealogical tree for this class of preparations begins with the distinguished pair of products, Brandy (*Spiritus Vini Vitis*) and Whisky (*Spiritis Frumenti*), and ends with a wide variety of products that comply with the definition given above. Physicians have debated the therapeutic value of the former products and these are no longer official in the compendia.

Some of these spirits are used internally for their medicinal value, a few medicinally by inhalation and a large number as flavoring agents. The latter group provides a convenient and ready means of obtaining the volatile oil in the proper quantity. For example, a spirit or spirit-like preparation may be used in the formulation of aromatic waters or other pharmaceuticals that require a distinctive flavor.

Spirits should be stored in tight, light-resistant containers and in a cool place. This prevents evaporation and volatilization of either the alcohol or the active principle.

Preparation—There are four classic methods of preparation:

Simple Solution—This is the method by which the majority of spirits are prepared. The formula and procedure given for Aromatic Ammonia Spirit USP illustrate this method of preparation.

Aromatic Ammonia Spirit USP

Ammonium Carbonate, in translucent pieces	34 g
Strong Ammonia Solution	36 mL
Lemon Oil	10 mL
Lavender Oil	1 mL
Nutmeg Oil	1 mL
Alcohol	700 mL
Purified Water, a sufficient quantity to make	1000 mL

Dissolve the ammonium carbonate in the strong ammonia solution and 195 mL of purified water by gentle agitation and allow the solution to stand for 12 hours. Dissolve the oils in the alcohol, contained in a graduated bottle or cylinder, and gradually add the ammonium carbonate solution and enough purified water to make the product measure 1000 mL. Set the mixture aside in a cool place for 24 hours, occasionally agitating it, then filter, using a covered funnel.

The spirit is a respiratory stimulant and is administered by inhalation of the vapor as required. It is marketed in suitable tight, light-resistant containers but is also available in a single-dose glass vial wrapped in a soft cotton envelope. The vial is broken easily; the cotton acts as a sponge for the spirit.

Ammonium carbonate is a mixture of ammonium bicarbonate and ammonium carbamate (NH_2COONH_4). The carbamate reacts with water to form the carbonate. An ammonium carbonate solution is, therefore, a solution of ammonium bicarbonate and ammonium carbonate in water. However, it decomposes in water, the decomposition products being ammonia, carbon dioxide and water. The stability of the spirit is improved by the addition of strong ammonia solution. This represses the hydrolysis of ammonium carbonate and, in this way, decreases the loss of dissolved gases.

Solution with Maceration—In this procedure, the leaves of a drug are macerated in purified water to extract water-soluble matter. They are expressed and the moist, macerated leaves are added to a prescribed quantity of alcohol. The volatile oil is added to the filtered liquid. Peppermint Spirit USP is made by this process. Peppermint Spirit PC differs from the official product in that it is a solution of the volatile oil in alcohol only. The concentration of volatile oil in the final product is about the same but the official preparation possesses a green color. The ready availability of soluble chlorophyll and other coloring agents had led to the frequent suggestion that a more uniform product could be obtained through their use. However, these agents cannot be used in preparing the official article.

The formula and procedure for Peppermint Spirit USP (page 798) illustrate this method of preparation.

Chemical Reaction—No official spirits are prepared by this process. Ethyl nitrite is made by the action of sodium nitrite on a mixture of alcohol and sulfuric acid in the cold. This substance then is used to prepare Ethyl Nitrite Spirit, a product no longer official.

Distillation—Brandy and Whisky are made by distillation. The latter is derived from the fermented mash of wholly or partially germinated malted cereal grains and the former from the fermented juice of ripe grapes.

Incompatibilities—Spirits are, for the most part, preparations of high alcoholic strength and do not lend themselves well to dilution with aqueous solutions or liquids of low alcoholic content. The addition of such a solution invariably causes separation of some of the material dissolved in the spirit, evidenced by a turbidity which, in time, may disappear as distinct layering occurs. Salts may be precipi-

tated from their aqueous solutions by the addition of spirits due to their lesser solubility in alcoholic liquids.

Some spirits show incompatibilities characteristic of the ingredients they contain. For example, Aromatic Ammonia Spirit cannot be mixed with aqueous preparations containing alkaloids (eg, codeine phosphate). An acid-base reaction (ammonia-phosphate) occurs and, if the alcohol content of the final mixture is too low, codeine will precipitate.

Toothache Drops

Toothache drops are preparations used for temporary relief of toothache by application of a small pledget of cotton saturated with the product into the tooth cavity. Anesthetic compounds include clove oil, eugenol or benzocaine; other ingredients include camphor, creosote, menthol and alcohol.

These preparations no longer are recognized officially. Furthermore, dentists do not recommend the use of toothache drops if the patient has ready access to adequate dental services. The preparations may damage the gums and produce complications more severe than the original toothache. However, many areas do not have adequate dental services and the pharmacist will, of necessity, handle these preparations, and he should warn the patient of possible hazards associated with their use.

Toothache Drops NF XI contains 25 g of chlorobutanol in sufficient clove oil to make the product measure 100 mL. Another formulation contains creosote, clove oil, benzocaine and alcohol in a flexible collodion base.

Emulsions

An emulsion is a two-phase system prepared by combining two immiscible liquids, one of which is dispersed uniformly throughout the other and consists of globules that have diameters equal to or greater than those of the largest colloidal particles. The globule size is critical, of course, and must be such that the system achieves maximum stability. However, even under the best conditions, separation of the two phases will occur unless a third substance, an *emulsifying agent*, is incorporated. The basic emulsion must, therefore, contain three components, but the products of commerce may consist of a number of therapeutic agents dissolved in either of the two phases.

Most emulsions incorporate an aqueous phase into a nonaqueous phase (or *vice versa*). However, it is possible to prepare emulsions that are basically nonaqueous. For example, investigations of the emulsifying effects of anionic and cationic surfactants on the nonaqueous immiscible system, glycerin and olive oil, have shown that certain amines and three cationic agents produced stable emulsions. This broadening of the basic definition for the term *emulsion* is recognized in the USP.

An emulsion is a two-phase system in which one liquid is dispersed in the form of small droplets throughout another liquid. The dispersed liquid is known as the internal or discontinuous phase, whereas the dispersion medium is known as the external or continuous phase. Where oil is the dispersed phase and an aqueous solution is the continuous phase, the system is designated as an oil-in-water (O/W) emulsion and can be diluted easily and uniformly with water. Conversely, where water, or an aqueous solution is the dispersed phase, and oil, or oleaginous material, is the continuous phase, the system is designated as a water-in-oil (W/O) emulsion.

Many emulsifying agents (or emulsifiers) are available, among them the following:

Natural Emulsifying Agents—These substances may be derived from either animal or vegetable sources. Examples of those obtained from the former source are gelatin, egg yolk, casein, wool fat or cholesterol. Acacia, tragacanth, chondrus or pectin are representative of those obtained from vegetable sources. Various cellulose derivatives, eg, methylcellulose and carboxymethylcellulose, are used to increase the viscosity of the aqueous phase and thereby enhance emulsion stability.

Finely Divided Solids—Examples are bentonite, magnesium hydroxide, aluminum hydroxide or magnesium trisilicate.

Synthetic Emulsifying Agents—This group may be subdivided further into the anionic, cationic or nonionic agents. Examples are, in order of presentation, sodium lauryl sulfate, benzalkonium chloride or polyethylene glycol 400 monostearate.

Many of these emulsifying agents are described in greater detail in Chapter 66.

In NF XIII it was suggested that only O/W emulsions are suitable for oral use because these are water-miscible and thus their oiliness is masked. This compendium gave specific directions for the preparation of emulsions using gelatin as an emulsifying agent. These preparations are based on either type A or type B gelatin.

Type A gelatin is prepared by acid-treated precursors and is used at a pH of about 3.2. It is incompatible with anionic emulsifying agents such as the vegetable gums. The following formula was recommended:

Gelatin (Type A)	8 g
Tartaric Acid	0.6 g
Flavor as desired	
Alcohol	60 mL
Oil	500 mL
Purified Water, to make	1000 mL

Add the gelatin and the tartaric acid to about 300 mL of purified water, allow to stand for a few minutes, heat until the gelatin is dissolved, then raise the temperature to about 98° and maintain this temperature for about 20 min. Cool to 50°, add the flavor, the alcohol and sufficient purified water to make 500 mL. Add the oil, agitate the mixture thoroughly and pass it through a homogenizer or a colloid mill until the oil is dispersed completely and uniformly.

This emulsion cannot be prepared by trituration or by the use of the usual stirring devices.

Type B gelatin is prepared from alkali-treated precursors and is used at a pH of about 8.0. It may be used with other anionic emulsifying agents but is incompatible with cationic types. If the emulsion contains 50% oil, 5 g of Type B gelatin, 2.5 g of sodium bicarbonate and sufficient tragacanth or agar should be incorporated into the aqueous phase to yield 1000 mL of product of the required viscosity.

The emulsion type (O/W or W/O) is of lesser significance if the final preparation is to be applied to the skin. If there are no breaks in the skin, a W/O emulsion can be applied more evenly since the skin is covered with a thin film of sebum. The latter substance favors the oily phase and contributes to the ease of application. The choice of emulsion type will, however, depend on many other factors. This particularly is true for those preparations which have basic cosmetic characteristics. It may be advantageous to formulate an O/W emulsion if ease of removal is an important consideration to the patient.

An emulsion that may be prepared by the mortar and pestle method is the following Mineral Oil Emulsion USP.

Mineral Oil	500 mL
Acacia, in very fine powder	125 g
Syrup	100 mL
Vanillin	40 mg
Alcohol	60 mL
Purified Water, a sufficient quantity	1000 mL

The mineral oil and acacia are mixed in a dry Wedgwood mortar. Water (250 mL) is added and the mixture triturated vigorously until an emulsion is formed. A mixture of the syrup, 50 mL of purified water and the vanillin dissolved in alcohol is added in divided portions with trituration; sufficient purified water is then added to the proper volume, the mixture mixed well and homogenized.

Very few emulsions are included now in the official compendia. The PC suggests that the term "emulsion" be restricted to preparations, usually O/W, intended for internal use and contains the following: Liquid Paraffin Emulsion, Liquid Paraffin and Magnesium Hydroxide Emulsion, Liquid Paraffin and Phenolphthalein Emulsion and Concentrated Peppermint Emulsion.

This, however, should not lead the reader to the conclusion that emulsions are a relatively unimportant class of pharmaceuticals. While it is true that few preparations carry the term *emulsion* in their titles, they are of great significance as bases for other types of preparations, particularly in the dermatological and cosmetic areas. Academically, they illustrate the importance of the relationship between the theory and practice of emulsion technology and, practically, they possess a number of important advantages over other liquid forms. These may be summarized in the following way:

1. In an emulsion, the therapeutic properties and the spreading ability of the constituents are increased.
2. The unpleasant taste or odor of an oil can be masked partially or wholly, by emulsification. Secondary masking techniques are available to the formulator but these must be used with caution. If flavors and sweetening agents are added to the emulsion, only minimal amounts should be used in order to prevent the nausea or gastric distress that results on ingestion of larger quantities of these.
3. The absorption and penetration of medicaments are controlled more easily if they are incorporated into an emulsion.
4. Emulsion action is prolonged and the emollient effect is greater than that observed with comparable preparations.
5. Water is an inexpensive diluent and a good solvent for the many drugs and flavors that are incorporated into an emulsion.

The effects of viscosity, surface tension, solubility, particle size, complexation and excipients on the bioavailability of oral suspensions and emulsions have been discussed in detail by Rettig.[14]

The aqueous phase of the emulsion favors the growth of microorganisms and, because of this, a preservative usually is added to the product. Some of the preservatives that have been used include chlorocresol, chlorobutanol, mercurial preparations, salicylic acid, the esters of *p*-hydroxybenzoic acid, benzoic acid, sodium benzoate or sorbic acid. The preservative should be selected with regard for the ultimate use of the preparation and possible incompatibilities between the preservative and the ingredients in the emulsion, eg, binding between the surface-active agent and the preservative. Low pH values of 5 to 6 and low concentrations of water are characteristics also likely to inhibit microbiological growth in emulsions.

Most emulsions consist of a nonaqueous (or oil or lipid) phase and an aqueous (or water) phase, thus some of the preservative may pass into the oil phase and be removed from the aqueous phase. It is in the aqueous phase that microorganisms tend to grow. As a result, water-soluble preservatives are more effective since the concentration of the unbound preservative in the aqueous phase assumes a great deal of importance in inhibiting the microbial growth. Esters of *p*-hydroxybenzoic acid appear to be the most satisfactory preservatives for emulsions. Many mathematical models have been used to determine the availability of preservatives in emulsified systems. However, because of the number of factors which reduce the effectiveness of the preservative, a final microbiological evaluation of the emulsion should be performed.

While emphasis concerning preservation of emulsions deals with the aqueous phase, microorganisms can reside also in the lipid phase. Consequently, it has been recommended that pairs of preservatives be used to ensure adequate concentration in both phases. Esters of *p*-hydroxybenzoic acid can be used to ensure appropriate concentrations in both phases because of their difference in oil and water solubilities.

An emulsion can be diluted with the liquid that constitutes, or is miscible with, the external phase. The diluting liquid, however, will decrease the viscosity of the preparation and, in certain instances, invert the emulsion. The latter phenomena may occur if the emulsifier-in-water method (see below) is used to prepare the emulsion.

Preparation

The theory of emulsion preparation is discussed in Chapter 19. The following procedures are those suggested by Griffin *et al.*[15]

The formulator must first determine the physical and chemical characteristics of the active ingredient. He must know the following:

1. Structural formula
2. Melting point
3. Solubility
4. Stability
5. Dose
6. Specific chemical incompatibilities

It also is necessary, at this stage, to decide on the type of emulsion required. Washable emulsions are of the O/W type; nonwashable, the W/O type. In general, O/W emulsions contain over 70% water. W/O emulsions usually will contain higher concentrations of oils and waxes. The preparation of cream and ointment emulsions for topical use is given in Chapter 87.

Experimental formulations may be prepared by the following procedure:

1. Group the ingredients on the basis of their solubilities in the aqueous and nonaqueous phases.
2. Determine the type of emulsion required and calculate an approximate HLB (hydrophile-lipophile balance) value.
3. Blend a low HLB emulsifier and a high HLB emulsifier to the calculated value. For experimental formulations, use a higher concentration of emulsifier (eg, 10 to 30% of the oil phase) than that required to produce a satisfactory product. Emulsifiers should, in general, be stable chemically, nontoxic and suitably low in color, odor and taste. The emulsifier is selected on the basis of these characteristics, the type of equipment being used to blend the ingredients and the stability characteristics of the final product. Emulsions should not coalesce at room temperature, when frozen and thawed repeatedly or at elevated temperatures of up to 50°. Mechanical energy input varies with the type of equipment used to prepare the emulsion. The more the energy input, the less the demand on the emulsifier. Both process and formulation variables can affect the stability of an emulsion.
4. Dissolve the oil-soluble ingredients and the emulsifiers in the oil. Heat, if necessary, to approximately 5° to 10° over the melting point of the highest melting ingredient or to a maximum temperature of 70° to 80°.
5. Dissolve the water-soluble ingredients (except acids and salts) in a sufficient quantity of water.
6. Heat the aqueous phase to a temperature which is 3° to 5° higher than that of the oil phase.
7. Add the aqueous phase to the oily phase with suitable agitation.
8. If acids or salts are employed, dissolve them in water and add the solution to the cold emulsion.
9. Examine the emulsion and make adjustments in the formulation if the product is unstable. It may be necessary to add more emulsifier, to change to an emulsifier with a slightly higher or lower HLB value or to use an emulsifier with different chemical characteristics.

The technique of emulsification of pharmaceutical preparations has been described by White.[16] The preparation of an emulsion requires work to reduce the internal phase into small droplets and disperse them through the external phase. This can be accomplished by a mortar and pestle or a high-speed emulsifier. The addition of emulsifying agents not only reduces this work but also stabilizes the final emulsion. Emulsions may be prepared by four principle methods.

Addition of Internal Phase to External Phase—This is usually the most satisfactory method for preparing emulsions since there is always an excess of the external phase present which promotes the type of emulsion desired. If the external phase is water and the interal phase is oil, the water-soluble substances are dissolved in the water and the oil-

soluble substances mixed thoroughly in the oil. The oil mixture is added in portions to the aqueous preparation with agitation. Sometimes, in order to give a better shearing action during the preparation, all of the water is not mixed with the emulsifying agent until the primary emulsion with the oil is formed; subsequently, the remainder of the water is added. An example using gelatin Type A is given above.

Addition of the External Phase to the Internal Phase—Using an O/W emulsion as an example, the addition of the water (external phase) to the oil (internal phase) will promote the formation of a W/O emulsion due to the preponderance of the oil phase. After further addition of the water, phase inversion to an O/W emulsion should take place. This method especially is useful and successful when hydrophilic agents such as acacia, tragacanth or methylcellulose are first mixed with the oil, effecting dispersion without wetting. Water is added and, eventually, an O/W emulsion is formed. This "dry gum" technique is a rapid method for preparing small quantities of emulsion. The ratio 4 parts of oil, 2 parts of water and 1 part of gum provides maximum shearing action on the oil globules in the mortar. The emulsion then can be diluted and triturated with water to the appropriate concentrations. The preparation of Mineral Oil Emulsion described above is an example.

Mixing Both Phases after Warming Each—This method is used when waxes or other substances which require melting are used. The oil-soluble emulsifying agents, oils and waxes are melted and mixed thoroughly. The water-soluble ingredients dissolved in the water are warmed to a temperature slightly higher than the oil phase. The two phases then are mixed and stirred until cold. For convenience, but not necessity, the aqueous solution is added to the oil mixture. This method frequently is used in the preparation of ointments and creams.

Alternate Addition of the Two Phases to the Emulsifying Agent—A portion of the oil, if an O/W emulsion is being prepared, is added to all of the oil-soluble emulsifying agents with mixing, then an equal quantity of water containing all the water-soluble emulsifying agents is added with stirring until the emulsion is formed. Further portions of the oil and water are added alternately until the final product is formed. The high concentration of the emulsifying agent in the original emulsion makes the initial emulsification more likely and the high viscosity provides effective shearing action leading to small droplets in the emulsion. This method often is used successfully with soaps.

Multiple Emulsions—A recent innovation in emulsion technology is the development of multiple emulsions. The dispersed phase of these emulsions contains even smaller droplets which are miscible with the continuous phase. Thus, the multiple emulsion may be O/W/O where the aqueous phase is between two oil phases, or W/O/W where the internal and external aqueous phases are separated by an oil phase. In these systems both hydrophobic and hydrophilic emulsifiers are used and both have an effect on the yield and stability, as noted by Florence and Whitehill.[17]

It appears that O/W/O emulsions are formed better by lipophilic, nonionic surfactants using gum acacia-emulsified simple systems, while W/O/W multiple emulsions were formed better by nonionic surfactants in a two-stage emulsification procedure. A specific formulation for a W/O/W emulsion may be prepared by forming the primary (W/O) emulsion from isopropyl myristate (47.5%), sorbitan monooleate (2.5%) and distilled water (100%). This primary emulsion (50%) is added to a polyoxyethylene sorbitan monooleate (2% *w/v*) solution in water. While the technique of preparing these emulsions is more complicated, research indicates potential use of these emulsions for prolonged action, taste-masking, more effective dosage forms, parenteral preparations, protection against the external environment and enzyme entrapment.

Microemulsions—The coarse pharmaceutical macroemulsions appear white and tend to separate on standing. Microemulsions are translucent or transparent, do not separate and have a droplet diameter in the nanometer size range. The microemulsions are not always distinguishable from micellar solutions.

Both O/W and W/O types are possible and may be converted, one to the other, by adding more of the internal phase or by altering the type of emulsifier. As the internal phase is added, the emulsion will pass through a viscoelastic gel stage; with further addition, an emulsion of the opposite type will occur.

The most obvious benefit of microemulsions is their stability, thus providing dose uniformity. Usually, the emulsifier should be 20 to 30% of the weight of the oil used. The W/O systems are prepared by blending the oil and emulsifier with a little heat, if required, and then adding the water. The order of mixing for O/W systems is more flexible. One of the simplest methods is to blend the oil and the emulsifier and pour this into water with a little stirring. In no case can a microemulsion be formed unless there is a match between the oil and emulsifier.

If the emulsifier has been selected properly, microemulsification will occur almost spontaneously, leading to a satisfactory and stable preparation. The details of various preparations and the relationship between microemulsions and micellar solutions have been reviewed by Prince *et al.*[18] Microemulsions containing hydrocortisone have been prepared.

Equipment

When emulsions are prepared, energy must be expended to form an interface between the oily and aqueous phases. Emulsification equipment includes, therefore, a wide variety of agitators, homogenizers, colloid mills, jet mixers and ultrasonic devices. Griffin *et al*,[15] Becher[19] and Peck *et al*,[20] have evaluated the emulsification equipment used by pharmacists and drug manufacturers. These publications, along with journals such as *Pharmaceutical Technology*, should be consulted for further details on the use of such apparatus.

The preparation of emulsions on a large scale usually requires the expenditure of considerable amounts of energy for heating and mixing. Careful consideration of these processes has led to the development of low-energy emulsification by using an appropriate emulsification temperature and selective heating of the ingredients. This process, described by Lin,[21] involves the preparation of an emulsion concentrate subsequently diluted with the external phase at room temperature.

Agitators—Ordinary agitation or shaking may be used to prepare the emulsion. This method frequently is employed by the pharmacist, particularly in the emulsification of easily dispersed, low-viscosity oils. Under certain conditions, intermittent shaking is considerably more effective than ordinary continuous shaking. Continuous shaking tends to break up not only the phase to be dispersed but also the dispersion medium and, in this way, impairs the ease of emulsification. Laboratory shaking devices may be used for small-scale production.

