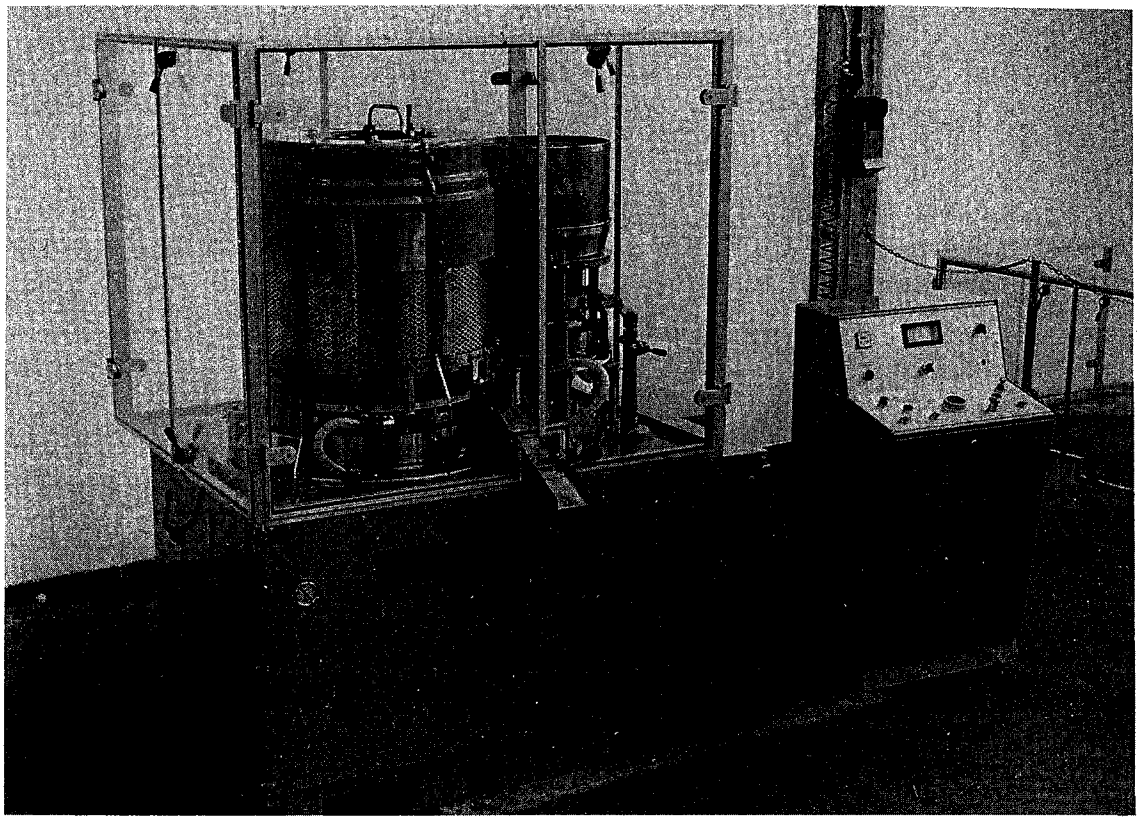

Fig. 10.56. The Zanasi BZ-72 automatic rotary capsule-filling machine.

of weight variation. The body and cap are then aligned and closed (6).

Pellets can be filled in a similar way. This vacuum-assisted method gives good weight consistency.

The Zanasi BZ-150

This machine, illustrated in Fig. 10.58, has an output of up to 150 000 capsules per hour. It is a continuous motion machine, and is claimed to be suitable for powders, granules, and tablets.

A plan of the layout of the machine is shown in Fig. 10.59. The operating sequence is similar in some respects to the method of compressing tablets on a rotary tablet machine. The mechanisms of opening, filling, and closing the capsules are similar to those of the BZ-72. There is a central turret (1), an empty-capsule feed hopper (2), and a powder supply hopper (3), all supported on a rectangular base (4). The turret houses the annular powder trough into which powder is fed from the powder hopper, 72 bushes into which empty capsules are fed from the empty-capsule hopper, and 72 dosators to fill the capsules.

Powder flows from the powder hopper, aided by a single flat-bladed stirrer similar to that used in the AZ-60, into the central powder trough through a tube fitted with a screw feeder. The powder flow can be controlled (a) by a valve fitted in the tube, and (b) by the screw feeder being activated by high- and low-level probes fitted with a mixing device which ensures the uniformity of composition and density of the powder in the trough, despite the disturbance due to withdrawal of the powder plug. It is necessary to raise the turret to allow the trough to be emptied for cleaning, and also for fitting different bushes, pistons and dosators when a different size of capsule is to be filled.

The turret rotates at a maximum speed of 35 rpm, whilst the empty-capsule hopper rotates at 70 rpm as it has only 36 empty-capsule filling

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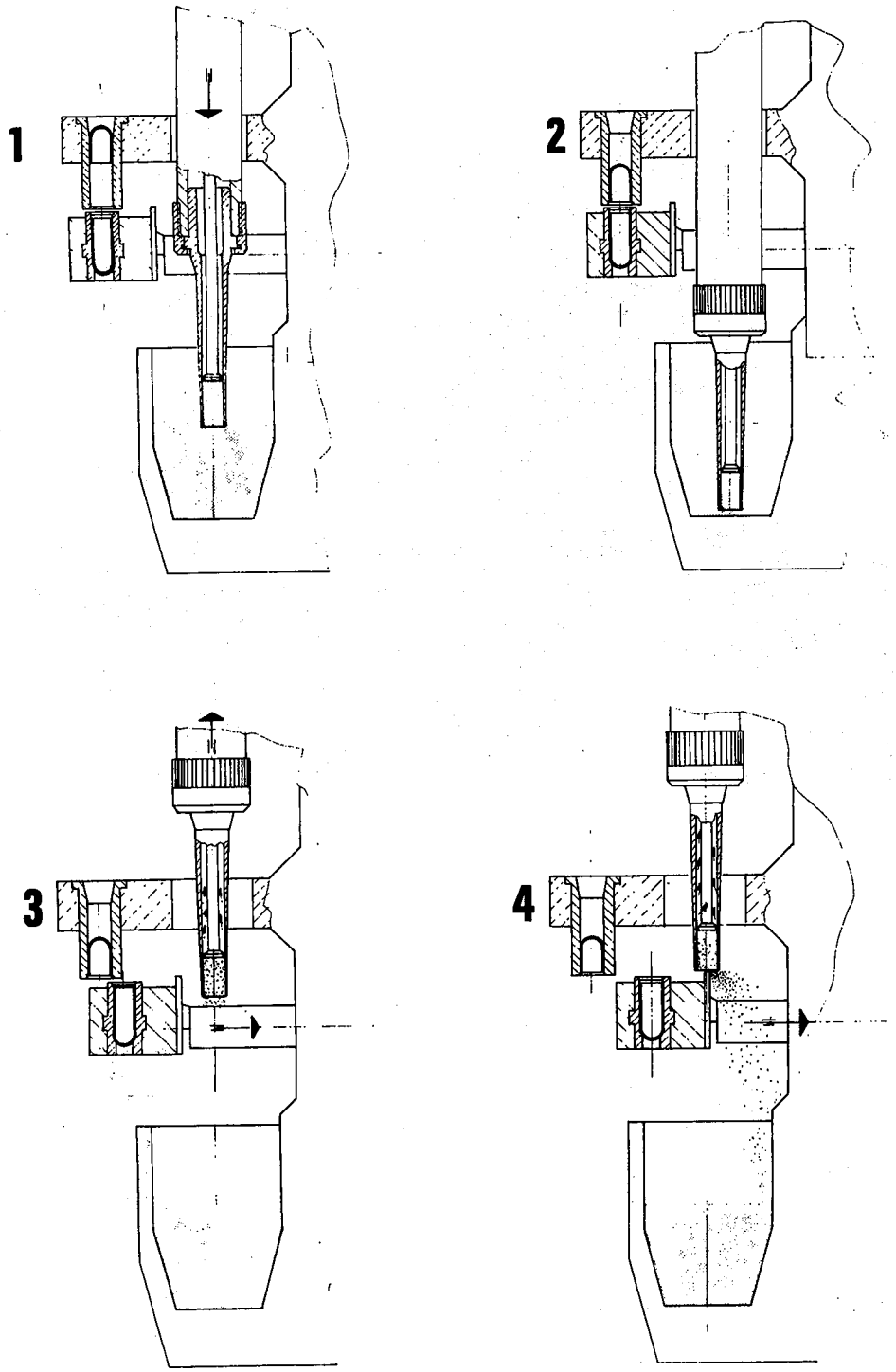

Fig. 10.57. Schematic diagram of the operation of the Zanasi BZ-72 capsule-filling machine. 1, capsule separation; 2, filling of the dosator; 3, removal of powder plug; 4, removal of excess fill; 5, ejection of powder into capsule body; 6, closing of the capsule.

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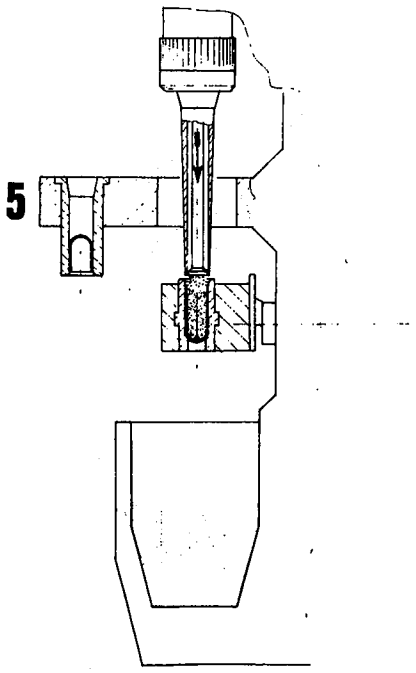

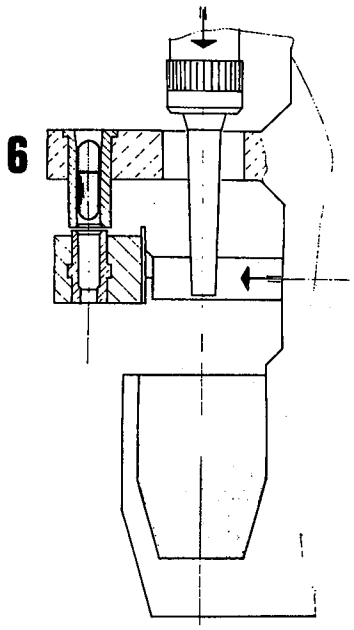

tubes. The hopper has a very low effective capacity considering its size, because the capsules tend to be thrown outwards by centrifugal force, which poses a problem of supply when the machine is running at full speed. The level of capsules in this hopper must be kept fairly low so that the operator can remove damaged capsules quickly when blockages occur in the feed tubes.

The following problems may occur in operating the machine.

1. The capacity of the empty-capsule hopper is low so that it requires replenishing too frequently.
2. The effect of damaged empty capsules is much more apparent on this machine than on, for example, the AZ-60. Since 2500 capsules are filled every minute, a defect level of only 0.04% will cause a feed tube blockage every minute.
3. The dust extraction and the number of cleaning points on the machine are not fully capable of dealing with the excess powder and the dust that are created during filling.
4. It is basically a single capsule-size machine. The estimated time for change-over to another size of capsule is of the order of one to two days. The change parts required are 72 dosators, pistons, bushes and push rods for ejecting the filled capsules, and 36 empty-capsule feed tubes.

Tables 10.6 and 10.7 show typical results obtained from filling a placebo formulation and an in-line product.

Figure 10.60 shows the layout of three BZ-150 machines at the Merck Sharp and Dohme plant at Cramlington, England.

Table 10.6. Statistical analysis of weight variation of two batches of capsules filled on the Zanasi BZ-150 encapsulation machine at 152 000 capsules per hour, taking three samples of each batch. The target weight was 300 mg.

Batch number	1	1	1	2	2	2
Mean weight (mg)	309.7	311.4	312.1	297.9	299.5	299.3
Degrees of freedom	62	57	59	58	55	55
Variance	37.64	25.82	54.65	128.21	77.47	56.51
Standard deviation (mg)	6.13	5.08	7.39	11.32	8.80	7.52
Coefficient of variation (%)	1.98	1.63	2.36	3.80	2.93	2.51

Table 10.7. Statistical analysis of one batch of capsules filled on the Zanasi BZ-150 encapsulation machine at a speed of 152 000 capsules per hour. The target weight was 290 mg.

Batch number	3	3	3
Mean weight (mg)	284.5	286.7	287.8
Degrees of freedom	60	60	60
Variance	65.91	44.65	70.45
Standard deviation (mg)	8.12	6.68	8.40
Coefficient of variation (%)	2.85	2.33	2.91

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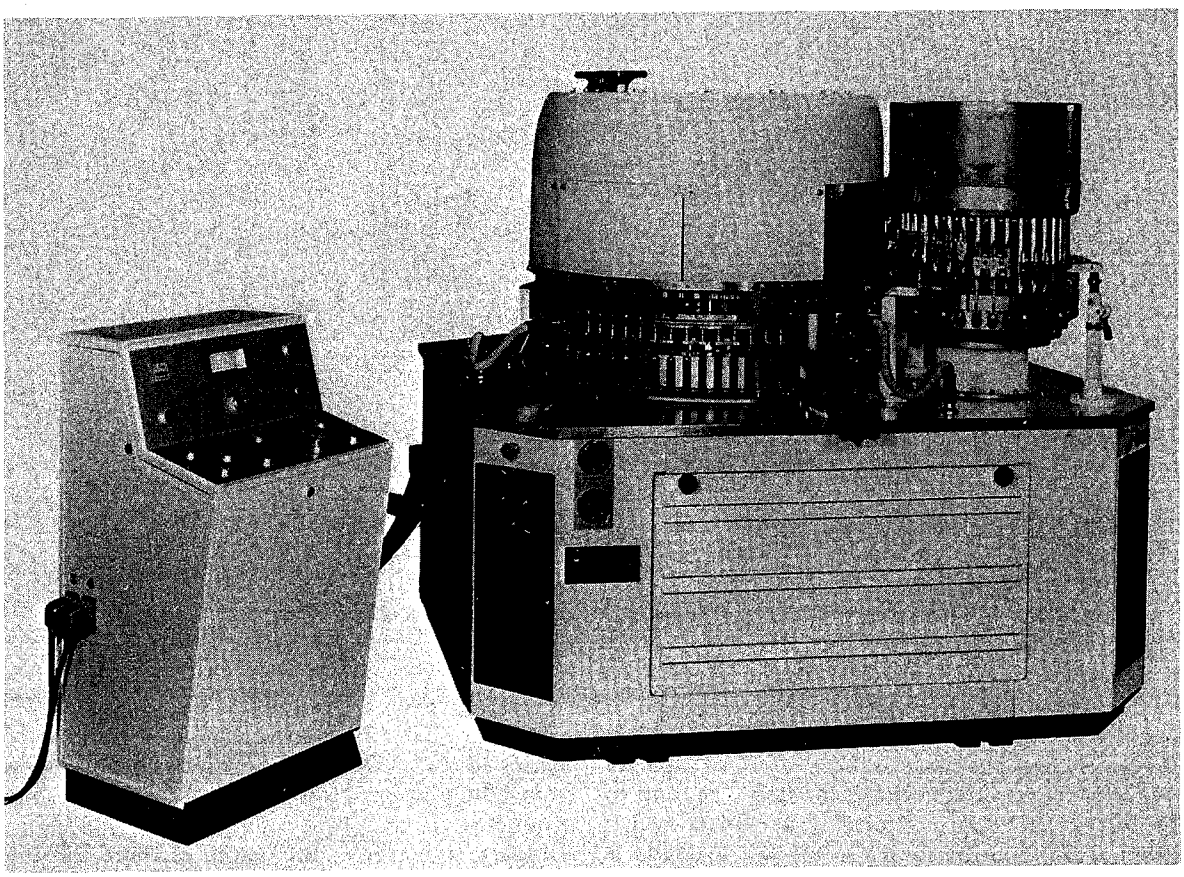

Fig. 10.58. The Zanasi BZ-150 automatic rotary capsule-filling machine.

The Zanasi Z 5000 Range

The Zanasi BZ range of fillers has been replaced by the Z 5000-R series. One of these machines is illustrated in Fig. 10.61. There are three models, the Z 5000-R1, Z 5000-R2, and Z 5000-R3, with maximum outputs in capsules per hour of 70 000, 110 000, and 150 000, respectively.

The dimensions of the machines in this series have been reduced, and the control console has been attached to the main frame of the machine. A reduction in noise level to 79–85 dB(A) has been achieved. The d.c. motor of the BZ series has been replaced by an a.c. motor which requires less maintenance and is more reliable. A schematic diagram of the operation of the Z 5000 is shown in Fig. 10.62.

The control console incorporates a small built-in computer control system for a more detailed analysis of capsule weight. Any part of the machine which has a fault can be quickly identified by this system. The Siemens fan has been replaced by compressed air for the capsule transfer system, which has led to a reduction in noise level and in heat generation during capsule filling. A better guarding system is fitted, which is lighter, and which allows adjustment of weight and compression without removing the guard and stopping the machine. The two vacuum pumps have been replaced by one, with savings in noise, size, dimensions, and maintenance. Improvements have been made to the method of fitting the lower pins which assist in the opening, closing, and ejection of unseparated capsules. These pins cannot now free themselves during the operation of the machine and yet a quick change from one size to another can be accomplished without tools. A modification has also been made to the location of the upper and lower pins at the point where the cap and

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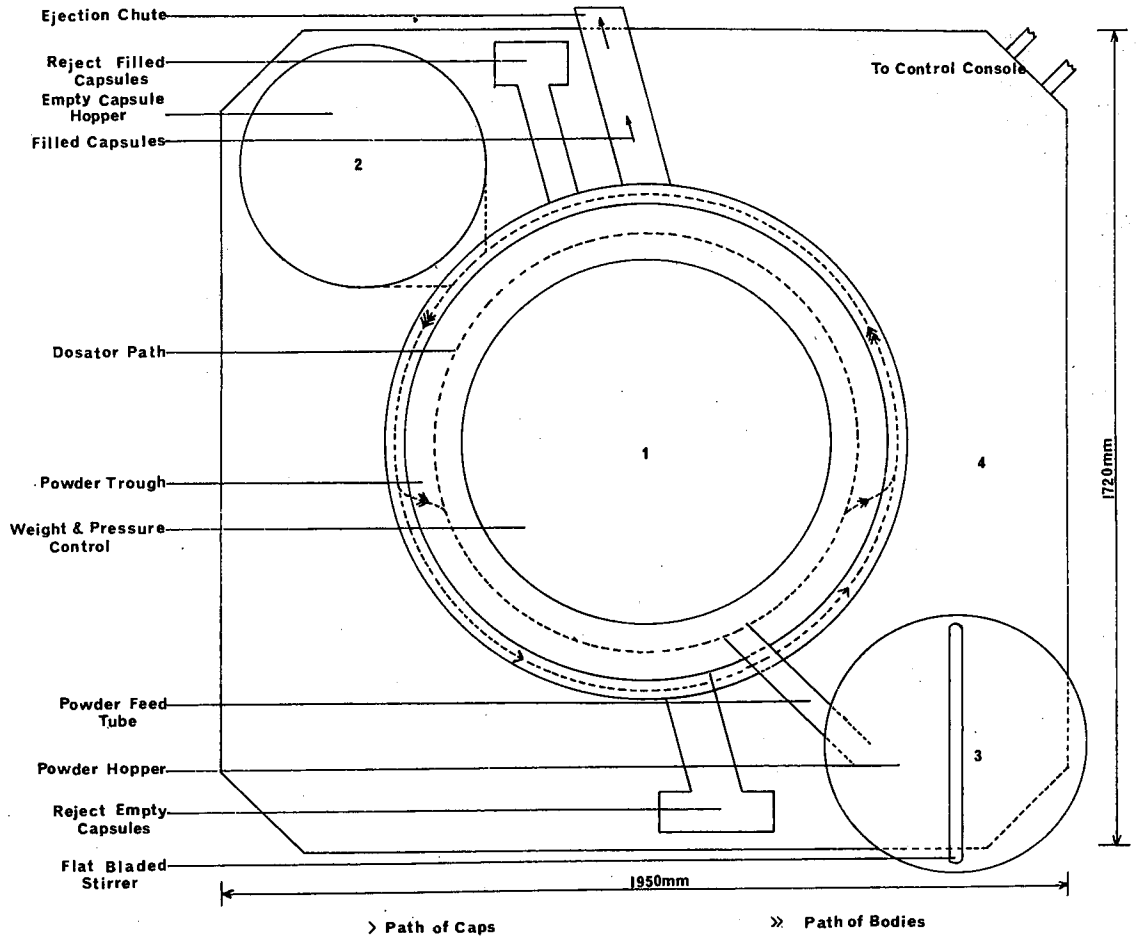

Fig. 10.59. Plan of the Zanasi BZ-150 capsule-filling machine. 1, central turret; 2, empty-capsule feed hopper; 3, powder supply hopper; 4, rectangular base.

filled body are reunited. The two bushes are now better aligned, which reduces the likelihood of splitting in the body or cap.

The annular hopper from which the dosators pick up powder has been separated from the main drive of the machine and its speed relative to the turret has been altered. This ensures that the dosator does not enter the powder at the same point on each revolution, resulting in better dosage weight uniformity.

The sequence of operations is illustrated in Fig. 10.63. Powder dosing is effected by means of a cylindrical tube in which a piston is used to regulate volume. The dosator enters the powder bed then rises holding the volume volume of powder. The capsule body is brought under the dosator and the powder charge is ejected by means of the piston.

For the filling of pellets, the volumetric principle is again employed with the assistance of vacuum for transfer of the product. By this means, even micro-capsules containing liquid or pellets with soft coatings such as wax can be handled without damage. High-accuracy filling is achieved by means of a dosator levelling system which operates after the dosator enters the product bed. Employment of this principle, rather than gravity filling, enables pellets with poor electrostatic qualities to be handled without affecting accuracy.

An attachment which is available for the Z 5000-R1 allows feeding of a tablet into the capsule body followed by a powder dose (Fig. 10.64). Every

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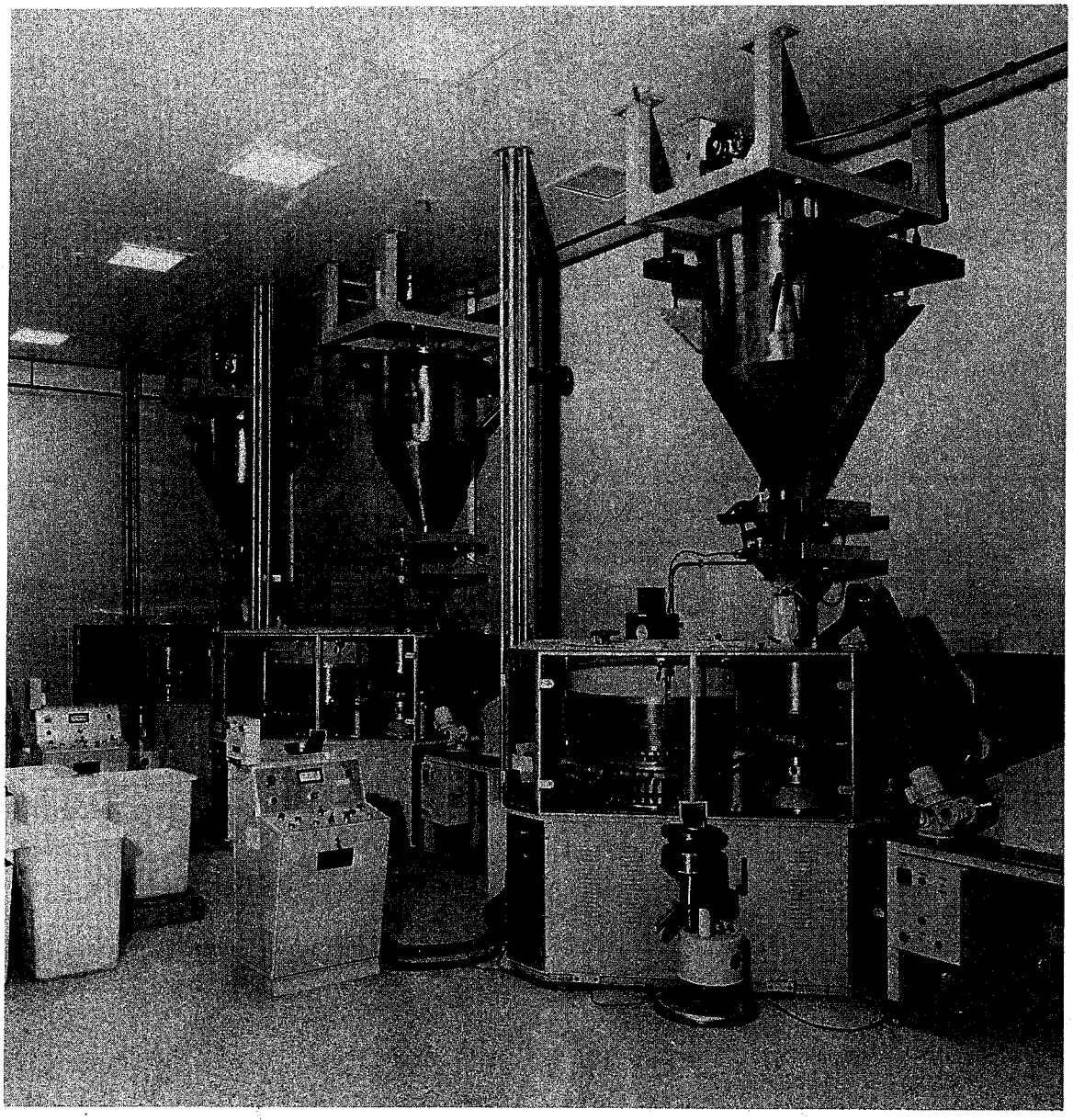

Fig. 10.60. A general view of three Zanasi BZ-150 machines at the Cramlington plant of MSD.

capsule is checked for the presence of a tablet. Capsules without tablets are automatically ejected. Regulation of the dosing volume and the compression of the plug are effected by single controls operating on all dosators simultaneously. Control can be effected while the machine is in motion without nullifying the safety interlocks. In the event of excessive compression, a safety interlock protects the working parts against mechanical damage.

The overall design of the equipment and parts is to the highest standard of good manufacturing practice, and allows simple, effective, and speedy cleaning. Most components are smooth shapes

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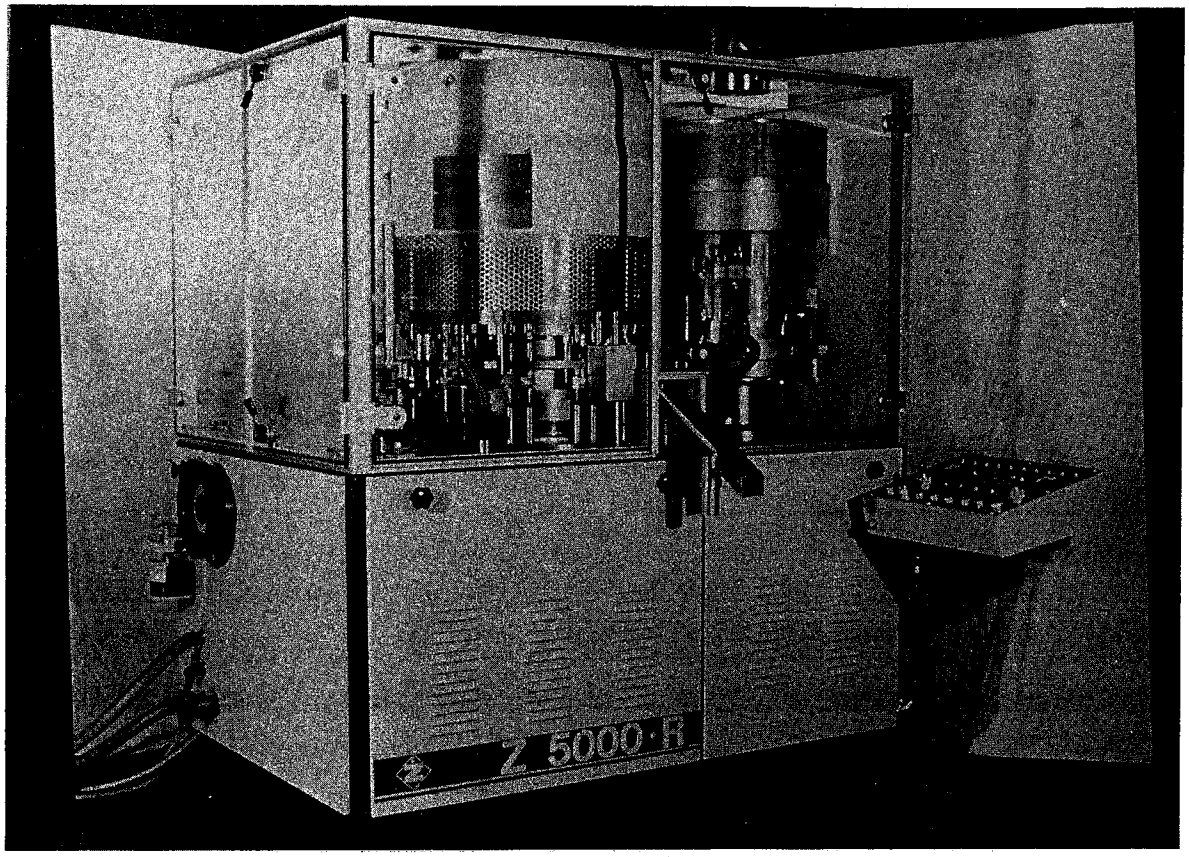

Fig. 10.61. The Zanasi Z 5000-R automatic rotary capsule-filling machine.

without corners or joins where the product might lodge. The manufacturers claim that a change in the size of capsules to be filled can be accomplished in less than one hour.

Farmatic Machines

This series consists of 3 machines, the 2000/15, 2000/30, and 2000/60, with maximum outputs of 40 000, 80 000, and 160 000 capsules per hour, respectively.

These machines have a single operating tower (Fig. 10.65), with a separate turret to hold the powder. A central hopper holds the empty capsules which are fed into special scoops for intercepting and rejecting damaged and distorted capsules. In a lower part of this central turret, the capsules are rectified, separated, filled, and reunited. If a capsule is missing from a dosing station, the powder plug is ejected from the machine. Selection of samples for check-weighing is accomplished by an electronic pneumatic device which monitors the dosator.

The Elanco Rotofil

The Elanco Rotofil (Eli Lilly & Co.), shown in Fig. 10.66, is a continuous motion pellet filler capable of a maximum rate of 60 000 capsules per hour. A weight variation of ±2% is claimed. It is essentially a volume filler, and the product has to be formulated specifically for the volume of the capsule to be filled. Capsule sizes 0 to 4 can be filled and it is claimed that the size change-over and cleaning take 2 hours. Excess pellets can be recycled to the filling hopper.

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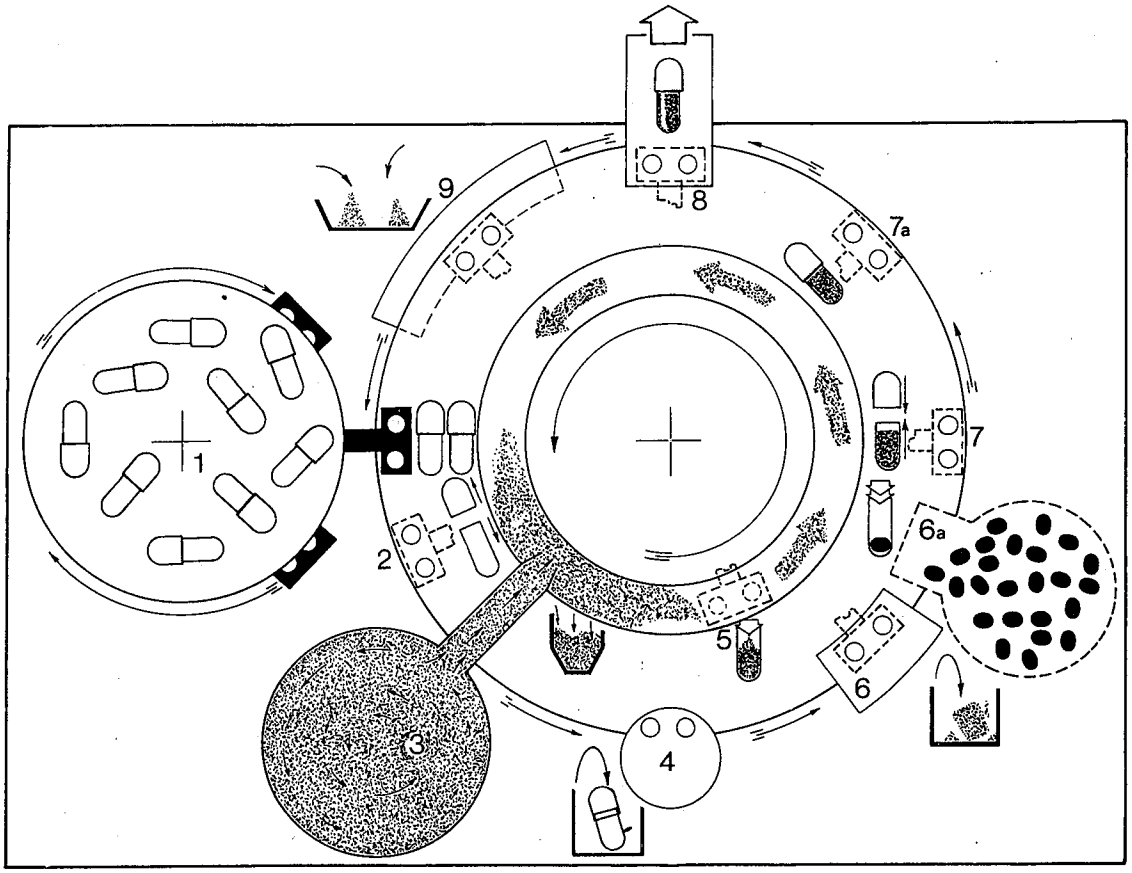

Fig. 10.62. Schematic diagram of the operation of the Zanasi Z 5000-R series of machines. 1, capsule feed; 2, capsule opening; 3, powder or pellet feeding; 4, unopened-capsule rejection; 5, dosing; 6, product ejection in case of empty bushings; 6a, tablet feeding; 7, commencement of capsule closure; 7a, end of capsule closure; 8, finished-capsule ejection; 9, cleaning of bushings.

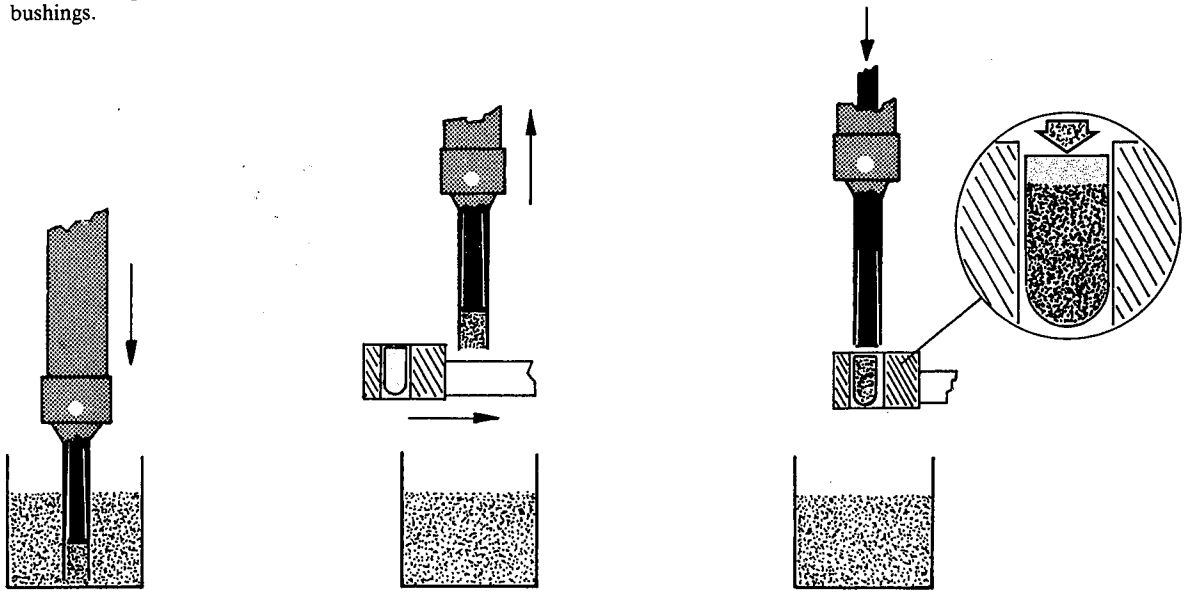

Fig. 10.63. Schematic diagram of powder dosing in the Zanasi Z5000-R series.

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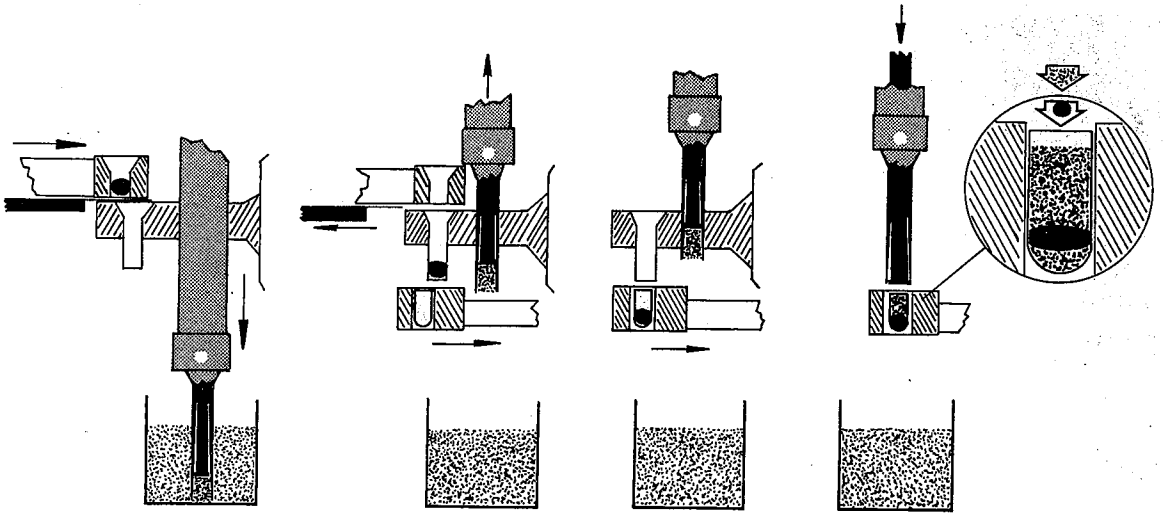

Fig. 10.64. Schematic diagram of the dosing of a tablet and powder on the Zanasi Z5000-R1.

The Filling of Liquids and Pastes into Hard Capsules

There have been a number of significant developments in the use of hard shell two-piece capsules for liquids, pastes, and thixotropic formulations. Both Nuova Zanasi, and Höfliger and Karg have produced machines based on their existing model range which are capable of this technique. Walker *et al.* (1980) and Francois and Jones (1979) describe the process and its requirements in detail. The important physical properties of the formulated mass are its viscosity, surface tension, and melting point, which govern how the product can withstand handling and storage. If the thixotropic effect is low then the problems of leakage will be greater.

A variety of medicines which are normally filled into soft gelatin capsules can now be presented in hard capsules. The limitations to this technique are the interactions of the materials with hard gelatin; materials with low moisture content, and oils, are preferable. One advantage of this process is that a simple machine can be placed at the formulator's bench and relatively small amounts of material are sufficient for filling trials. Greater accuracy can also be claimed for this method compared to normal powder filling and, since the amount of gelatin used for a hard shell capsule is less than for a soft shell one, it is cheaper as well.

Machines which are available for filling liquids into hard capsules include the Zanasi RM/L-75, Zanasi RM/P-75, a series of machines from Höfliger and Karg, and the Harro Höfliger unit.

The Zanasi RM/L-75

The basic machine, illustrated in Fig. 10.67, can carry out six sequential operations: feeding of empty capsules, and rectification; opening of capsules by vacuum; sorting and ejection of faulty capsules; filling of capsules with liquid products by means of dosing pistons and liquid-injecting needles; closing of capsules, and the ejection of filled capsules. The machine must be fitted with the size-parts relating to both the capsules and the product.

The two-piece hard shell capsules must meet the standard dimensional requirements, but can be either the standard or the self-locking type. The range of sizes that can be handled is listed below, and the contained volumes are also given here for ease of reference: size 000 (1.37 ml), size 00 (0.95 ml), size 0 (0.68 ml), size 1 (0.50 ml), size 2 (0.37 ml), size 3 (0.30 ml), size 4 (0.21 ml), and size 5 (0.13 ml).

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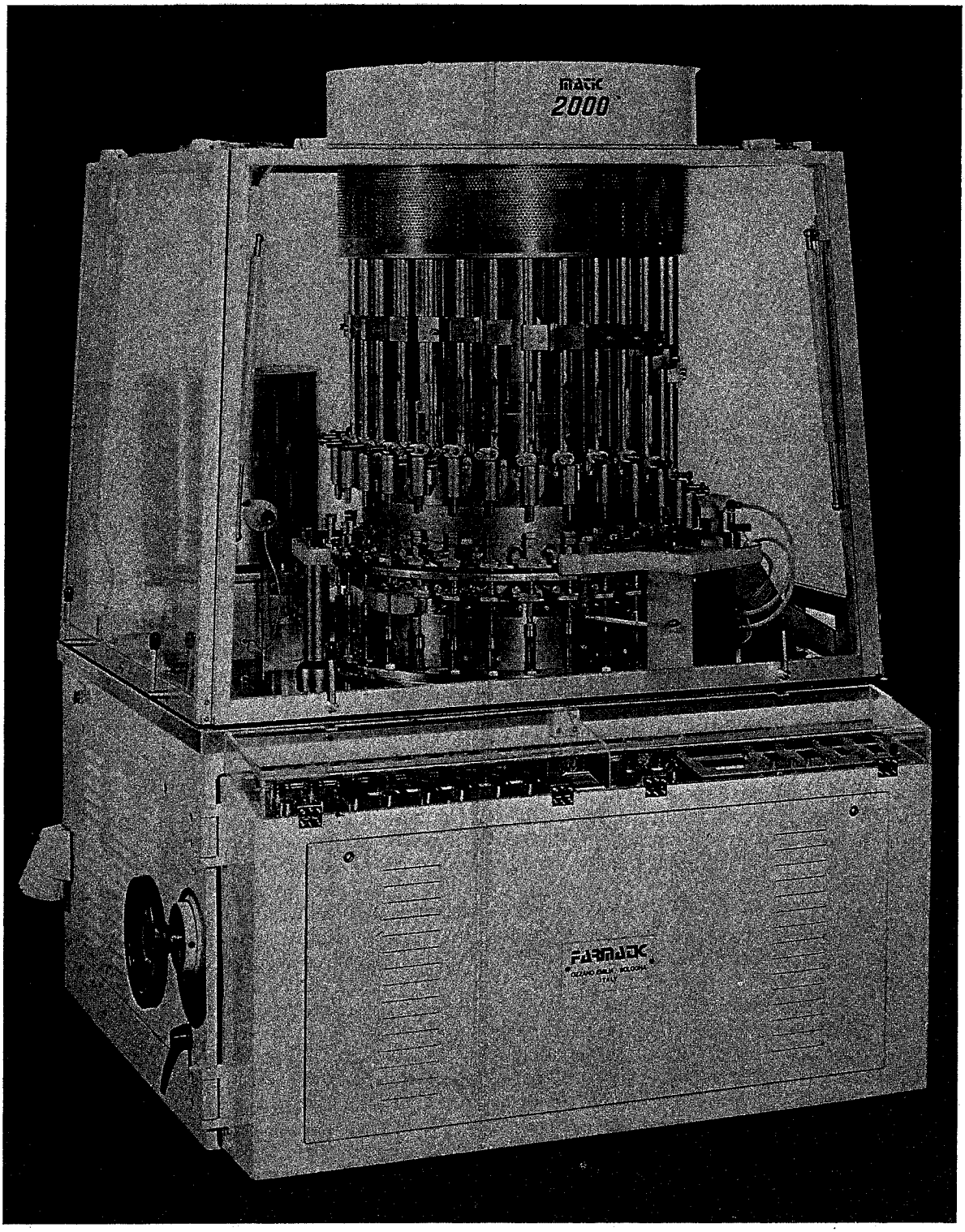

Fig. 10.65. The Farmatic model 2000 automatic rotary capsule-filling machine.

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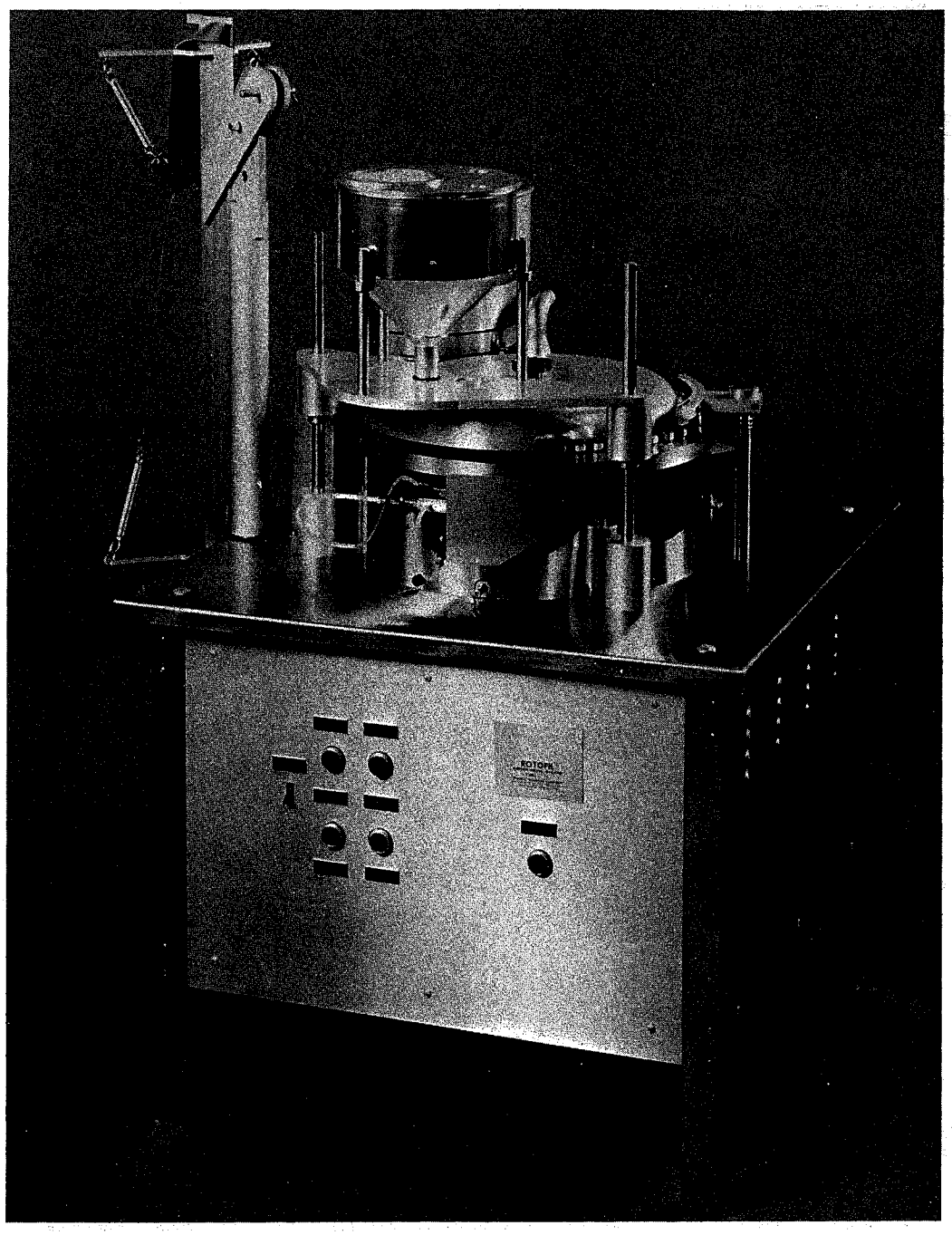

Fig. 10.66. The Elanco Rotofil automatic pellet filler.

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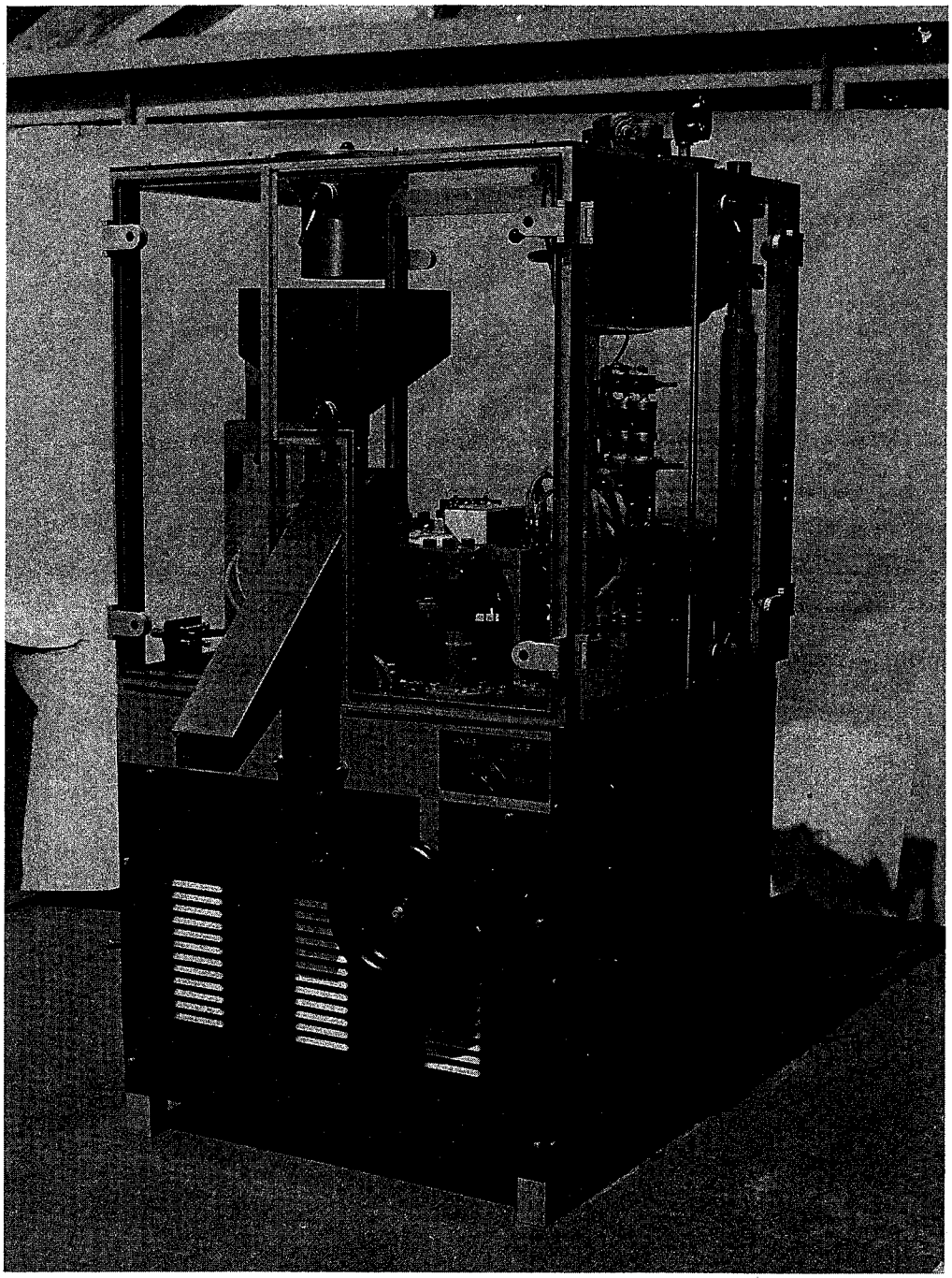

Fig. 10.67. The Zanasi RM/L-75 automatic machine for filling liquids into hard capsules.