The mortar and pestle are used widely by the prescription pharmacist in the extemporaneous preparation of emulsions. This equipment has very definite limitations because its usefulness depends largely on the viscidity of the emulsifying agent. A mortar and pestle cannot be used to prepare an emulsion if the emulsifying agent lacks viscidity (eg, gelatin solutions). These emulsifying agents will produce stable emulsions only if other types of equipment are used to mix the ingredients and the agent together.

Small electric mixers may be used to prepare emulsions at the prescription counter. They will save time and energy and produce satisfactory emulsions when the emulsifying agent is acacia or agar. However, the mixers cannot be used if the emulsifying agent is gelatin.

The commercially available *Waring Blendor* disperses efficiently by means of the shearing action of rapidly rotating blades. It transfers large amounts of energy and incorporates air into the emulsion. If an emulsion first is produced by using a blender of this type, the formulator must remember that the emulsion characteristics obtained in the laboratory will not be duplicated necessarily by the production-size agitators.

Production-size agitators include high-powered propeller-shaft stirrers immersed in a tank or self-contained units with

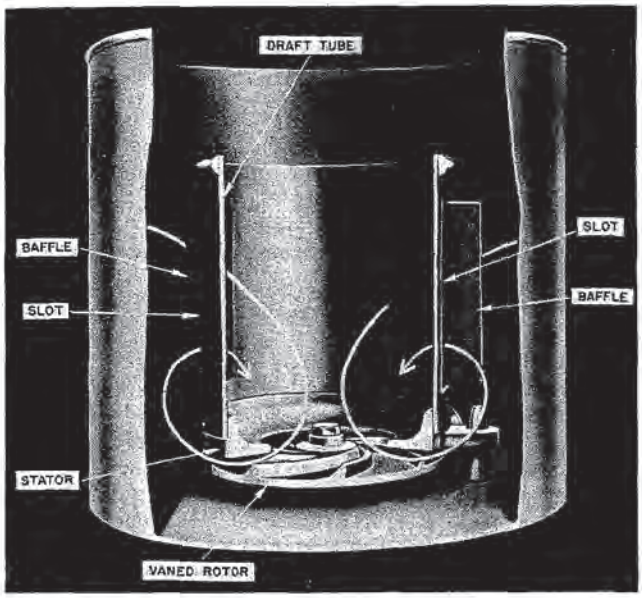


Fig 83-2. Standard slurry-type dispersall mixer with vaned-rotor "mixing" element and slotted draft-tube circulating element (courtesy, Abbe Eng).

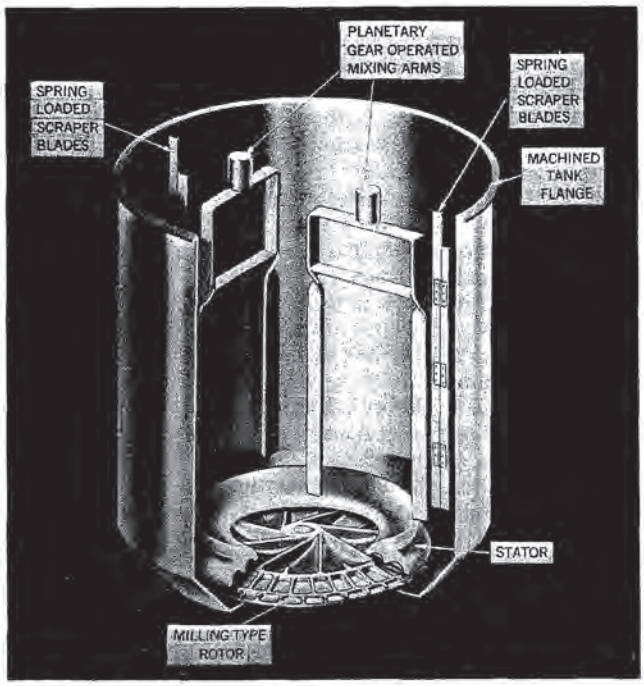


Fig 83-3. Standard paste-type dispersall mixer with "cupped-rotor" milling element and double-rotating mixing arm circulating element (courtesy, Abbe Eng).

propeller and paddle systems. The latter usually are constructed so that the contents of the tank either may be heated or cooled during the production process. Baffles often are built into a tank and these increase the efficiency of agitation. Two mixers manufactured by the same company are shown in Figs 83-2 and 83-3.

Colloid Mills—The principle of operation of the colloid mill is the passage of the mixed phases of an emulsion formula between a stator and a high-speed rotor revolving at speeds of 2000 to 18,000 rpm. The clearance between the rotor and the stator is adjustable, usually from 0.001 in upward. The emulsion mixture, in passing between the rotor and stator, is subjected to a tremendous shearing ac-

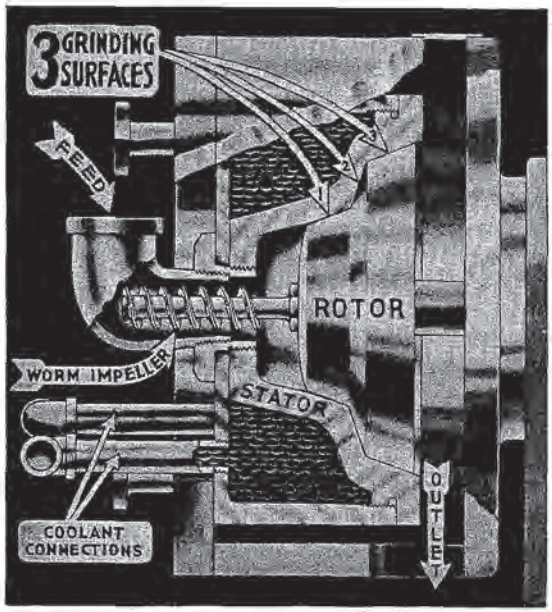


Fig 83-4. A colloid mill shown in cross section (courtesy, Tri-Homo).

Fig 83-5. Types of rotors used in colloid mills. These may be smooth (for most emulsions), serrated (for ointments and very viscous products) or of vitrified stone (for the paints and pigment dispersions) (courtesy, Tri-Homo).

tion which effects a fine dispersion. A colloid mill and various rotors are shown in Figs 83-4 and 83-5. The operating principle is the same for all, but each manufacturer incorporates specific features which result in changes in operating efficiency. The shearing forces applied in the colloid mill may result in a temperature increase within the emulsion. It may be necessary, therefore, to cool the equipment when the emulsion is being produced.

Homogenizers and Viscolizers—In these two types of equipment the mixed phases are passed between a finely ground valve and seat under high pressure. This, in effect, produces an atomization which is enhanced by the impact received by the atomized mixture as it strikes the valve head. They operate at pressures of 1000 to 5000 psi and produce some of the finest dispersions obtainable in an emulsion.

Homogenizers may be used in one of two ways:

1. The ingredients in the emulsion are mixed and then passed through the homogenizer to produce the final product.
2. An emulsion is prepared in some other way and then passed through a homogenizer for the purpose of decreasing the particle size and obtaining a greater degree of uniformity and stability.

Two-stage homogenizers are constructed so that the emulsion, after treatment in the first valve system, is conducted directly to another where it receives a second treatment. A single homogenization may produce an emulsion which, although its particle size is small, has a tendency to clump or form clusters. Emulsions of this type exhibit increased creaming tendencies. This is corrected by passing the emulsion through the first stage of homogenization at a high

pressure (eg, 3000 to 5000 psi) and then through the second stage at a greatly reduced pressure (eg, 1000 psi). This breaks down any clusters formed in the first step.

For small-scale extemporaneous preparation of emulsions, the inexpensive *hand homogenizer* (available from *Med Times*) is particularly useful. It is probably the most efficient emulsifying apparatus available to the prescription pharmacist. The two phases, previously mixed in a bottle, are hand pumped through the apparatus. Recirculation of the emulsion through the apparatus will improve its quality.

A homogenizer does not incorporate air into the final product. Air may ruin an emulsion because the emulsifying agent is adsorbed preferentially at the air/water interface, followed by an irreversible precipitation termed *denaturization*. This is particularly prone to occur with protein emulsifying agents.

Homogenization may spoil an emulsion if the concentration of the emulsifying agent in the formulation is less than that required to take care of the increase in surface area produced by the process.

The temperature rise during homogenization is not very large. However, temperature does play an important role in the emulsification process. An increase in temperature will reduce the viscosity and, in certain instances, the interfacial tension between the oil and the water. There are, however, many instances, particularly in the manufacturing of cosmetic creams and ointments, where the ingredients will fail to emulsify properly if they are processed at too high a temperature. Emulsions of this type are processed first at an elevated temperature and then homogenized at a temperature not exceeding 40°.

Figure 83-6 shows the flow through the homogenizing valve, the heart of the high-pressure APV Gaulin homogenizer. The product enters the valve seat at high pressure, flows through the region between the valve and the seat at high velocity with a rapid pressure drop and then is discharged as a homogenized product. It is postulated that circulation and turbulence are responsible mainly for the homogenization that takes place. Different valve assemblies, two stage valve assemblies and equipment with a wide range of capacities are available.

The Macro Flow-Master *Kom-bi-nator* employs a number of different actions, each of which takes the ingredients a little further along in the process of subdividing droplets, until complete homogenization results. The machine is equipped with a pump which carries the liquid through the various stages of the process. In the first stage, the ingredients are forced between two specially designed rotors (gears) which shoot the liquid in opposite directions in a small chamber and, in this way, are mixed thoroughly. These rotors also set up a swirling action in the next chamber into

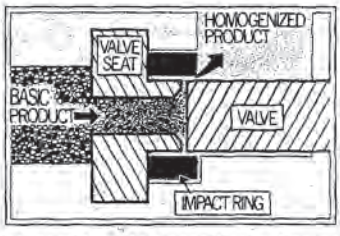


Fig 83-6. Operation of the homogenizer value assembly (Courtesy APV Gaulin).

which the liquid is forced and swirled back and forth in eddies and crosscurrents. The second stage is a pulsing or vibrating action at rapid frequency. The product then leaves this chamber, goes through a small valve opening and is dashed against the wall of the homogenizing chamber. Pressure is applied, but it is not as great as that used in other types of homogenizers. Pressure is controlled accurately by adjusting devices on the front of the machine, and temperature is controlled by passing coolants through the stators.

Ultrasonic Devices—The preparation of emulsions by the use of ultrasonic vibrations also is possible. An oscillator of high frequency (100 to 500 kHz) is connected to two electrodes between which is placed a piezoelectric quartz plate. The quartz plate and electrodes are immersed in an oil bath and, when the oscillator is operating, high-frequency waves flow through the fluid. Emulsification is accomplished by simply immersing a tube containing the emulsion ingredients into this oil bath. Considerable research has been done on ultrasonic emulsification, particularly with regard to the mechanism of emulsion formation by this method. Limited data indicate that these devices will produce stable emulsions only with liquids of low viscosity. The method is not practical, however, for large-scale production of emulsions.

Special techniques and equipment in certain instances, will produce superior emulsions, including rapid cooling, reduction in particle size or ultrasonic devices. A wide selection of equipment for processing both emulsions and suspensions has been described by Eisberg.[22] A number of improvements have been made to make the various processes more effective and energy-efficient.

General methods are available for testing the instability of emulsions including bulk changes, centrifugal and ultracentrifugal studies, dielectric measurement, surface-area measurement and accelerated-motion studies. Low-shear rheological studies measuring viscoelasticity are suggested as the optimal method of stability testing.

Suspensions

The physical chemist defines the word "suspension" as a two-phase system consisting of a finely divided solid dispersed in a solid, liquid or gas. The pharmacist accepts this definition and can show that a variety of dosage forms fall within the scope of the preceding statement. There is, however, a reluctance to be all-inclusive, and it is for this reason that the main emphasis is placed on solids dispersed in liquids. In addition, and because there is a need for more specific terminology, the pharmaceutical scientist differentiates between such preparations as suspensions, mixtures, magmas, gels and lotions. In a general sense, each of these preparations represents a suspension, but the state of subdivision of the insoluble solid varies from particles which settle gradually on standing to particles which are colloidal in nature. The lower limit of particle size is approximately 0.1 μm, and it is the preparations containing dispersed solids of this magnitude or greater that are defined pharmaceutically as suspensions.

Certain authors also include liniments, and the newer sustained-release suspensions, in any discussion of this particular subject. The former preparations now usually are considered as solutions although a number of older liniments were, in fact, suspensions. The sustained-release suspensions represent a very specialized class of preparation and, as such, are discussed in more detail in Chapter 91. Some insoluble drugs also are administered in aerosol form; one example is dexamethasone phosphate suspended in a propellant mixture of fluorochlorocarbons. More detail on aerosols is available in Chapter 92.

Suspension formulation and control is based on the prin-

ciples outlined in Chapters 19 and 20. Formulation involves more than suspending a solid in a liquid. A knowledge of the behavior of particles in liquids, of suspending agents and of flavors and colors is required to produce a satisfactory suspension.

Briefly, the preparation of a stable suspension depends upon the appropriate dispersion of the drug in the suspending medium. To ensure that the particles are wetted by the dispersion medium, a surface-active agent should be used, especially if the dispersed phase is hydrophobic. The suspending agent in the aqueous medium then can be added. Alternatively, the dry suspending agent can be mixed thoroughly with the drug particles and then triturated with the diluent. Other approaches to suspension preparation include the formation of a flocculated suspension and also a flocculated preparation in a suspending vehicle. Details of these procedures are given in Chapter 19.

The most efficient method of producing fine particles is by dry milling prior to suspension. Suspension equipment such as colloid mills or homogenizers normally are used in wet-milling finished suspensions to reduce particle agglomerates. These machines (Fig 83-4) usually have a stator and a rotor which effects the dispersion action. Several methods of producing small uniform dry particles are micropulverization fluid-energy grinding, spray-drying and controlled precipitation with ultrasound as described by Nash.[23]

The choice of an appropriate suspending agent depends upon the use of the products (external or internal), facilities for preparation and the duration of storage.

Preparations made extemporaneously for internal use may include, as suspending agents, acacia, methylcellulose or other cellulose derivatives, sodium alginate or tragacanth.

Extemporaneous preparations of suspensions for internal use showing good flow and suspending properties are provided by sodium carboxymethylcellulose 2.5%, tragacanth 1.25% and guar gum 0.5%. Avicel RC-591, a coprecipitate of microcrystalline cellulose and sodium carboxymethylcellulose stabilized with hydroxypropyl methylcellulose, has been used as a suspending vehicle for propranolol and orphenadrine hydrochloride dispersions prepared from tablets. It also may serve as a general-purpose suspending agent. Carbopol 934, 0.3% or greater, was a satisfactory suspending agent for sulfamethazine 10%, maintaining a permanent suspension for more than 6 months.

Agents suitable for external use include bentonite, methylcellulose or other cellulose derivatives, sodium alginate or tragacanth. Agents which may require high-speed equipment and which are suitable for internal or external use include aluminum magnesium silicates and carbomer.[24]

Preparations such as those mentioned above possess certain advantages over other dosage forms. Some drugs are insoluble in all acceptable media and, therefore, must be administered as a solid, nonsolution dosage form (tablet, capsule, etc), or as a suspension. Because of its liquid character, the last preparation insures some uniformity of dosage but does present some problems in maintaining a consistent dosage regimen. Disagreeable tastes can be covered by using a suspension of the drug or a derivative of the drug, an example of the latter being chloramphenicol palmitate. Suspensions prepared from ion-exchange resins containing an ionic drug can be used not only to minimize the taste of the drug but also to produce a prolonged-action product, since the drug is exchanged slowly for other ions within the gastrointestinal tract.

Suspensions also are chemically more stable than solutions. This particularly is important with certain antibiotics, and the pharmacist often is called on to prepare such a suspension just prior to dispensing the medication. In addition, a suspension is an ideal dosage form for patients who have difficulty swallowing tablets or capsules, which is particularly important in administering drugs to children. An alternate method to enhance compliance includes flavored nystatin "popsicles" which can be prepared by freezing a suspension of the drug so that the taste is improved during the treatment of oral candidiasis.

Suspensions should possess certain basic properties. The dispersed phase should settle slowly and be redispersed readily on shaking. They should not cake on settling and the viscosity should be such that the preparation pours easily. As with all dosage forms, there should be no question as to the chemical stability of the suspension. Appropriate preservatives should be incorporated in order to minimize microbiological contamination. The suspension must be acceptable to the patient on the basis of its taste, color and cosmetic qualities (elegance), the latter two factors being of particular importance in preparations intended for external use.

Gels

Pharmaceutical terminology is, at best, confusing and no two authors will classify gels, jellies, magmas, milks and mixtures in the same way. The NF described Gels as a special class of pharmaceutical preparations but considered Jellies under the same heading. The latter preparations usually contain water-soluble active ingredients and, therefore, are considered in another part of this chapter. The USP definition for Gels is

> Gels are semisolid systems of either suspensions made up of small inorganic particles or large organic molecules interpenetrated by a liquid. Where the gel mass consists of a network of small discrete particles, the gel is classified as a two-phase system (eg, Aluminum Hydroxide Gel). In a two-phase system, if the particle size of the dispersed phase is relatively large, the gel mass sometimes is referred to as a magma (eg Bentonite Magma). Both gels and magmas may be thixotropic, forming semisolids on standing and becoming liquid on agitation. They should be shaken before use to ensure homogeneity and should be labeled to that effect.
>
> Single-phase gels consist of organic macromolecules distributed uniformly throughout a liquid in such a manner that no apparent boundaries exist between the dispersed macromolecules and the liquid. Single-phase may be made from synthetic macromolecules (eg, Carbomer) or from natural gums (eg, Tragacanth). The latter preparations also are called mucilages. Although these gels are commonly aqueous, alcohol and oils may be used as the continuous phase. For example, mineral oil can be combined with a polyethylene resin to form an oleaginous ointment base.

The USP states that each 100 g of Aluminum Hydroxide Gel contains the equivalent of not less than 3.6 and not more than 4.4 g of aluminum oxide (Al_2O_3), in the form of aluminum hydroxide and hydrated oxide, and it may contain varying quantities of basic aluminum carbonate and bicarbonate. The gel itself usually is prepared by the interaction of a soluble aluminum salt, such as a chloride or sulfate, with ammonia solution, sodium carbonate or bicarbonate. The reactions which occur during the preparation are

$$3CO_3^{2-} + 3H_2O \rightarrow 3HCO_3^- + 3OH^-$$

$$[Al(H_2O)_6]^{3+} + 3OH^- \rightarrow [Al(H_2O)_3(OH)_3] + 3H_2O$$

$$2HCO_3^- \rightarrow CO_3^{2-} + H_2O + CO_2$$

The physical and chemical properties of the gel will be affected by the order of addition of reactants, pH of precipitation, temperature of precipitation, concentration of the reactants, the reactants used and the conditions of aging of the precipitated gel.

Aluminum Hydroxide Gel is soluble in acidic (or very strongly basic) media. The mechanism in acidic media is

$$\text{Aluminum Hydoxide Gel} + 3H_2O \rightarrow [Al(H_2O)_3(OH)_3]^0$$

$$[Al(H_2O)_3]^0 + H_3O^+ \rightarrow [Al(H_2O)_4(OH)_2]^+ + H_2O$$

$$[Al(H_2O)_4(OH)_2]^+ + H_3O^+ \rightarrow [Al(H_2O)_5(OH)^{2+} + H_2O$$
$$[Al(H_2O)_5(OH)]^{2+} + H_3O^+ \rightarrow [Al(H_2O)_6^{3+} + H_2O$$

It is unlikely that the last reaction given proceeds to completion. Since the activity of the gel is controlled by its insolubility (solubility will decrease with an increase in the pH of the gastric media), there is no acid rebound. Further, since a certain quantity of insoluble gel always is available, the neutralizing capability of the gel extends over a considerable period of time.

Aluminum hydroxide gels also may contain peppermint oil, glycerin, sorbitol, sucrose, saccharin and various preservatives. Sorbitol improves the acid-consuming capacity, apparently by inhibiting a secondary polymerization that takes place on aging. In addition, polyols such as mannitol, sorbitol and inositol have been shown to improve the stability of aluminum hydroxide and aluminum hydroxycarbonate gels.

Aluminum Hydroxide and Belladonna Mixture PC

Belladonna Tincture	100 mL
Chloroform Spirit	50 mL
Aluminum Hydroxide Gel to	1000 mL

It should be noted, however, that the addition of other drugs (eg, antibiotics) to the gel may result in a loss of the activity anticipated for that active ingredient.

Generally, if left undisturbed for some time, gels may become semisolid or gelatinous. With some gels, small amounts of water may separate on standing.

The single-phase gels are being used more frequently in pharmacy and cosmetics because of several properties: semisolid state, high degree of clarity, ease of application and ease of removal and use. The gels often provide a faster release of drug substance, independent of the water solubility of the drug, as compared to creams and ointments. Some drugs used in medication gels include urea, hydrogen peroxide, ephedrine sulphate, erythromycin and povidone-iodine.

Gels may be used as lubricants for catheters, bases for patch testing, sodium chloride gels for electrocardiography, fluoride gels for topical dental use and for intravaginal administration (prostaglandin-E_2 gel).

Gels can be prepared from a number of pharmaceutical agents such as tragacanth 2 to 5%, sodium alginate 2 to 10%, gelatin 2 to 15%, methylcellulose 2 to 4%, sodium carboxymethyl-cellulose 2 to 5%, carbomer 0.3 to 5% or polyvinyl alcohols 10 to 20% as noted by Carter.[25] Other gelling agents include methylhydroxyethyl cellulose, polyoxyethylene-polyoxypropylene, hydroxyethyl cellulose and gelatin. Gels prepared from nonpolar materials such as magnesium soap-hydrocarbon and hydrocarbons are being investigated.

The percentages above indicate the concentration ranges of the gelling agent. The lower-percentage preparations may be used as lubricants and the higher-percentage preparations as dermatological bases. Some of the gelling agents are available in different grades indicating the viscosity at a definite concentration. In general, high-viscosity grades result in gels at lower concentrations.

Gels recently have been prepared in adhesive form in order to increase the contact time of the active ingredients, such as insulin with the oral and nasal mucosa, leading to a decrease in plasma glucose. This system also has been investigated as a vaginal dosage form for cervical cancer and a topical dosage form for aphthous stomatitis.

Preservatives should be incorporated into the gels, especially those prepared from natural sources. Appropriate preservatives, depending upon use and the gelling agent, include the parabens at about 0.2%, benzoic acid 0.2% (if the product is acidic) and chlorocresol 0.1%.

The preparation of a few gel bases is given below:

Sodium Alginate Gel Base

Sodium Alginate	2–10 g
Glycerin	2–10 g
Methyl Hydroxybenzoate	0.2 g
a soluble calcium salt (calcium or gluconate)	0.5 g
Purified Water, to make	100 mL

The sodium alginate is wetted in a mortar with glycerin, which aids the dispersion. The preservative is dissolved in about 80 mL of water with the aid of heat, allowed to cool and the calcium salt added, which will increase the viscosity of the preparation. This solution is stirred in a high speed stirrer and the sodium alginate-glycerin mixture added slowly while stirring, until the preparation is homogeneous. The preparation should be stored in a tightly sealed container in a wide mouth jar or tube.

Carbomer Jelly

Carbopol 934	2 g
Triethanolamine	1.65 mL
Parabens	0.2 g
Purified Water, to make	100 mL

The parabens are dissolved in 95 mL of water with the aid of heat and allowed to cool. The Carbopol 934, a commercial grade of carbomer, is added in small amounts to the solution using a high speed stirrer and, after a smooth dispersion is obtained, the preparation is allowed to stand permitting entrapped air to separate. Then the gelling agent, triethanolamine, is added, dropwise, stirring with a plastic spatula to avoid entrapping air and the remaining water incorporated. Other concentrations of carbomer can be used to prepare gels, creams or suspensions.

The USP lists a number of gels: Sodium Fluoride and Phosphoric Acid Gel for application to the teeth to reduce cavities, Betamethasone Benzoate Gel and Fluocinonide Gel, anti-inflammatory corticosteroids, Tolnaftate Gel, an antifungal agent and Tretinoin Gel for the treatment of acne. Refer to the specific monographs in this text for more information.

Lotions

Lotions usually are liquid suspensions or dispersions intended for external application to the body. They may be prepared by triturating the ingredients to a smooth paste and then adding the remaining liquid phase cautiously. High-speed mixers or homogenizers produce better dispersions and, therefore, are the tools of choice in the preparation of larger quantities of lotion. Calamine Lotion USP is the classic example of this type of preparation and consists of finely powdered, insoluble solids held in more or less permanent suspension by the presence of suspending agents and/or surface-active agents. Many investigators have studied Calamine Lotion and this has led to the publication of many formulations, each possessing certain advantages over the others but none satisfying the collective needs of all dermatologists.

Phenolated Calamine Lotion USP contains 10 mL of liquefied phenol in sufficient calamine lotion to make the product measure 1000 mL. Formulations containing Avicel R (hydrated microcrystalline cellulose, *FMC*) and carboxymethylcellulose settle less than the official preparations.

Calamine Lotion

Calamine	8 g
Zinc Oxide	8 g
Glycerin	2 mL
Avicel R Gel	2 g
Carboxymethylcellulose	2 g
Calcium Hydroxide Solution, a sufficient quantity, to make	100 mL

Mix 45 g of Avicel R with 55 g of water with a suitable electric mixer. This gel is used in the preparation of the calamine lotion. Mix the calamine and the zinc oxide with the glycerin, the gel and the carboxymethylcellulose. Add sufficient calcium hydroxide solution to make the product measure 100 mL.

To prepare Phenolated Calamine Lotion add 1 mL of Liquefied Phenol during the mixing stage.

Suspensions also may be formed by chemical interaction in the liquid. White Lotion is an example.

White Lotion

Zinc Sulfate	40 g
Sulfurated Potash	40 g
Purified Water, a sufficient quantity to make	1000 mL

Dissolve the zinc sulfate and the sulfurated potash separately, each in 450 mL of purified water and filter each solution. Add slowly the sulfurated potash solution to the zinc sulfate solution with constant stirring. Then add the required amount of purified water, and mix.

Sulfurated potash is a solid of variable composition but usually is described as $K_2S_3 \cdot K_2S_2O_3$. The chemical reaction which occurs when sulfurated potash solution is added to the zinc sulfate is

$$ZnSO_4 \cdot 7H_2O + K_2S_3 \cdot K_2S_2O_3 \rightarrow ZnS + S_2 + K_2SO_4 + K_2S_2O_3 + 7H_2O$$

This lotion must be prepared fresh and does not contain a suspending agent. Bentonite Magma has been used in some formulations. Coffman and Huyck[26] include a detailed discussion of the chemistry and the problems involved in the preparation of a suitable product.

The USP recognizes a second type of lotion. These are emulsions of the O/W type stabilized by a surface-active agent. Benzyl Benzoate Lotion is an example. Some lotions are clear solutions and, in fact, the active ingredient of one official lotion, Dimethisoquin Hydrochloride Lotion USP XX is a water-soluble substance. However, one unofficial formulation for this lotion lists dimethisoquin hydrochloride, menthol and zinc oxide as active ingredients and the preparation thus becomes a suspension. Several lotions are listed in the USP and contain, for example, antibiotics, steroids, keratolytics and scabicides.

A formula for hydrocortisone lotion is given in the PC.

Hydrocortisone Lotion

Hydrocortisone, in ultrafine powder	10.0 g
Chlorocresol	0.5 g
Self-emulsifying monostearin	40.0 g
Glycerol	63.0 g
Purified water, freshly boiled and cooled to make	1000.0 g

To prepare the base, the chlorocresol is dissolved in 850 mL of water with the aid of gentle heat, the self-emulsifying monostearin is added and the mixture heated to 60° with stirring until completely dispersed. The hydrocortisone is triturated with the glycerol and the trituration is then incorporated, with stirring, into the warm base, allowed to cool while stirring, then added the remainder of the water and mixed.

Lotions usually are applied without friction. Even so, the insoluble matter should be divided very finely. Particles approaching colloidal dimensions are more soothing to inflamed areas and effective in contact with infected surfaces. A wide variety of ingredients may be added to the preparation to produce better dispersions or to accentuate its cooling, soothing, drying or protective properties. Bentonite is a good example of a suspending agent used in the preparation of lotions. Methylcellulose or sodium carboxymethylcellulose will localize and hold the active ingredient in contact with the affected site. A formulation containing glycerin will keep the skin moist for a considerable period of time. The drying and cooling effect may be accentuated by adding alcohol to the formula.

Dermatologists frequently prescribe lotions containing anesthetics, antipruritics, antiseptics, astringents, germicides, protectives or screening agents, to be used in treating or preventing various types of skin diseases and dermatitis. Antihistamines, benzocaine, calamine, resorcin, steroids, sulfur, zinc oxide, betamethasone derivatives, salicylic acid, safflower oil, minoxidil and zirconium oxide are ingredients common in unofficial lotions. In many instances the cosmetic aspects of the lotion are of great importance. Many lotions compare badly with cosmetic preparations of a similar nature. The manufacture of fine lotions to meet the specialized needs of the dermatologist provides the pharmacist with an excellent opportunity to demonstrate his professional competence. Recent extensive studies on lotions, as described by Harb,[27] will assist the pharmacist to attain this goal.

Lotions tend to separate or stratify on long standing, and they require a label directing that they be shaken well before each use. All lotions should be labeled "For External Use Only."

Microorganisms may grow in certain lotions if no preservative is included. Care should be taken to avoid contaminating the lotion during preparation, even if a preservative is present.

Magmas and Milks

Magmas and milks are aqueous suspensions of insoluble, inorganic drugs and differ from gels mainly in that the suspended particles are larger. When prepared, they are thick and viscous and, because of this, there is no need to add a suspending agent.

Bentonite Magma USP is prepared by simple hydration. Two procedures are given in the compendium for the preparation of this product.

Magmas also may be prepared by chemical reaction. Magnesium hydroxide is prepared by the hydration of magnesium oxide.

$$MgO + H_2O \rightarrow Mg(OH)_2$$

Milk of Magnesia USP is a suspension of magnesium hydroxide containing 7.0–8.5% $Mg(OH)_2$. It has an unpleasant, alkaline taste which can be masked with 0.1% citric acid (to reduce alkalinity) and 0.05% of a volatile oil or a blend of volatile oils.

Milk of Bismuth contains bismuth hydroxide and bismuth subcarbonate in suspension in water. The Magma is prepared by reacting bismuth subnitrate with nitric acid and ammonium carbonate with ammonia solution and then mixing the resulting two solutions.

The following reactions occur during the preparation of the magma.

$$(NH_4)_2CO_3 \rightarrow 2NH_4^+ + CO_3^{2-}$$

$$NH_3 + H_2O \rightarrow NH_4^+ + OH^-$$

$$2BiO^+ + CO_3^{2-} \rightarrow (BiO)_2CO_3$$

$$BiO^+ + OH^- \rightarrow BiO(OH)$$

If the insoluble substance is precipitated fresh by mixing hot, dilute solutions, there is only slight sedimentation on standing. This characteristic of magmas sometimes is enhanced by passing the product through a colloid mill.

For the most part, magmas and milks are intended for internal use, although Bentonite Magma is used primarily as a suspending agent for insoluble substances eg, Milk of Magnesia USP and Dihydroxy Aluminum Aminoacetate Magma USP, either for local application or for internal use. All magmas require a "Shake Well" label. Freezing must be avoided.

Several antimicrobial preservatives have been tested in liquid antacid preparations for their stability and effectiveness, such as benzoic acid, chlorhexidine, methylparaben,

propylparaben, sorbic acid, propylene glycol or ethanol. It was found that a combination of methylparaben and sorbic acid was superior to the parabens alone.

Mixtures

The official mixtures are aqueous, liquid preparations which contain suspended, insoluble, solid substances and are intended for internal use. The insoluble substance does not make the mixture very viscous, and the particles may be held in suspension by using suitable suspending or thickening agents. This class was introduced originally to secure uniformity in the formulas of certain well-known and largely used preparations. Frequently, the term *mixture* is applied loosely to aqueous preparations of every description. The term *shake mixture* is used often for liquid preparations which contain insoluble ingredients and, therefore, must be shaken before use. The USP does not recognize the term. The term *suspension* now is used to describe a number of similar preparations. The PC uses the term *mixtures* and includes suspensions in this category, for example:

Ammonium Chloride Mixture PC

Ammonium Chloride	100 g
Aromatic Ammonia Solution	50 mL
Liquorice Liquid Extract	100 mL
Water, for preparations to	1000 mL

It should be prepared recently.

The term mixture occurs in the expression dry mixture, which may be used to describe many USP products, in particular, antibiotic powders for oral solutions which are described on page 1527.

The pectin and the tragacanth in Kaolin Mixture with Pectin (page 796) act as suspending agents. An alternate formula, based on Veegum (*Vanderbilt*) and sodium carboxymethylcellulose, has been proposed by Kalish.[28]

Kaolin Mixture with Pectin

Veegum	0.88 g
Sodium Carboxymethylcellulose	0.22 g
Purified Water	79.12 g
Kaolin	17.50 g
Pectin	0.44 g
Saccharin	0.09 g
Glycerin	1.75 g

Add the Veegum and the sodium carboxymethylcellulose to the water with continuous stirring. Add, with mixing, the kaolin. Mix the pectin, saccharin and glycerin and add to the suspension. A preservative and flavoring agent may be added to the product.

The insoluble material in mixtures must be in a very finely divided state and uniformly distributed throughout the preparation. This is accomplished with colloid mills, special methods of precipitation and suspending agents. There are three main reasons for having the insoluble substances in as fine a state of subdivision as possible.

1. The more nearly the colloidal state is approached by protectives, such as kaolin, magnesium trisilicate or magnesium phosphate, the more active they become as adsorbents and protectives when in contact with inflamed surfaces.
2. Finely divided particles are suspended more readily and settle out much more slowly than large particles, thus enabling the patient to obtain uniform doses of suspended substances. Homogeneous mixtures are desirable especially when administering medication to form an evenly distributed, protective coating on the gastrointestinal tract.
3. The palatability of many preparations is enhanced by the use of colloidal suspending agents.

Mixtures containing suspended material should have a "Shake Well" label affixed to the container in which they are dispensed.

Mixtures, including suspensions, are subject to contamination by microorganisms that remain viable and are a potential health hazard during the period of use of the products. Survival times of organisms depend on the preservative used. A kaolin pediatric mixture that contains benzoic acid kills organisms rapidly, whereas organisms survived for more than a week in a magnesium trisilicate mixture that contained no more than a trace of peppermint oil, as noted by Westwood.[29]

Occasionally, it is necessary to prepare suspensions from crushed tablets. A general formula for this purpose is given.[24]

Methylcellulose 20	0.75
Parabens	0.1
Purified Water	60.0
Propylene Glycol	2.0
Simple Syrup, to make	100.0

An extemporaneous suspension of cimetidine tablets which retained its potency at 40° over 14 days is:

Cimetidine 300-mg tablets	24 (7.2 g)
Glycerin	10 mL
Simple Syrup, to make	120 mL

The tablets are triturated to a fine powder using a mortar, the mixture is levigated with the glycerin, simple syrup added, mixed well, placed in a blender until smooth and then refrigerated.[30]

Satisfactory suspensions have been compounded from diazepam tablets and propranolol hydrochloride tablets, and they possess chemical stability for 60 days and 4 months, respectively, at room temperature or under refrigeration. Frequently, since the drug may be soluble, it is the excipients which are being suspended.

A comprehensive checklist of suspension formulations has been reported in the literature by Scheer.[31]

Official Suspensions

The USP places particular emphasis on the term suspension by providing specific definitions for a variety of oral, parenteral and ophthalmic preparations formulated in such a way that an insoluble substance is suspended in a liquid at some stage of the manufacturing or dispensing process. The USP definition begins as follows:

Suspensions are preparations of finely divided, undissolved drugs dispersed in liquid vehicles. Powders for suspension are preparations of finely powdered drugs intended for suspension in liquid vehicles. An example of the ready-to-use type is *Trisulfapyrimidines Oral Suspension*, in which the three sulfapyrimidines are already suspended in a liquid flavored vehicle in a form suitable for oral administration. *Tetracycline for Oral Suspension* is finely divided tetracycline mixed with suspending and dispersing agents. It is intended to be constituted with the prescribed volume of purified water and mixed before it is dispensed by the pharmacist for oral administration to the patient.

Neither this definition nor the monographs give specific directions for the preparation of the suspension, although pharmacopeias usually permit the addition of suitable flavoring agents, suspending agents, preservatives and certified color additives. One procedure for the preparation of the commonly used Trisulfapyrimidines Oral Suspension is given below.

Trisulfapyrimidines Oral Suspension

Veegum	1.00 g
Syrup USP	90.60 g
Sodium Citrate	0.78 g
Sulfadiazine	2.54 g
Sulfamerazine	2.54 g
Sulfamethazine	2.54 g

Add the Veegum, slowly and with continuous stirring, to the syrup. Incorporate the sodium citrate into the Veegum-syrup mixture. Premix the sulfa drugs, add to the syrup, stir and homogenize. Add sufficient 5% citric acid to adjust the pH of the product to 5.6. A preservative and a flavoring agent may be added to the product.

Methods of preparation for those formulations which contain several active ingredients and are produced in large quantities tend to be more complex than that given above.

Many formulations for suspensions are given in the PC under *Mixtures*.

A properly prepared suspension has a number of desirable properties:

1. The suspended material should not settle rapidly.
2. Particles that do settle should not form a hard cake and easily should be resuspended uniformly on shaking.
3. The suspension should pour freely from the container.

Insoluble powders that do not disperse evenly throughout the suspending medium, when shaken, should be powdered finely and levigated with a small amount of an agent such as glycerin, alcohol or a portion of the dispersion of the suspending agent. The other ingredients are incorporated and the remainder of the dispersion of the suspending agent is incorporated gradually by trituration to produce the appropriate volume.

Suspensions intended for parenteral or ophthalmic use also are described in the USP. For a discussion of these suspensions, see Chapter 84 and 86.

Extracts

Extraction

Extraction, as the term is used pharmaceutically, involves the separation of medicinally active portions of plant or animal tissues from the inactive or inert components by using selective solvents in standard extraction procedures.

The products so obtained from plants are relatively impure liquids, semisolids or powders intended only for oral or external use. These include classes of preparations known as decoctions, infusions, fluidextracts, tinctures, pilular (semisolid) extracts and powdered extracts. Such preparations popularly have been called galenicals, after Galen, the 2nd century Greek physician. For additional information concerning extraction and extractives, see RPS 15, Chapter 86.

Extraction continues to be of considerable interest in order to obtain improved yields of drugs derived from plant and animal sources. For example, improved extraction of digitalis glycosides has been carried out using a pulsating, perforated, bottom column. Other techniques include ultrasonics, rotary-film evaporators, liquid and supercritical carbon dioxide, hydrodistillation, liquid chromatography, multiple-solvent extraction, countercurrent extraction and gravitation dynamics.

In this discussion we are concerned primarily with basic extraction procedures for crude drugs to obtain the therapeutically desirable portion and eliminate the inert material by treatment with a selective solvent, known as the menstruum. Extraction differs from solution in that the presence of insoluble matter is implied in the former process. The principal methods of extraction are maceration, percolation, digestion, infusion and decoction. The quality of the finished product can be enhanced by standardizing primary extracts and carrying out analytical assays during production on the raw materials, intermediate products and manufacturing procedures.

The processes of particular importance, insofar as the USP is concerned, are those of maceration and percolation. Most pharmacopeias refer to such processes for extraction of active principles from crude drugs.

Maceration—In this process the solid ingredients are placed in a stoppered container with the whole of the solvent and allowed to stand for a period of at least 3 days, with frequent agitation, until soluble matter is dissolved. The mixture then is strained, the marc (the damp solid material) pressed and the combined liquids clarified by filtration or by decantation, after standing.

Percolation—This is the procedure used most frequently to extract the active ingredients in the preparation of tinctures and fluidextracts. Certain specific procedural details are provided in the USP, which should be consulted for such information. In the PC general procedure, a percolator (a narrow, cone-shaped vessel open at both ends) is used. The solid ingredient(s) are moistened with an appropriate amount of the specified menstruum and allowed to stand for approximately 4 hr in a well-closed container, after which the drug mass is packed into the percolator. Sufficient menstruum is added to saturate the mass and the top of the percolator is closed. When the liquid is about to dip from the neck (bottom) of the percolator, the outlet is closed. Additional menstruum is added to give a shallow layer above the mass, and the mixture is allowed to macerate in the closed percolator for 24 hr. The outlet of the percolator then is opened and the liquid contained therein allowed to drip slowly, additional menstruum being added as required, until the percolate measures about three-quarters of the required volume of the finished product. The marc is pressed and the expressed liquid is added to the percolate. Sufficient menstruum is added to produce the required volume, and the mixed liquid clarified by filtration or by allowing it to stand and then decanting.

Digestion—This is a form of maceration in which *gentle heat* is used during the process of extraction. It is used when moderately elevated temperature is not objectionable and the solvent efficiency of the menstruum is increased thereby.

Infusion—An infusion is a dilute solution of the readily soluble constituents of crude drugs. Fresh infusions are prepared by macerating the drugs for a short period of time with either cold or boiling water. US official compendia have not included infusions for some time. An example is Concentrated Compound Gentian Infusion BP 1973.

Decoction—This once-popular process extracts water-soluble and heat-stable constituents from crude drugs by boiling in water for 15 min, cooling, straining and passing sufficient cold water through the drug to produce the required volume.

Extractive Preparations

After a solution of the active constituents of a crude drug is obtained by maceration or percolation, it may be ready for use as a medicinal agent, as with certain tinctures or fluidextracts, or it may be processed further to produce a solid or semisolid extract.

For a discussion of *resins* and *oleoresins* obtained by solvent extraction of plant exudates see Chapter 23, under *Plant Exudates*.

Tinctures—Tinctures are defined in the USP as being alcoholic or hydroalcoholic solutions prepared from vegetable materials or from chemical substances, an example of the latter being Iodine Tincture. Traditionally, tinctures of potent vegetable drugs essentially represent the activity of 10 g of the drug in each 100 mL of tincture, the potency being adjusted following assay. Most other tinctures of vegetable drugs represent the extractive from 20 g of the drug in 100 mL of tincture.

The USP specifically describes two general processes for preparing tinctures, one by percolation designated as Process P, and the other by maceration, as Process M. These utilize the methods described under *Extraction*.

Process P includes a modification so that tinctures that require assay for adjustment to specified potency thus may be tested before dilution to final volume. A tincture prepared by Process P as modified for assayed tinctures is Belladonna Tincture.

Examples of tinctures prepared by Process M are Compound Benzoin Tincture and Sweet Orange Peel Tincture (the latter contains the extractive from 50 g of sweet orange peel in 100 mL of tincture).

Fluidextracts—The USP defines fluidextracts as being liquid preparations of vegetable drugs, containing alcohol as a solvent or as a preservative, or both, so made that each mL contains the therapeutic constituents of 1 g of the standard

drug that it represents. While the USP states that pharmacopeial fluidextracts are made by percolation, the official compendia previously have described general procedures for three percolation methods used in making fluidextracts.

Process A is a percolation method that can be modified for fluidextracts that must be assayed.

Process E is an alternative for Process A in which percolation is conducted on a column of drug much greater in length than in diameter.

Process D is used for preparing fluidextracts with boiling water as the menstruum, alcohol being added as a preservative to the concentrated percolate; this is the procedure used for preparing Cascara Sagrada Fluidextract.

The BP and PC use the designation *Liquid Extracts* for fluidextracts.

Extracts—Extracts are defined in the USP as concentrated preparations of vegetable or animal drugs obtained by removal of the active constituents of the respective drugs with suitable menstrua, evaporation of all or nearly all of the solvent and adjustment of the residual masses or powders to the prescribed standards.