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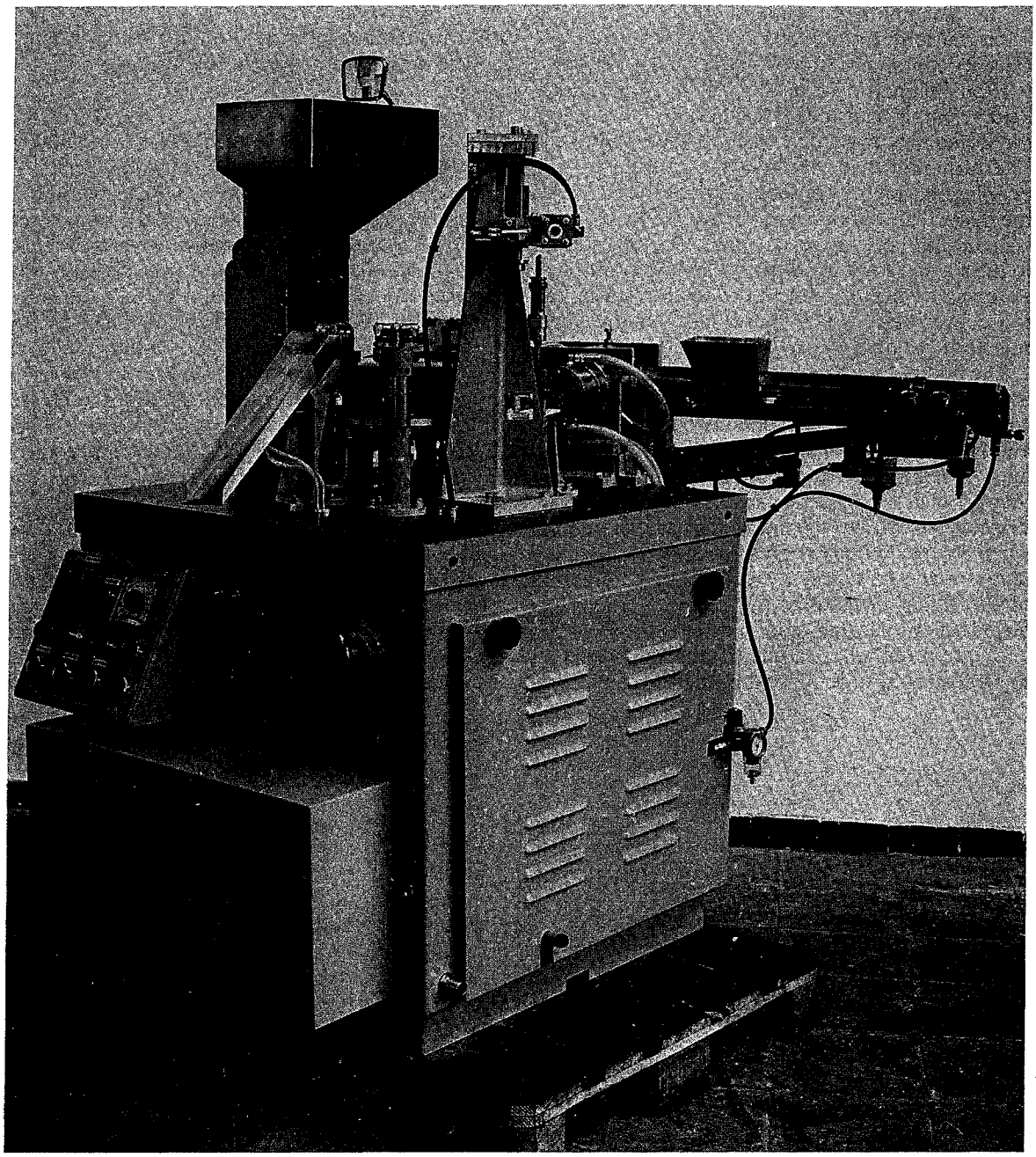

Fig. 10.68. The Zanasi RM/P-75 automatic machine for filling pastes into hard capsules.

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The machine has a general rotary motion but is intermittent. Empty capsules are fed into a high-capacity container inside which is a plate, with two vertical channels each having a slightly larger diameter than the capsules. The capsules fall through these channels and are rectified, body downwards. The turntable then transfers the capsules to the opening station for the separation of the cap from the body. This operation is performed by pins and vacuum. In their passage from the opening station to the sorting station, all the bodies are positioned at the same height, and at the sorting station all those capsules which have not opened are rejected.

The bodies then move to the filling station which has a container for the liquid, two dosing pistons with micrometric adjustments, two filling needles, and two valves for suction and delivery of the product. When the bodies are under the filling station, they are checked by a 'no capsule body—no filling' device which allows the needle to be lowered only when a capsule body is present. The whole filling unit is made of stainless steel. After completion of the filling operation, the capsules are transferred to the closing station where the cap and body are reunited. The filled and closed capsules are transferred to the last station, where ejection is brought about by two hollow pins, which push the capsules out and down a chute into a container.

The output is up to 12 000 capsules per hour.

The Zanasi RM/P-75

The Zanasi model RM/P-75, illustrated in Fig. 10.68, will fill pastes into hard shell capsules by means of special dosators fitted with a micrometric adjustment. The basic machine is the same as the RM/L-75, but the filling station consists of a hopper, paste-extruding unit, and four dosators with micrometric adjustment. When the bodies are under the filling station, they are filled by two dosators, whilst the other two dosators pick up the paste as formed by the extruder to repeat the filling cycle. The paste is extruded in the desired shape and size by a piston and screw feeder, working inside a cylinder which has a cavity and cooling-water jacket. Waste material is retained on a plate, and can be recycled. After filling, the capsules are transferred to the closing station where the cap and body are reunited.

All moving parts on both these Zanasi machines are located within a single base and are surrounded on all sides by safety guards with safety devices on the doors. The working table can be protected by means of a transparent anti-dust and anti-noise

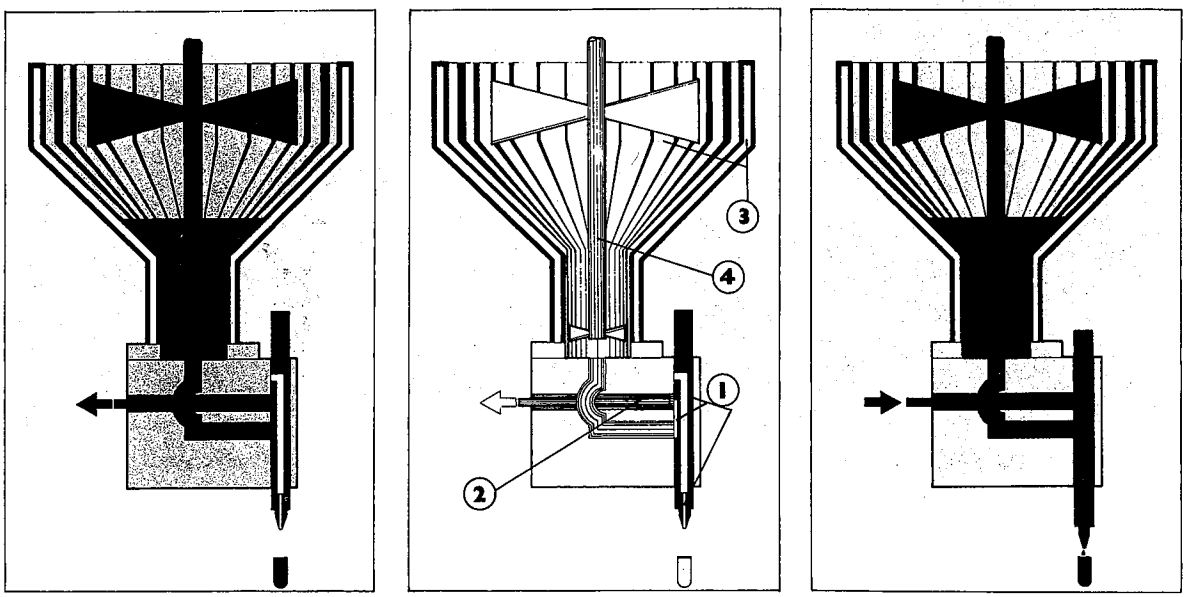

Fig. 10.69. The mechanism of filling liquids into hard capsules on the Höfliger and Karg machines. 1. control valve, outlet valve, and filling needle; 2, dosing piston; 3, jacketted product container; 4, stirrer.

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protection hood, which is also fitted with safety devices on the doors.

Höfliger and Karg Machines

Höfliger and Karg offer three versions of their standard range of capsule fillers equipped to fill liquids into hard shell capsules. Table 10.8 shows the variations that are possible. The dosing mechanism is shown in Fig. 10.69. In the left-hand illustration, the control valve is in the upper position and product is drawn into the dosing cylinder. The stroke of the piston is adjustable. The dosing stroke is shown in the right-hand illustration. The downward movement of the control valve causes the outlet valve to shut off the product flow. Simultaneously, the dosing piston forces the measured dose through the dosing needle into the capsule.

References

Francois, D. and Jones, B. E., *Mfg Chem.*, 1979, *50*(3), 37, 38, 41.

Walker, S. E. *et al.*, *J. Pharm. Pharmac.*, 1980, *32*, 389–393.

Table 10.8. Applications for liquid pumps on Höfliger and Karg machines

Model	*No. of holes in carrier segment*	*Dosing possibilities (in order of sequence with the stations on the machine)*	*Description of liquid pump*	*Output* (caps/min) *tablets pellets powder*	*liquids*
330L*	3	liquids only	3-Head pump with drive motor in place of powder filling station (brake-clutch combination). Dosing impulse comes from cam-operated switches. Dosing disk can be stopped manually, whilst the dosing piston continues to operate.	—	50–60
330	3	pellets-powder-pellets tablets-powder-pellets pellets-liquids-pellets tablets-liquids-pellets	As for 330L	110	50–60
603	6	liquids-powder-pellets pellets-powder-pellets tablets-powder-pellets	6-Head pump, drive synchronised with main drive shaft. Dosing disk can be manually stopped, whilst the dosing piston continues to operate.	105	70
603L*	6	liquids only	As for 603	—	70
1200L*	12	liquids only	Two 6-head pumps in place of pellet stations. Otherwise same as for 603.	—	70

* These models cannot be equipped with additional dosing systems

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Chapter 11

Capsule Types, Filling Tests, and Formulation

G. C. Cole

Capsule Sizes and Types

There are eight sizes of hard gelatin capsules commercially available:

Capsule size	000	00	0	1	2	3	4	5
Volume in ml	1.37	0.95	0.68	0.50	0.37	0.30	0.21	0.13

For pharmaceutical products it is unusual to use a size larger than 0 because of the difficulty in swallowing larger sizes, whilst size 5 is rarely used due to difficulties in the automatic filling process. Other sizes are available to order but are used mainly in veterinary practice.

The main suppliers of capsules are the Elanco Qualicaps division of Eli Lilly & Co., the Capsugel Division of Parke, Davis & Co. Ltd, and R. P. Scherer Ltd. The sizes and specifications adopted by the three manufacturers are very similar, which allows any of their sizes to be used on standard automatic filling machines. Each manufacturer produces a range of standard capsules which are designed so that the body and the cap do not separate before the filling operation takes place. They each also make a range of capsules which are locked after filling to ensure that the contents do not leak during packaging and distribution. Each company uses its own brand name to market its regular and locking capsules.

Self-locking Capsules

The self-locking capsule was developed as an alternative to the dot-sealing or banding of capsules which was used by Parke, Davis & Co. for a number of their products and was a costly, difficult, and lengthy process. To eliminate this process, Eli Lilly produce the Lok-Cap and Posilok capsules, Parke, Davis the Snap-Fit and Coni-Snap capsules, and R. P. Scherer the Star-Lock and Lox-It capsules. These are described and illustrated below.

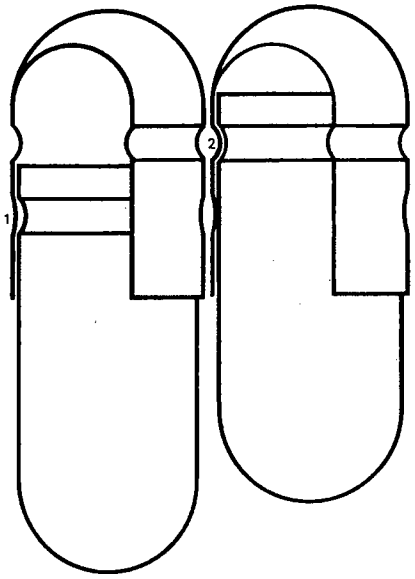

Fig. 11.1 The Snap-Fit capsule. The protuberances (1) prevent premature opening; the grooves (2) lock the two halves together once the capsule has been filled.

The Snap-Fit principle is shown in Fig. 11.1. A development of this design is the Coni-Snap (Fig. 11.2) which is claimed to reduce defects during the filling operation. In 1983, Parke, Davis introduced the Coni-Snap Supro capsule, claiming it to be virtually tamper proof. To achieve this, the dimensions of the capsule have been changed and given new designated sizes from A to E. The capacity is related to the standard Coni-Snap capsules as shown in Table 11.1(b) The cap is so designed that after filling and closing only the rounded end of the body is visible. Due to this change in dimensions, additional machine change parts are required for the filling and packaging operations. The dimensions of capsules made by Parke, Davis are given in Table 11.1(a) and (b).

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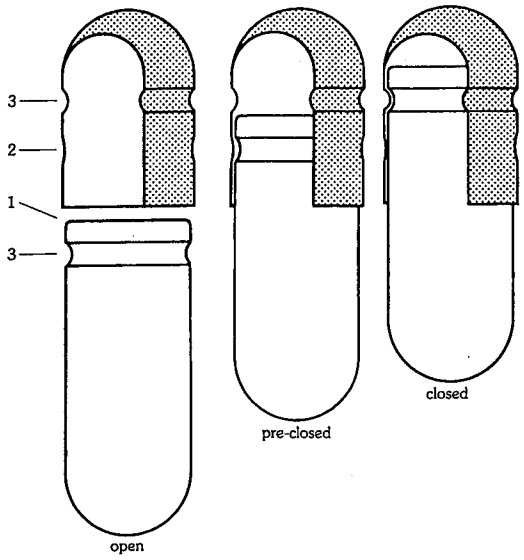

Fig. 11.2 The Coni-Snap capsule. The tapered rim (1) avoids telescoping; the protuberances (2) prevent premature opening; the grooves (3) lock the two halves together once the capsule has been filled.

Table 11.1(a). Dimensions of Coni-Snap capsules made by Parke, Davis, measured at a moisture content of 12–16%

Capsule size	*Cap length* mm	*Body length* mm	*Cap diam.* mm	*Body diam.* mm
00	11.74*	20.22*	8.53	8.18
0	10.72*	18.44*	7.64	7.33
1	9.78	16.61	6.91	6.63
2	8.94	15.27	6.35	6.07
3	8.08	13.59	5.83	5.57
4	7.21	12.19	5.32	5.05
Tolerance	*±0.51 ±0.46	*±0.51 ±0.46	—	—

Table 11.1(b). Dimensions of Coni-Snap Supro capsules compared with standard Coni-Snap capsules.

	Coni-Snap Supro capsules			
	External diam. body/cap	*Volume*	*Standard capsule size with same*	
Size	mm	ml	*volume*	*diameter*
A	8.18/8.53	0.68	0	00
B	8.18/8.53	0.50	1	00
C	7.33/7.64	0.37	2	0
D	6.63/6.91	0.30	3	1
E	6.07/6.35	0.21	4	2

Standard and Lox-It capsules are illustrated in Fig. 11.3. R. P. Scherer also manufacture capsules with the registered name 'Star-Lock'. The dimensions of capsules made by Scherer are shown in Table 11.2. The manufacturers recommend storage at 24°C and about 50% relative humidity.

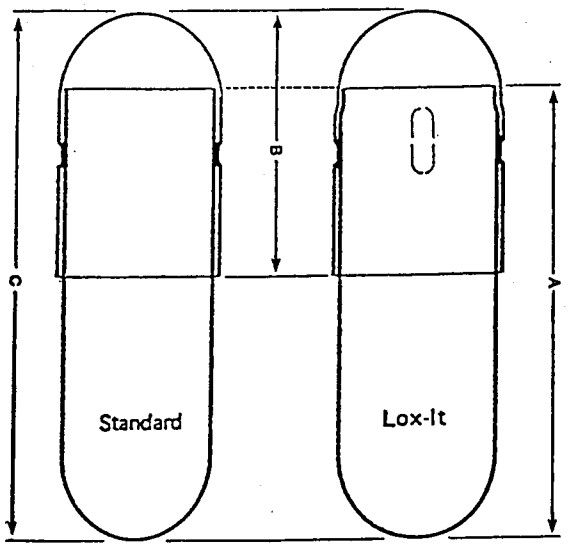

Fig. 11.3 Standard (or Star-Lock) and Lox-It capsules.

A Posilok capsule is illustrated in Fig. 11.4. The pre-lock feature is designed to prevent the cap and body from separating during transit from the manufacturer to the purchaser. Air is released through vents during closure with a resultant increase in the final holding force between the cap and the body. The dimensions of capsules made by Elanco Qualicaps are shown in Table 11.3. Target weights for empty shells are shown in Table 11.4.

Capsules can be manufactured with elongated bodies to meet specific requirements, and specifications for these capsules are supplied to individual customers. Capsule diameters are not a directly controlled parameter and various factors, e.g. moisture content, wall thickness, length, etc., can influence them.

Hard gelatin capsules with a larger volume than size 000 (1.37 ml) are available (e.g. from Kruger, Willi K. G.). In the United Kingdom they are supplied by Davcaps. The sizes range from 3.5 ml to 51.5 ml; dimensions of these capsules are shown in Fig. 11.5.

Experimental Filling Tests

The results of a number of filling trials, comparing Coni-Snap and conventional capsules, are given in Table 11.5 (Latchem, 1979; Mallory, 1980).

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Table 11.2. Dimensions of capsules made by Scherer, measured at a moisture content of 12–16%

Capsule size	*Body length (A)* mm	*Cap length (B)* mm	*Body diameter* mm	*Cap diameter* mm	*Filled length (C)* mm	*Volume of standard length* ml	*Volume of elongated length* ml
0	18.69	11.05	7.35	7.65	22.0	0.7	0.76
1	16.55	9.82	6.65	6.90	19.6	0.5	0.54
2	15.29	9.04	6.10	6.36	18.0	0.4	0.45
3	13.66	8.12	5.60	5.85	16.2	0.3	0.34
4	12.39	7.36	5.09	5.34	14.7	0.21	0.22
Tolerance	±0.3	±0.3	±0.05	±0.05	—	—	—

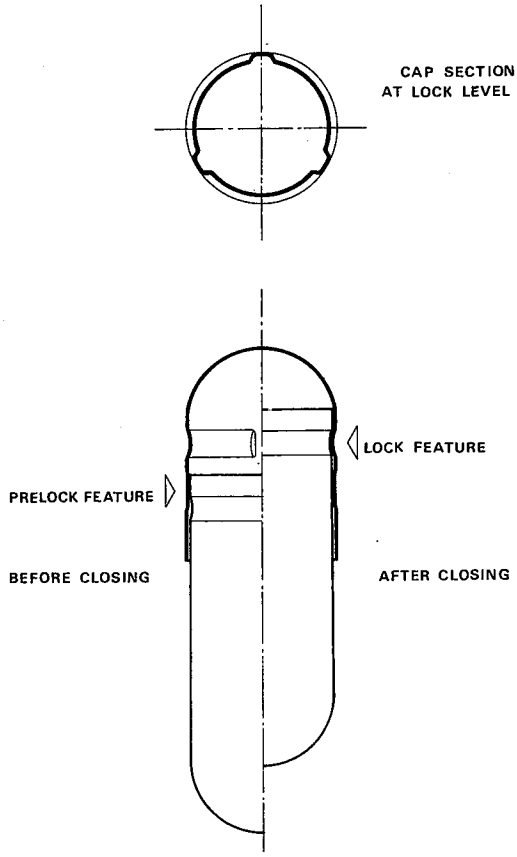

Fig. 11.4 The Posilok capsule.

These results show a reduction in the number of filling defects when the Coni-Snap design is used.

The results from a series of fillings of Elanco Qualicaps capsules followed by controlled inspections are shown in Tables 11.6, 11.7, and 11.8.

An examination of the results shown in these tables will illustrate that the fault levels are reasonably constant for each machine. One reason

Table 11.3. Dimensions of capsules made by Elanco Qualicaps, measured at a moisture content of 13 to 16% w/w

Capsule size	*Cap length* mm	*Body length* mm	*Cap diameter* mm	*Body diameter* mm	*Closed joined length* mm
00	11.4	20.2	8.51	8.16	22.9
0	10.9	18.5	7.63	7.33	21.8
1	9.7	16.5	6.90	6.62	19.5
2	8.9	15.1	6.35	6.07	17.8
3	7.9	13.5	5.82	5.56	15.9
4	7.2	12.3	5.32	5.06	14.5
Tolerance	±0.3	±0.3	±0.05	±0.05	±0.3

Table 11.4. Average weights of 100 capsules manufactured by Elanco Qualicaps

Capsule size	*Average weight* mg	*Limit* mg
00	126	±12
0	98	±9
1	76	±7
2	63	±6
3	50	±5
4	40	±4

for this may be the age of the capsule bushings. If they are very worn, the number of telescoped capsules increases, whilst if the bushings are new the tightness of fit results in more cracked ends. Generally, the level of defects in the empty capsules from all manufacturers is very low and the quality high. There can be considerable batch-to-batch variation in capsules from the same supplier, and the conditions of storage can affect the quality significantly. For instance, in a trial to examine the performance of capsules from two different suppliers, one manufacturer supplied capsules containing only 8% moisture, which were very brittle.

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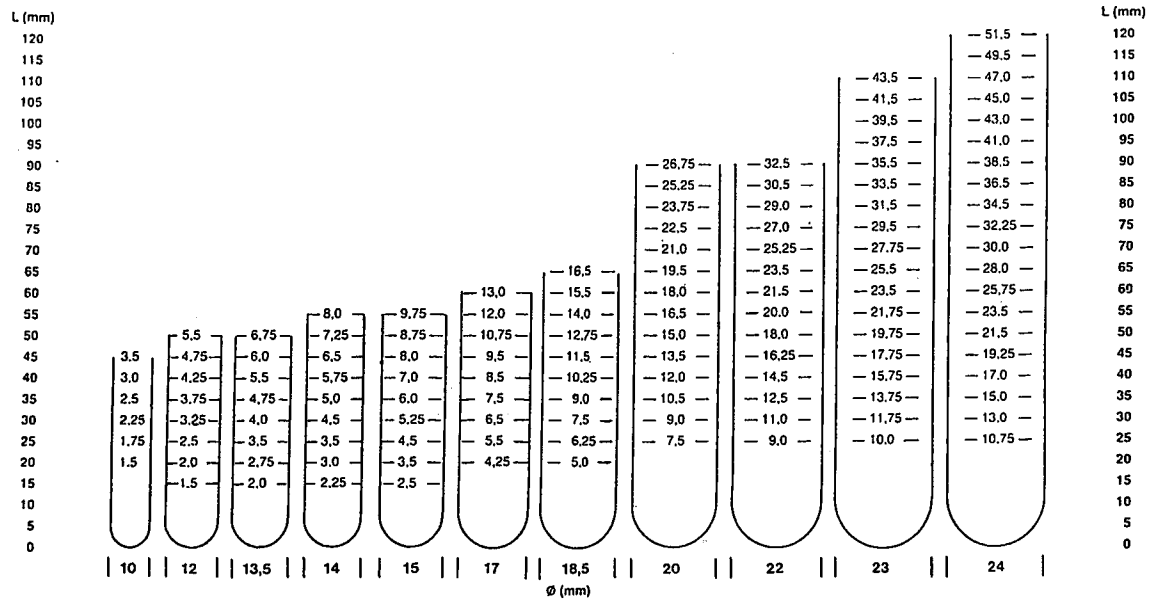

Fig. 11.5 The dimensions of capsule bodies larger than size 000, showing diameter (ø), length (L), and the volume (ml) contained at various filling levels.

Table 11.5. Summary of trials comparing filling defects between Coni-Snap and conventional capsules on different capsule-filling machines

Machine	*Filling rate* c.p.h.	*Defects per 100 000 capsules*			
		Split capsules		*Punched ends*	
		Conventional	*Coni-Snap*	*Conventional*	*Coni-Snap*
AZ-25[a]	32 000	37	0	6	0
AZ-30[a]		167	3	49	2
AZ-30[a]	32 000	19	0	0	0
AZ-60[a]	58 000	9	0	4.5	0
AZ-60[a]	60 000	11	2	1	1
GFK-600[b]	36 000	30	5	105	55
GFK-700[b]	38 000	20	2	1	1
GFK-1000[b]		11	2	36	16
GFK-1200[b]	73 000	1	0.1	14	0.3
GFK-1200[b]	70 000 to 80 000	18	0.2	2	0
G-37[c]	70 000 to 80 000	6	0	17	0

[a]Zanasi
[b]Höfliger and Karg
[c]mG2

The type of capsule-filling machine may also have a significant effect on the level of defects. In a trial which compared Coni-Snap capsules with Posilok capsules, the former fared better when filled on a Zanasi BZ-72 machine, whereas the Posilok capsules showed a lower level of defects when filled on an mG2 G37/N machine.

When pellets are being filled into Coni-Snap capsules, material can lodge on the lip of the body and hinder closure. This is also true if the powder plugs are loosely packed. The body-edge chamfer also reduces the area of contact between the body and the cap when the capsules are empty, which causes a higher than normal level of separated

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Table 11.6. Faults in a batch of filled capsules (Opaque Yellow, size 3), from three Zanasi BZ-150 fillers; sample size, 1200 capsules

	Sample 1	*Sample 2*	*Sample 3*	*Total (%)*
Machine No. 1				
Telescopes	9	4	8	0.58
Crush cracks	1	2	2	0.14
Other faults	2	1	3	0.17
Total	12	7	13	0.89
Machine No. 2				
Telescopes	1	4	2	0.19
Crush cracks	22	18	16	1.56
Other faults	0	2	2	0.11
Total	23	24	20	1.86
Machine No. 3				
Telescopes	2	2	12	0.44
Crush cracks	5	10	8	0.64
Other faults	5	1	1	0.19
Total	12	13	21	1.27

Table 11.7. Faults in two samples, each of 10 000 capsules (Opaque Yellow, size 3), from one Zanasi BZ-150 filler

	Sample 1	*%*	Sample 2	*%*
Telescopes	63	0.63	22	0.22
Dented	6	0.06	4	0.04
Crush cracks	16	0.16	6	0.06
Split	4	0.04	3	0.03
Holed body	1	0.01	0	0
Overclosure	0	0	0	0
Thin spot	0	0	1	0.1
Halves	12	0.12	0	0
Empty	1	0.01	0	0
Dirty	10	0.10	0	0
Total	113	1.13	36	0.36
Print defects	8	0	0	0

empty capsules. However, some tests have shown a considerable reduction in the number of splits and telescoped capsules when Coni-Snap capsules have been used.

The Formulation of Capsule Products

There are a number of factors to be considered in the formulation of capsules. These include the size and colour of the shell, powder characteristics, stability, bioavailability, filling method, and packaging, storage, and marketing.

The size of the shell is governed largely by the bulk density of the contents (see Chapter 7). The colour of the shell must be different from that used for other capsules and must be acceptable in the country to be supplied (see Chapter 4). Powder

Table 11.8. Summary of defects found after inspections of 50 different batches of capsules from three different Zanasi BZ-150 fillers

	Defect	*Highest %*	*Lowest %*	*Mean %*
Machine 1	Telescopes	0.70	0.09	0.25
(36 inspections)	Crush cracks	0.44	0	0.13
	Others	0.21	0	0.09
	Total			0.47
Machine 2	Telescopes	0.64	0	0.16
(33 inspections)	Crush cracks	0.35	0	0.10
	Others	0.18	0	0.07
	Total			0.33
Machine 3	Telescopes	0.70	0	0.13
(33 inspections)	Crush cracks	0.26	0	0.10
	Others	0.32	0	0.11
	Total			0.34

Overall mean defects from 102 inspections = 0.38%

characteristics (Chapter 7) are a significant factor in the filling process and it must be remembered that a formulation which is suitable for a hand-operated filling machine may need to be changed when an automatic machine using compression filling is to be used. The particle size and other formulation factors may affect bioavailability (Chapter 13).