Three forms of extracts are recognized: semiliquids or liquids of syrupy consistency, plastic masses (known as *pilular* or *solid extracts*) and dry powders (known as *powdered extracts*). Extracts, as concentrated forms of the drugs from which they are prepared, are used in a variety of solid or semisolid dosage forms. The USP states that pilular extracts and powdered extracts of any one drug are interchangeable medicinally, but each has its own pharmaceutical advantages. Pilular extracts, so-called because they are of a consistency to be used in pill masses and made into pills, are suited especially for use in ointments and suppositories. Powdered extracts are suited better for incorporation into a dry formulation, as in capsules, powders or tablets. Semiliquid extracts, or extracts of a syrupy consistency, may be used in the manufacture of some pharmaceutical preparations.

Most extracts are prepared by extracting the drug by percolation. The percolate is concentrated, generally by distillation under reduced pressure. The use of heat is avoided where possible because of potential injurious effect on active constituents. Powdered extracts which are made from drugs that contain inactive oily or fatty matter may have to be defatted or prepared from defatted drug. For diluents that may be used to adjust an extract to prescribed standards, see the USP.

Pure Glycyrrhiza Extract USP is an example of a pilular extract; Belladonna Extract USP and Hyoscyamus Extract PC are examples of powdered extracts (the former is prepared also as a pilular extract and the latter as a liquid extract).

References

1. Ostendorf JP: *J Soc Cosmet Chem 16:* 203, 1965.
2. Chalmers L: *Soap Perfum Cosmet 44:* Jan. 29, 1971.
3. Bruch CW: *Drug Cosmet Ind 111:* 51, Oct. 1972.
4. Coates D: *Manuf Chem Aerosol News 44 (Jun):* 35, *(Aug):* 41, *(Oct):* 34, *(Dec):* 19, 1973; *45 (Jan):* 19, 1974.
5. Hickman K *et al: Science 180:* 15, 1973.
6. Bergen A: *Can J Hosp Pharm 30 (Jul–Aug):* 109, 1977.
7. Meer T: *Flavoring Pharmaceutical Preparations* (SK&F Selected Pharm Res Refs No 4), SmithKline Corp, Philadelphia, Feb 11, 1957.
8. Schumacher GE: *Am J Hosp Pharm 24:* 588, 713, 1967; *25:* 154, 1968.
9. *Am Drug 175:* 24, May 1977.
10. Ryder J: *Int J Pharm Technol Prod Manuf 1(1):* 14, 1979.
11. *The Chemistry and Rheology of Water-Soluble Gums and Colloids*, Society of Chemical Industry Monograph, No 24, London, 1966.
12. Sumner ED: *JAPhA NS8:* 250, 1968.
13. Reynolds JEF, ed: *Martindale's, The Extra Pharmacopoeia*, 28th ed, The Pharmaceutical Press, London, 425, 1982.
14. Rettig H: *Acta Pharm Technol 24:* 143, 1978 through *Int Pharm Abstr 19:* 5096, 1982.
15. Griffin WC *et al: Drug Cosmet Ind 101 (Oct):* 41, *(Nov):* 52, 1967.
16. White RF: *Pharmaceutical Emulsions and Emulsifying Agents*, 4th ed, The Chemist and Druggist, London, 1964.
17. Florence AT, Whitehill D: *Int J Pharm 11:* 277, 1982.
18. Prince LM, ed: *Microemulsions Theory and Practice*, Academic, New York, 1977.
19. Becher P: *Emulsions: Theory and Practice*, Reinhold, New York, 267, 1965.
20. Peck GE *et al: JAPhA Sci Ed 49:* 75, 1960.
21. Lin TJ: *J Soc Cosmet Chem 29:* 117, 1978; *35:* 357, 1984.
22. Eisberg N: *Mfg Chem 53 (Jan):* 27, 1982.
23. Nash RA: *Drug Cosmet Ind 97:* 843, 1965; *98:* 39, 1966.
24. See Ref 13, 947, 948.
25. Carter SJ: "*Cooper and Gunn's Dispensing for Pharmaceutical Students*," 12th ed, Pitman Medical, London, 214, 1975.
26. Coffman HL, Huyck CL: *Am J Hosp Pharm 20:* 132, 1963.
27. Harb NSA: *Cosmet Perfum 89 (Apr):* 67, 1974 through *Int Pharm Abstr 11:* 3304, 1974; Shapiro WB: *Cosmet Toiletries 97 (Mar):* 27, 1982 through *Int Pharm Abstr 20:* 3134, 1983.
28. Kalish J: *Drug Cosmet Ind 94:* 276, 1964.
29. Westwood N: *Pharm J 208:* 153, 1972.
30. Tortorici MP: *Am J Hosp Pharm 36:* 22, 1979.
31. Scheer AJ: *Drug Cosmet Ind 128 (Apr):* 40, *(May):* 39, *(Jun):* 52, 1981.

CHAPTER 88

Powders

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Powders are encountered in almost every aspect of pharmacy, both in industry and in practice. Drugs and other ingredients, when they occur in the solid state in the course of being processed into a dosage form, usually are in a more or less finely divided condition. Frequently, this is a powder whose state of subdivision is critical in determining its behavior both during processing and in the finished dosage form. Apart from their use in the manufacture of tablets, capsules, suspensions, etc, powders also occur as a pharmaceutical dosage form. While the use of powders as a dosage form has declined, the properties and behavior of finely divided solid materials are of considerable importance in pharmacy.

This chapter is intended to provide an introduction to the fundamentals of powder mechanics and the primary means of powder production and handling. The relationships of the principles of powder behavior to powders as dosage forms are discussed.

Production Methods

Molecular Aggregation

Precipitation and Crystallization—These two processes are fundamentally similar and depend on achieving three conditions in succession: a state of supersaturation (supercooling in the case of crystallization from a melt), formation of nuclei and growth of crystals or amorphous particles.

Supersaturation can be achieved by evaporation of solvent from a solution, cooling of the solution if the solute has a positive heat of solution, production of additional solute as a result of a chemical reaction or a change in the solvent medium by addition of various soluble secondary substances. In the absence of seed crystals, significant supersaturation is required to initiate the crystallization process through formation of nuclei. A nucleus is thought to consist of from ten to a few hundred molecules having the spatial arrangement of the crystals that will be grown ultimately from them.

Such small particles are shown by the Kelvin equation to be more soluble than large crystals and, therefore, to require supersaturation, relative to large crystals, for their formation and subsequent growth. It is a gross oversimplification to assume that, for a concentration gradient of a given value, the rate of crystallization is the negative of the rate of dissolution. The latter is generally somewhat greater.

Depending on the conditions of crystallization, it is possible to control or modify the nature of the crystals obtained. When polymorphs exist, careful temperature control and seeding with the desired crystal form are often necessary. The habit or shape of a given crystal form is often highly dependent on impurities in solution, pH, rate of stirring, rate of cooling and the solvent. Very rapid rates of crystallization can result in impurities being included in the crystals by entrapment.

Spray-Drying—Atomization of a solution of one or more solids *via* a nozzle, spinning disk or other device, followed by evaporation of the solvent from the droplets is termed spray-drying. The nature of the powder that results is a function of several variables, including the initial solute concentration, size distribution of droplets produced and rate of solvent removal. The weight of a given particle is determined by the volume of the droplet from which it was derived and by the solute concentration. The particles produced are aggregates of primary particles consisting of crystals and/or amorphous solids, depending on the rate and conditions of solvent removal. This approach to the powdered state provides the opportunity to incorporate multiple solid substances into individual particles at a fixed composition, independent of particle size, and avoiding difficulties that can arise in attempting to obtain a uniform mixture of several powdered ingredients by other procedures.

Particle-Size Reduction

Comminution in its broadest sense is the mechanical process of reducing the size of particles or aggregates. Thus, it embraces a wide variety of operations including cutting, chopping, crushing, grinding, milling, micronizing and trituration, which depend primarily on the type of equipment employed. The selection of equipment in turn is determined by the characteristics of the material, the initial particle size and the degree of size reduction desired. For example, very large particles may require size reduction in stages simply because the equipment required to produce the final product will not accept the initial feed, as in crushing prior to grinding. In the case of vegetable and other fibrous material, size reduction generally must be, at least initially, accomplished by cutting or chopping.

Chemical substances used in pharmaceuticals, in contrast, generally need not be subjected to either crushing or cutting operations prior to reduction to the required particle size. However, these materials do differ considerably in melting point, brittleness, hardness and moisture content, all of which affect the ease of particle-size reduction and dictate the choice of equipment. The heat generated in the mechanical grinding, in particular, presents problems with materials which tend to liquefy or stick together and with the thermolabile products which may degrade unless the heat is dissipated by use of a flowing stream of water or air. The desired particle size, shape and size distribution also must be considered in the selection of grinding or milling equipment. For example, attrition mills tend to produce spheroidal,

more free-flowing particles than do impact-type mills, which yield more irregular-shaped particles.

Fracture Mechanics—Reduction of particle size through fracture requires application of mechanical stress to the material to be crushed or ground. Materials respond to stress by yielding, with consequent generation of strain. Depending on the time course of strain as a function of applied stresses, materials can be classified according to their behavior over a continuous spectrum ranging from brittle to plastic. In the case of a totally brittle substance, complete rebound would occur on release of applied stress at stresses up to the yield point, where fracture would occur. In contrast, a totally plastic material would not rebound nor would it fracture. The vast majority of pharmaceutical solids lie somewhere between these extremes and thus possess both elastic and viscous properties. Linear and, to a lesser extent, nonlinear viscoelastic theory has been developed well to account for quantitatively and explain the simultaneous elastic and viscous deformations produced in solids by applied stresses.

The energy expended by comminution ultimately appears as surface energy associated with newly created particle surfaces, internal free energy associated with lattice changes and as heat. Most of the energy expressed as heat is consumed in the viscoelastic deformation of particles, friction and in imparting kinetic energy to particles. Energy is exchanged among these modes and some is, of course, effective in producing fracture. It has been estimated that 1% or less of the total mechanical energy used is associated with newly created surface or with crystal lattice imperfections.

While the grinding process has been described mathematically, the theory of grinding has not been developed to the point where the actual performance of the grinding equipment can be predicted quantitatively. However, three fundamental laws have been advanced:

Kick's Law—The work required to reduce the size of a given quantity of material is constant for the same reduction ratio regardless of the original size of the initial material.

Rittinger's Law—The work used for particulate size reduction is directly proportional to the new surface produced.

Bond's Law—The work used to reduce the particle size is proportional to the square root of the diameter of the particles produced.

In general, however, these laws have been useful only in providing trends and qualitative information on the grinding process. Usually laboratory testing is required to evaluate the performance of particular equipment. A work index, developed from Bond's Law, is a useful way of comparing the efficiency of milling operations.[1] A grindability index, which has been developed for a number of materials, also can be used to evaluate mill performance.[2]

A number of other factors also must be considered in equipment selection. Abrasion or mill wear is an important factor in the grinding of hard materials, particularly in high-speed, close-clearance equipment (eg, hammer mills). In some instances mill wear may be so extensive as to lead to highly contaminated products and excessive maintenance costs that make the milling process uneconomical. Hardness of the material, which is often related to abrasiveness, also must be considered. This usually is measured on the Moh's Scale. Qualitatively, materials from 1 to 3 are considered as soft and from 8 to 10 as hard. Friability (ease of fracture) and fibrousness can be of equal importance in mill selection. Fibrous materials, eg, plant products, require a cutting or chopping action and usually cannot be reduced in size effectively by pressure or impact techniques. A moisture content above about 5% will in most instances also create a problem and can lead to agglomeration or even liquefaction of the milled material. Hydrates will often release their water of hydration under the influence of a high-temperature milling process and thus may require cooling or low-speed processing.

Methods and Equipment—When a narrow particle-size distribution with a minimum of fines is desired, closed-circuit milling is advantageous. This technique combines the milling equipment with some type of classifier (see *Particle-Size Measurement and Classification*). In the simplest arrangement, a screen is used to make the separation, and the oversize particles are returned to the mill on a continuous basis while the particles of the desired size pass through the screen and out of the grinding chamber. Overmilling, with its subsequent production of fines, thereby is minimized. Equipment also has been designed to combine the sieving and milling steps into a single operation (see *Centrifugal-Impact Mills and Sieves*).

In order to avoid contamination or deterioration, the equipment used for pharmaceuticals should be fabricated of materials which are chemically and mechanically compatible with the substance being processed. The equipment should be disassembled readily for ease in cleaning to prevent cross-contamination. Dust-free operation, durability, simplified construction and operation and suitable feed and outlet capacities are additional considerations in equipment selection.

While there is no rigid classification of large-scale comminution equipment, it generally is divided into three broad categories based on feed and product size:

1. *Coarse crushers* (eg, jaw, gyratory, roll and impact crushers).
2. *Intermediate grinders* (eg, rotary cutters, disk, hammer, roller and chaser mills).
3. *Fine grinding mills* (eg, ball, rod, hammer, colloid, and fluid-energy mills; high-speed mechanical screen and centrifugal classifier).

Machines in the first category are employed ordinarily where the size of the feed material is relatively large, ranging from 1½ to 60″ in diameter. These are used most frequently in the mineral crushing industry and will not be considered further. The machines in the second category are used for feed materials of relatively small size and provide products which fall between 20- and 200-mesh. Those in the third category produce particles, most of which will pass through a 200-mesh sieve, though, often the particle size of the products from fine grinding mills is well into the micron range.

The comminution effect of any given operation can be described mathematically in terms of a matrix whose elements represent the probabilities of transformation of the various-size particles in the feed material to the particle sizes present in the output. The numerical values of the elements in the transition matrix can be determined experimentally and the matrix serves to characterize the mill. Matrices of this type are frequently a function of feed rate and feed particle-size distribution but are useful in predicting mill behavior. Multiplication of the appropriate comminution matrix with the feed-size distribution line-matrix yields the predicted output-size distribution.

Intermediate and Fine Grinding Mills—The various types of comminuting equipment in this class generally employ one of three basic actions or, more commonly, a combination of these actions.

1. *Attrition*—This involves breaking down of the material by a rubbing action between two surfaces. The procedure is particularly applicable to the grinding of fibrous materials where a tearing action is required to reduce the fibers to powder.
2. *Rolling*—This uses a heavy rolling member to crush and pulverize the material. Theoretically, only a rolling-crushing type of action is involved, but in actual practice some slight attrition takes place between the face of the roller and the bed of the mill.
3. *Impact*—This involves the operation of hammers (or bars) at high speeds. These strike the lumps of material and throw them against each other or against the walls of the containing chamber. The impact causes large particles to split apart, the action continuing until small particles of

required size are produced. In some instances high-velocity air or centrifugal force may be used to generate high-impact velocities.

Roller Mills in their basic form consist of two rollers revolving in the same direction at different rates of speed. This principle, which provides particle-size reduction mainly through compression (crushing) and shear has been applied to the development of a wide variety of roller mills. Some use multiple smooth rollers or corrugated, ribbed or saw-toothed rollers to provide a cutting action. Most allow adjustment of the gap between rollers to control the particle size of the product. The roller mill is quite versatile and can be used to crush a variety of materials.

An example of a pharmaceutical roller mill is the Crack-U-Lator, in which a series of ribbed rollers are adjusted to reduce sequentially the particle size of the product to produce the desired distribution. The design allows particles which are smaller than the gap between the rollers to pass to the next stage without unnecessary size reduction, thus reducing fines.

Hammer Mills consist of a rotating shaft on which are mounted either rigid or swing hammers (beaters). This unit is enclosed with a chamber containing a grid or removable screen through which the material must pass. On the upper part is the feed hopper. As the material enters the chamber, the rapidly rotating hammers strike against it and break it into smaller fragments. These are swept downward against the screen where they undergo additional "hammering" action until they are reduced to a size small enough to pass through the openings and out. Oversize particles are hurled upward into the chamber where they also undergo further blows by the revolving hammers.

These mills operate at high speed and generally with controlled feed rate. Both impact and attrition provide the grinding action. Particle size is regulated by rotor speed, feed rate, type and number of hammers, clearance between hammers and chamber wall and discharge openings. At a constant screen opening, the speed of the mill and the thickness of the screen will affect the particle size of the milled powder,[3] as shown in Fig 88-1. The higher the speed, the steeper the approach angle of the particle to the screen hole. Thus, for any screen size opening, the higher the blade speed, the smaller the particle obtained. Increasing the screen thickness will have a similar effect. In general flat-edged blades are most effective for pulverizing, while sharp-edged blades will act to chop or cut fibrous materials.

The FitzMill Comminutor (Fig 88-2) is an example of this type of mill. It can be used in either the hammer or knife-blade configuration and can be fitted with a wide range of screen sizes to fulfill a variety of milling specifications.

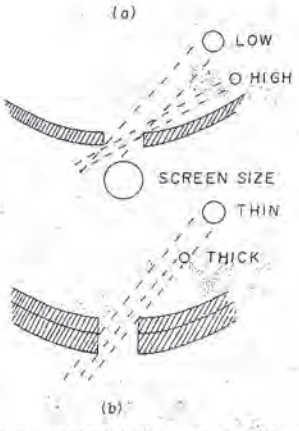

Fig 88-1. The influence of (*a*) mill speed and (*b*) screen thickness on particle size at a constant screen-opening size.[3]

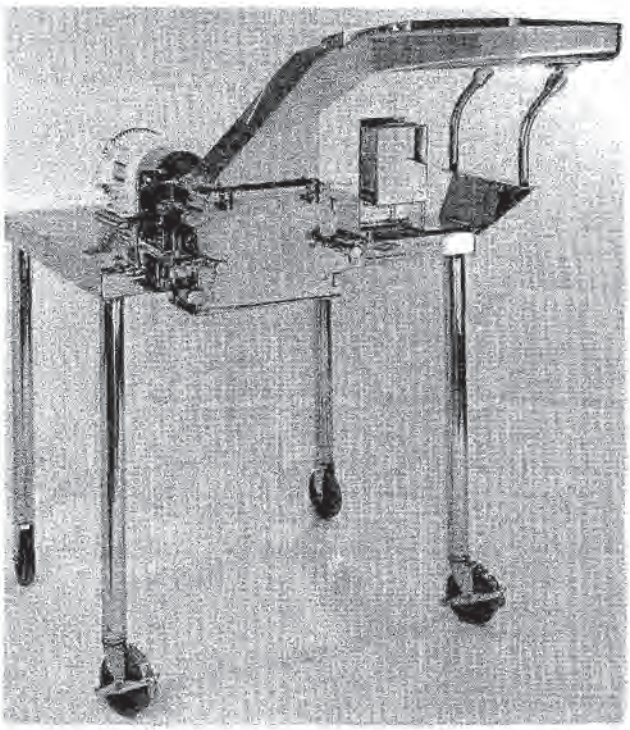

Fig 88-2. EZ-Clean FitzMill Comminutor (courtesy, Fitzpatrick).

A wide range of particle sizes down to the micron size can be produced by these mills. The particle shape, however, is generally sharper and more irregular than that produced by compression methods. When very fine particles are desired, hammer mills can be operated in conjunction with an air classifier. Under such conditions a narrower particle-size distribution and lower grinding temperatures are obtained. Fine pulverizing of plastic material can be accomplished in these mills by embrittlement with liquid N_2 or CO_2 or by jacketing the grinding chamber.

Centrifugal-Impact Mills and Sieves are useful to minimize the production of fine particles, since their design combines sieving and milling into a single operation. The mill consists of a nonrotating bar or stator which is fixed within a rotating sieve basket. The particles which are smaller than the hole size of the sieve can pass through the mill without comminution; however, the particles or agglomerates larger than the hole size are directed by centrifugal force to impact with the stator. The sieve baskets also can be constructed to have a cutting edge which can aid in particle-size reduction without impact with the stator. The Quick Sieve (Fig 88-3), Turbo Sieve and CoMill are examples of this type of mill.

Cutter Mills are useful in reducing the particle size of fibrous material and act by a combined cutting and shearing action. They consist of a horizontal rotor in which are set a series of knives or blades. This rotor turns within a housing into which are set stationary bed knives. The feed is from the top and a perforated plate or screen is set into the bottom of the housing through which the finished product is discharged. The particle size and shape is determined by the plate size, gap between rotor and bed knives and size of the openings. A number of rotor styles are available to provide different particle shapes and sizes, though cutter mills are normally not designed to produce particles finer than 80- to 100-mesh.

Attrition Mills make use of two stone or steel grinding plates, one or both of which revolve to provide grinding mainly through attrition. These mills are most suitable for friable or medium-hard, free-flowing material.

The Sprout-Waldron double runner attrition mill is an

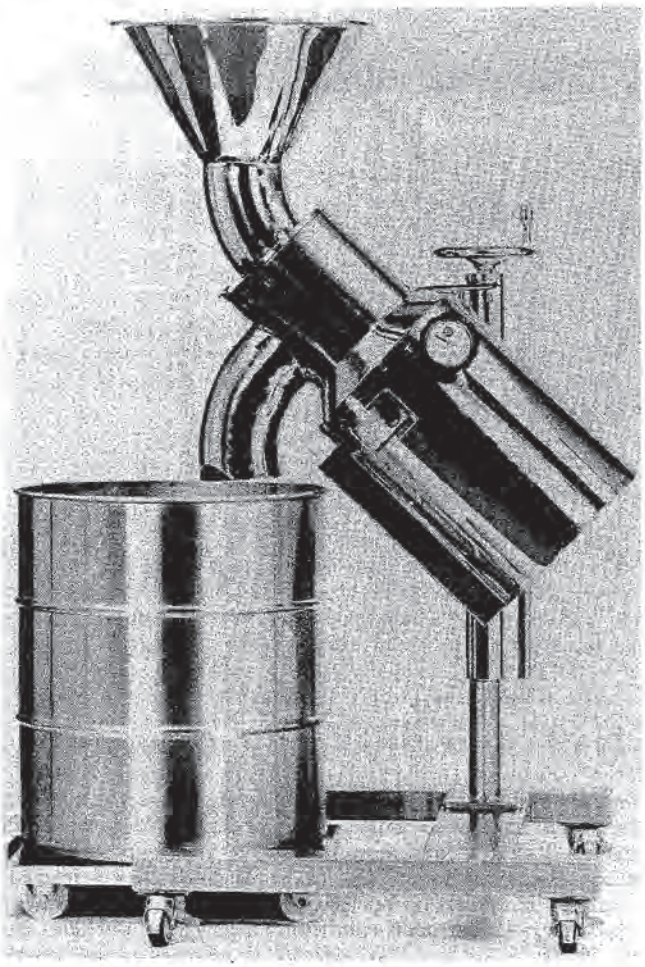

Fig 88-3. Quick Sieve (courtesy, Glatt Air).

example of a mill which uses two rotating disks revolving in opposite directions. The particle-size reduction is controlled by varying the speed at which the disks revolve, the space between the disks and the size and number of ridges and indentations in the face of the disks. By appropriate combination with a classifier, particle sizes ranging from 10-mesh to 20 μm can be obtained by these attrition mills.