Formulation for High-speed Filling

A lubricant, such as magnesium stearate, is essential for high-speed filling. One difficulty that arises is that there is no generally accepted method for quantitatively assessing lubrication capability. It has been suggested (Butcher and Jones, 1972) that particle densities, packing characteristics, tensile strength measurements, surface area measurements, and shear strength measurements may give a clearer indication of the lubrication properties of batches of magnesium stearate. Considerable batch-to-batch variation has been shown to exist, sufficient to produce large differences in compression properties (Hanssen *et al.*, 1970). Some materials, such as corn starch, that are commonly used as excipients in formulation work, possess some lubricating properties, whilst others, like lactose, do not.

The concentration of glidants is also important as quantities above 1% tend to decrease the flow rate; about 0.1% is usually adequate. Not all authors agree that glidants and lubricants are separate, different, classes of compound (King, 1970). Magnesium stearate can certainly act as both a glidant and lubricant.

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Investigation of Factors Affecting Filling

In an attempt to define the formulation process more accurately, Cole and May (1975) used an instrumented Zanasi LZ-64 capsule-filling machine to investigate the filling characteristics of some commonly used excipients by measuring the forces exerted in the transfer of powder. The machine was fitted with a modified dosator assembly, shown in Fig. 11.6.

The capsule fill-weight depends on (a) the position of the dosator in the dosator nozzle (distance X in Fig. 11.6), (b) the powder depth in the dosator hopper, (c) the bulk density of the material in the dosator hopper, and (d) the filling speed of the machine.

In this machine, the tubular nozzle was dipped into a powder bed of constant depth and, during plug formation, the distance X was always less than the depth of powder in the hopper. To eject the powder plug into the capsule body, the piston was moved to the end of the dosator nozzle, pushing the plug before it, after which the spring returned it to its original position. In these studies, the axial forces exerted by the powder on the end of the dosator piston were measured during formation, carry-over, and ejection of the powder plug.

The small values of the forces made measurement difficult. On a tablet machine the punch forces during compression are typically 3×10^4 N, whereas in capsule filling the values rarely exceed 400 N, and are more typically in the range 20–30 N. To measure forces of this order with strain gauges, a large degree of amplification is necessary, with its attendant drift and signal-to-noise ratio problems.

The piston of the dosator assembly was fitted with four strain gauges, two active and two passive, the active pair being fitted on opposite sides of the stem so that only axial forces were recorded: lateral bending forces were automatically compensated and had no effect. To prevent the leads becoming twisted during operation, the dosator was driven so that it turned in the opposite direction to, and at the same angular velocity as, the rotating head on which it was carried. The system was calibrated in compression and in tension.

Experiments were made using size 00 capsules at a filling speed of 50 per minute. The materials used were microcrystalline cellulose (Avicel), a modified corn starch (Starch 1500, formerly Sta-Rx 1500), and two grades of lactose, 50T and 80 mesh. These were all used either alone or after the addition of 0.5% w/w magnesium stearate as a lubricant. The machine was run for several revolutions before fitting the dosator nozzle to stabilise the powder level in the dosator hopper. When using the lubricated materials, several capsules were filled before taking recordings of pressure, but with the unlubricated materials recordings

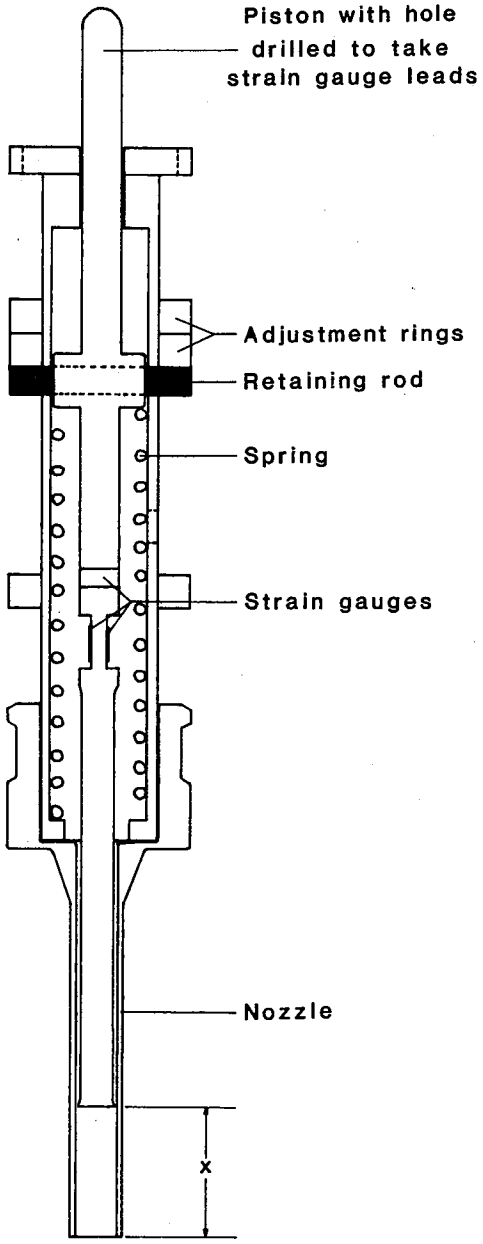

Fig. 11.6 The modified dosator assembly used on an instrumented Zanasi LZ-64 capsule-filling machine (Cole and May, 1975).

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were started immediately to enable the onset of binding to be studied. A recording was made with the machine running but with the powder hopper removed, to ascertain the effects of machine movement on the oscillograph trace.

The particle sizes and bulk densities of the materials examined are shown in Tables 11.9 and 11.10, and the traces in Fig. 11.7. The first event

Table 11.9. Particle size distribution (% retained on sieves) of powders used in experimental filling tests

Sieve mesh no.	*Lactose 80-mesh* %	*Lactose 50T* %	*Avicel pH 101* %	*Sta-Rx 1500* %
60	0	0	0	1.2
100	3.8	18.3	1.5	6.0
150	12.6	38.0	6.5	11.7
200	14.8	20.0	12.4	14.6
350	30.3	18.5	33.4	22.6
through 350	39.3	4.2	46.2	43.6

Table 11.10. Bulk density of powders used in experimental filling tests

	Untapped g/cm^3	*Tapped* g/cm^3
Lactose 80-mesh	0.500	0.877
+0.5% magnesium stearate	0.658	0.926
Lactose 50T	0.758	0.909
+0.5% magnesium stearate	0.840	0.917
Avicel pH 101	0.309	0.455
+0.5% magnesium stearate	0.373	0.463
Sta-Rx 1500	0.625	0.840
+0.5% magnesium stearate	0.690	0.877

marker on each trace shows when the powder plug was picked up, and the second when it was ejected into the capsule.

Figure 11.7C is a typical trace, which is modified in detail by the characteristics of the material being filled. An initial compaction force was produced at *a*, as the plug was formed, and was partially retained, *b*, during carry-over of the plug to the capsule body. A second force was produced at *c*, as the powder plug was ejected into the capsule body. This second force changed considerably according to the extent of lubrication of the material.

The amount of compression which is given to the powder during plug formation is governed by the combined effects of the depth of powder in the filling hopper and the distance of the end of the dosator piston from the end of the nozzle. These were both kept constant so that any differences in the resulting forces were attributable to the nature of the powder.

Lactose requires lubrication before tablets can be produced. That this is also true of capsule filling when using the plug method can be seen from the rapid ejection force build up in lactose 50T. Figure 11.7C is the trace taken after about 20 capsules had been filled, and Fig. 11.7D after about 50 (note the change of vertical scale). At this stage the noise from the machine was sufficient to indicate that a binding problem existed. The cause was the entrapment of small particles between the inner wall of the dosator nozzle and the flared end of the dosator push rod. Magnesium stearate, added at a concentration of 0.5%, overcame this (Fig. 11.7E).

Addition of magnesium stearate to lactose 80 mesh resulted in an increase in compaction pressure, a possible explanation for which is that the pressure increase is due to the 5.5% increase in bulk density caused by the glidant effect of the lubricant. Addition of magnesium stearate to the lactose 50T produced little change in either compaction pressure or bulk density, probably because the coarser and more evenly sized particles of this grade of lactose are more free-flowing than those of the lactose 80 mesh, and rapidly assume a maximum packing density in the dosator hopper, whether lubricated or not. Sta-Rx showed an increase in bulk density of similar magnitude to that of lactose 80 mesh after lubrication (4.4%) but did not show the same increase in compaction pressure. It is possible that the Sta-Rx particles deform more easily under compaction than the lactose particles and so absorb the energy of compaction more easily.

The effect of 0.5% magnesium stearate on the Avicel was slight. The compression force was not reduced, and the carry-over or retention force was only slightly reduced, as was the ejection force. This material would fill satisfactorily without lubrication, which supports the claim by Fox *et al.* (1963), that Avicel has some lubricant properties. The bulk density of the material did not increase appreciably after lubrication (1.73%).

Mehta and Augsburger (1981) suggested that increased levels of lubricant might be required to improve the dissolution characteristics of the capsule when an insoluble filler such as Avicel is used. This could probably be explained by the reduction in hardness of the plug more than offsetting the

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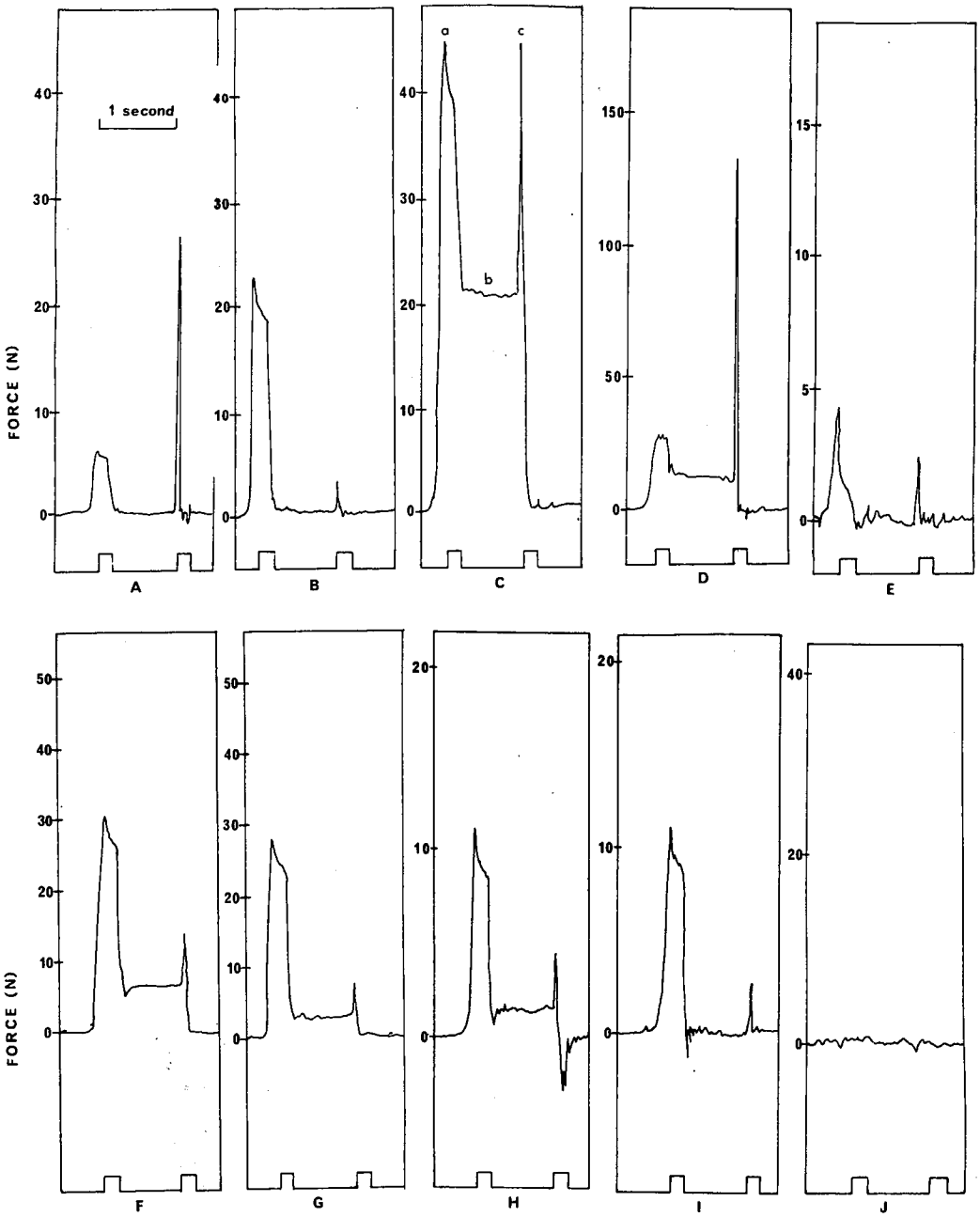

Fig. 11.7 Recorder traces of the forces operative in the filling of capsules with some commonly-used excipients, on a Zanasi LZ-64 machine. A, lactose 80-mesh; B, lactose 80-mesh with 0.5% magnesium stearate; C, lactose 50T after 20 capsules; D, lactose 50T after 50 capsules; E, lactose 50T with 0.5% magnesium stearate; F, Avicel; G, Avicel with 0.5% magnesium stearate; H, Sta-Rx 1500; I, Sta-Rx 1500 with 0.5% magnesium stearate; J, machine noise.

hydrophobic properties of the magnesium stearate. Where the filler is soluble (e.g. lactose) some increase in dissolution with increased lubrication level was shown.

The retention and ejection forces seen on the Sta-Rx trace (Fig. 11.7H) were almost eliminated after the addition of 0.5% magnesium stearate (Fig. 11.7I), as was the tensile force, which can

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be seen just after ejection in the trace of the unlubricated material. This was due to tension in the dosator rod, arising from the frictional resistance to its return caused by particles of powder getting between it and the inner surface of the nozzle. This happened only with Sta-Rx.

Measurements such as these can help in the determination of minimum lubricant levels during the formulation of powders for encapsulation, and of the optimum mixing time for the powders.

Another method, using the piezo-electric principle of measuring force (Money *et al.*, 1976), is shown in Fig. 11.8. The device was fitted to a

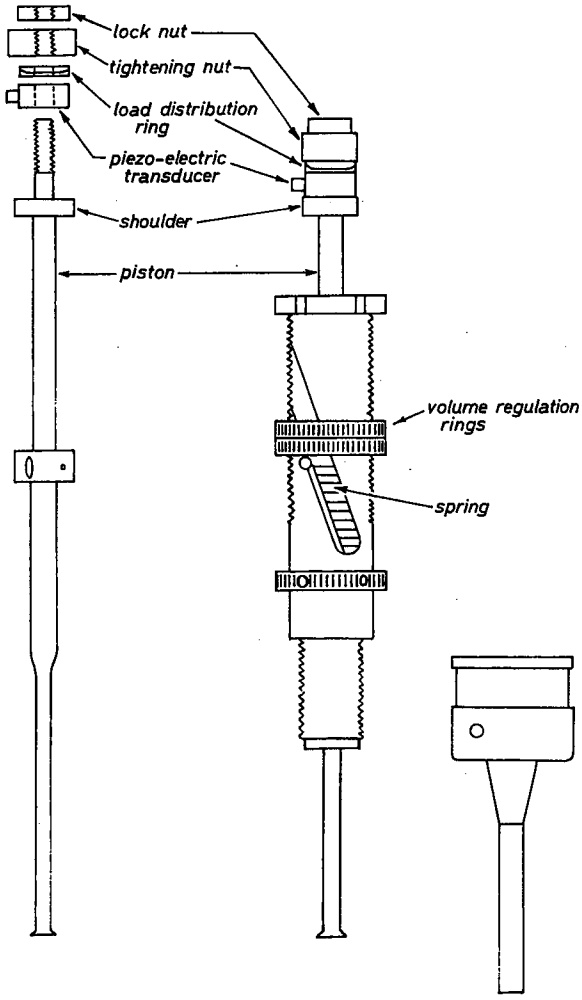

Fig. 11.8 The dosator assembly with piezo-electric transducer, used on a Zanasi RV-59 capsule-filling machine.

Zanasi RV-59 capsule filler, and the following excipients and lubricants were examined: lactose, extra-fine and fine; microcrystalline and granulated cellulose; maize, rice, and potato starch, and sodium starch glycolate; talc; and magnesium stearate. No details were given of such parameters as particle size or surface area. The type of trace produced is shown in Fig. 11.9.

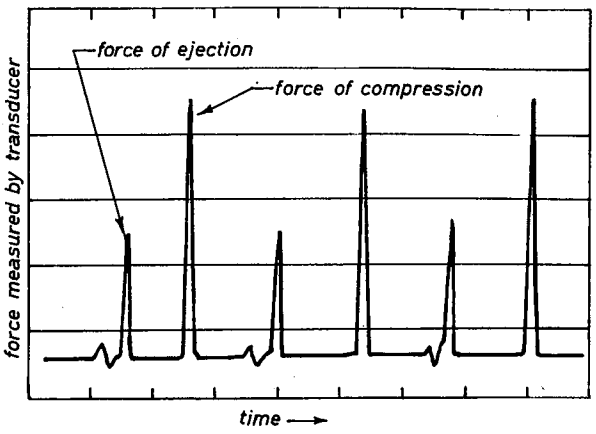

Fig. 11.9 Trace of the forces operative in the filling of capsules, measured by the piezo-electric transducer.

Further work in this field was conducted by Small and Augsburger (1977) who essentially repeated the work of Cole and May (1972, 1975) but used a slip ring between the instrumented dosator and monitoring equipment. They also used a mercury contact swivel to minimise the possibility of noise in the output. Their results supported the conclusions reached earlier by Cole and May.

Small and Augsburger (1978) extended their work to study in detail the behaviour of a number of lubricants commonly used for capsule formulations. They used an instrumented Zanasi LZ-64 capsule filler to study the behaviour of a number of fillers (compressible starch, microcrystalline cellulose, and anhydrous lactose) with several lubricants such as magnesium stearate, stearic acid, and magnesium lauryl sulphate. The results for compressible starch are shown in Fig. 11.10.

Comparative Evaluation of Capsule-filling Machines

When testing a new machine's suitability for a new product, or even for an old product that is required in greater quantity, certain basic information can be obtained by using placebo formulations. But it is not possible to estimate mechanical reliability

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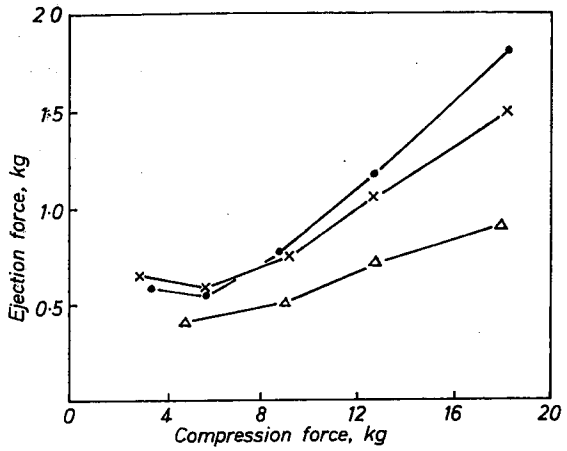

Fig. 11.10 The effect of lubricant type on the ejection force of compressible starch blends containing 0.1% of lubricant. Depth of powder bed, 50 mm, piston height, 15 mm. • magnesium lauryl sulphate, × stearic acid, △ magnesium stearate.

using this method, because it is necessary to run it over a long period in a production area. The tests which are described here are designed for high-speed equipment capable of filling from 30 000 to 150 000 capsules per hour. For smaller output, the quantities of materials may be adjusted accordingly.

When evaluating a new machine, the following points should be considered.

1. Overall comparison of the new model with the existing machines of similar capacity.
2. The time needed to set up the machine, and the degree of technical competence required.
3. The time needed to dismantle and/or to change over from one capsule size to another.
4. Ease of maintenance, quantity of spare parts required for maintenance and for handling different capsule sizes.
5. Extent of services required.
6. Delivery and cost.

Testing the Performance of a Machine

At least three different powders are needed for satisfactory evaluation. Suitable mixtures are as follows.

Coarse powder (fill-weight 250.0 mg): lactose 50T, hydrous, dense, 246.0 mg + colloidal silicon dioxide, 1.5 mg + magnesium stearate, 2.5 mg.
Fine powder I (fill-weight 250.0 mg): lactose 80-mesh, 246.0 mg + colloidal silicon dioxide, 1.5 mg + magnesium stearate, 2.5 mg.
Fine powder II (fill-weight 200.0 mg): lactose 80 mesh, 160.0 mg + maize starch, 38.0 mg + magnesium stearate, 2.0 mg.

The test will require 2 000 000 Posilok capsules, 2 000 000 Coni-Snap (Star-Lock could be used as an alternative) and 200 kg of the Company's product.

To carry out the test, set up the machine with each type of powder in turn, and run under ideal conditions, applying the following criteria for the appraisal of the machine.

1. Uniformity of weight between individual capsules.
2. Uniformity of weight between groups of capsules.
3. Uniformity of closure of capsules.
4. Need for polishing capsules.
5. General appearance of capsules.
6. Proportion of rejects.
7. Time spent clearing operating faults.
8. Output of capsules.
9. In-process control of fill-weights.

The machine should then be run under non-ideal conditions.

1. Allow the powder to fall to a low level in the hopper, and check the weight variation of the filled capsules.
2. Examine the effects of changing the temperature and, if possible, the humidity.
3. Vary the speed of the machine over as wide a range as is possible.
4. Estimate the amount of dust produced, the smooth running or vibration of the machine, and examine for overheating.
5. List any modifications that are going to be needed.
6. Consider the noise level near the machine, the extent to which moving parts are protected, and how easy it is to load the machine with empty capsules and material for filling.

To compare the weight variation at various speeds of the Zanasi AZ-60 and the BZ-150, the following scheme was used by the author.

1. Run both machines at 60 000 capsules per hour, using a single batch of 700 000 capsules divided in two. After the machines have been adjusted for a specific target weight, the gross individual

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weights of samples of 50 capsules taken at intervals of 25 minutes of actual encapsulation time from each machine (including an initial and final sample) are measured for statistical analysis. A timed log detailing events occurring during the run (e.g. capsule blockage, shutdowns, weight adjustments made, etc.) should be kept.

2. Compare the performance of the BZ-150 at a speed of 60 000 capsules per hour with that at a speed of 100 000 capsules per hour, using a single 700 000 capsule batch divided in two. Estimate the total process time and divide into 10 equal intervals to give the sampling times. At each sampling time withdraw 100 capsules and weigh 20 of these capsules using a suitable balance. If the data can be stored in a retrieval system then progressive analysis during the evaluation may be possible.

3. Compare the performance of the BZ-150 at filling speeds of 60 000 capsules per hour with that at a speed of 150 000 capsules per hour in a similar way to run 2.

4. Compare the performance of the BZ-150 at a speed of 100 000 capsules per hour with that at a speed of 150 000 capsules per hour in a similar way to run 2.

Determine the effect of sampling time on weight uniformity, i.e. is the weight variation occurring between samples taken at different times greater than the weight variation of samples at those times? This is a one-way ANalysis Of VAriance, and such an ANOVA table for each group of data shows whether sampling time is important. This table gives a significance value for the F-ratio which, when compared with tabulated values, shows whether the batch is homogeneous for statistical purposes.

If there is no effect of sampling time then the batch can be considered as a whole and a single parameter (variance) generated which can be examined to show the effect of machine speed, batch, type of machine, production conditions, etc. If the batch is not homogeneous (i.e. sampling time has an effect), then the direct comparison of two variables, e.g. sampling time and machine speed, is required. This is a two-way ANalysis Of VAriance and produces a two-way ANOVA table.

Determination of more elementary statistics, such as the mean weight, standard deviation, and coefficient of variation is also conducted on each sample.

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Chapter 12

Capsule Handling Systems

G. C. Cole

CAPSULE WEIGHING EQUIPMENT

This section contains a description of equipment used to monitor the weight of capsules after the filling process, and to sort batches that are likely to be rejected due to wider variation than is acceptable. There are a number of pieces of equipment that can sort capsules into pass and reject fractions, but generally they operate at a much lower speed than the filling equipment.

Capsule Balances for Rapid Check-weighing

THE INQUISITOR CAPSULE BALANCE

This may be used for either in-process control or in a quality control function.

The Inquisitor balance (C.I. Electronics Ltd) is shown in Fig. 12.1. This balance automatically check-weighs samples of capsules from production batches to give a print-out of any or all of the following information: the number of samples weighed, the target weight, the mean weight, the percentage drift of the mean weight from the target weight, the standard deviation, the coefficient of variation, all the individual weights in ascending order with an indication of any that are outside the set limits, and a histogram to show the weight distribution.

It consists of a weighing unit with a vibratory feeder, weighing head with opening pan, and a

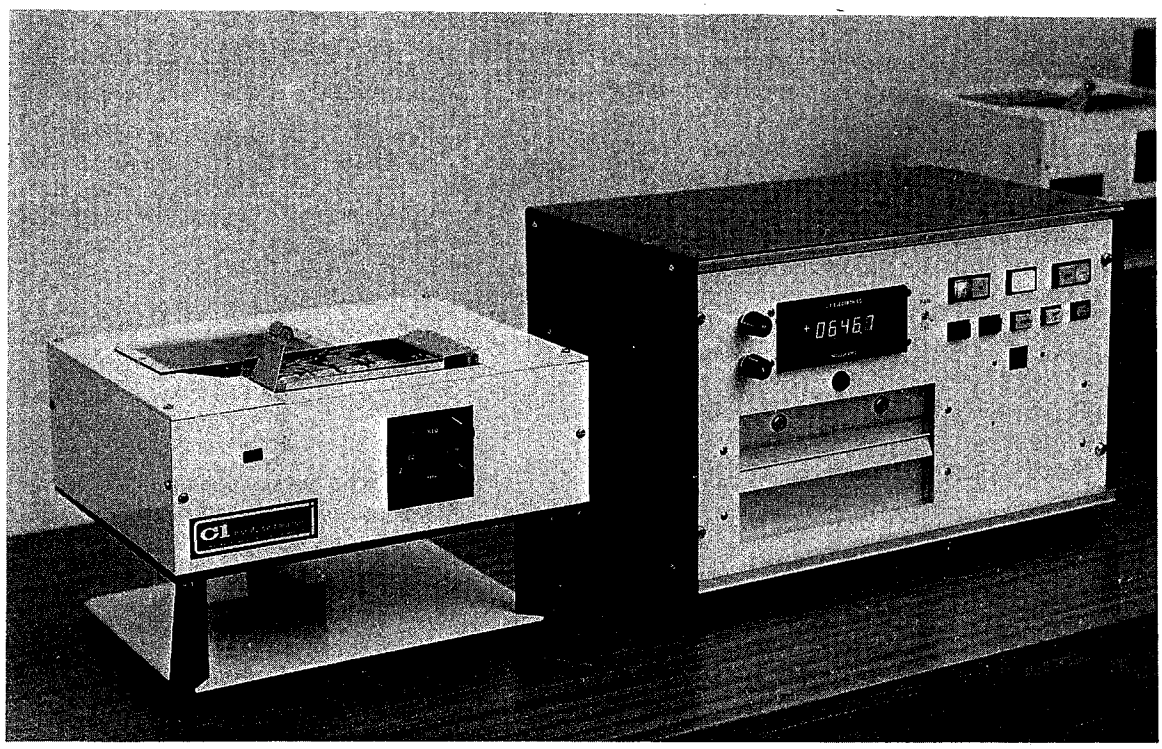

Fig. 12.1 The C.I. Electronics Inquisitor tablet and capsule balance.

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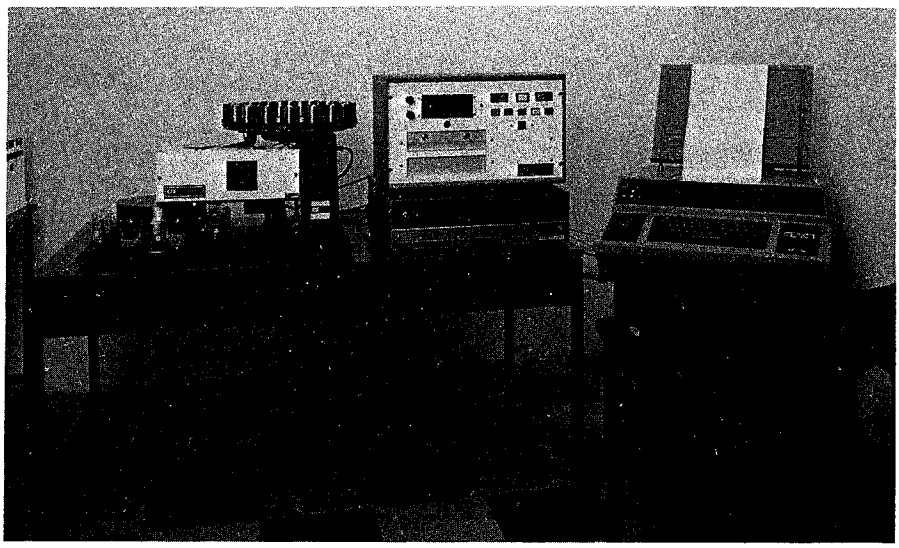

Fig. 12.2 The C.I. Electronics Carousel tablet and capsule balance.

semi-automatic calibration mechanism. The balance control unit has a digital weight display, on/off switch, zero control, calibration control, and a set/run switch. The mini-computer has a core memory of 16K. As an optional extra, a teletype to produce hard copy and eight-hole punched paper tape may be fitted.

The balance is checked, set to zero, and calibrated at the start of the day. Batch identification, product code, etc., are entered into the system on the teletype, together with the sample quantity required. The samples are placed on the vibrator and the balance started. Thereafter the operation is fully automatic. When the required number have been weighed, the surplus of capsules is flushed through the system and a print-out given of the results. The weighing rate is 20 capsules per minute with a precision of ±1 mg, and the maximum individual capsule weight is 1.5 g.

A typical print-out shows: product name, date, number of batches, individual weights, histogram of weight distribution, target weight, mean weight, number of samples, time of sample, limits, and number outside limits.

The Carousel Capsule Balance

An alternative to the Inquisitor is the Carousel balance (C.I. Electronics Ltd) shown in Fig. 12.2 The print-out is similar to that from the Inquisitor. This balance will automatically check-weigh samples of capsules from up to 16 batches, sequentially. It has 16 acceptance and delivery units with a vibratory feeder. It will weigh at either 12 or 20 capsules per minute from a minimum weight of 15 mg up to a maximum of 1.5 g. The delivery unit holds up to 50 capsules, the unit being programmed to weigh an exact number from each position and then reject the excess. The control unit has a digital display, the mini-computer has a 16K memory, and data transfer is to an ASR 33 teletype.

The Vigilante Weight Control System

The Vigilante system (C.I. Electronics Ltd) is designed for the control of a number of filling machines. It has the following features: fast initial set-up, regular or continuous weight monitoring for each production machine, immediate analysis during or at the end of each production batch, daily production records and comprehensive weight data for quality control.

The coupling of the Vigilante to weighing units and sampling stations is shown schematically in Fig. 12.3. Capsules can be taken from production machines either automatically or manually. Sampling is supervised by the system which records the time at which each sample is taken. Samples are taken from the exit chute of each capsule machine in a coded scoop which is identified with that machine by a series of coded slots on one edge. The scoop is inserted into a verification unit, shown in Fig. 12.4, near the filling machine and this unit relays, via a cable to the system control, the time and the identity of the machine from

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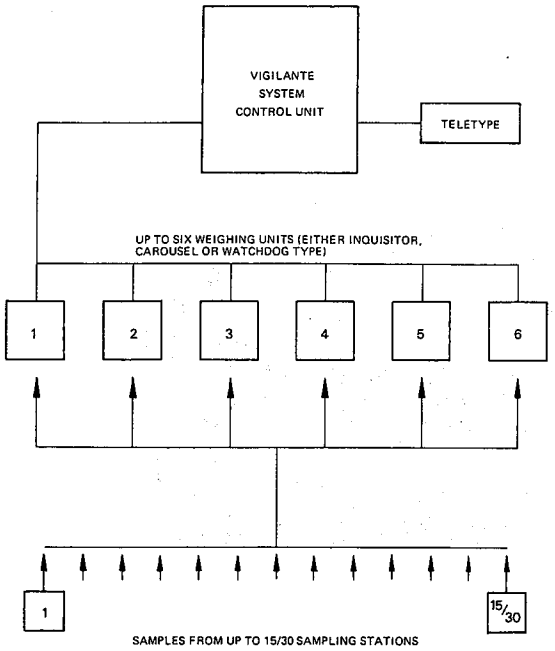

Fig. 12.3 Schematic diagram of the optimum usages of the Vigilante weight control system.

which the sample has been taken. A small lamp on the control unit indicates that the scoop has been identified.

The capsules contained in the scoop are then fed, by the operator, into a weighing unit. When this has been done, the verification unit will digitally display the mean weight of the sample, and will light a red lamp if the mean weight or any individual capsule weight is outside the pre-set limits. For resampling, or for normal sampling after the next appropriate time interval, the unit lights a green lamp. There is a reset button to restore the unit to normal operation after it has given an alarm signal.

Capsule Weighing and Sorting

This section describes equipment which is designed for sorting batches of capsules, which have been rejected for excessive weight variation, into 'accept' and 'reject' batches, or for tightening up the weight control. Such units can also be used to divide capsule lots into various weight fractions.

The SADE Balance

The Sorting Automatic Device Electronic (SADE) balance (C.I. Electronics Ltd) is illustrated in Fig. 12.5. This balance will weigh and

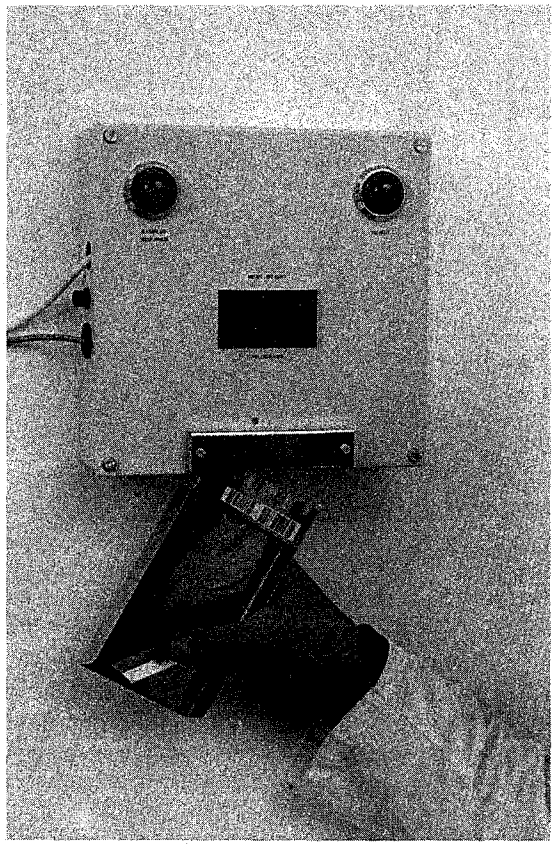

Fig. 12.4 The C.I. Electronics verification system.

sort capsules at the rate of 2400 per hour into 'accept' and 'reject' fractions between 0 and 2.0 g with a precision of ±1 mg. The capsules pass from the large 100-litre hopper into a rotary bowl which divides them into two streams. The capsules in each stream are then passed singly into a bucket-type pan on one of the two electronic balances that make up the unit. The digital panel meter displays the weight and, after weighing, the bucket opens and allows the capsule to fall into one of two chutes, for acceptance or rejection. The unit has an automatic self-calibrating facility which permits it to operate unattended for long periods. An audio-alarm sounds when attention is required.

The Anritsu-Zanasi Check-weigher

This check-weigher, illustrated in Fig. 12.6, can sort capsules of sizes 0–4 into three fractions according to upper and lower pre-set limits which are adjustable up to ±50 mg from a mean value. The machine has five weighing channels, each of which operates at speeds of up to 7200 capsules

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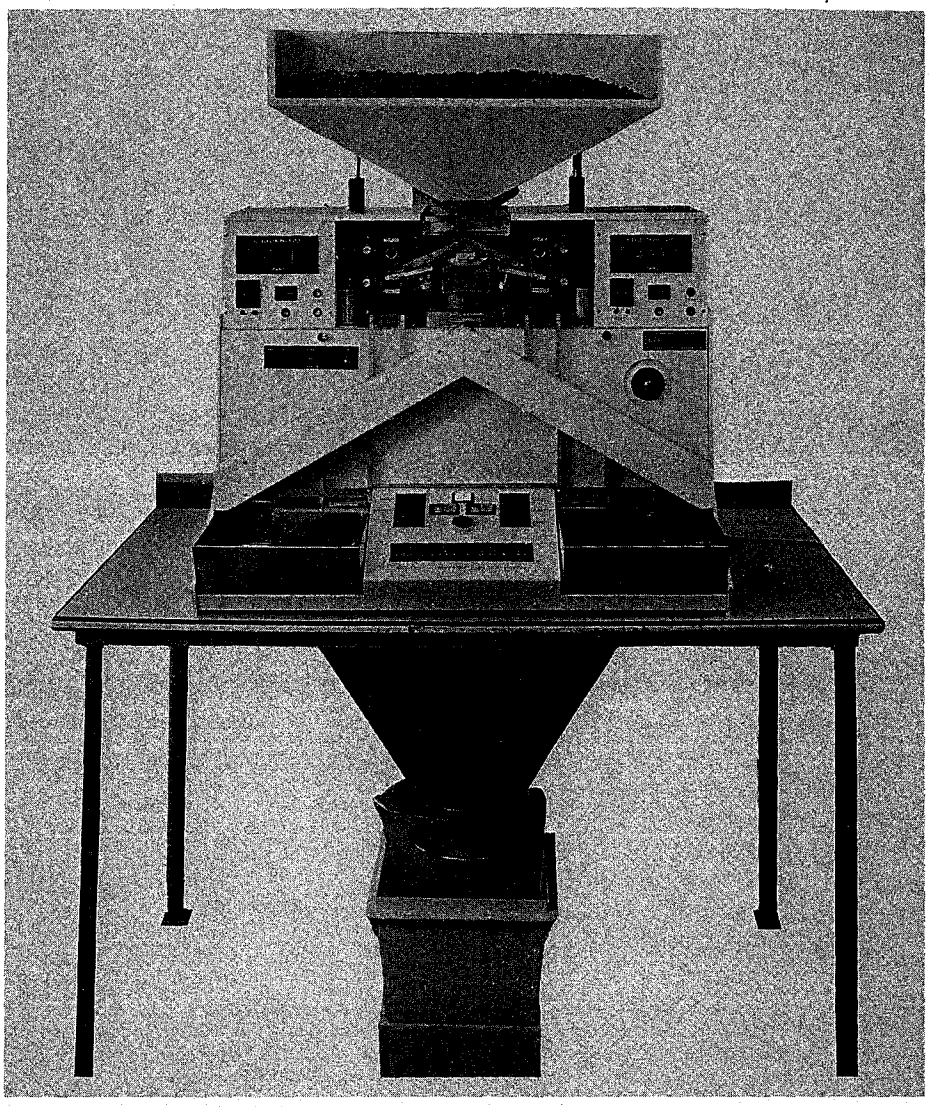

Fig. 12.5 The C.I. Electronics SADE balance.

per hour, giving a total throughput of 36 000 capsules per hour. Three counters provide read-outs of the number of capsules in each fraction.

Capsules are fed from a hopper through conventional capsule handling techniques onto the weighing head (Figs 12.7 and 12.8). This head is a linear variable differential transformer (LVDT) the output of which is proportional to the linear displacement and hence to the capsule weight. The capsule is ejected from the weighing head by the succeeding capsule, and falls down a chute, past a photoelectric counter. The counter is an electromagnetic type, and counts one digit for every ten capsules. After passing the photoelectric counter the capsule takes one of three paths depending on its weight and the calibrated machine settings. Capsules within the set limits pass straight along the chute into a receiving container, whilst the overweight or underweight capsules fall through one of two flaps which are connected to the counting mechanism, so that separate counts are recorded for overweight, underweight, and normal capsules.

If any of the five channels become blocked by a damaged capsule, or if the hopper becomes empty, an alarm is sounded and the machine stops.

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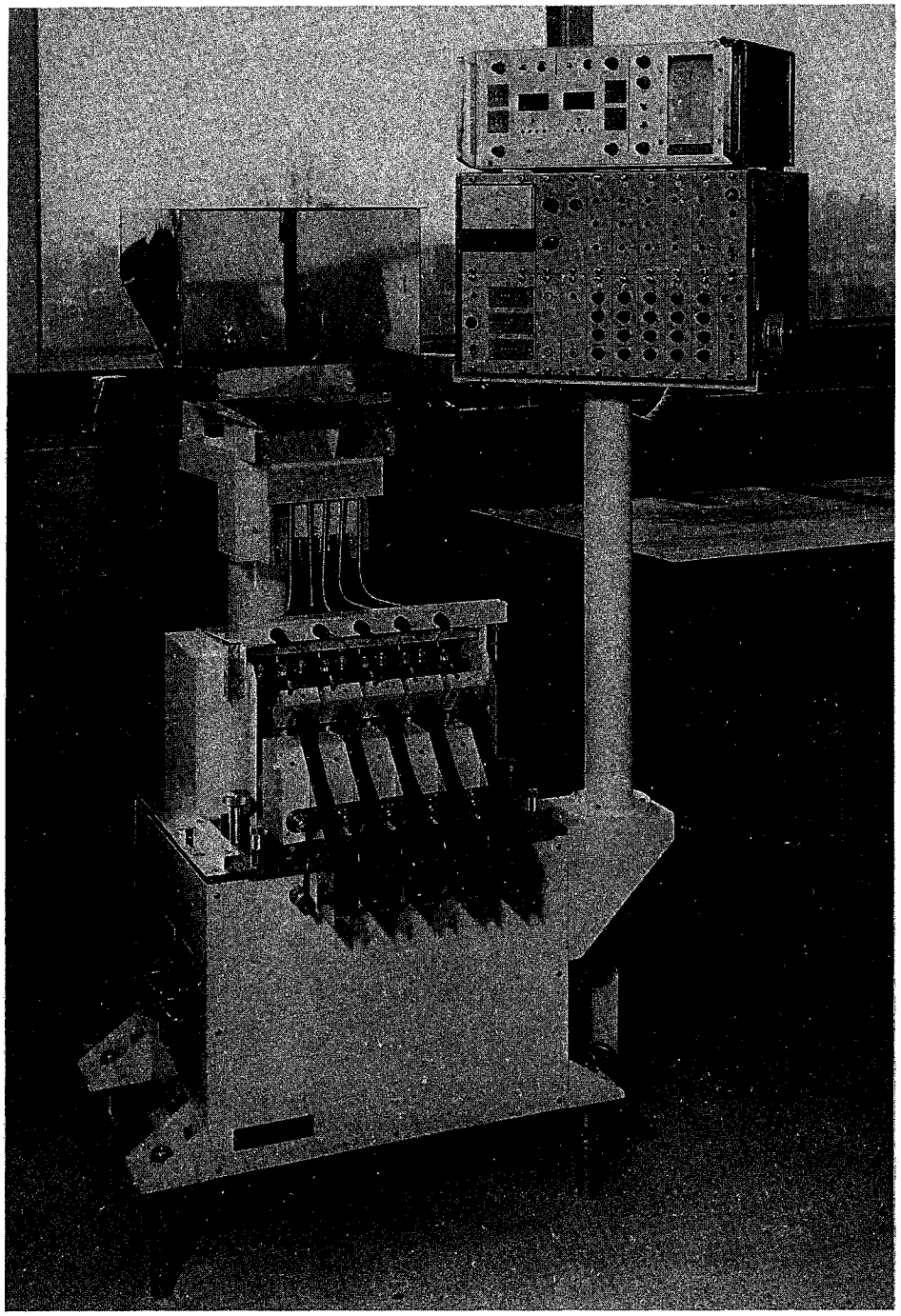

Fig. 12.6 The Anritsu-Zanasi K515B check-weigher.

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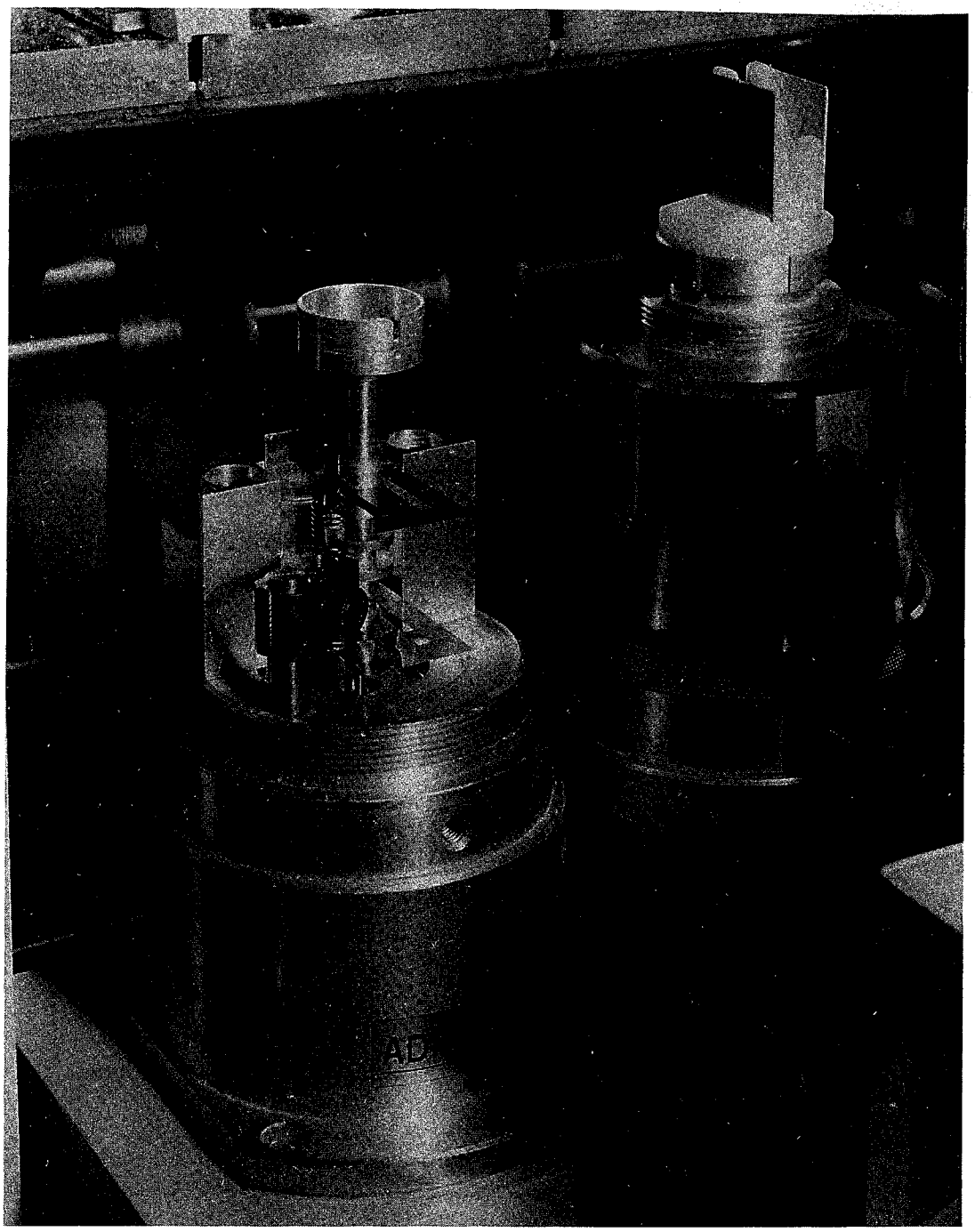

Fig. 12.7 The weighing head (with cover removed) on the Anritsu-Zanasi K515B.

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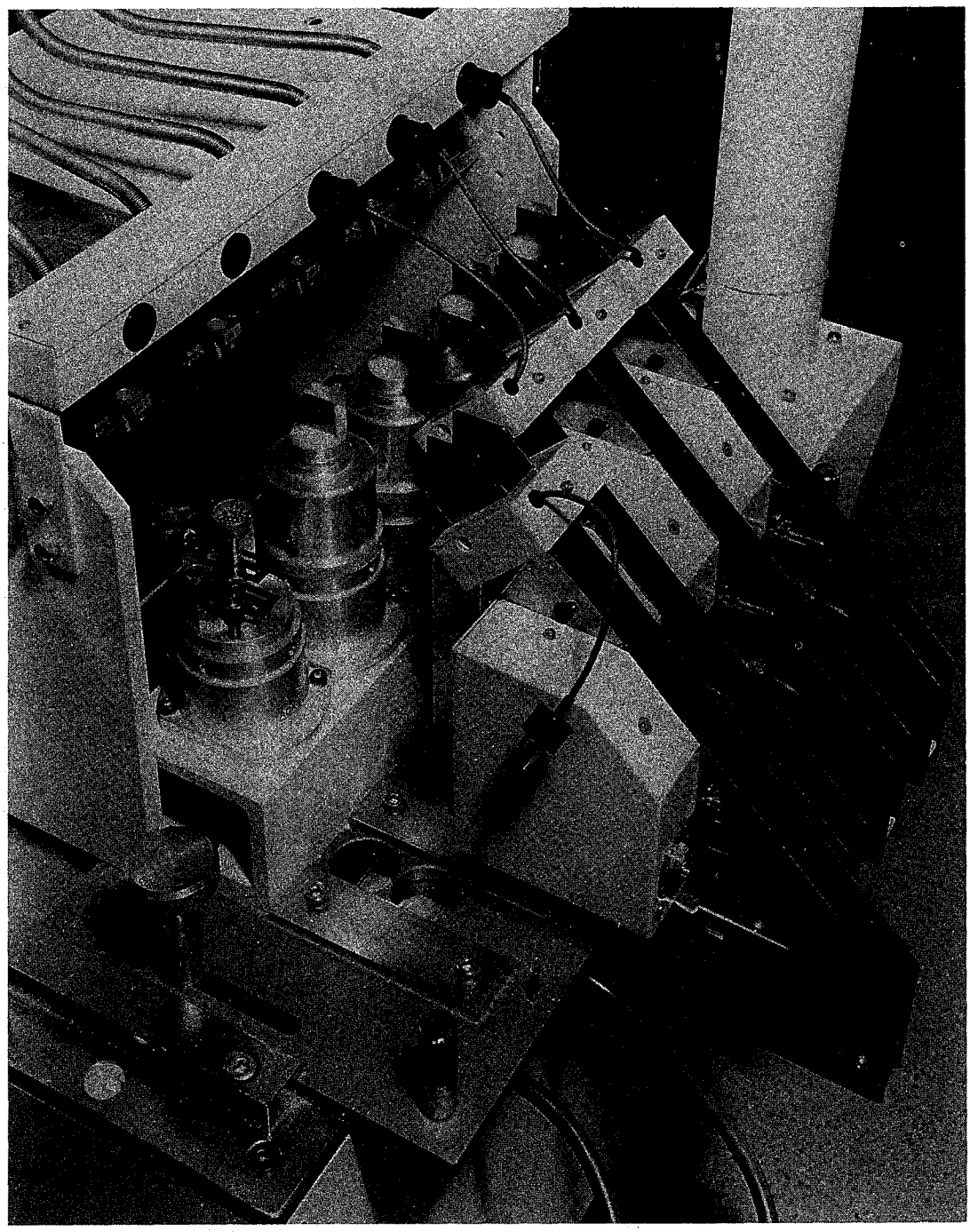

Fig. 12.8 The arrangement of weighing heads and outlet chutes (channel 1 chute removed) on the Anritsu-Zanasi K515B.

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The change from one capsule size to another takes approximately 10–15 minutes and is effected by changing (a) the hopper feed mechanism, which is fixed by two hexagonal socket screws and five bayonet fasteners, where the ends of five tubes enter the transfer mechanism to the weighing heads, (b) five transfer arm pieces, each of which is fixed by one hexagonal socket screw, and (c) five weighing heads which rest on top of the LVDT mechanisms.

The performance of one of these machines is indicated in Table 12.1.

Table 12.1. The drift (mg) away from the set weight of a capsule sorting machine, measured after each 1000 capsules

	Channel number				
	1	2	3	4	5
Initial	0	0	0	0	0
1000	+5	0	0	+1	0
2000	+6	+1	+2	+2	+1
3000	+9	+1	+2	+4	+2
4000	+10	0	+2	+3	+1
5000	+7	+1	+2	+3	+2
6000	+10	+1	+3	+5	+2
7000	+10	+2	+3	+5	+3
After cleaning	+8	0	−1	0	+1
Drift after 15 000 capsules had been sorted					
Total drift	+3	+5	+6	+2	+6
Electronic drift	+2	+1	+3	+1	+2
Dust	+1	+4	+3	+1	+4
Drift after 30 000 capsules had been sorted					
Total drift	+12	+5	+7	+1	+1
Electronic drift	+6	+2	+4	0	−2
Dust	+6	+3	+3	+1	+3

The Elanco Rotoweigh Check-weigher

This machine is illustrated in Fig. 12.9 and is available from Manesty Machines Ltd under licence from Eli Lilly & Co. It operates by measuring the back-scattered X-ray intensity from a capsule and its contents. The claimed throughput is 73 000 capsules per hour, with an accuracy of ±3%. A schematic diagram is shown in Fig. 12.10.