Chaser Mills are so called because two heavy granite stones, or chasers, mounted vertically like wheels and connected by a short horizontal shaft, are made to revolve or *chase* each other upon a granite base surrounded by a curb. Revolution of the chasers produces an upward current of air; this carries over the lighter particles, which fall outside the curb and subsequently are collected as a fine powder.

Pebble or Ball Mills, sometimes called "pot mills" or "jar mills," are operated on the principle of attrition and impact, the grinding being effected by placing the substance in jars or cylindrical vessels, lined with porcelain or a similar hard substance and containing "pebbles" or "balls" of flint, porcelain, steel or stainless steel. These cylindrical vessels revolve horizontally on their long axis and the tumbling of the pebbles or balls over one another and against the sides of the cylinder produces pulverization with a minimum loss of material. Ball-milling is a relatively slow process and generally requires many hours to produce material of suitable fineness. In order to keep the grinding time within reasonable limits, coarse material (>10-mesh) should be preground before introduction into a ball mill. Fig 88-4 shows a sectional view of a single jar mill. Rod mills are a modification in which rods about 3 in shorter than the length of the mill are used in place of balls. This results in a lower production of fines and a somewhat more granular product.

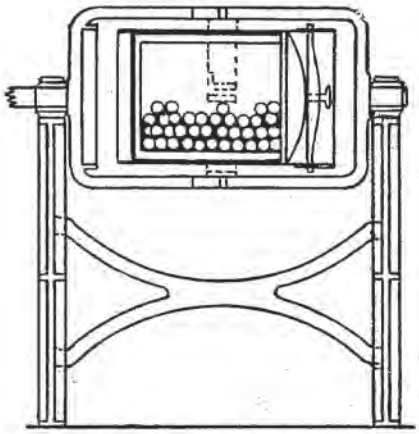

Fig 88-4. Single jar mill.

Vibrating Ball Mills, which also combine attrition and impact, consist of a mill shell containing a charge of balls similar to rotating ball mills. However, in this case the shell is vibrated at some suitable frequency, rather than rotated. These mills offer the advantage of being free of rotating parts, and thus can be integrated readily into a particle classifying system or other ancillary equipment. Furthermore, there have been several studies which have demonstrated that the vibrating ball mill will grind at rates often as high as 20 to 30 times that of the conventional tumbling mill and offer a higher order of grinding rate and efficiency than other prevailing milling procedures.

Fluid-Energy Mills are used for pulverizing and classifying extremely small particles of many materials. The mills have no moving parts, grinding being achieved by subjecting the solid material to streams of high velocity elastic fluids, usually air, steam or an inert gas. The material to be pulverized is swept into violent turbulence by the sonic and supersonic velocity of the streams. The particles are accelerated to relatively high speeds and when they collide with each other the impact causes violent fracture of the particles.

One type of fluid-energy mill is shown in Fig 88-5. The elastic grinding fluid is introduced through nozzles in the lower portion of the mill under pressures ranging from 25 to 300 psi. In this way, a rapidly circulating flow of gas is generated in the hollow, doughnut-shaped mill. A Venturi feeder introduces the coarse material into the mill and the

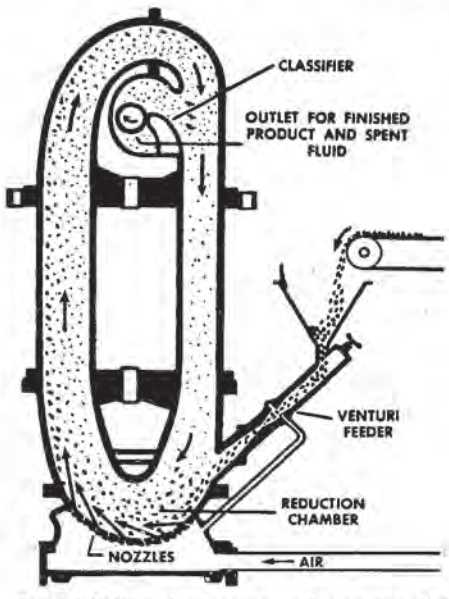

Fig 88-5. The Jet-O-Mizer fluid energy mill (courtesy, Fluid Energy).

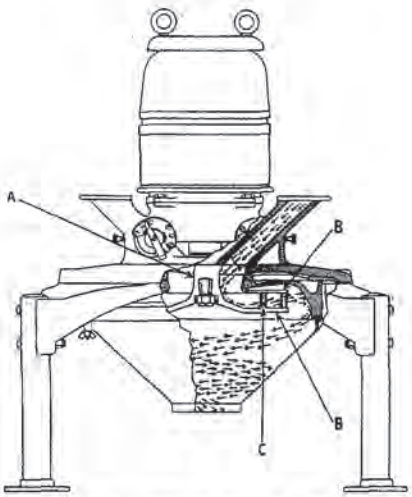

Fig 88-6. CentriMil, a centrifugal-impact mill, available in models ranging from 2 to 250 hp. A: Spinning rotor; B: rotor hub disks; C: impacters (courtesy, Entoleter).

particles enter into the jet stream of rapidly moving gas. The raw material is pulverized quickly by mutual impact in the reduction chamber. As the fine particles form they are carried upward in the track. Particles are ground simultaneously and classified in this process. The smaller particles are entrapped by the drag of gas leaving the mill and are carried out to a collecting chamber or bag. Centrifugal force at the top of the chamber stratifies the larger, heavy particles and their greater momentum carries them downward and back to the grinding chamber.

A major advantage of the fluid-energy mill is that the cooling effect of the grinding fluid as it expands in the grinding chamber more than compensates for the moderate heat generated during the grinding process. Another advantage is the rather narrow range of particle sizes produced. When precise control of particle size is an important factor, the fluid-energy mill produces very narrow ranges of particles with minimum effort.

One major disadvantage is the necessity of controlling the feeding of the coarse, raw material into the jet stream. Often, the feeding device becomes clogged by a clump of material, and special feeding devices must be built to produce a uniform rate of feed.

Centrifugal-Impact Pulverizers also have been found to be effective for the reduction of the particle size of a wide variety of materials ranging from very soft, organic chemicals to hard, abrasive minerals. In addition, this type of mill is suited well for the size reduction of heat-sensitive substances. Basically, in these pulverizers, the material is fed into the center of a spinning rotor which applies a high centrifugal force to the particles. The material, thus accelerated, moves toward the impactor set at the periphery of the rotor. On striking these impactors the material is hurled against the outer casing where final reduction is achieved. Processed material is removed from the bottom of the conical discharge hopper (Fig 88-6). Particle-size reduction in the range of 10- to 325-mesh can be obtained with this type of mill with a minimum of fines.

Particle-Size Measurement and Classification

Size and Distribution

Statistical Parameters—Monodisperse systems of particles of regular shape, such as perfect cubes or spheres, can be described completely by a single parameter, ie, length of a side or diameter. However, when either nonuniform size distributions or anisometric shapes exist, any single parameter is incapable of totally defining the powder. Measurements must be made over the total range of sizes present. Statistical diameters, for example, are useful measures of central size tendency and are computed from some measured property that is a function of size and related to a linear dimension. For irregular particles the assigned size will depend strongly on the method of measurement.

Table I—Definition of Statistical Diameters[a]

Type of mean diameter	Statistical definition	Description
Arithmetic	$\Sigma nd/\Sigma n$	Mean diameter weighted by number
Diameter moment	$\Sigma nd^2/\Sigma nd$	Mean diameter weighted by particle diameter
Surface moment	$\Sigma nd^3/\Sigma nd^2$	Mean diameter weighted by particle surface
Volume moment	$\Sigma nd^4/\Sigma nd^3$	Mean diameter weighted by particle volume
Surface	$(\Sigma nd^2/\Sigma n)^{1/2}$	Root mean square
Volume	$(\Sigma nd^3/\Sigma n)^{1/3}$	

[a] When grouped data are used, n is the number of particles in a size interval characterized by a diameter, d.

Once a method of assignment of numerical value for the diameter, surface area or other parameter has been established, the average value computed for the parameter is dependent on the weighting given the various sizes. Mean particle diameter is the most important single statistical parameter since, if the proper diameter is chosen, the various other parameters of interest such as specific surface area, number, mean particle weight, etc, often may be calculated. Thus, the choice of the mean diameter to be measured or calculated is based on its intended use. For example, specific surface area, which may control drug dissolution, frequently can be related to the root-mean square diameter. Depending on the method of measurement, various diameters are obtained; these will be discussed later. The particle diameters most commonly used are listed in Table I.

Size Distributions—As has been pointed out, size distributions are often complex and no single particle size parameter is sufficient to characterize or permit prediction of the many bulk properties of pharmaceutical interest, eg, flow characteristics, packing densities, compressibility or segregation tendencies. Thus, descriptions beyond the central tendency provided by the various mean diameters are needed. These generally take the form of equations or charts that describe in detail the distribution of particle size. In measuring particle size it is important first to select the parameter that is related to the ultimate use of the product, and then select the method that will measure this parameter.

Certainly, more-useful information would be gained if the particle size of a powder used in a suspension were determined by sedimentation than by microscopy, or if the total surface area of the particles were the critical factor (as in use as an adsorbant) by the more useful method of permeability or gas adsorption.

Particles can be classified by determining the number of particles in successive size ranges. The distribution can be represented by a bar graph or histogram (Fig 88-7), where the widths of the bars represent the size range and the heights represent the frequency of occurrence in each range. A smooth curve drawn through the midpoints of the tops of the bars in this case results in a normal probability size-distribution curve. A line drawn through the center of the curve to the abscissa divides the area into two equal parts and represents the mean value. Since a number of other

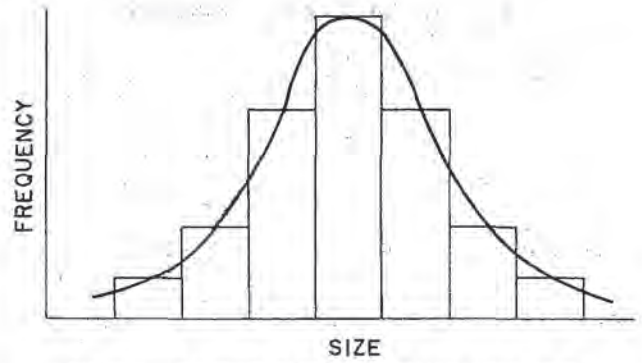

Fig 88-7. Symmetrical particle-size distribution curve.

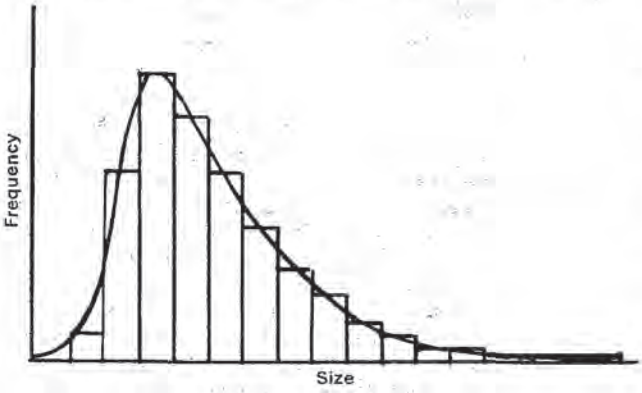

Fig 88-8. Skewed particle-size distribution curve.

symmetrical distributions could have this same midpoint, a term to describe the scatter about the mean value is needed. Standard deviation (the root-mean square deviation about the mean) serves to define the spread of the curve on either side of the midpoint.

Most particulate material cannot, however, be described by a normal distribution curve. The resultant curves are usually skewed as shown in Fig 88-8, making mathematical analysis complex. In a skewed size distribution the mean value is affected by very large or very small values. In these cases the median (ie, the central value of a series of observations) is a more useful average. In a symmetrical distribution the mean and the median values are the same. Most asymmetrical size distribution curves relating to powders can be converted into symmetrical curves by using the logarithm of the size, ie, Log Normal Distribution curve. The symmetrical shape of the latter curve allows for simplified mathematical analysis.

Cumulative plots are also useful for particle-size distribution analysis. Here the cumulative percent of the particles which are finer (or larger) than a given size is plotted against the size. By use of logarithmic–probability paper the median size (geometric mean) and standard deviation (geometric standard deviation) can be obtained readily by graphical solution. The median is the 50% size and the standard deviation is the slope of the line and equal to the ratio 50% size/15.87% size (Fig 88-9).

Size Measurement

Frequently, particle-size measurements are made in conjunction with separation of the powder into fractions on the basis of size. Methods that lead primarily to size distribution analysis only are discussed first, followed by methods in which classification by size is a central feature.

The basic processes employed for measurement, classification or fractionation of fine solid particles involve direct and indirect techniques. Direct methods measure the actual dimensions of the particle by use of a calibration scale as in microscopy and sieving. Indirect measurements make use of some characteristic of the particle that can be related to particle size; eg, sedimentation rates, permeability and optical properties.

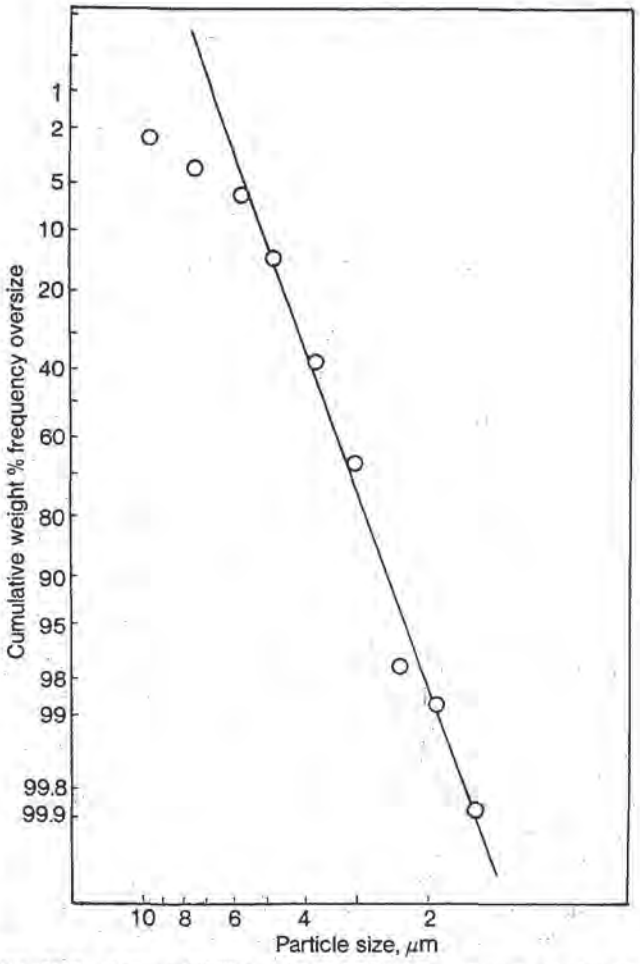

Fig 88-9. Log-probability plot of particle size versus cumulative weight % frequency oversize.

Microscopy—Microscopic techniques have been classified as one of the most accurate of *direct* methods. Here, particles are sized directly and individually, rather than being grouped statistically by some other means of classification. The linear measurement of particles is made by comparison with a calibrated scale usually incorporated into the microscope. For spherical particles the size is defined by the measurement of the diameter. However, for other-shaped particles some other single size designation is generally used; eg, the diameter of a sphere with the same projected area as the nonspheroidal particle being measured. Other characteristic diameters based on various aspects of the projected particle outline as seen through the microscope also have been reported in the literature to describe nonspheroidal particles.

The method is rather tedious and other limitations are found in the techniques required for preparation of the slides and in the maximum resolution which sets the lower limits of particle size measurement using visible light. White light can resolve particles within the range of 0.2 to 100 μm. This lower limit can be decreased to about 0.1 μm by the use of ultraviolet light and to about 0.01 μm by the use of the ultramicroscope. The electron microscope finds its greatest usefulness in particle-size measurements in the range of 0.2 to 0.001 μm.

While microscopic methods for particle size determination are time consuming, tedious, and generally require more skill than some of the other techniques, they offer a number of advantages. They supply information about the shape and thickness that cannot be obtained by other methods and, in addition, supply a permanent record through use of photomicrographs.

A variety of semiautomated procedures have been developed to reduce the fatigue and tedium associated with manual counting of particles. These are represented by instruments such as the Imanco Quantimet 720 and the πMC System (*Millipore*), which scan the powder image in a manner similar to a TV scanner. The signal obtained is analyzed by a pulse-height analyzer and expressed as a particle-size distribution.

Adsorption of Gases—Adsorption of a solute from solution or of a gas at low temperatures onto powdered material serves as a measure of the particle surface area, generally reported as specific surface (area/unit mass). Common adsorption techniques use the adsorption of nitrogen and krypton at low temperatures. The volume of the gas adsorbed by a powdered sample is determined as a function of gas pressure, and an appropriate plot is prepared. The point at which a monomolecular layer of adsorbate occurs is estimated from the discontinuity that shows in the curve. The specific surface area then can be calculated from a knowledge of the volume of gas required to achieve this monolayer, and the area/molecule occupied by the gas, its molecular weight and density. Frequently, more complex expressions such as the Brunauer, Emmett and Teller (BET) equation must be used to describe the surface adsorption of some materials and determine the volume of gas required to produce an adsorbed monolayer. The surface properties of a number of pharmaceuticals have been investigated by this technique.

Permeability—When a gas or liquid is allowed to flow through a powdered material, the resistance to this flow is a function of such factors as specific surface of the powder, area of the bed, pore space, pressure drop across the bed and viscosity of the fluid. This resistance can be described and the specific surface calculated by the Kozeny-Carmen equation, which relates these factors. This method, while it does not provide a size distribution analysis, offers a rapid and convenient means of size estimation that is useful for some industrial operations.

Instruments that measure the rate of flow of a gas through a powder bed under controlled pressure differential are available commercially. The Sub-Sieve Sizer (*Fisher*) permits the reading of average particle size directly. The Blaine Permeameter (produced by *Precision Scientific*) uses the principle of filling the void spaces in a powder with mercury and then weighing it. The void fraction is calculated from the known density of mercury at different temperatures.

The calculations involved in permeability techniques are often complicated and yield only an average size of particles. In measuring particles in the subsieve ranges, rather large deviations may be encountered. With larger mesh sizes, some good agreement is found between the results obtained by techniques employing permeability and microscopy, particularly if the powders are made up of spherical or near-spherical particles.

Impaction and Inertial Techniques—The laws that govern the trajectories of particles in fluid streams are used in several methods of particle-size measurement. Impaction devices are based on the dynamics of deposition of fine particles in a moving air stream when directed past obstacles of defined geometric form, or when forced from a jet device onto a plane surface.

The *cascade impactor*, described by Pilcher et al,[3] forces particle laden air at a very high speed and fixed rate through a series of jets (each smaller than the preceding one) onto glass slides; impaction takes place in a series of stages. The velocities of the air stream and the particles suspended in it are increased as they advance through the impactor. As a result, the particles are classified by impaction on the different slides, with the larger particles on the top slides and the smaller ones on the downstream slides. Figure 88-10 illustrates the principle of the cascade impactor. The exact size of impacted particles on each slide subsequently must be determined. Size analyses may be obtained directly by theoretical treatment or prior calibration of the instrument.

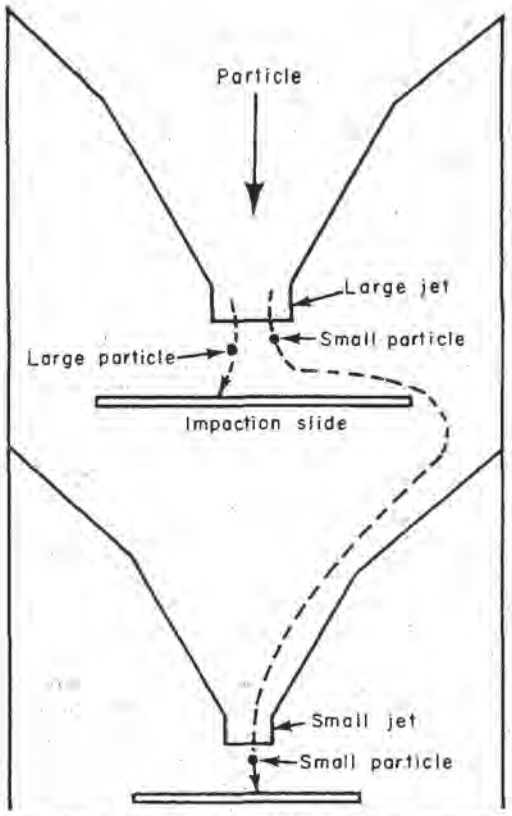

Fig 88-10. The principle of the cascade impactor.[3]

Tillotson[4] described an instrument based on inertial principles similar to those of the cascade impactor. This instrument may be adapted for automatic readout of size distribution by means of light-scattering techniques and electronic counters. The method is claimed to provide complete particle-size distribution data in a few minutes.

Automatic Particle-Size Counters—The Coulter Counter, HIAC Counter and Gelman Automatic Particle Counter represent three examples of automatic counting equipment.