Filled capsules are placed in the hopper (1). They move under gravity into the chamfered holes in plate (2) and are fed into the tubes in the rotating turret (3). The capsules drop one at a time from the tubes into sleeves (4) mounted on pins in the perimeter of an inspection wheel. The wheel carries the capsules past a low-energy X-ray beam (5). The energy back-scattered by the capsule is in direct proportion to the mass of its contents. This energy is detected by a scintillation crystal

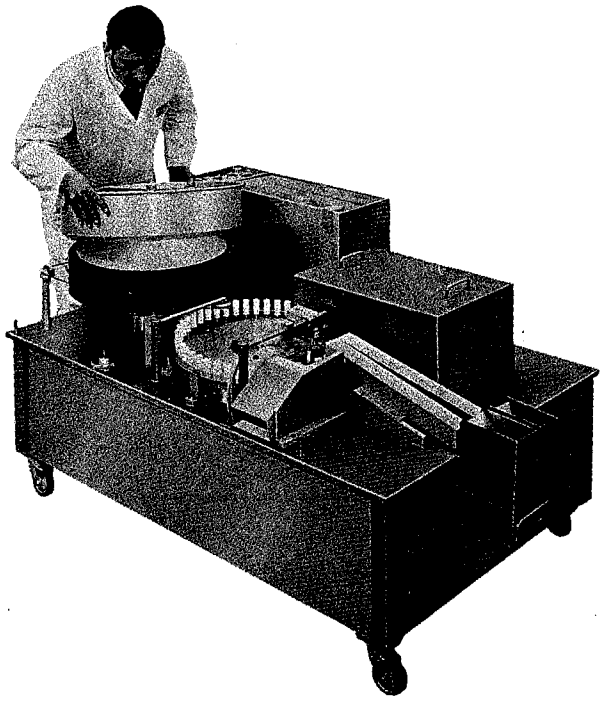

Fig. 12.9 The Elanco Rotoweigh check-weigher.

(6) which is read by a photomultiplier tube to provide a voltage in proportion to the intensity of the reflected energy.

If the mass of a capsule is lower than a pre-set standard, the voltage is processed so as to activate a valve, releasing an air jet which blows the underweight capsule into low-mass chute (7). If the mass is higher than a pre-set standard, another valve is opened which blows the capsule into the high-mass rejection chute (8). If the mass of the capsule falls within the accepted range, a third air jet blows the capsule into a hopper for packaging (9).

The inspection wheel carrying the capsules past the inspection beam rotates 26 times per minute and there are 47 inspection pins in the wheel. Thus, 1222 capsules will pass through the unit in one minute. A 48th pin (10) carries a standard mass which passes the inspection beam 26 times per minute. The purpose of this mass is to restabilise the detection system to offset any drift in sensitivity which may be caused by changes in temperature, component age, line voltage, or other factors. Some typical test results are shown in Table 12.2.

The results in Table 12.2 show that out of a total of 171 000 capsules, only 17 (0.01%) would

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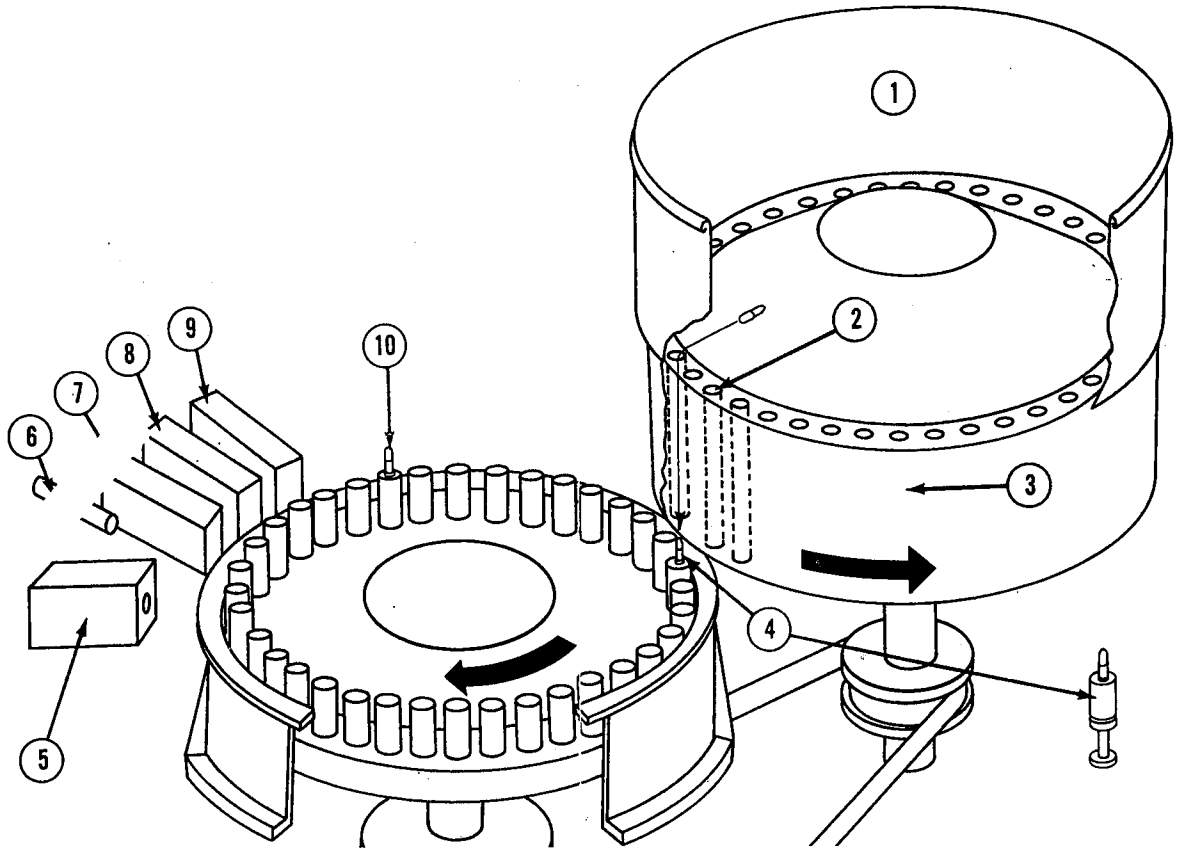

Fig. 12.10 Schematic diagram of the operation of the Elanco Rotoweigh. 1, hopper; 2, plate containing chamfered holes; 3, rotating turret; 4, capsule sleeves; 5, low-energy X-ray beam; 6, scintillation crystal; 7, low-mass rejection chute; 8, high-mass rejection chute; 9, acceptance chute to hopper; 10, 48th pin carrying a standard mass.

Table 12.2. Test results from five sub-batches, each containing 34 200 capsules, obtained from the Rotoweigh check-weigher

			Number of rejects		
Sub-batch	*Weight category*	*Total rejects*	*Within set limits*	*Outside set limits*	*Outside U.S.P. XX limits*
1	high	144	106	38	0
	low	22	0	22	5
2	high	64	51	13	0
	low	203	188	15	2
3	high	77	55	22	0
	low	28	14	14	4
4	high	159	131	28	0
	low	45	38	7	4
5	high	30	18	12	1
	low	37	31	6	1

fail the *U.S.P.* XX weight variation test. To determine the reliability of these results, several capsules known to be outside the pre-set limits were inserted into the batches; they were all rejected by the machine. Two of the sub-batches were passed through the machine a second time; no further rejects were recovered.

The average time for each sub-batch to pass through the Rotoweigh was 30 minutes, which is equivalent to 68 400 capsules per hour. Fine tuning of the calibration at the start of the batch reduced the number of capsules rejected without affecting those rejects which were outside the normal limits. The majority of capsules rejected were on the borderline of the pre-set limits but did not amount to more than 1% of the total.

The Vericap 1800 Check-weigher

A schematic diagram of the Vericap 1800 (MOCON/Modern Controls Inc.) is shown in Fig. 12.11. The system is based on the change in capacitance which occurs when a non-conducting object, such as a capsule, is placed between two oppositely-charged plates. The average dielectric

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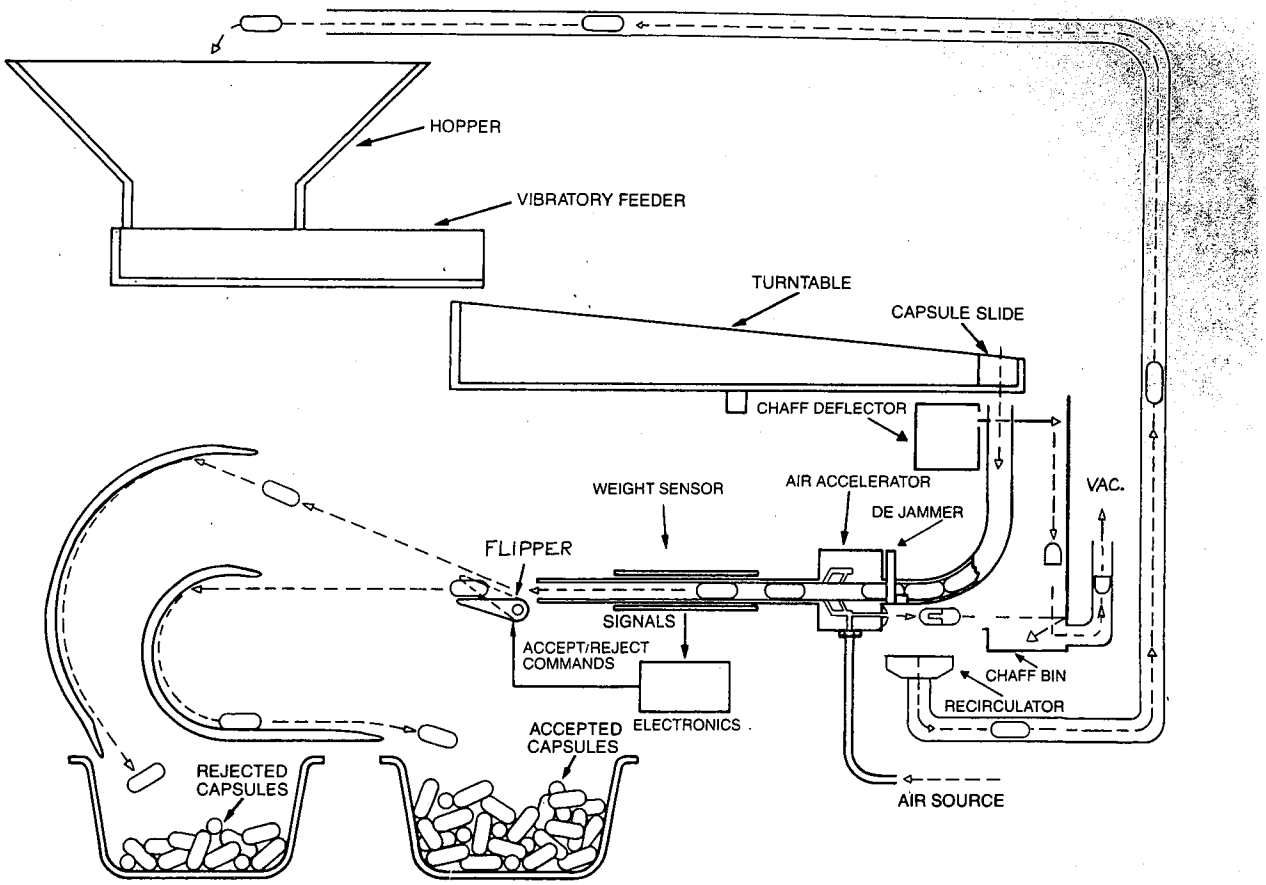

Fig. 12.11 Schematic diagram of the operation of the Vericap 1800 check-weigher.

constant between the plates when separated by air is 1, and a significant and measureable change takes place when a capsule is passed through the electric field. The system is calibrated so that the weight of the capsule can be related to the change in capacitance. A detailed description of this type of system has been given by Demorest (1980). The machine is claimed to have a throughput of 72 000 to 108 000 capsules per hour. An advantage of this system is that the air used to propel the capsules has a de-dusting effect.

CAPSULE HANDLING EQUIPMENT

The Parke, Davis Capsule-finishing System

In this system, the constituent units clean, polish, inspect and count the capsules, and may be arranged in various combinations to suit different requirements. One arrangement is shown in Fig. 12.12.

The drum dumper is designed to handle a 24-gallon (100-litre) cylindrical drum, 655 mm long × 440 mm diameter, weighing approximately 300 kg when full. The operator loads a drum into the drum carrier and raises it to an inverted position above the capsule cleaner/polisher. When the drum reaches the upper limit of its travel, the operating motor is automatically stopped.

As part of this dumping process, after a few millimetres of upward movement, the drum contacts a spring-loaded conical cover which clamps tightly to the drum and serves as a retaining cover for it and its contents. The cone prevents the capsules from leaving the drum when the drum is inverted. When the drum has reached its final position, the operator opens a valve on the cone to release the capsules into the cleaner unit. The drum remains in its inverted position until it is empty.

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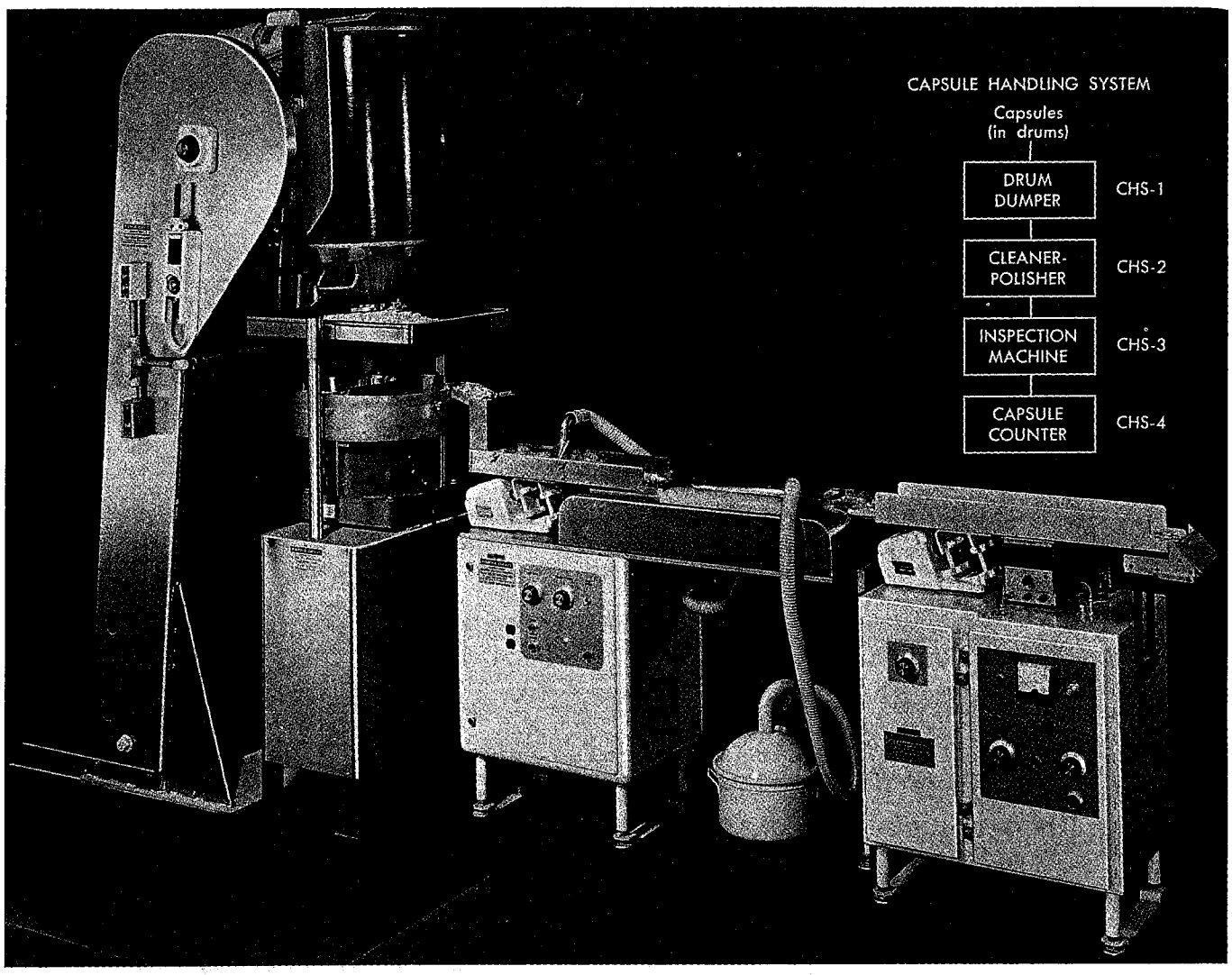

Fig. 12.12 The Parke, Davis capsule-finishing system showing, in order, the drum dumper, the cleaner-polisher, the inspection machine, and the capsule counter.

When the drum is empty, the operator presses a pushbutton to return it to floor level, the spring-loaded cone being automatically released from the drum as it descends. The cone is made of stainless steel and is easily cleaned between batches to eliminate cross-contamination of products. To save time, extra cones are available so that washing can be off-line.

The dumper is driven by an electric motor with a spring-operated mechanical brake: when power is removed, the brake locks the drum carriage, preventing further travel. Limit switches prevent inadvertent manual operation that might drive the drum carrier too far in the wrong direction, and a slip clutch prevents damage to the equipment if the drum carrier sticks at any point within its normal travel.

The cleaner/polisher is designed to clean and polish capsules by tumbling them in moisturised salt or other cleaning agent. It consists of a hopper, feeding capsules into a bowl mounted on a vibratory drive, all supported on a heavy steel base. The vibrating bowl is the heart of the cleaning system. There are several blades in the bottom

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of the bowl that serve to tumble and rotate the salt and capsule mixture. The capsules are cleaned by this tumbling process because the powder on the capsule exterior has a greater affinity for the damp salt than it has for the gelatin of the capsules. In addition, the capsules are polished by the vibration. Salt is separated from the capsules as they ascend a perforated metal ramp to discharge from the cleaning bowl into an empty capsule extractor and thence into a drum or an inspection machine.

The capsule feed rate is controlled by varying the distance between the bottom of the hopper and the feed chute of the bowl, though minor feed rate adjustments can be made with the vibrator potentiometer. When used in conjunction with the inspection machine, the throughput of the cleaner/polisher is held to between 40 000 and 80 000 capsules per hour by the operator's inspection rate.

The hopper is designed to hold at least 150 litres of capsules. Used with the inspection line, the drum remains inverted in the drum dumper where it is used as a supply hopper for the cleaner, with only a minimum quantity of capsules in the cleaner hopper. The salt has to be changed periodically, depending on the amount of powder on the capsules. This is accomplished by stopping the inflow of capsules to the bowl and raising a slide valve that connects the drain at the bottom of the bowl to the central vacuum system. As soon as the dirty salt has been sucked out, the valve is closed, new salt placed in the bowl, and the capsule feed restarted. This takes only 20 to 30 seconds.

If moisturised salt is used, the capsule feed must be stopped and all the capsules removed from the bowl whenever the machine stops operating for ten minutes or more. If this is not done, the damp salt will fuse to the capsules and will not be removed by further tumbling or vibrating.

The hopper and the bowl are made of stainless steel, and are removable for cleaning to prevent product cross-contamination. Such cleaning is required between different batches of the same or different products, but not between drums of the same batch. When used after filling, it is manually stopped and started by a built-in switch, but when used as part of an inspection line, a relay in the inspection machine stops and starts the cleaner at the end of a predetermined count or whenever the operator manually stops the inspection machine.

Capsules are fed into the inspection machine by a linear vibrating feeder consisting of a grooved orientating plate that feeds capsules in single file into a 12-track grille slanting across a moving conveyor belt. Since the grille guides the capsules at an angle to the conveyor belt, they rotate as they move past the operator, enabling the entire capsule to be seen. The operator sits in front of the grille to inspect the capsules, removing defective ones with a hand-held vacuum pick-up tube. The remainder are conveyed by the belt into the capsule counter. Built into the input feeder of this machine is a vacuum-operated hood that removes empty capsules and any loose dust, and the belt itself is vacuum-cleaned by a brush and vacuum connection located underneath it.

The rate at which capsules leave the capsule cleaner and discharge directly into the inspection section is set according to capsule size, capsule quality, and the operator's inspection rate. It ranges from about 40 000 capsules per hour for size 0 to 70 000 capsules per hour for size 4. There is a belt speed-control on the machine, a vibrator control, and an on/off switch. This latter is used by the operator to stop and start the cleaner/polisher, the inspection machine, and the capsule counter during operation. When the predetermined count is reached, the counter automatically stops the system.

All metal parts that come into contact with the product are made of stainless steel, anodised aluminium, or are nickel-plated. The conveyor belt is removable for washing, as is the grille. The only change parts are the two grilles, each of which accommodates three sizes of capsule.

The final unit in the inspection system is a 12-channel electronic pre-set counter. Capsules leaving the inspection machine are conveyed through the counter by a vibrating grooved pan which aligns the capsules in 12 rows and feeds them through the 12-channel electronic detector. Signals from the detector are fed through an electronic system that counts the capsules and shuts off the counter, the inspection machine, and cleaner/polisher when the pre-selected count is reached. These counts are manually selected, according to capsule size and drum capacity, by means of a rotary switch. The counter will count capsules passing the detector whether they pass one or twelve at a time. The counter has a six-digit visual display counter that indicates the actual count at all times. Its primary purpose is to enable non-standard amounts of capsules to be counted.

The counter is designed so that if a detector lamp fails, the system will stop, but the lamp can be changed and the system restarted without losing

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the stored count. A reset button is provided to clear and reset the counter when necessary. The operator, using a switch on the inspection machine, can stop the whole system, including the counter, without the counter losing its stored count. Mounted on the front panel are 12 small lamps. As a capsule passes a particular detector, its lamp momentarily blinks, as the capsule is sensed. These lights are useful for quickly checking the performance of the counter. Finally, a rate meter and an associated rate-alarm signal are provided. The rate per hour can be read directly from the rate meter, and the alarm circuit can be pre-set so that a piercing audio alarm will sound at a count rate slightly above the desired production rate. This prevents the counter from being flooded with capsules without the operator knowing it. Too many capsules attempting to pass the detector will 'piggyback' and cause miscounts, and the alarm is provided to alert the operator to this condition.

All parts in contact with the capsules are nickel- or chrome-plated. The counter itself is built with sophisticated but robust solid-state circuitry, providing extremely long life. Most of the critical circuitry is mounted on plug-in circuit boards, and procedures exist for rapid trouble-shooting by non-technical personnel for locating a defective board and replacing it with a new one.

The following predetermined count settings are provided for various capsule sizes: size 0, 65 000; size 1, 80 000; size 2, 100 000; size 3, 150 000; size 4, 200 000; size 5, 250 000. Other counts, such as those at the end of a run or for special lots, can be made by reading and recording numbers on the built-in visual display counter. The counter cannot run independently of the inspection machine.

The Perry CCP/2 Polisher and BFD/2 Descagger

These two machines (Perry Industries Inc.) may be used as a combination unit or independently. The polisher is a saltless cleaner, designed to ensure the maximum cleaning of two problem areas, the ends of the capsule and the ledge where the cap forms a trap with the body. The descagger removes all empty shells and broken pieces of shell before the cleaning and polishing operation. The polisher is shown in Fig. 12.13 and incorporates a two-stage process.

The first stage consists of a pre-cleaning section to remove heavy deposits or the results of a capsule opening and spilling its contents. The pre-cleaning is followed by a final buffing operation to remove any remaining dust. The system is variable in speed, with two adjustments, and is designed as a continuous-flow machine which can be operated at the outlet of a filling machine or can be fed from a belt or vibratory feed system.

The object of pre-cleaning is to reduce contamination of the buffing medium and to extend the time before changing or cleaning it is required. The pre-cleaner also enhances the cleaning of the trap areas. The pre-cleaner utilises a combination of reduced pressure (partial vacuum), air propulsion, and impact with a high-voltage screen. Each of these brings about some cleaning, and in combination they remove between 85 and 95% of the dust.

In operation, capsules are fed into an input chute and carried into an air jet which propels the capsules and dust forward through a tube. At the end of the short air path, the capsules hit a stainless steel screen at a potential of 5000 volts. The high voltage, the high-velocity air stream, and the impact, cause dust to be released. The dust-collection suction is applied behind the high-voltage screen, accelerating particles of dust through the screen and on to the dust collection system. The combination of suction and air jet create a negative pressure within the system from the input chute to the output. The pre-cleaning system is designed for easy dismantling and cleaning.

The capsules pass through the pre-cleaner and drop from a chute into a rotating tube for final cleaning and buffing. The stainless steel rotating tube is fitted with a synthetic fabric liner to clean and polish the capsules. The tube liner and the entire tube assembly is quickly and easily removed; changing a liner requires about two minutes, and they are both washable for re-use, and are long-lasting. This final buffing section has two adjustments: a dial speed control adjustment, and an angle adjustment.

The services that the system requires are, besides electricity, clean air at about 60 litres/minute at 0.2 MPa for size 0 capsules, and a negative pressure equivalent to a vacuum cleaner, approximately 1 metre water gauge, for dust collection. There must be a negative pressure at both the inlet and the outlet chutes.