The *Coulter Counter* will determine the particle volume distribution of material suspended in an electrolyte-con-

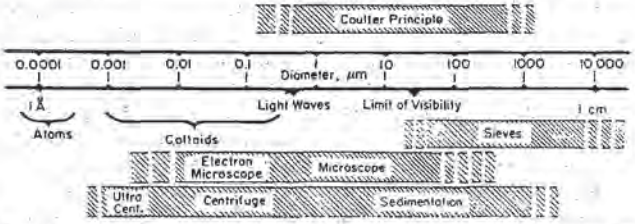

Fig 88-11. Size range of Coulter method compared with coverage of sieve, sedimentation and microscopic methods, and overlap of electron microscope and centrifuge ranges (courtesy, Coulter).

taining solution. A table of size ranges of several methods compared with the Coulter principle is shown in Fig 88-11. The principle underlying use of this instrument is described on page 496.

The *HIAC Counter* measures the size distribution of particles suspended in either liquids or gases. The standard models will measure sizes from 2 to 2500 μm at pressures up to 3000 psi. Basically, in this instrument the particles pass a window one-by-one. Each particle as it passes, depending on its size, interrupts some portion of a light beam. This causes an instantaneous reduction in the voltage from a photodetector which is proportional to the size of the particle. Several counting circuits with preset thresholds tally the particles by size.

The *Gelman Counter* uses the principles of light-scattering to count particles in the air in the range of 0.5 μm and larger.

Size Classification

Sieving—This is one of the simplest and probably the most frequently used method for determining particle-size distribution. The technique basically involves size classification followed by the determination of the weight of each fraction.

In this technique, particles of a powder mass are placed on a screen made up of uniform apertures. By the application of some type of motion to the screen, the particles smaller than the apertures are made to pass through. The sieve motion generally is either (1) horizontal, which tends to loosen the packing of the particles in contact with the screen surface, permitting the entrapped subsieve particles to pass through or (2) vertical, which serves to agitate and mix the particles as well as to bring more of the subsieve particles to the screen surface.

One major difficulty associated with this method is the production of screens with uniform apertures, particularly in the very fine mesh sizes. As a result the practical lower limit for woven-wire mesh screens is about 43 μm (325-mesh). However, with the introduction of electroformed screens, sieves capable of analyzing particles in the 5-μm range are now available. In addition, "blinding" of the openings by oversized or irregular particles and inefficient presentation of the particles to the screen surface are problems associated with this technique. The use of horizontal and vertical screening motions, airjets, sudden periodic reversal of the sieve motion and continuous cycling all have been used in an attempt to eliminate these problems.

For continuous operations, the screens are attached to mechanical or electromagnetic devices which supply the energy required to shake the particles through the openings in the screen and also prevent accumulation of fines within the openings as this tends to clog them and slow down the operation. The use of an electromagnetic instead of mechanical drive provides a more-gentle sieving action with a resultant decrease in sieve wear, blinding and less machine noise. Sieves may be used either in a sequence of sizes through which the material must pass or singly in the required size.

This apparatus is useful in obtaining size-analysis data under controlled conditions. The sample is placed in the top of the nest of standard sieves arranged in a descending order. The length of time and force of vibration to which the sample is subjected may be preset by variable time and voltage controls. The controlled vibration causes the powder particles to pass through the sieves, each fraction coming to rest in the sieve through which it cannot pass. For the purpose of analysis, the weight of each fraction is determined and the percentage calculated.

The Sonic Sifter (*Allen-Bradley* and *ATM*) is a laboratory sifter that uses sonic oscillation to classify particles. A mechanical pulse action is used to reduce blinding and agglomeration in the subsieve sizes. This combination of sonic and mechanical agitation permits dry sifting down to 5 μm. US Standard Sieves are available for this unit from 3½- to 400-mesh and in precision electroformed mesh sizes from 150 to 5 μm.

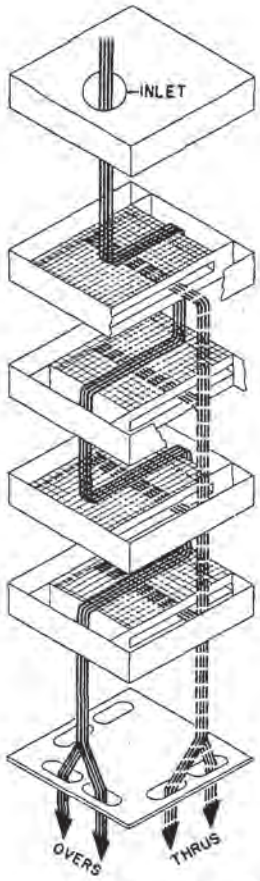

Fig 88-12. Gyro-Whip sifter (courtesy, Sprout-Waldron).

Industrial-size mechanical sieves are varied in design and capacity, and include the gyratory, circular rotatory, vibrating, shaking and revolving sifters. In gyratory sifters the motion is in a single horizontal plane, but may vary from circular to reciprocal from the feed to the discharge end. The circular sifter also confines the screen motion to a horizontal plane, but in this case the total motion applied to the sieve is circular. The Gyro-Whip (*Sprout-Waldron*) is an example of such a sifter in which the material enters the top and spreads over the first sieve. Some of the finer particles drop through and are discharged into the "throughs" channel. The remaining powder moves to the next sieve in order, the process is repeated until complete separation is accomplished (Fig 88-12).

Centrifugal screening is used in the Symons V-Screen (developed by *Nordberg*). Here the material is pushed through a spinning vertical wire cloth cylinder. Sharp cuts in particle size can be obtained with this equipment. Downward air flow, instead of shaking and tapping, has been used to move the particles through the screen openings; alternating with a reverse air flow serves to prevent "blinding," particularly with fine-mesh sieves.

Wet Screening—The addition of water sometimes is employed to dissolve out any unwanted binders, remove fines or surface contamination, and to reduce surface forces, particularly in micromesh sieves, that oppose the flow of particles through the sieve. Particles that tend to agglomerate or react with oxygen or moisture and thus cannot be dry-sieved

often can be handled by wet-sieving. Particles in the 6 to 150-μm range have been classified with good precision using electroformed sieves. Some hydrophobic substances which resist wetting by water may be wet screened by the use of organic liquids such as petroleum ether, acetone or alcohol. Wet-screening may be accomplished by spraying both the screen surface and the material as it is fed onto the screen or by feeding a slurry of material directly onto the screen.

Screening Surfaces—A number of factors must be considered in selecting screening surfaces. Primary consideration is given to the size and shape of the aperture opening, the selection of which is determined by the particle size that is to be separated. Screens commonly used in pharmaceutical processing include *woven wire screens*, *bolting cloth*, *closely spaced bars* and *punched plates*. Punched plates are used for coarse sizing; their holes may be round, oval, square or rectangular. The plates must be sturdy and withstand rough service. Sizes in common use range upward from $\frac{1}{4}$ in.

Most screening, however, is accomplished with woven-wire screens ranging in size from those with 400 openings/in to screens with 4-in square openings or larger. There are numerous types of woven wire screens, including plain, twilled and braided weave. An example of the plain and twilled weave is shown in Figs 88-13 and 88-14.

In the US, the two common standards are the *Tyler Standard* and *US Standard* sieves. In both these series the sieve number refers to the number of openings per linear inch. For most purposes, screens from the two series are interchangeable, though in a few instances the number designations are different. Since these numbers do not define the size of the openings the Bureau of Standards has established specifications for *Standard Sieves*, as given in Table II. These specifications also establish tolerances for the evenness of weaving, as irregularities from careless weaving might permit much larger particles to pass the sieve than would be indicated. The standard sieves used for pharmaceutical testing are of wire cloth.

Table II—Nominal Dimensions of Standard Sieves

No	Sieve opening, mm	Sieve opening, μm	Permissible variation in average opening, %	Permissible variation in maximum opening, %	Wire diameter, mm
2	9.52	9520	±3	+ 5	2.11 to 2.59
4	4.76	4760	±3	+10	1.14 to 1.68
8	2.38	2380	±3	+10	0.74 to 1.10
10	2.00	2000	±3	+10	0.68 to 1.00
20	0.84	840	±5	+15	0.38 to 0.55
30	0.59	590	±5	+15	0.29 to 0.42
40	0.42	420	±5	+25	0.23 to 0.33
50	0.297	297	±5	+25	0.170 to 0.253
60	0.250	250	±5	+25	0.149 to 0.220
70	0.210	210	±5	+25	0.130 to 0.187
80	0.177	177	±6	+40	0.114 to 0.154
100	0.149	149	±6	+40	0.096 to 0.125
120	0.125	125	±6	+40	0.079 to 0.103
200	0.074	74	±7	+60	0.045 to 0.061

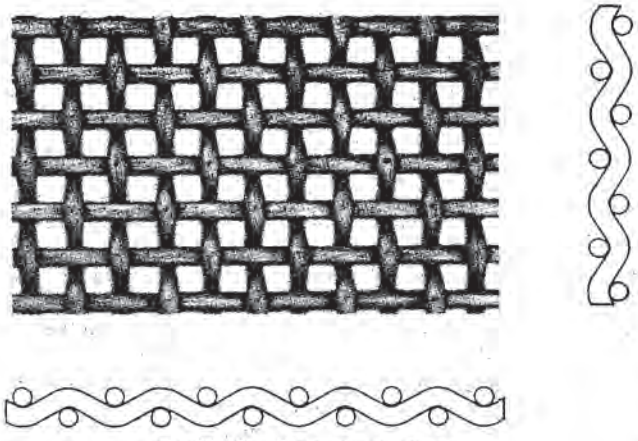

Fig 88-13. Plain weave screen.

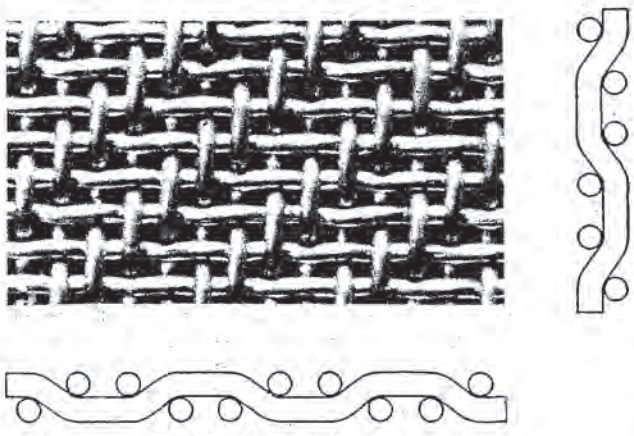

Fig 88-14. Twilled weave screen.

Sedimentation—This method employs the settling of particles in a liquid of a relatively low density, under the influence of a gravitational or centrifugal field. In free-settling (ie, no particle–particle interference) the particles are supported by hydraulic forces and their fall can be described by Stokes' law. However, in most real situations particle–particle interference, nonuniformity and turbulence are all present, resulting in more complex settling patterns. The Andreason pipet, which is based on sampling near the bottom of a glass sedimentation chamber, is perhaps the best known of the early instruments. With centrifugation, entrainment of particles in the currents produced by other particles also may interfere with fractionation.

Gravitational settling chambers often are used for large-scale separation of relatively coarse particles in the range of 100 μm. Centrifugal devices are useful for the separation of much smaller particles (5 to 10 μm).

Sedimentation balances are available which provide a means of directly weighing particles at selected time intervals as they fall in a liquid system. For continuous observations, automatic recording balances are also available. A commercially available instrument called a *Micromerograph* uses the principle of sedimentation in an air column. This instrument and others related to it in principle offer more rapid determinations than those which use a liquid medium. There are, however, serious uncertainties in the method which must be taken into consideration. Deviations from Stokes' law and impaction of particles against the inner wall of the settling chamber are sources of possible error.

The Carey and Stairmand *photosedimentometer* photographs the tracks of particles as they fall in a dispersion medium. The size determination is derived from the length of the photographic track, which is an indication of the distance traveled by the particles, and the time of exposure of the photograph.

Elutriation—In this process the particles are suspended in a moving fluid, generally water or air. In vertical elutriation at any particular velocity of the fluid, particles of a given size will move upwards with the fluid, while larger particles will settle out under the influence of gravity. In horizontal

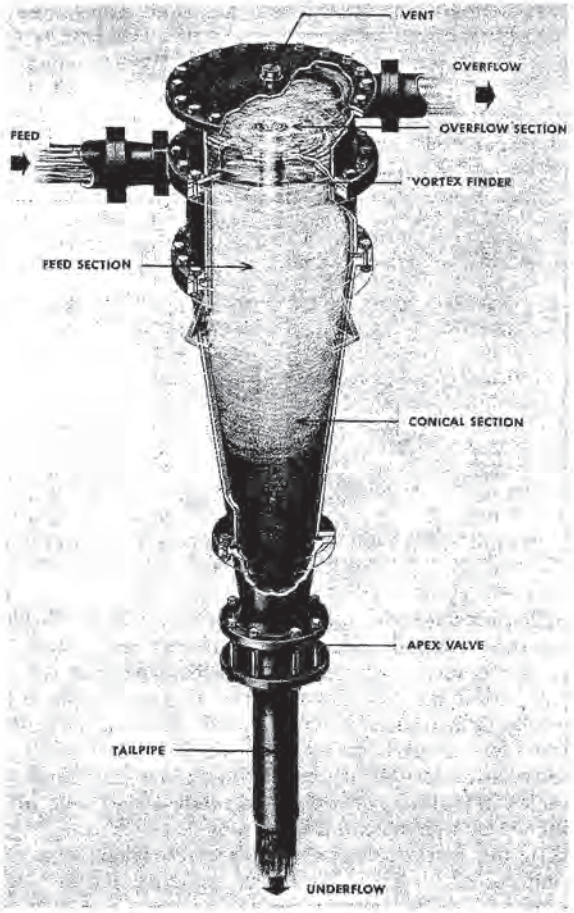

Fig 88-15. DorrClone, a hydrocentrifugal classifier (courtesy, Dorr-Oliver).

elutriation a stream of suspended particles is passed over a settling chamber. Particles that leave the stream are collected in the bottom of the chamber. Normally, for all elutriation techniques, both undersize and oversize particles appear in each fraction and recycling is required if a clean cut is desired. By varying the fluid velocities stepwise the sample may be separated into fractions. The amount in each fraction then can be determined and the size limits calculated by the use of the Stokes' equation or measured directly by microscopy. Air elutriation usually will give a sharper fractionation in a shorter time than will water elutriation.

Centrifugal elutriation is basically the same process, except in this case the fluid stream is caused to spin so as to impart a high centrifugal force to the suspended particles. Those particles which are too large to follow the direction of flow separate out on the walls or bottom of the elutriator or cyclone. The finer particles escape with the discharge stream. Separation down to about 0.5 μm can be achieved with some centrifugal classifiers.

The DorrClone (*Dorr-Oliver*) (Fig 88-15) is an example of a centrifugal-type classifier. The feed enters tangentially into the upper section. Centrifugal forces in the vortex throw the coarser particles to the wall where they collect and then drop down and out of the unit. The fine particles move to the inner spiral of the vortex and are displaced upward and finally out of the top of the unit.

The Super Classifier (*Sharples*) (Fig 88-16) is another example of a centrifugal classifier useful for the high-speed separation of fine particles. It has a capacity of about 250 lb/hr and operates at an air flow of about 100 cu ft/min at a maximum rotor speed of about 15,000 rpm.

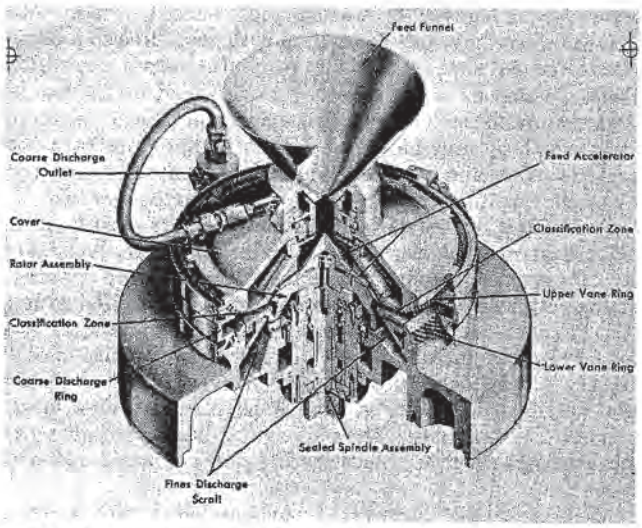

Fig 88-16. The Sharples K-8 Super Classifier (courtesy, Sharples).

The Donaldson air classifier subjects the feed particles to a high degree of dispersion just prior to classification and thus is able to make sharp separations in production quantities as low as 0.5 μm.

Inertial elutriators, which use an abrupt change in direction of the fluid stream to produce separation, are effective down to about 200-mesh. However, as with other elutriators a clean cut usually cannot be obtained without recycling.

Felvation is a unique process that combines elutriation and sieving along with a varying fluid flow rate and a turbulent fluidized bed to achieve particle separation. The particles are fluidized within the felvation column. By gradually increasing the fluid flow rate the very fine particles are brought up to and then through a sieve surface set into the upper section of the column. These fines are filtered subsequently out of the fluid stream. A further increase in the fluid flow rate causes larger and larger particles to move through the sieve. The final stage is reached when particles just larger than the sieve aperture are elutriated up to the sieve. Because of the way in which the particles are presented to the sieve, very little blinding of the openings occur. Furthermore, since the sieve need only serve as a "go, no go" gauge and not as a supporting surface for the powder, a relatively small sieve surface is required. Thus, the more-uniform but more-expensive electroform sieves, even down to a 10-μm size, can be used in this process.

Miscellaneous Methods—Numerous other methods have been applied to particle-size determination, including X-ray and electron diffraction, ultrasound, flotation and electrostatic, magnetic and dielectrophoretic methods. These techniques either are used principally as research tools or are industrial-scale methods of use outside the pharmaceutical industry. Detailed descriptions of their principles of operation and their applications can be found in the *Bibliography*.

Solids Handling

Packing and Bulk Properties

Bulk Density; Angles of Repose—Systems of particulate solids are the most complex physical systems encountered in pharmacy. No two particles in a powder are identical and the nature of momentum and energy exchange between particles defies description except in the most idealized and approximate terms. Bulk properties of pow-

ders are determined in part by the chemical and physical properties of their component solids and in part by the manner in which the various components interact. These interactions in turn frequently depend on the past history of the powder bed as well as on the ambient conditions.

The static properties of a particulate bed depend on particle–particle interactions and, in particular, on the way in which applied stresses are distributed through the bed. The number of contacts between particles and, hence, the average number of interparticulate contact points per particle increases as bed-packing increases. Packing may be expressed in terms of porosity, percent voids or fraction of solids by volume. Packings for regular arrangements of uniform spheres can be calculated and range in fractional solids from 0.53 for cubic to 0.74 for tetrahedral lattices. Powders comprised of irregular-shaped particles in a distribution of sizes can pack to fractional densities approaching unity.

The manner in which stresses are transmitted through a bed and the bed's response to applied stress are reflected in the various angles of friction and repose. The most commonly used of these is the angle of repose which may be determined experimentally by a number of methods, with slightly differing results. The typical method is to pour the powder in a conical heap on a level, flat surface and measure the included angle with the horizontal. Angles of repose range from 23° for smooth uniform glass beads to 64°for granular limestone. Cohesive materials frequently behave in an anomalous manner yielding values in excess of 90°.

The angle of internal friction is a measure of internal stress distributions and is the angle at which an applied stress diverges as it passes through the bed. This angle together with the angle of slide are useful parameters in the design of storage/discharge bins. The latter angle is defined as the least slope at which a powder will slide down an inclined plane surface. Various other angles are in lesser use and will not be discussed here.

Statics—Powders at rest experience stresses that vary with location throughout their volume and arise from pressures exerted by the container as well as from the weight of the bed above. Each point within the bed experiences both normal and shear stresses in general. Normal stresses may be either tensile or compressive. The powder bed will remain motionless and no flow will occur unless the normal and/or the shear strength is exceeded at some point within the bed. In general, the yield strengths, both normal and shear, are functions of the normal and shear stresses at the point of interest and depend upon the orientation of the axes of reference and the nature of the powder itself. It is apparent that to understand powder flow it is necessary to understand the conditions under which bed failure occurs and powder flow is initiated and sustained.

Consider the stresses which are applied to the faces of a small cube that is centered about a point chosen at random within a powder bed. Normal stresses are designated σ_i, where the subscript indicates the axis normal to the face and shear stresses are designated τ_{ij}, where the first subscript indicates the face and the second indicates the direction of the applied force. If the cube has an edge length, l, which is not infinitesimal, and if a stress gradient exists within the region, the corresponding stresses on opposite faces of the cube will not be equal. However, if the cube is made progressively smaller and as l approaches zero, the stress values will converge to those at the point of interest. These forces are illustrated in Fig 88-17. It can be seen from this diagram that the state of stress at a point can be described by nine stress components.

If the system is in static equilibrium, and is not being accelerated translationally or rotationally, the forces which otherwise would result in movement must be in balance and

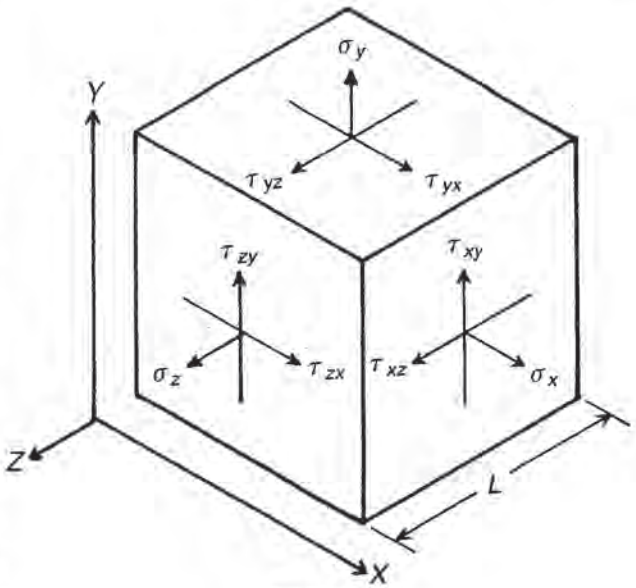

Fig 88-17.

have the effect of canceling each other. For example, τ_{xy} must equal τ_{yx} if rotation about the z-axis is not to occur. In a similar manner, shear and normal stresses, which would lead to translational movement along any of the three axes, also must balance.

Because the directions of the mutually perpendicular axes in Fig 88-17 were chosen arbitrarily, any other orientation of the cube corresponding to another set of axes also must result in a balance of forces. However, the distribution of stress among normal and shear components will depend on the particular axes selected. Thus, the stress condition of a powder can be analyzed in terms of the dependence of the normal and shear stresses on the direction chosen for the reference axes. This can be done by a method of analysis devised by Mohr, and can be visualized using a Mohr circle diagram, which permits stresses at any given point within a powder bed to be graphically resolved into normal, σ, and shear, τ, stresses for any arbitrary choice of axes.

For simplicity, assume that stress in the z-direction is not a function of z and that stress gradients exist in the x and y directions only. Stresses then can be analyzed in the xy plane without reference to the z-axis. Fig 88-18 shows the relationship between stresses relative to two xy coordinate systems at an angle θ to each other. If the condition of stress in the powder remains constant and only the angle θ between the two sets of reference axes is allowed to change, the resolution of stress into normal and shear components will be different for each set of axes and will depend on θ. By means of trigonometry, the relationships between these two sets of stresses is shown to be

$$\sigma_{x'} = \frac{\sigma_x + \sigma_y}{2} + \frac{\sigma_x - \sigma_y}{2}\cos 2\theta + \tau_{xy}\sin 2\theta$$

$$\sigma_{y'} = \frac{\sigma_x + \sigma_y}{2} - \frac{\sigma_x - \sigma_y}{2}\cos 2\theta - \tau_{xy}\sin 2\theta$$

$$\tau_{x'y'} = -\frac{\sigma_x - \sigma_y}{2}\sin 2\theta - \tau_{xy}\cos 2\theta$$

These equations permit the calculation of σ and τ values for any desired set of axes if the values are known for any given set of axes. In particular, if θ is chosen properly, $\tau_{x'y'}$ can be made to vanish and normal stresses only will remain. The set of axes for which this is true are called the *principal*

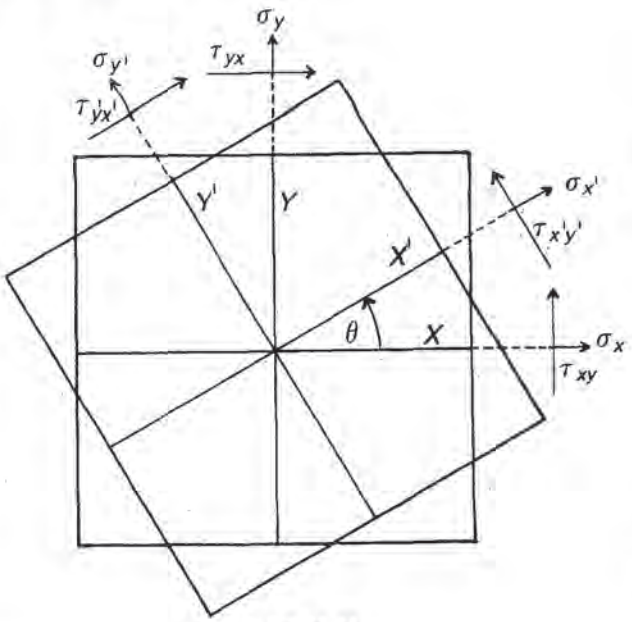

Fig 88-18.

axes of stress and the corresponding σ's are called the *principal stresses*. All points within static beds of powders can be characterized by principal axes and stresses which will, in general, vary from point to point throughout the bed. The principal axes do not correspond necessarily to the orientation of the walls of the powder container.

These concepts can be extended to three dimensions. Thus, it is possible to find a set of three mutually perpendicular planes, on which there are no shear stresses acting, for each location within the powder. The normals to these planes are the principal axes. It also is possible to find a set of planes for which the shear stresses are a maximum and the normal stresses are equal. The associated axes are called the axes of maximum shear. These two sets of axes are important since they represent directions of bed failure were it to occur.

The relationships between stresses, as functions of θ, can be illustrated and determined graphically. Figure 88-19 is an example of a Mohr's circle diagram for stress. Such diagrams are based on the stress equations. This can be seen by comparing Fig 88-19 with the equations, noting the relationships of the stresses of θ. A Mohr diagram can be constructed for any point within the powder, permitting stresses to be resolved graphically into normal and shear components for any arbitrary choice of axes.

Steps in constructing a diagram are

Plot the center of the circle, p, on the σ axis at the average normal stress, $(\sigma_x + \sigma_y)/2$.

Plot point x and y with coordinates (σ_x, τ_{xy}) and (σ_y, τ_{xy}), respectively. Note that these three points lie on a diameter of the circle.

Draw a circle with its center at p and passing through points x and y.

Locate the $x'y'$ diameter using the angle 2θ.

The stress components corresponding to the new axes can be read off the graph. Both $\sigma_{x'}$ and $\sigma_{y'}$ are read off the same axes on the graph since both are normal stresses.

For the particular case in Fig 88-19, the principal axes lie at an angle of θ^* to the original axes. The axes of maximum shear stress lie at an angle of θ^* from the original axes since the xy line corresponding to maximum shear is perpendicular to the σ axis. Depending on the state of the powder, it is possible to have negative σ values, where the Mohr circle passes to the left of the τ axis.

The application of stress normal to a plane of shear influences the shear stress at which the powder fails. Because of this, a given powder will fail at various combinations of normal and shear stresses. These combinations can be expressed graphically by a line in the σ,τ plane which separates regions on the graph at which the powder either flows or is stable. This is shown in Fig 88-20 for a typical powder. Various powders will display curves which uniquely define their failure characteristics. Each point on such a curve corresponds to a σ,τ combination at which failure occurs and can be analyzed by constructing a Mohr circle which passes through the point and is centered on the intersection of a line perpendicular to the point, q, and the σ axis. An example is shown in Fig 88-20.

Bulk Properties—In addition to the angles of repose and friction which reflect bulk behavior, tensile and shear strength and dilatancy are of interest. Tensile strength is measured by forming a powder bed on a roughened and split plate. Half of the plate is laterally movable and the force necessary to rupture the bed by pulling the plate halves apart, minus sliding plate friction corrections, represents the bed tensile strength. Various methods of applying force to the movable plate are used, including tipping the plate from the horizontal and allowing it to react to gravity by rolling on steel balls.

Shear strength is determined from the force necessary to shear horizontally a bed of known cross-section. The Jenike

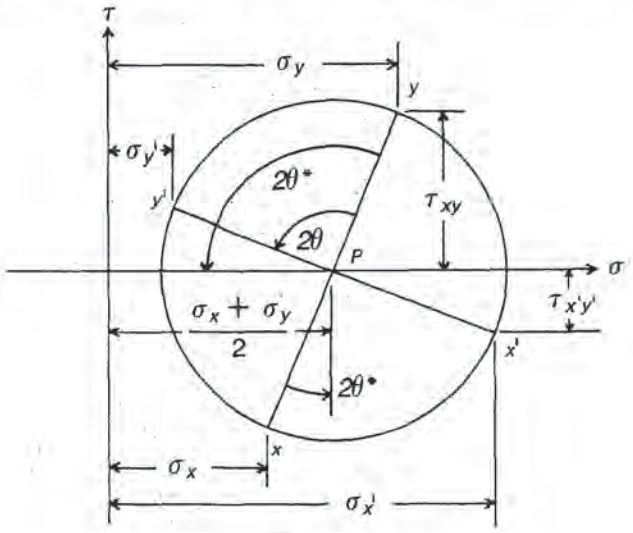

Fig 88-19.

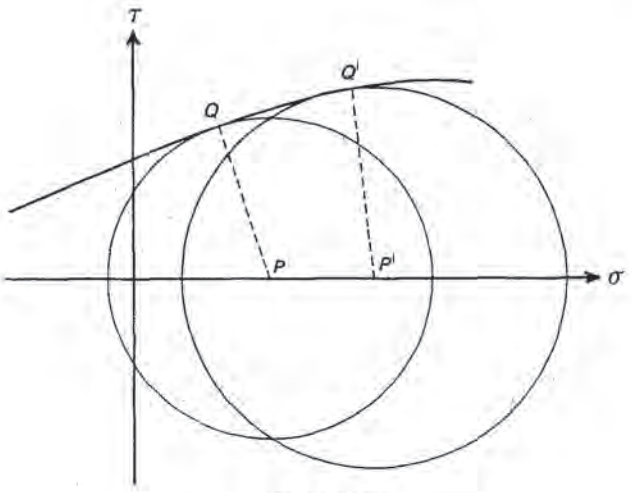

Fig 88-20.

shear cell is typical of those in use. It permits various loads to be applied normal to the plane of shear, whereby a shear failure locus can be determined. With the desired normal load applied, a steadily increasing shearing force is applied until failure occurs. These measurements are the basis for constructing powder-failure curves such as that in Fig 88-20.

When packed powder beds are deformed, local expansion occurs along the failure planes, barring fracture of the particles themselves. This phenomenon is termed dilatancy and is a direct consequence of the micromechanics of interparticulate movement. For one particle to move past another it is necessary for it to move to the side in order to move forward when the particles are in an "interlocked" arrangement. Such arrangements predominate in packed beds with the consequence that the collective sideways movements in the failure zone produce bed expansion. Room for expansion therefore must be provided when packed beds are forced to flow.

Mixing of Powders

Degree of Homogeneity—Many mathematical expressions have been proposed and used to express the degree of homogeneity of powders comprised of two or more components. For the most part measures of mixture uniformity have been statistical and based on either the standard deviation or variance of the composition from its mean value. It should be recognized that these indices of mixing are scalar quantities and are incapable of uniquely describing the composition profile of a given powder bed. A practical definition of mixing uniformity should be selected to relate as closely as possible to the desired properties of the mix. The manner in which samples are taken (number, size and location of samples) largely determines the validity and interpretation of the derived index.

The standard deviation is presented here as a representative index. It can be estimated solely from a set of n samples. If sample number i has composition x_i, and all samples are of uniform size, the sample standard deviation is defined in the usual way as

$$s = \sqrt{\sum_{i=1}^{n} (x_i - \bar{x})^2/(n-1)}$$

where $\bar{x}$ is the mean composition estimated from the samples alone.

In sampling a bed, there should be assurance that the bed is sampled uniformly over its entirety. This can be done either by use of a sampling "thief" designed to probe the bed and collect samples at selected points or serially as the powder is discharged from the mixer.

The "scale of scrutiny" at which the powder is examined for uniformity is determined by the sample size. This should be chosen based on the ultimate use of the powder. For a tablet or capsule formulation the appropriate sample size is that of the dosage form.

Two important concepts related to mixing uniformity have been described by Danckwerts as the scale and intensity of segregation. Assuming that zones having uniform but differing compositions exist in a powder bed, the scale of segregation is a function of the size of the zones. The intensity of segregation is in turn a function of the composition differences among zones. Generally, the process of mixing tends to reduce the intensity of segregation while the scale of segregation passes through a minimum.

Mechanisms of Mixing and Segregation—Three primary mechanisms are responsible for mixing:

Convective movement of relatively large portions of the bed.
Shear failure which primarily reduces the scale of segregation.
Diffusive movement of individual particles.

Most efficient mixers operate to induce mixing by all three mechanisms. Thus, mixing can be considered to be a random shuffling-type operation involving both large and small particle groups and even individual particles. However, it should be noted that the use of random motion to achieve random distribution assumes that no other factors influence this distribution. This is rarely if ever the case in practice. Instead, a variety of properties of the powders being mixed influence this approach to complete randomness. Stickiness or slipperiness of particles must be considered, among other factors. As might be expected, the stickier the material, the less readily it mixes and demixes. Electrostatic forces on the particle surface also can produce marked effects on the mixing process, and in fact may produce sufficient particle–particle repulsion to make random mixing impossible.

By enabling particles to undergo movement relative to each other, mixers also provide the conditions necessary for segregation to occur. Any manipulation of a powder bed for purposes of conveying, discharge from a hopper, etc, provides the opportunity for segregation. Thus, many of the so-called mechanisms of segregation are actually conditions under which segregation can happen.

The segregation that occurs in free-flowing solids usually does so as a result of differences in particle size and, to a lesser extent, to differences in particle density and shape. The circumstances leading to segregation can be generalized from a fundamental physical standpoint. The necessary and sufficient conditions for segregation to occur are that (1) various mixture components exhibit mobilities for interparticulate movement which differ and (2) the mixture experience either a field which exerts a directional motive force on the particles or a gradient in a mechanism capable of inducing or modifying interparticulate movement. The combination of these conditions results in asymmetric particle migrations and leads to segregation.

Rates of Mixing and Segregation—Rate expressions analogous to those of chemical kinetics can be derived using any of the various indices of mixing as time dependent variables. When this is done, it usually is found that mixing follows a first-order approach to an equilibrium state of mixedness. More recently, mixing has been described as a stochastic process (by means of stationary and nonstationary Markov chains) in which the probabilities of particle movement from place to place in the bed are determined. When applied to a mixer, this approach is capable of indicating zones of greater and lesser mixing intensity.

Large-Scale Mixing Equipment—The ideal mixer should produce a complete blend rapidly with as gentle as possible a mixing action to avoid product damage. It should be cleaned and discharged easily, be dust-tight and require low maintenance and low power consumption. All of these assets generally are not found in any single piece of equipment, thus requiring some compromise in the selection of a mixer.

Rotating-Shell Mixers—The drum-type, cubical-shaped, double-cone and twin-shell blenders are all examples of this class of mixers. Drum-type blenders with their axis of rotation horizontal to the center of the drum are used quite commonly. These, however, suffer from poor crossflow along the axis. The addition of baffles or inclining the drum on its axis increases crossflow and improves the mixing action. Cubical- and polyhedron-shaped blenders with the rotating axis set at various angles also are available. However, in the latter, because of their flat surfaces, the powder is subjected more to a sliding than a rolling action, a motion which is not conducive to the most efficient mixing.

Double-cone blenders, an important class of rotating-shell or tumbling mixers, were developed in an attempt to overcome some of the shortcomings of the previously discussed

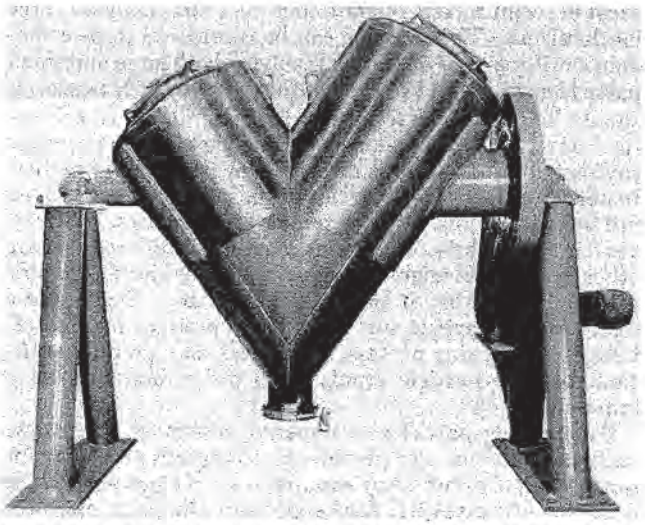

Fig 88-21. Cross-Flow twin-shell blender (courtesy, Patterson-Kelley).

mixers. Here, the mixing pattern provides a good crossflow with a rolling rather than a sliding motion. Normally, no baffles are required so that cleaning is simplified. The twin-shell blender is another important tumbling-type blender. It combines the efficiency of the inclined drum-type with the intermixing that occurs when two such mixers combine their flow.

The Cross-Flow blender (*Patterson-Kelley*) (Fig 88-21) is an example of a twin-shell blender. The uneven length of each shell in this blender provides additional mixing action when the powder bed recombines during each revolution of the blender. The Zig-Zag blender, an extension of the twin-shell blender, provides efficient continuous precision blending.

Fixed-Shell Mixers—The ribbon mixer, one of the oldest mechanical solid–solid blending devices, exemplifies this type of mixer. It consists of a relatively long troughlike shell with a semicircular bottom. The shell is fitted with a shaft on which are mounted spiral ribbons, paddles or helical screws, alone or in combination. These mixing blades produce a continuous cutting and shuffling of the charge by circulating the powder from end to end of the trough as well as rotationally. The shearing action that develops between the moving blade and the trough serves to break down powder agglomerates. However, ribbon mixers are not precision blenders; in addition, they suffer from the disadvantage of being more difficult to clean than the tumbler-type blenders and of having a higher power requirement.

Sigma-Blade and Planetary Paddle Mixers also are used for solid–solid blending, although most generally as a step prior to the introduction of liquids. Mixers with high-speed impeller blades set into the bottom of a vertical or cylindrical shell have been shown to be very efficient blenders. This type, in addition to its ability to produce precise blends, serves also to break down agglomerates rapidly. The mechanical heat buildup produced within the powder mix and the relatively high power requirement are often drawbacks to the use of this type of mixer; however; the shorter time interval necessary to achieve a satisfactory blend may offset these factors.

Muller Mixers are a specialized class of mixers, useful for heavy-duty operations requiring high shearing forces. The mulling action is a shearing mechanism, and is the closest to the type of mixing achieved by the hand-operated mortar and pestle.

Vertical Impeller Mixers, which have the advantage of requiring little floor space, employ a screw-type impeller which constantly overturns the batch (Fig 88-22). The fluidized mixer is a modification of the vertical impeller type. The impeller is replaced by a rapidly moving stream of air fed into the bottom of the shell. The body of the powder is fluidized and mixing is accomplished by circulation and overtumbling in the bed (Fig 88-23). Generally, when precision solid–solid blending is required, the rotating twin-shell or the double-cone-type blenders are recommended.

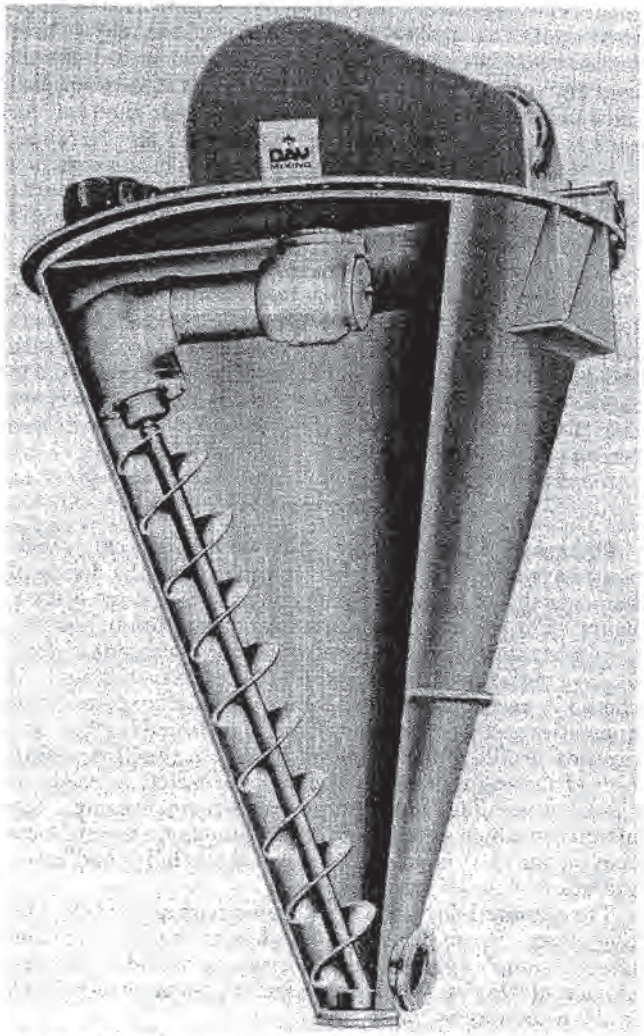

Fig 88-22. Cutaway view of the Mark II Mixer (courtesy, JH Day).

Motionless Mixers—These are in-line continuous processing devices with no moving parts. They consist of a series of fixed flow-twisting or flow-splitting elements. The Blendex (*Ross & Son*), designed for blending of free-flowing solids, is constructed to operate in a vertical plane. Four pipes interconnect with successive tetrahedral chambers, the number of chambers needed depending on the quality of mix desired. The powders enter the mixer from overhead hoppers and free fall through the mixer and are mixed by what is described as Interfacial Surface Generation. For two input streams entering this mixer the number of layers, L, emerging from each of the successive chambers, C, is $L = 2(4)^C$. Thus for 10 chambers over 2 million layers are generated. This type provides efficient batch or continuous mixing for a wide variety of solids without particle-size reduction or heat generation and essentially no maintenance. Units are available to mix quantities ranging from 100 to 5000 lb/hr.