Capsule-inspecting Machines from mG2

The mG2 model SC filled-capsule selecting machine (see Chapter 10, Fig. 10.53), is designed to process up to 100 000 capsules per hour at the ejection side of a capsule-filling machine, and it

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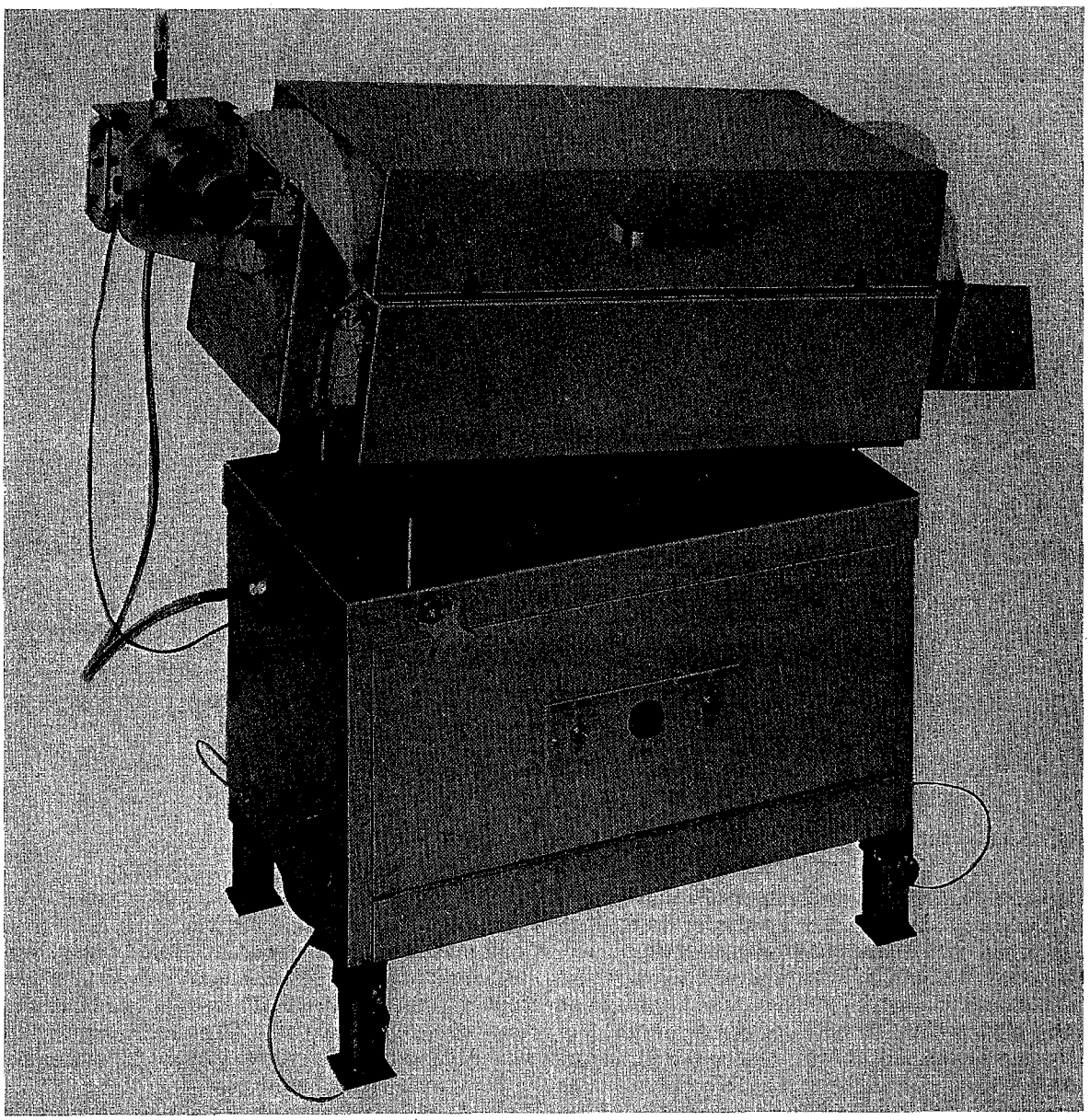

Fig. 12.13 The Perry Model CCP/2 automatic capsule cleaner and polisher.

can be used in conjunction with the cleaning and inspecting machine, also manufactured by mG2, Fig. 12.14. The selecting machine removes capsule fragments and open or empty capsules from the filled capsules. It has two independently-driven vibrating grooved plates, each controlled by its own rheostat; the capsules pass across one of them and then the other, travelling in the grooves and being propelled by the vibration. Loose powder, dust, and capsule fragments are removed by suction. If several capsule sizes are to be selected, the second vibrating plate is replaced. A static charge eliminator can be fitted for neutralising the charge on the capsules.

The mG2 cleaning and inspecting machine, model P1, is shown in Fig. 12.14 and is intended

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Fig. 12.14 The mG2 Model P1 capsule cleaning and inspecting machine.

for use with any capsule filling machine. Its function is to remove powder from the outside of capsules, to polish them, and to detect broken or ill-shaped capsules. The latter are manually selected for removal through a suction nozzle. The machine can handle over 100 000 capsules per hour. For a better performance, the machine can be linked to the exit of the filled-capsule selecting machine model SC.

Capsules are introduced into the hopper and are conveyed on to two lambswool belts, where powder is removed and the capsules are polished by the relative movement of the belts. Capsules are subsequently moved on to the inspection unit where they can be checked by the operator as they move downwards on rollers, passing over a luminous surface. The convenient height of the inspection unit and its oblique orientation enable the operator to check and to remove faulty capsules with the suction nozzle.

The Elanco Rotosort Capsule-sorting Machine

This machine is available from Manesty Machines Ltd under licence from Eli Lilly & Co. It can remove the following defective items: uncapped capsule bodies containing powder, uncapped empty capsule bodies, loose capsule caps, unfilled joined capsules, and loose powder.

The gentle conveying motion is produced by a crank and rod mechanism. The crank is driven by a variable speed motor which allows the output rate to be set for optimum sorting. The capsules travel through three sections (Fig. 12.15): powder separation (A), dual-plate sorter (B), and vacuum pick-up (C).

The powder-separation screen removes and contains the loose powder from unjoined capsules and other sources. The dual-plate sorter allows the joined capsules to pass, but removes the unjoined caps and bodies. The vacuum pick-up

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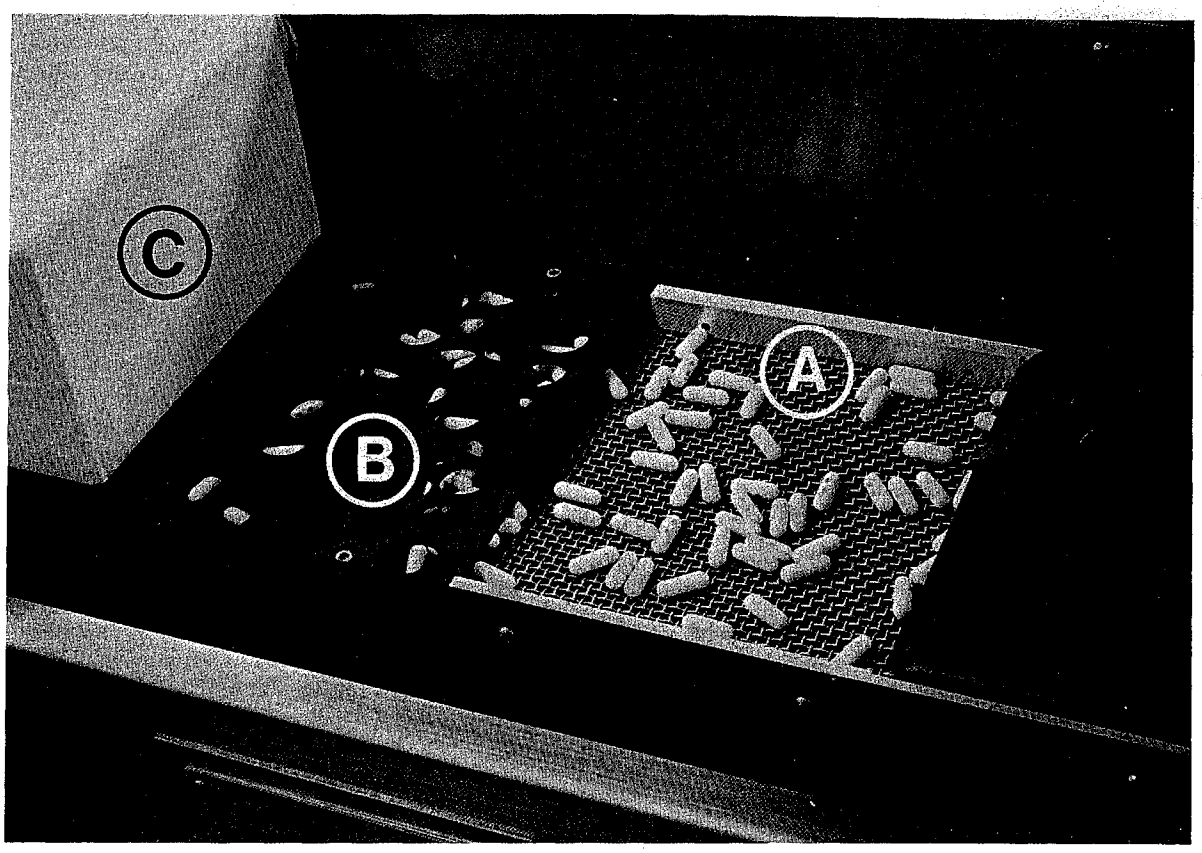

Fig. 12.15 The three sections on the Elanco Rotosort capsule-sorting machine. A, powder separation; B, dual-plate sorter; C, vacuum pick-up.

removes joined capsules which are empty or contain very little powder. A removable empty-capsule catch-basket is located in the vacuum line. All contact parts of the machine are washable and are made of aluminium alloy, stainless steel, or polyurethane. It is a compact automatic unit requiring only one operator.

Zanasi Capsule Sorters

The Zanasi DS/71 capsule selection device (Fig. 12.16) removes empty capsules, partially-filled capsules, and bodies or caps from amongst the filled capsules on ejection from the filling machine. It has no moving parts. The capsules are balanced on a fluidised bed and the difference in weight between empty and filled capsules enables separation to take place. Excess dust on the capsule surface is removed. Generally the only maintenance required is the periodic cleaning of the filter.

The Zanasi empty-capsule preselector, model L/34, has been designed to prevent faulty capsules from obstructing the feed channels of any capsule filler. It is illustrated in Fig. 12.17. It does not eliminate capsules with every kind of fault, but only those whose diameter is different from the norm. The channels of the feed plate of the L/34 machine are the same as those mounted in all the capsule fillers made by Zanasi Nigris.

The empty capsules contained in the feed hopper pass into the channels of the feed plate, by the continuous vibratory motion of the hopper towards the plate. If the capsules are of the size intended for the filling machine and if their cylindrical section is not deformed, they will pass through the plate channels under gravity and will fall into the underlying collecting funnel, which will discharge them into the buckets of the conveyor.

Any fault in the cylindrical section of the

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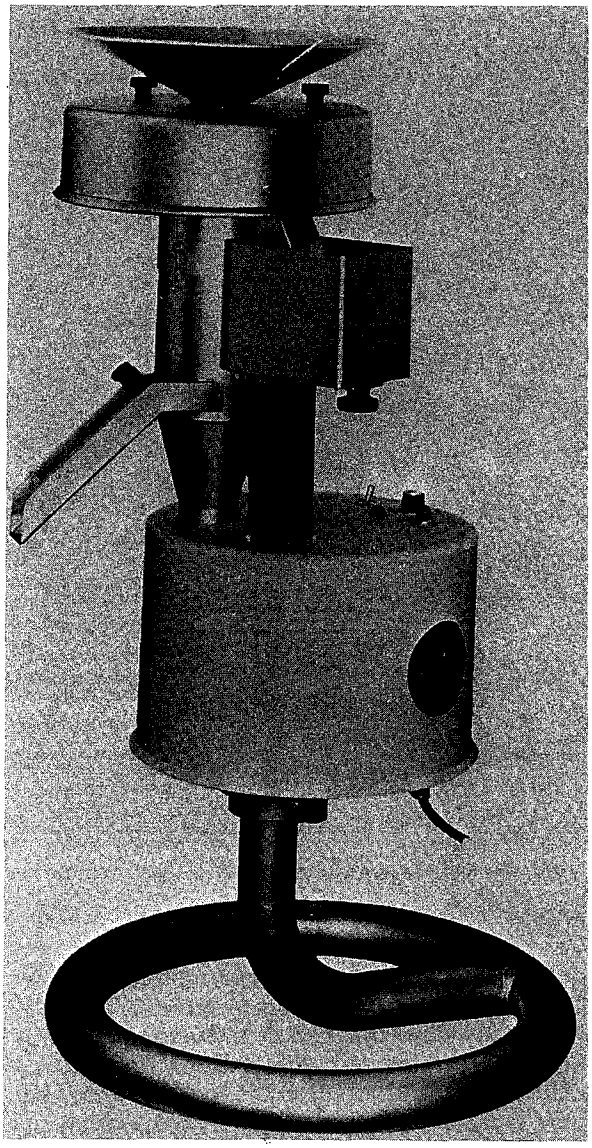

Fig. 12.16 The Zanasi DS/71 capsule selection device.

capsule, which would cause it to obstruct the feed channels of the capsule filler, will only cause the blocking of one of the plate channels of the L/34 machine, which is much easier to clear. The operator checks the plate and removes the faulty capsules, thus keeping the feed channels clear.

Banding and Sealing of Capsules

The sealing of capsules has several advantages. It can ensure that filled capsules do not open, thereby releasing powder, it can protect the contents against the atmosphere to some degree, and can protect against substitution. The main methods of sealing capsules are banding with gelatin, sealing the overlapping section of the capsule, and spot welding the gelatin.

Until the early 1980s the increased use of self-locking capsules had largely eliminated the use of banding machines for sealing the two halves of the hard gelatin capsule. In recent years interest in banding and sealing has grown following some cases of deliberate contamination of paracetamol capsules in the U.S.A. Sealing of a self-locking capsule provides a product that is virtually tamper proof. Sealing has also become more important for use with liquid or semisolid formulations to avoid leakage and to contain substances with a strong odour.

For many years, Parke, Davis have used a band of gelatin (which may be coloured) around their capsules as an identification, under the trade-mark Kap-Seal.

Banding capsules is a time-consuming and messy operation, but it is 100% effective. Where Zanasi equipment is used, the filled capsules are transferred directly from the filler into the banding unit. Here the capsules are fed into a revolving plate and onto the banding station. The gelatin solution is contained in a heated tank underneath the plate holding the capsules. Banding wheels rotate half immersed in the gelatin solution and take up a quantity of gelatin which is deposited around the junction of the gelatin capsule. The width and thickness of the band may be adjusted. The turntable then deposits the capsule in the cradles of a drying chamber through which a current of cold air is blown. The capsules remain in the cradles long enough to ensure complete drying of the gelatin. Other polymers may be used in place of the gelatin, e.g. cellulose acetate phthalate in a suitable solvent such as methyl ethyl ketone.

More recently, the Capsugel division of Parke, Davis have introduced a sealing process under the trademark Licaps, and Elanco Qualicaps have introduced the Qualiseal process, which is effectively a refinement of the older banding process.

The Licaps process has three stages which ensure that the contact areas of the cap and body are thermally bonded by using a solution, such as water and alcohol, which lowers the melting point of gelatin. Capillary action ensures that in stage 1 the solution is uniformly distributed in the area of overlap between the cap and body. In stage 2 the excess liquid is removed by draining and air

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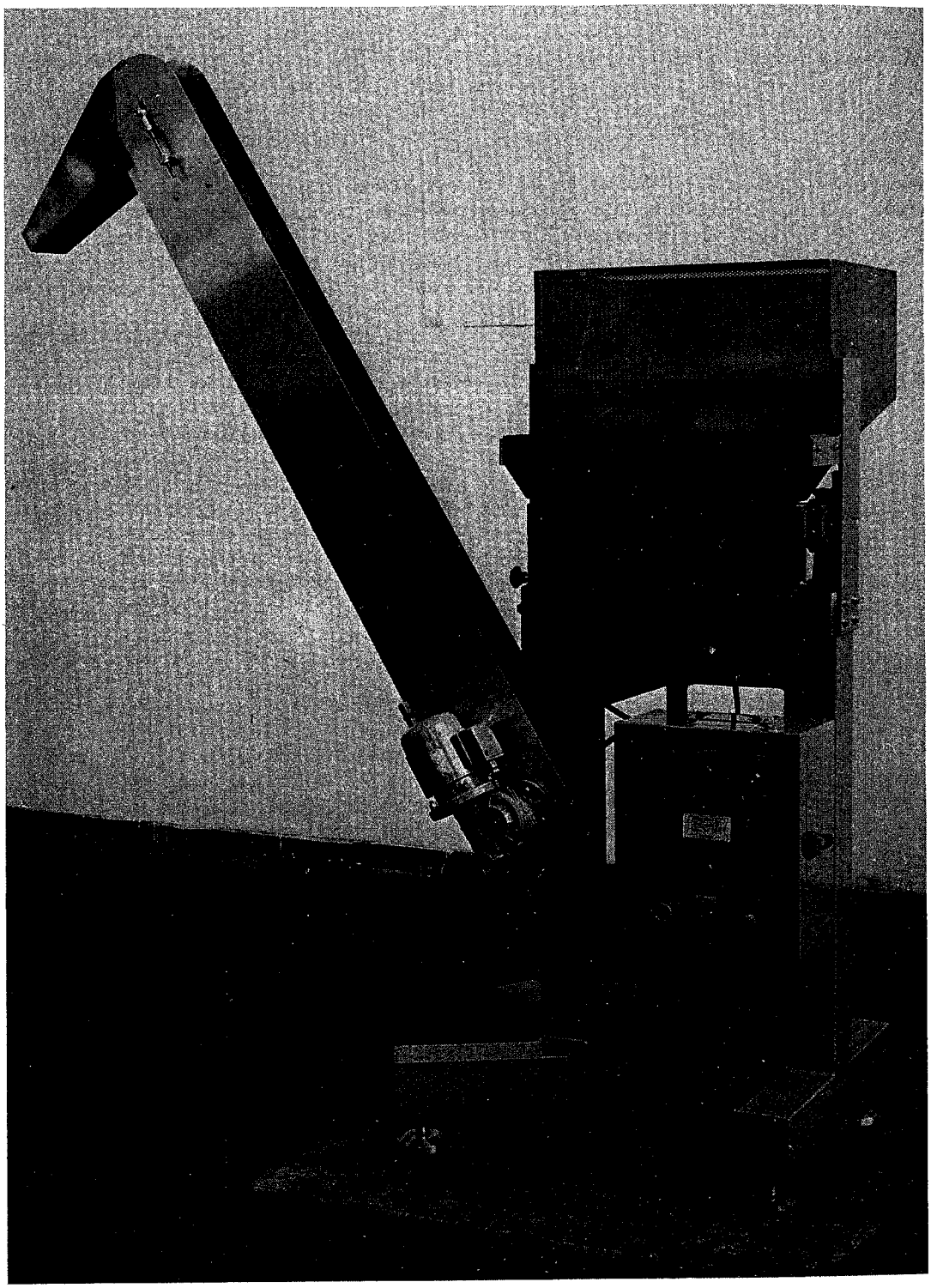

Fig. 12.17 The Zanasi Model L/34 empty-capsule preselector.

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drying of the capsule. Stage 3 strengthens the bond between the cap and body by heating in a fluidised bed. A laboratory model is described by Withered (1986) for sealing 16 capsules, and this model duplicates the cycle time of the production equipment for which outputs of up to 150 000 capsules per hour are claimed.

Elanco Qualicaps have developed and improved the gelatin banding process to seal the open edge of the cap to the body of filled capsules in the Qualiseal process.

The process consists of applying two bands of gelatin onto the open edge of the cap and body sequentially. This eliminates any imperfections such as air bubbles, an uneven band, or a discontinuous band and generally ensures a stronger seal than one thick application. Capsule seals are then dried using filtered air at 25° and 50% RH. The advantage of this method is the use of an aqueous solution of gelatin, which does not introduce any new material or solvent into the process.

There are three stages to the Qualiseal process. In stage 1, the filled capsules from a storage hopper are passed through the feed roller, the rectifier roller, and the transfer roller, and fed continuously into the pockets of the conveyor belt slats. In stage 2, the capsules are positioned uniformly in the slat pockets regardless of the joined length of the capsule, and sealed once around their circumference while being rotated by the roller of the first sealing unit. The second seal is applied by the second sealing unit in a similar manner to the first. The sealing solutions are maintained under constant conditions by circulating water at a thermostatically controlled temperature through the jackets of the holding tanks. In stage 3, the sealed capsules are transferred by carriers from the conveyor belt to the drying unit, where filtered air is used to dry the gelatin seals.

Laboratory equipment is available with an output of 100 capsules per hour, and production equipment with an output of 80 000–100 000 capsules per hour.

In addition to these two methods there is a process for ultrasonic welding which uses high-frequency sound waves as an energy source to generate heat for fusing body and cap together.

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Demorest, R. L., *Pharm. Technol.*, 1980, *4*(12), 41–44.
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Chapter 13

Drug Release from Capsules

J. M. Newton

Concepts of Bioavailability

After administration of an oral preparation, the active substance is delivered to the site of pharmacological activity by a complex process which involves solution of the drug in the gastro-intestinal fluid, absorption, usually by passive diffusion across the membrane of the gastro-intestinal wall into the capillary blood supply, and distribution via the portal circulation to the systemic circulation and the site of action. The dissolution of the drug at the site of absorption is frequently, though not always, the rate-limiting factor in the distribution process. It has been established that the formulation of the dosage form and the physicochemical characteristics of the drug may have a marked influence on the dissolution process and hence on the pharmacological performance of the drug. The rate at which, and the extent to which, the active ingredient is delivered to the circulation is referred to as the bioavailability.

To evaluate the performance of a formulated product, the bioavailability can be assessed by measuring the concentration of the drug in plasma or serum over a period of time after administration. The variation in the plasma concentration with time gives an indication of the amount and rate of absorption of the drug. Increasing the rate of absorption will increase the peak concentration, and decrease the time taken to reach it, but will not change the total area under the plasma concentration-time curve (total amount absorbed). Changing the extent of the absorption will change both the peak height and the total area under the curve.

Alternatively, the rate and extent of urinary excretion of the drug or its metabolites can be measured.

Another approach, which is less time-consuming, is to use *in vitro* tests which attempt to simulate the *in vivo* performance of the dosage form.

Such tests are based on the ability of the dosage form to disintegrate in a fluid under given conditions (disintegration test), or upon the amount of drug that is released into solution in a specified fluid under given conditions (dissolution test). These tests are used in official standards for certain preparations in the *B.P.* and the *U.S.P.* Dissolution tests provide reproducible conditions for the solution process and can indicate the way in which formulation variables influence the solution rate process. However, some caution is necessary in the interpretation of *in vitro* tests in terms of *in vivo* performance as they do not always correlate.

No single test procedure has been devised which can simulate accurately what happens to a dosage form after administration, mainly because individuals vary in their responses. The apparent simplicity of capsule formulations as a blend of powders which will be readily available for dissolution promotes the belief that hard gelatin capsules are a readily bioavailable oral dosage form.

However, evidence that capsule formulations may be subject to problems of bioavailability can be obtained by comparison of the plasma concentration-time curve with that of other preparations containing the drug. These may be other commercial products, such as capsules or tablets, which have been found to be clinically acceptable. Alternatively, an intravenous injection or other type of preparation such as a solution or a suspension may be used as a reference.

Comparison with an intravenous injection will give a measure of the absolute bioavailability because it eliminates the absorptive phase. Comparison with other types of preparation only indicates the relative bioavailability of the formulation.

A solution of the drug is considered to be the most useful oral reference preparation as it eliminates the dissolution phase. Hence, comparison with a solution should indicate whether dissolution is the rate-limiting factor.

Intravenous injections and solutions may not be

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feasible for insoluble drugs, yet these are the ones that are more likely to give rise to bioavailability problems. Solutions in non-aqueous polar solvents or in oils may offer an alternative as reference formulations for such drugs.

A drug which is clinically effective over a wide range of blood concentrations would provide products which may not differ significantly in bioavailability. However, if there is a narrow range between the minimum therapeutic concentration and the minimum toxic concentration, then changes in bioavailability may have serious clinical consequences. For example, phenytoin has dose-dependent elimination kinetics and a narrow therapeutic range, and even small differences in bioavailability may be hazardous. The earliest reports (Eadie *et al.*, 1968; Martin, 1968; Rail, 1968) indicated that patients had shown the toxic effects of phenytoin overdosage when the capsule formulation of an established brand was changed. In this particular example, the difficulty was shown to be due to the substitution of lactose for calcium sulphate dihydrate as the excipient. Since then, numerous studies of this drug have shown that different formulations may not be bioequivalent. The bioavailability of phenytoin has been reviewed by Neuvonen (1979).

Consideration of published papers should provide an answer to the question as to whether hard gelatin capsules do present problems in terms of ensuring bioequivalence. Unfortunately, individual papers taken in isolation may provide conflicting evidence. For example, Tannenbaum *et al.* (1968) concluded that a commercial capsule formulation of triamterene and hydrochlorothiazide was less effectively absorbed than an experimentally formulated tablet. Randolph *et al.* (1985), however, found that a capsule formulation of the same two drugs was bioequivalent to an aqueous solution, suggesting that the capsule formulation of the earlier study was probably not optimised.

Since many published papers lack details of formulation, it is generally impossible to make an accurate assessment of which formulation factors are important. It is also important to realise that reports of capsule formulations being less bioavailable than other preparations could be due to a particular drug being poorly absorbed by the oral route for various reasons. For example, Sasahara *et al.* (1980) concluded that the relatively low absolute bioavailability of levodopa in capsules is probably due to first pass metabolism.

An alternative source of difference between the various preparations of the same drug is the use of non-optimum formulations in the comparison. Wagner *et al.* (1966) provided clear evidence that a capsule formulation of indoxole was inferior to emulsion, soft gelatin capsule and suspension formulations. Whether this was the best hard gelatin capsule formulation cannot be judged from the evidence available in the paper. Thus comparison of capsules with other formulations must be judged with caution.

Another factor to be considered in assessing the comparison of formulations is the physiology of the gastro-intestinal tract and its involvement in drug absorption. For example, Stewart and others (1979) compared an experimental capsule formulation with a solution of riboflavine as a standard. The higher urinary excretion observed after administration of capsule formulations could be associated with the rapid transit of the solution past the limited area of the intestine capable of absorbing riboflavine.

Comparison of different capsule formulations of the same drug should provide better evidence that formulation needs to be considered to ensure comparable bioavailability of capsule formulations, but even here caution must be used in interpretation of some of the papers listed in the Bibliography. In several instances conclusions are drawn from poor *in vivo* experimental data, e.g. Brice and Hammer (1969), where serum levels produced by commercial formulations of oxytetracycline were compared at only four time intervals, providing insufficient data for a reasonable pharmacokinetic analysis.

The evidence of the papers contained in the Bibliography, while not being unequivocal, does lead to the conclusion that it is necessary to consider formulation to ensure an adequate *in vivo* performance of certain drugs.

Formulation and the Release of Drugs from Capsules

Because the release of drugs from hard gelatin capsules can be influenced by the formulation, it is important to consider the ways in which maximisation and/or consistency of drug release can be achieved. For this purpose, it is necessary to understand the mechanism of absorption of the drug to be formulated, and especially to know which stage is the rate-controlling step in the process. Much time can be wasted in attempting to improve the formulation, in terms of drug release, if this is only a minor aspect of the absorption

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process. In the present account, it will be assumed that the drug is in the correct crystalline form; there will be no consideration of the influence of crystal structure, nor the existence of solvates or hydrates.