Small-Scale Mixing Equipment—The pharmacist most generally employs the mortar and pestle for the small-scale

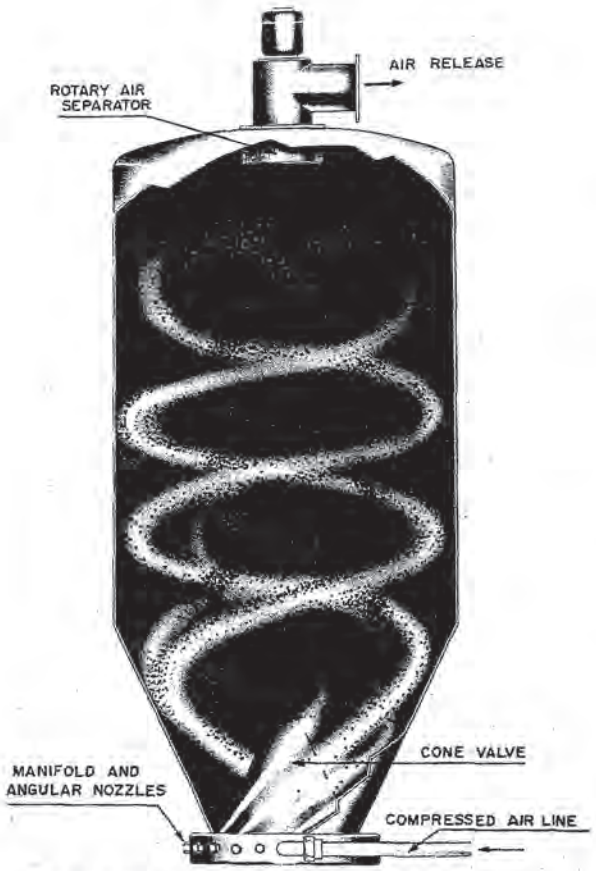

Fig 88-23. Air Mix mixer (courtesy, Sprout-Waldron).

mixing usually required for prescription compounding. However, the use of spatulas and sieves also may be utilized on occasion. The mortar and pestle method combines comminution and mixing in a single operation. Thus, it is particularly useful where some degree of particle-size reduction as well as mixing is required as in the case of mixtures of crystalline material.

The blending of powders with a spatula on a tile or paper, or spatulation, is used sometimes for small quantities of powders often as an auxiliary blending technique or when the compaction produced by the mortar and pestle technique is undesirable. Spatulation is a relatively inefficient method of mixing and is used rarely to prepare a finished dosage form.

Sieving usually is employed as a pre- or post-mixing method to reduce loosely held agglomerates and to increase the overall effectiveness of a blending process. When used alone as a solid–solid blending technique, several passes through the sieve are required to produce a reasonably homogeneous mix.

Storage and Flow

Flow Patterns—Discharge of powders from large-scale mixers, storage bins or machine-feed hoppers primarily generates flow in the form of shear failure, ie, the powder behaves in a manner analogous to a viscous liquid in laminar flow. The analogy ends at that point since conditions are then present in the powder bed conducive to segregation. The overall pattern of discharge from a bin takes the form of either funnel-flow or mass-flow. Bin-design characteristics, which take into account the powder's angles of slide and internal friction and its yield locus in terms of normal and shear stresses, determine which flow pattern will occur.

In funnel flow the powder moves in a column down the center of the bin toward the exit orifice at the bottom. Material surrounding this relatively rapidly moving core remains stationary or is drawn slowly into the core, which is fed primarily from the top where powder moves to the center and then down in the manner of a funnel.

The powder in a mass-flow bin moves downward toward the orifice as a coherent mass. When it reaches the tapered section of the bin leading to the orifice, it is compressed and flows in shear analogous to a plastic mass being compressed. This type of bin is advantageous for use with powders having a strong tendency to segregate.

The rate of discharge from a hopper varies as a function of the cube of the orifice diameter and is nearly independent of the height of the bed. An arch forms over the orifice which in effect is a boundary between material in essentially free fall and material in the closely packed condition of the powder bed. The rate of mass transport across this constantly renewed surface determines the rate of orifice flow. It has been shown that flow can be increased substantially if gas is pumped through the bed and across the orifice in the direction of solids flow. Flow conditioners are also an important means of improving flow and are discussed in Chapter 19.

Pneumatic Transport—This method of transporting powders is of interest since it can be used to mix powders at the same time as they are being conveyed. The method consists of propelling a solids–gas mixture along a conduit *via* a gas pressure drop. The solids are held in suspension by the turbulence of the gas stream. At low-solids concentrations, where the particles are relatively small, the solids are dispersed uniformly over the pipe cross-section. However, at higher solids content or with larger particles some stratification will occur in a horizontal pipe and solids will settle out if the pipe is overloaded.

Gas flow must be turbulent so as to suspend the solids; however, the solids behave as in laminar flow. Slippage between gas and solid occurs, particularly in vertical pipes, with the consequence that gas and solids flow rates are not in proportion to flow-stream composition. Further, smaller and less dense particles flow more rapidly than large and dense material and a chromatographic-like separation occurs. This is not a problem, however, once steady state is achieved. Because of the industrial importance of this process in many fields it has been investigated extensively and a number of useful theoretical and empirical expressions have been derived and may be used to predict conditions necessary for satisfactory pneumatic transport.

Powders as a Dosage Form

Historically, powders represent one of the oldest dosage forms. They are a natural outgrowth of man's attempt to prepare crude drugs and other natural products in a more conveniently administered form. However, with declining use of crude drugs and increasing use of many highly potent compounds, powders as a dosage form have been replaced largely by capsules and tablets.

In certain situations powders possess advantages and thus still represent a portion (although small) of the solid dosage forms currently being employed. These advantages are flexibility in compounding and relatively good chemical stability. The chief disadvantages of powders as a dosage form are they are time-consuming to prepare and they are not suited well for dispensing the many unpleasant-tasting, hygroscopic or deliquescent drugs.

Bulk powders have another serious disadvantage when compared with divided and individually weighed powders—inaccuracy of dose. The dose is influenced by many factors, including size of measuring spoon, density of pow-

der, humidity, degree of settling, fluffiness due to agitation and personal judgment. Not only do patients measure varying amounts of powder when using the same spoon but they often select one differing in size from that specified by their physician.

Extemporaneous Techniques

In both the manufacturing and extemporaneous preparation of powders the general techniques of weighing, measuring, sifting, mixing, etc, as described previously are applied. However, the following procedures should receive special attention.

1. Use of geometric dilution for the incorporation of small amounts of potent drugs.
2. Reduction of particle size of all ingredients to the same range to prevent stratification of large and small particles.
3. Sieving when necessary to achieve mixing or reduction of agglomerates, especially in the preparation of dusting powders or powders into which liquids have been incorporated.
4. Heavy trituration, when applicable, to reduce the bulkiness of a powder.
5. Protection against humidity, air oxidation and loss of volatile ingredients.

Powders are prepared most commonly either as divided powders and bulk powders which are mixed with water or other suitable material prior to administration, or as dusting powders which are applied locally. They also may be prepared as dentifrices, products for reconstitution, insufflations, aerosols and other miscellaneous products.

The manually operated procedures usually employed by the pharmacist today are *trituration, pulverization by intervention* and *levigation.*

Trituration—This term refers to the process of reducing substances to fine particles by rubbing them in a mortar with a pestle. The term also designates the process whereby a mixture of fine powders is intimately mixed in a mortar. The circular mixing motion of the pestle on the powders contained in a mortar results in blending them and also breaking up soft aggregates of powders. By means of the application of pressure on the pestle, crushing or grinding also can be effected.

When granular or crystalline materials are to be incorporated into a powdered product, these materials are comminuted individually and then blended together in the mortar.

Pulverization by Intervention—This is the process of reducing the state of subdivision of solids with the aid of an additional material which can be removed easily after the pulverization has been completed. This technique often is applied to substances which are gummy and tend to reagglomerate or which resist grinding. A prime example is camphor which cannot be pulverized easily by trituration because of its gummy properties. However, on the addition of a small amount of alcohol or other volatile solvent, this compound can be reduced readily to a fine powder. Similarly, iodine crystals may be comminuted with the aid of a small quantity of ether. In both instances the solvent is permitted to evaporate and the powdered material is recovered.

Levigation—In this process a paste is first formed by the addition of a suitable nonsolvent to the solid material. Particle-size reduction then is accomplished by rubbing the paste in a mortar with a pestle or on an ointment slab using a spatula. Levigation generally is used by the pharmacist to incorporate solids into dermatological and ophthalmic ointments and suspensions.

The Mortar and Pestle—These are the most frequently used utensils in small-scale comminution. Mortars made of various materials and in diverse shapes are available and while these often are used interchangeably the different kinds of mortars have specific utility in preparing or grinding different materials.

Modern mortars and pestles are prepared usually from Wedgwood ware, porcelain or glass. While pharmacists often use different mortars interchangeably, each type has a preferential range of utility which makes its use more efficient. Glass mortars, for example, are designed primarily for use in preparing solutions and suspensions of chemical materials in a liquid. They also are suitable for preparing ointments which require the reduction of soft aggregates of powdered materials or the incorporation of relatively large amounts of liquid. Glass also has the advantage of being comparatively nonporous and of not staining easily and thus is particularly useful when substances such as flavoring oils or highly colored substances are used. Glass cannot be used for comminuting hard solids.

Wedgwood mortars are suited well for comminution of crystalline solids or for the reduction in particle size of most materials used in modern prescription practice. They are capable of adequately powdering most substances which are available only as crystals or hard lumps. However, Wedgwood is relatively porous and will stain quite easily. A Wedgwood mortar is available with a roughened interior which aids in the comminution process but which requires meticulous care in washing since particles of the drugs may be trapped in the rough surface and cause contamination of materials subsequently comminuted in the mortar.

Porcelain mortars are very similar to Wedgwood, except that the exterior surface of the former is usually glazed and thus less porous. Porcelain mortars may be used for comminution of soft aggregates or crystals but more generally are used for blending powders of approximately uniform particle size.

Pestles are made of the same material as the mortar. Pestles for Wedgwood or porcelain mortars are available with hard rubber or wooden handles screwed into the head of the pestle. Also available are one-piece Wedgwood pestles. Pestles made entirely of porcelain are objectionable, because they are broken easily.

Pestles and mortars should not be interchanged. The efficiency of the grinding or mixing operation depends largely on a maximum contact between the surfaces of the head of the pestle and the interior of the mortar. The pestle should have as much bearing on the interior surface of the mortar as its size will permit. A pestle which does not "fit" the mortar will result in a waste of labor.

Divided Powders

Divided powders (*chartula or chartulae*) are dispensed in the form of individual doses and generally are dispensed in papers, properly folded. They also may be dispensed in metal foil, small heat-sealed plastic bags or other containers.

Dividing Powders—After weighing, comminuting and mixing the ingredients, the powders must be divided accurately into the prescribed number of doses. In order to achieve accuracy consistent with the other steps in the preparation, *each dose should be weighed individually* and transferred to a powder paper. Following completion of this step the powder papers are folded.

Folding Powders—The operations of folding powder papers are illustrated in Fig 88-24. Care in making the several folds, and experience gained by repetition, are necessary to obtain uniformity when the powders are finally placed in the box for dispensing. Deviation from any of the three main folds will result in powders of varying height being formed, and variations in the folded ends likewise will be noticeable when the powders are placed side by side. A detailed de-

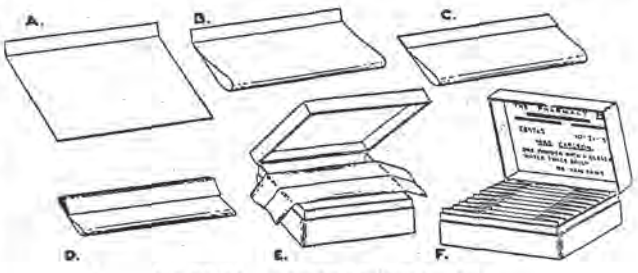

Fig 88-24. Folding powder papers.

scription of folding powder papers is contained in RPS-17 (page 1600).

Packaging Divided Powders—Specially manufactured paper and boxes are available for dispensing divided powders.

Powder Papers—Four basic types of powder papers are available.

1. Vegetable parchment, a thin semiopaque moisture-resistant paper.
2. White bond, an opaque paper with no moisture-resistant properties.
3. Glassine, a glazed, transparent moisture-resistant paper.
4. Waxed, a transparent waterproof paper.

Hygroscopic and volatile drugs can be protected best by using a waxed paper, double-wrapped with a bond paper to improve the appearance of the completed powder. Parchment and glassine papers offer limited protection for these drugs.

A variety of sizes of powder papers are available. The selection of the proper size depends on the bulk of each dose and the dimensions of the powder box required to hold the number of doses prescribed.

Powder Boxes—Various types of boxes are supplied in several sizes for dispensing divided powders. The hinged-shoulder boxes shown in Fig 88-24F are the most popular and have the advantage of preventing the switching of lids with the directions for use when several boxes of the same size are in the same home. The prescription label may be pasted directly on top of the lid or inside the lid. In the latter case the name of the pharmacy is lithographed on top of the lid.

Special Problems

The incorporation of volatile substances, eutectic mixtures, liquids and hygroscopic or deliquescent substances into powders presents problems that require special treatment.

Volatile Substances—The loss of camphor, menthol and essential oils by volatilization when incorporated into powders may be prevented or retarded by use of heat-sealed plastic bags or by double wrapping with a waxed or glassine paper inside of a bond paper.

Eutectic Mixtures—Liquids result from the combination of phenol, camphor, menthol, thymol, antipyrine, phenacetin, acetanilid, aspirin, salol and related compounds at ordinary temperatures. These so-called eutectic mixtures may be incorporated into powders by addition of an inert diluent. Magnesium carbonate or light magnesium oxide are used commonly and effective diluents for this purpose, although kaolin, starch, bentonite and other absorbents have been recommended. Silicic acid prevents eutexia with aspirin, phenyl salicylate and other troublesome compounds; incorporation of about 20% silicic acid (particle size, 50 μm) prevented liquefaction even under the compression pressures required to form tablets.

In handling this problem each eutectic compound should be mixed first with a portion of the diluent and gently blended together, preferably with a spatula on a sheet of paper. Generally, an amount of diluent equal to the eutectic compounds is sufficient to prevent liquefaction for about 2 wk. Deliberate forcing of the formation of the liquid state, by direct trituration, followed by absorption of the moist mass, also will overcome this problem. This technique requires use of more diluent than previously mentioned methods but offers the advantage of extended product stability. Thus, the technique is useful for dispensing a large number of doses that normally would not be consumed over a period of 1 or 2 wk.

Liquids—In small amounts, liquids may be incorporated into divided powders. Magnesium carbonate, starch or lactose may be added to increase the absorbability of the powders if necessary. When the liquid is a solvent for a nonvolatile heat-stable compound, it may be evaporated gently on a water bath. Lactose may be added during the course of the evaporation to increase the rate of solvent loss by increasing the surface area. Some fluidextracts and tinctures may be treated in this manner, although the use of an equivalent amount of a powdered extract, when available, is a more desirable technique.

Hygroscopic and Deliquescent Substances—Substances that become moist because of affinity for moisture in the air may be prepared as divided powders by adding inert diluents. Double-wrapping is desirable for further protection. Extremely deliquescent compounds cannot be prepared satisfactorily as powders.

Bulk Powders

Bulk powders may be classified as oral powders, dentifrices, douche powders, dusting powders, insufflations and triturations.

Oral Powders—These generally are supplied as *finely divided powders* or *effervescent granules.*

The finely divided powders are intended to be suspended or dissolved in water or mixed with soft foods, eg, applesauce, prior to administration. Antacids and laxative powders frequently are administered in this form.

Effervescent granules contain sodium bicarbonate and either citric acid, tartaric acid or sodium biphosphate in addition to the active ingredients. On solution in water, carbon dioxide is released as a result of the acid–base reaction. The effervescence from the release of the carbon dioxide serves to mask the taste of salty or bitter medications.

Granulation generally is accomplished by producing a moist mass, forcing it through a coarse sieve and drying it in an oven. The moisture necessary for massing the materials is obtained readily by heating them sufficiently to drive off the water of hydration from the uneffloresced citric acid. The completed product must be dispensed in tightly closed glass containers to protect it against the humidity of the air. For a formerly official general formula for preparing effervescent salts see RPS-15, page 1574.

Effervescent powders may be prepared also by adding small amounts of water to the dry salts in order to obtain a workable mass. The mass is dried and ground to yield the powder or granule. Care must be used in this procedure to ensure that the reaction which occurs in the presence of water does not proceed too far before it is stopped by the drying process. Should this happen, the effervescent properties of the product will be destroyed.

Other preparative techniques have been reported for effervescent powders such as a fluidized-bed procedure in which the powders are blended and then suspended in a stream of air in a Wurster chamber. Water is sprayed into the chamber resulting in a slight reaction and an expansion of the particles to form granules ranging in size from 10- to 30-mesh. This approach apparently offers a number of advantages over the older techniques. The extent of reaction and particle size are controlled during the manufacture. A drying oven, trays and even grinding devices are not required. Furthermore, the technique lends itself to a continuous as well as a batch operation.

The heat generated from the blending and mixing operation also has been used to mass the powders by causing the release of the water of hydration from the citric acid. The massed materials can be dried and sieved through a coarse sieve. This technique thus eliminates the need of an external heat source or a granulating solution.

Dentifrices—These may be prepared in the form of a

bulk powder, generally containing a soap or detergent, mild abrasive and an anticariogenic agent. These products are considered in more detail in Chapter 109.

Douche Powders—These products are completely soluble and are intended to be dissolved in water prior to use as antiseptics or cleansing agents for a body cavity. They most commonly are intended for vaginal use, although they may be formulated for nasal, otic or ophthalmic use. Generally, since aromatic oils are included in these powders, they are passed through a No 40 or 60 sieve to eliminate agglomeration and insure complete mixing. Dispensing in wide-mouth glass jars serves to protect against loss of volatile materials and permits easy access by the patient. Bulk-powder boxes may be used for dispensing douche powders, although glass containers are preferred because of the protection afforded by these containers against air and moisture.

Dusting Powders—These are locally applied nontoxic preparations that are intended to have no systemic action. They always should be dispensed in a very fine state of subdivision to enhance effectiveness and minimize irritation. When necessary, they may be micronized or passed through a No 80 or 100 sieve.

Extemporaneously prepared dusting powders should be dispensed in sifter-top packages. Commercial dusting powders are available in sifter-top containers or pressure aerosols. The latter, while generally more expensive than the other containers, offer the advantage of protection from air, moisture and contamination, as well as convenience of application. Foot powders and talcum powders are currently available as pressure aerosols.

Dusting powders are applied to various parts of the body as lubricants, protectives, absorbents, antiseptics, antipruritics, antibromhidrosis agents, astringents and antiperspirants.

While in most cases dusting powders are considered nontoxic, the absorption of boric acid through large areas of abraded skin has caused toxic reactions in infants. Accidental inhalation of zinc stearate powder has led to pulmonary inflammation of the lungs of infants. The pharmacist should be aware of the possible dangers when the patient uses these compounds as well as other externally applied products. See also Chapter 38.

Insufflations—These are finely divided powders introduced into body cavities such as the ears, nose, throat, tooth sockets and vagina. An insufflator (powder blower) usually is employed to administer these products. However, the difficulty in obtaining a uniform dose has restricted their general use.

Specialized equipment has been developed for the administration of micronized powders of relatively potent drugs. The Norisodrine Sulfate Aerohaler Cartridge (*Abbott*) is an example. In the use of this Aerohaler, inhalation by the patient causes a small ball to strike a cartridge containing the drug. The force of the ball shakes the proper amount of the powder free, permitting its inhalation. Another device, the Spinhaler turbo-inhaler (*Fisons*), is a propeller-driven device designed to deposit a mixture of lactose and micronized cromolyn sodium into the lung as an aid in the management of bronchial asthma.

Pressure aerosols also have been employed as a means of administering insufflations, especially for potent drugs. This method offers the advantage of excellent control of dose, through metered valves, as well as product protection.

Triturations—These are dilutions of potent powdered drugs, prepared by intimately mixing them with a suitable diluent in a definite proportion by weight. They were at one time official as 1–10 dilutions. The pharmacist sometimes prepares triturations of poisonous substances, eg, atropine, in a convenient concentration using lactose as the diluent, for use at the prescription counter. These medicinal substances are weighed more accurately and conveniently by using this method.

The correct procedure for preparing such triturations or any similar dilution of a potent powder medicament, to insure uniform distribution of the latter, is

Reduce the drug to a moderately fine powder in a mortar.

Add about an equal amount of diluent and mix well by thorough trituration in the mortar.

Successsively add portions of diluent, triturating after each addition, until the entire quantity of diluent has been incorporated.

Under no circumstance should the entire quantity of diluent be added at once to the drug that is to be diluted in the expectation that uniform dispersion of the latter will be more expeditiously achieved on brief trituration of the mixture.

References

1. Parrott EL. In Lachman L *et al: The Theory and Practice of Industrial Pharmacy*, 3rd ed, Lea & Febiger, Philadelphia, 32, 1986.
2. Perry RH *et al: Chemical Engineers' Handbook*, 4th ed, McGraw-Hill, New York, 8–8, 1963.
3. Parrott EL, *loc cit*, 39.
4. Pilcher JM *et al: Proc Chem Spec Mfrs Assoc Ann Mtg:* 66, 1956.
5. Tillotson D: *Aerosol Age 3(5):* 41, 1958.

Bibliography

Irani RR, Callis CF: *Particle Size: Measurement, Interpretation and Application*, Wiley, New York, 1963.

Cadle RD: *Particle Size*, Reinhold, New York, 1965.

Silverman L *et al:* Particle Size Analysis in Industrial Hygiene, Academic, New York, 1971.

Allen T: *Particle Size Measurement*, Chapman & Hall, London, 1968.

Orr C Jr, Dalla Valle JM: *Fine Particle Measurement*, Macmillan, New York, 1959.

Martin AN: *Physical Pharmacy*, 3rd ed, Lea & Febiger, Philadelphia, 1983.

Orr C Jr: *Particulate Technology*, Macmillan, New York, 1966.

Brown RL, Richards JC: *Principles of Powder Mechanics*, Pergamon, Oxford, 1970.

Uhl VW, Gray JW: Mixing, vol II, Academic, New York, 1967.

Stockman JD, Fochtman EG, eds: *Particle Size Analysis*, Ann Arbor Science Pub, Ann Arbor, MI 1977.

Jelinek IZK: *Particle Size Analysis*, Wiley, New York, 1970.

Sterbacek Z, Tausk P: *Mixing in the Chemical Industry*, Pergamon, Oxford, 1965.

DallaValle JM: *Micromeritics*, 2nd ed, Pitman, New York, 1948.

Parfitt GD, Sing KSW: *Characterization of Powder Surfaces*, Academic, London, 1976.