An important feature of formulation is to ensure that the capsule contains the correct, uniform dose of the drug. The formulation will only exist as a single-component system if the drug completely and reproducibly fills the capsule volume. Small dose levels of drug require prior blending with an inert diluent. Similarly, larger doses can be blended with a diluent if, by this addition, a greater reproducibility of bulk volume can be achieved. High-speed filling machines, which operate by preforming a plug of powder prior to transferring it to the capsule, often involve a degree of consolidation of the powder bed, and friction between this plug and metal makes necessary the addition of a powder/metal lubricant. Glidants may also be needed to improve powder flow and ensure reproducible bulk volume.

The work involved in studying formulation variables by *in vivo* techniques is costly and time consuming, hence many studies involving formulation factors use *in vitro* testing, particularly dissolution. This makes two important assumptions: that dissolution is the rate-controlling step in the absorption process, and that the particular *in vitro* dissolution test reflects the *in vivo* performance of the formulation.

Unfortunately, these two restrictions are only rarely assessed. Any deductions made from dissolution results should be used only as guidelines to formulation, not as absolute values.

In order to ensure adequate bioavailability when formulating hard gelatin capsules, it is necessary to consider various factors. These include the solubility, particle size, and wettability of the drug, together with the combination of possible additives, the filling process to be used, and the requirement to produce a granulation. An essential feature is to ensure that the capsule disintegrates both *in vitro* and *in vivo*. Whilst the application of the *in vitro* test may not be a conclusive indicator of a bioavailable capsule formulation, a capsule which does not disintegrate is very unlikely to be effective. These factors will now be considered.

Drug Solubility

Unless other factors dominate, the rate-controlling step in the absorption process is the rate at which the drug is transferred from the solid state into solution. For a wide range of compounds, the intrinsic rate of dissolution is directly proportional to the solubility (Hamlin *et al.*, 1965). Hence the lower the drug solubility, the lower will be the rate of dissolution and so absorption. The combined effects of drug solubility and of additives within the capsule on the dissolution rate of a range of drugs were studied by making measurements at two levels (20 and 80%) of three diluents, and in the presence or absence of magnesium stearate and sodium lauryl sulphate (Newton and Razzo, 1977a). There was a strong indication that the rate was proportional to the logarithm of the drug solubility (Fig. 13.1). Thus one can anticipate

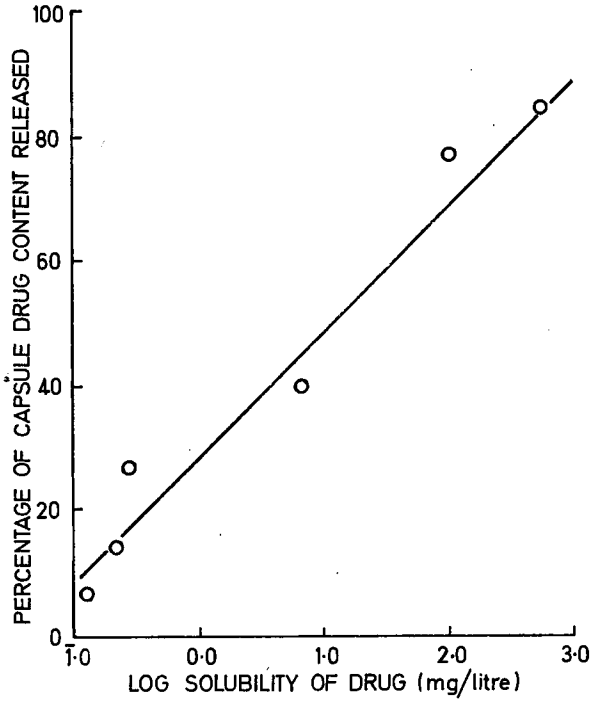

Fig. 13.1. The influence of drug solubility on the *in vitro* release of drugs from capsules.

problems when presenting drugs with low water solubility in capsules. Blending of simple additives did not overcome the formulation problems.

Particle Size

The standard method of increasing the rate of solution of a drug is to increase the surface area in contact with the solvent by reducing the particle size. However, the effectiveness of this method

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will depend on the contact between liquid and solid.

When nitrofurantoin, a relatively insoluble substance, was administered to rats in a hard gelatin capsule, the proportion of the dose excreted in the urine increased as the particle size was decreased (Fig. 13.2) (Paul *et al.*, 1967). Capsules

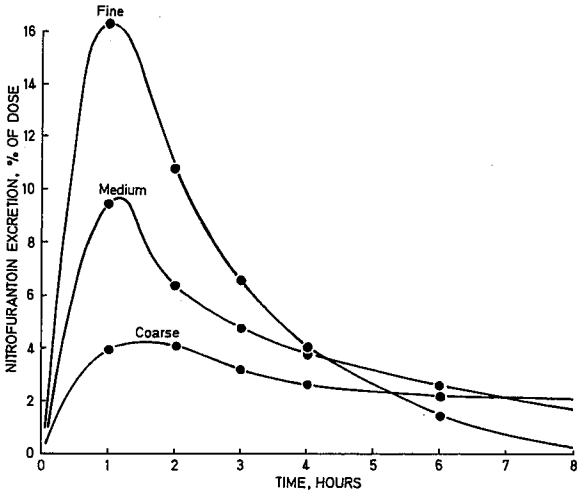

Fig. 13.2. The effect of particle size of orally-administered nitrofurantoin on urinary excretion in rats.

containing sulphafurazole of mean particle size 1.7, 39, and 95 μm were tested in dogs by Fincher *et al.*, (1965); the peak blood concentration increased with decreasing particle size.

Results such as these for relatively water-insoluble drugs make it appear that reduction of the particle size of the drug should solve the bioavailability problems of capsules. However, the opposite effect can occur. Capsules of ethinamate, a drug with a solubility of 1 in 400, were tested for dissolution *in vitro*, using various particle sizes packed to give different porosities. For equivalent packing densities as judged by porosity, a greater drug release was obtained with the largest particle size fraction (Fig. 13.3) (Newton and Rowley, 1970). This was because the powder bed with smaller particle sizes was less permeable to liquid. Similar effects were obtained with aspirin (Newton and Bader, 1980).

When four different particle size fractions of the same drug, <6, <10, <50 and <100 μm in size, were administered in capsules to dogs, there was no significant difference in absorption, but when

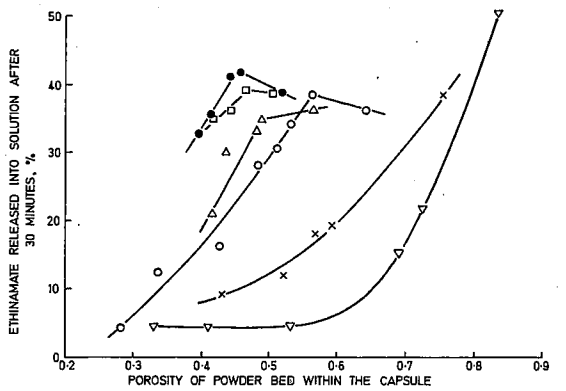

Fig. 13.3. The percentage of ethinamate released into solution after 30 minutes from capsules containing different particle size fractions packed to give different porosities.

● 251–420 μm ○ 125–152 μm
□ 177–251 μm × 66–76 μm
△ 152–177 μm ▽ 8.3 μm

the powder was more closely classified to give better-defined size ranges, namely between 6 and 12 μm, and between 60 and 100 μm, higher blood concentrations resulted from the administration of the capsules containing the larger particle size fraction (Ljungberg and Otto, 1970). Ridolfo *et al.* (1979) established that for capsules containing particles of 67 μm or 640 μm mean equivalent diameter of a relatively water-insoluble drug, benoxaprofen, the capsules containing the smaller size particles dissolved more rapidly and gave a higher *in vivo* bioavailability, judged by plasma concentration/time curves and urinary excretion. The capsules, however, contained nearly twice as much starch as drug. This could ensure water penetration between the fine particles, and thus adequate contact with their larger surface area. Confirmation of this result was reported from the same laboratories (Wolen *et al.*, 1979). Again, the drug was incorporated into a large quantity of starch within the capsules.

Wetting

As discussed in the previous section, decreasing the particle size of a drug, although it increases the surface area for dissolution, does not necessarily increase the dissolution rate because there may be a reduction in the contact between the liquid and the solid. This is particularly likely if the liquid does not wet the solid. Whether a liquid will spread over the surface of a solid is determined by the relative values of the attraction of the molecules

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of the liquid for those of the surface, and of those of the liquid molecules for each other. If the former exceed the latter, spreading of the liquid over the solid surface will occur. The ease of wetting is best expressed by the contact angle between the edge of the liquid meniscus and the solid surface. A zero value implies ready and complete wetting of the solid by the liquid while a value of 180° would correspond to absolute non-wetting. Water-insoluble drugs usually have a low affinity for aqueous fluids, and hence have high values of the contact angle, indicative of non-wetting (Lerk *et al.*, 1977). Similarly the addition of the hydrophobic lubricant, magnesium stearate, can also prevent wetting of powders and hence retard dissolution. Wetting, as indicated by the liquid penetration test of Studebaker and Snow (1955), and drug release as indicated by dissolution, have been shown to correlate inversely. The interesting behaviour of magnesium stearate is shown in Fig. 13.4 (Samyn and Jung, 1970).

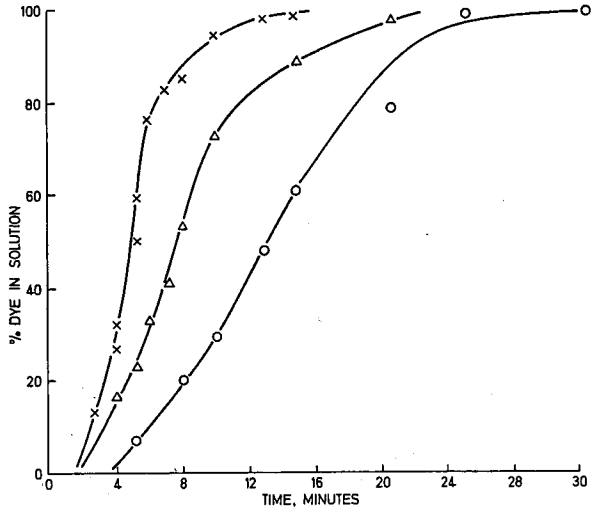

Fig. 13.4. The dissolution of dye from capsules containing lactose (×), and capsules containing lactose with 2% (△) or 5% (○) of magnesium stearate.

However, for more complex formulations, systems giving poor wetting do not necessarily give poor dissolution (Fig. 13.5) (Rowley and Newton, 1970). Sodium lauryl sulphate dissolves with swelling and it may retard penetration in the wetting test, yet aid disruption of the capsule in the dissolution test. Most surfactants produced only small increases in the dissolution rate of ethinamate in capsule formulations (Newton, 1972). An alternative method of increasing the wettability of a capsule formulation is to incorporate a hydrophilic material such as starch or lactose. Such additives may of course act by disintegration as well as wetting, and their effectiveness is not reliably disclosed by dissolution techniques (Newton, 1972). Large proportions (up to 80%) of the diluent may be needed to be effective and do not always guarantee complete drug release, especially of highly insoluble drugs (Newton and Razzo, 1974).

The inability of physical mixing to ensure wetting and drug release was confirmed by mixing hexobarbitone with hydroxymethyl or hydroxyethyl cellulose, which failed to reduce the contact angle or increase dissolution rate (Lerk *et al.*, 1978). However, by intimate mixing of the drug with a solution of the hydrophilic material, followed by drying to give minigranules, a reduction in the contact angle and a marked improvement in dissolution were achieved. The contact angles, although reduced, remained relatively high, so that the improved dissolution should perhaps be attributed to the structure introduced by granulation. Treating griseofulvin with hydroxypropyl cellulose, by a similar process, improved the drug release, as assessed by dissolution and urinary excretion of the major metabolite (Fell *et al.*, 1978). As no measurements of contact angles were reported, it could again be the granulation as well as the wetting process which is involved in improving drug release. The same process has been shown by Lerk *et al.* (1979) to improve the rate of absorption, relative to pure drug, when phenytoin capsule formulations were administered to human volunteers. The authors were able to show that the process improved water uptake into the powder plug, employing penetration tests. *In vitro* dissolution tests were found to reflect the improved liquid penetration, irrespective of the presence of surfactant in the dissolution fluid.

Granulation

Granulation provides a method of assembling the individual particles in a regular manner, as opposed to the random aggregation which occurs under the influence of the natural interparticulate forces between small particles, and it is known that granulation can increase the dissolution rate of fine particles (Finholt *et al.*, 1968). The technique is applicable to capsule formulations (Newton and Rowley, 1970). In this case a solvent is the only binder, so there is no change in contact angle;

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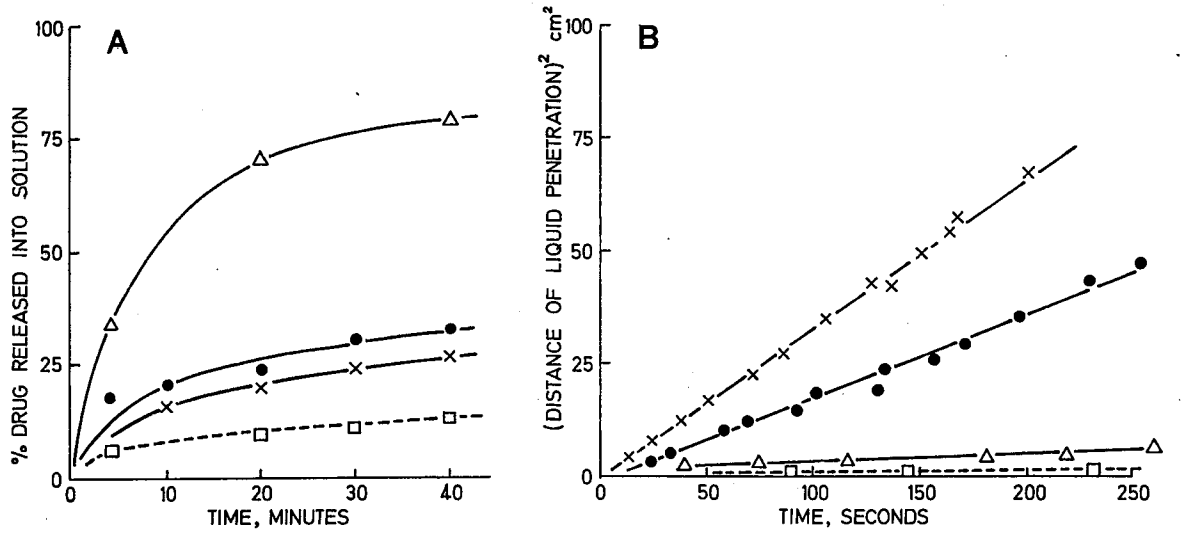

Fig. 13.5. A, the dissolution of a drug for four different capsule formulations. B, the liquid penetration test for the same formulations.

□ drug with 0.5% magnesium stearate
× drug with 0.5% magnesium stearate, 1% sodium lauryl sulphate, and 5% lactose
● drug with 0.5% magnesium stearate, 1% sodium lauryl sulphate, and 20% lactose
△ drug with 1% magnesium stearate, 1% sodium lauryl sulphate, and 50% lactose

only the particle arrangement is altered. The improvement in dissolution rate is related to the permeability of the structure produced (Fig. 13.6).

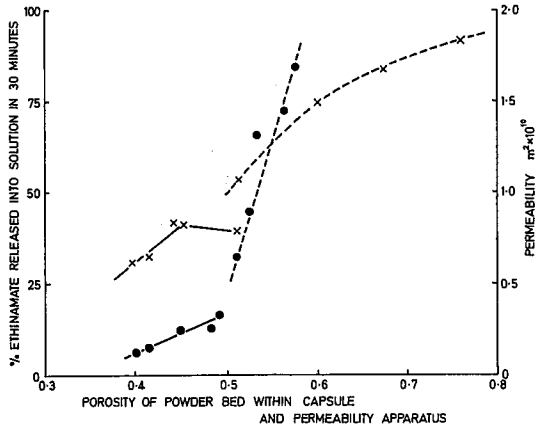

Fig. 13.6. The dissolution of drug from capsules containing crystals and granules of micronised ethinamate, packed to give different porosities, compared with the liquid permeability of beds of the same samples.

——— crystals, 251–420 μm × dissolution
--------- granules, 251–420 μm ● liquid permeability

Granulation appears to be an extremely beneficial process in capsule formulation; it should improve flow and uniformity of bulk density in addition to assisting drug release.

Disintegration

Disintegration of the capsule into primary particles is a necessary requirement, especially for high-dose drugs.

Deaggregation performance and serum level have been shown to be related for four chloramphenicol capsule formulations (Aguiar *et al.*, 1968). Incorporation of twice the drug weight of sodium bicarbonate into tetracycline capsules ensured disruption of the capsule and improved dissolution, (Nelson, 1960) but the incorporation of an equal weight of citric acid did not affect the drug release at all (O'Reilly and Nelson, 1961). Improved drug release, as indicated by dissolution testing, was claimed to follow the incorporation of sodium starch glycolate (Primojel, a tablet disintegrant) into capsule formulations, but as no disintegration test results are reported, improved drug release may also be a function of improved wetting as well as of disintegration (Newton and Rowley, 1975). This is also true of a comparison of capsule disintegrants by dissolution testing (Ryder and Thomas, 1977). A ranking order of

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starch glycolate (Primojel) > Nymcel > no disintegrant was established, and the results also suggested that maize starch is not an effective disintegrant.

To assess the *in vivo* disintegration of capsules, Eckert (1967) used capsules filled with sodium bicarbonate and determined the disintegration time by the change in pH of the gastric juice, measured by a radio-endoscope.

Casey *et al.* (1976) reported the use of external scintigraphy, using a gamma camera to estimate the dispersion of a gamma-emitting isotope (^{99m}Tc) contained in capsule formulations. They found that a more rapid disintegration occurred when the capsule contents were soluble (6 minutes) than when they were insoluble (30–40 minutes). Using the same technique, Hunter *et al.* (1980) found that the condition of the subjects was important. Capsules containing resin beads labelled with ^{99m}Tc provided little dispersion when administered to fasting subjects, whereas after food the dispersion was more rapid and reflected *in vitro* disintegration times. A profile scanning technique was used by Alpsten *et al.* (1979) to compare the *in vivo* and *in vitro* disintegration of granule formulations of aspirin labelled with ^{51}Cr. Subjects were scanned with a movable detector whilst sitting in a well-defined position in an armchair within a low-activity laboratory. The disintegration times were considerably longer *in vivo* for both formulations than those obtained from *in vitro* disintegration tests.

Combinations of Additives

The presentation of drugs in hard gelatin capsules is usually considered to be a relatively simple matter, but it is seldom possible to provide formulations which meet the needs of filling machines without resorting to a multicomponent system. The added components, however, do not always result in a simple additive effect on drug release (Newton *et al.*, 1971a and b; Newton and Razzo, 1974). The effect of changing the quantity of additives has been modelled for a single drug by fitting a second-degree equation to relate capsule composition to dissolution (Newton and Razzo, 1977b). Such a relationship is the simplest model that allows the interactions between pairs of factors to be represented. The results also include the influence of formulation combinations on the filling performance, allowing the feasibility of filling a particular combination of ingredients into the capsule to be assessed.

Capsule Filling

The method by which the capsules are filled is also important. The available processes vary in complexity, and hence the resultant powder-bed structures will be very different. For fine particles, decreasing the porosity resulted in a decrease in drug release (Newton and Rowley, 1970). This effect applied equally for capsules containing a drug with 10 or 50 per cent of lactose (Newton, 1972). For more complex formulations, packing seemed to be less important than other formulation factors (Newton *et al.*, 1971b). Loose and tight filling of capsules of cephalexin did not influence serum levels (O'Callaghan *et al.*, 1971), but it has been claimed that a high salicylate plasma level was obtained when the same quantity of aspirin and dibasic calcium phosphate was packed into a smaller size shell (McGee *et al.*, 1970). It would seem, however, desirable to ensure that the ingredients are filled into a capsule in such a manner as to allow rapid deaggregation of the particles, which means that they should be filled with a minimum of compression, or incorporate a disintegrant which will ensure deaggregation.

Drug Release from Soft Gelatin Capsules

There are only a few drugs which are of the correct consistency and dose level to form the total content of the capsule. Thus the vehicle used to present the drug within the shell is important. In general, the system must have the correct rheological characteristics to be handled by the filling process, and must be compatible with the gelatin shell. Water-immiscible oils are the most important type of vehicle although water-miscible polyethylene glycols and non-ionic surfactants have also been used.

Capsules Containing the Drug as the Major Component

Drugs which are oils or which are highly soluble in oils can be readily presented as a unit dose in a soft gelatin capsule, e.g. cod liver oil, clofibrate, ethchlorvynol, and paramethadione. There appears to be little published work establishing the 'absolute bioavailability' of such drugs, and indeed the low water solubility would present difficulties for formulation of an intravenous preparation.

Taylor and Chasseaud (1977) compared the bioavailability of clofibrate in a soft capsule with that of calcium clofibrate in a hard gelatin capsule

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formulation; the results indicated the bioequivalence of the two formulations. In a later paper, Taylor *et al.* (1978) compared the bioavailability of a soft gelatin clofibrate capsule with that of a film-coated tablet containing calcium clofibrate and calcium carbonate (1:1 mixture), under conditions approaching steady state. The results suggested that the two formulations did not differ significantly.

Fischler *et al.* (1973) compared soft gelatin capsule formulations containing chlormethiazole base with a tablet formulation containing chlormethiazole edisylate. They established that there was a more rapid and complete absorption from the capsules than from the tablets, due to drug forms of different solubility. The addition of arachis oil to the capsule formulation was found to result in a further increase in the peak drug concentration. As the dissolution rate was not improved by the addition of arachis oil, the authors suggested that a change in the absorptive conditions of the gastro-intestinal tract might take place in the presence of the arachis oil.

Angelucci *et al.* (1976) compared the bioavailability of flufenamic acid formulated as hard or soft gelatin capsules. The soft capsule contained vegetable oil, hydrogenated vegetable oils, beeswax, and soya lecithin in addition to the drug. Results using both dogs and humans indicated that the soft gelatin formulation produced consistently higher plasma concentration-time curves.

Capsules Containing the Drug as a Minor Component

The solution of a drug in a solvent allows the use of accurate methods to sub-divide the drug into unit-dose systems. If the solubility of the drug is high and the dose relatively low, it is possible to contain the dose within the volume of a soft gelatin capsule. Alternatively, the drug, especially if low-dose, may be dispersed in a fluid to provide an emulsion or a suspension. Such a dispersion must have suitable rheological properties.

Water-immiscible oils, which are compatible with the shell, provide only limited dissolving power. There is also the question of whether the drug is absorbed with the oily vehicle, an unlikely possibility, or has to transfer to the aqueous phase before absorption can take place. Water-miscible solvents which are compatible with the shell, e.g. polyethylene glycols or non-ionic surfactants, have solvent properties for a large range of drugs.

Mallis *et al.* (1975) administered soft gelatin capsules containing 0.2 mg of digoxin dissolved in polyethylene glycol and propylene glycol and compared them with a rapidly dissolving tablet containing 0.2 mg and two commercially available tablets containing 0.25 mg, in a single- and a multiple-dose study. Serum-digoxin concentrations achieved with the capsules were similar to those obtained with both the 0.25 mg tablets, and better than those achieved with the 0.2 mg tablets. The time to achieve peak concentration was equivalent for all four preparations, but the area under the curve was significantly greater for the capsules than for the equivalent dose of a rapidly-dissolving tablet, and equivalent to that achieved with the 0.25 mg tablets. There were no significant differences between any formulations in the serum concentrations on the 2nd, 8th or 10th days, nor in the steady-state urinary excretion.

In a second study, the capsules were compared with a solution of the capsule contents and with a commercially available elixir; results indicated that the mean area under the serum concentration-time curve was greater for the capsule than for either of the two liquids. The mean time to reach peak concentration was similar for all three preparations. These results imply that presenting the drug in a capsule has a beneficial influence on bioavailability, possibly due to changes in the rate of movement within the gastro-intestinal tract.

Marcus *et al.* (1976) compared the bioavailability of a soft gelatin capsule of digoxin (in ethanol, water, propylene glycol, and polyethylene glycol 400) with an oral alcoholic solution and a standard commercial tablet, relative to an intravenous solution (0.25 mg/ml in 40% propylene glycol, 10% ethanol, 0.3% sodium phosphate, and 0.08% anhydrous citric acid). The intravenous infusion was administered over 1 hour and 3 hours. The serum concentration peaked at 5 ng/ml at the end of the 1-hour infusion, and at 3.5 ng/ml after the second hour of the 3-hour infusion. The 6-day urinary excretion after the 3-hour infusion was 21% more than for the same dose given over 1 hour. Hence, the assessment of the absolute bioavailability will be affected by the choice of infusion rate. In general, the soft gelatin capsule had the highest level of bioavailability.

Lindenbaum (1977) compared a soft gelatin capsule formulation of digoxin (in polyethylene glycol 400, ethanol, water, and propylene glycol) with an equivalent dose in 10% aqueous ethanol, and with a tablet formulation. It was established that

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the area under the serum concentration-time curve, and the 6-day cumulative urinary excretion, were greater after administration of the capsule than for the other two formulations.

Wagner *et al.* (1979) compared the *in vivo* bioavailability of four commercial soft capsule formulations of digoxin, but no details of formulation were given. There were no significant differences in the amount of digoxin absorbed from each formulation, as judged by urinary excretion or area under the plasma concentration-time curve. There were significant differences in the time to reach peak plasma concentration, in the *in vitro* 'burst time', and in the time required to release 50 or 85% of digoxin in a dissolution test.

The possible involvement of the shell in the absorption process can present problems if the shell characteristics change on storage. Johnson *et al.* (1977) studied freshly-prepared digoxin capsules and capsules which had been stored at 5° and 37° for 10 months. There was some evidence that storage delayed the onset of peak plasma concentrations but there was no evidence that the extent of absorption was reduced.

Further indications of the enhanced bioavailability of digoxin when presented as soft gelatin capsules come from papers reporting the administration of commercially available formulations, e.g. Binnion (1976), Longhini *et al.* (1977), O'Grady *et al.* (1978) and Alvisi *et al.* (1979). Padeletti and Brat (1978), however, compared equivalent doses of commercially available soft capsules and tablets and reported that they were bioequivalent.

The use of polyhydric alcohols with non-ionic surfactants to provide solutions or dispersions in soft gelatin capsules was proposed as a method of improving the bioavailability of water-insoluble drugs by Hom and Miskel (1970). The suggestion was based on the *in vitro* dissolution performance of soft gelatin capsules of dicoumarol, stilboestrol, digitoxin, ethinyloestradiol, hydrocortisone, phenobarbitone, phenylbutazone, propylthiouracil, and sulphadiazine. In all cases, the drug appeared in solution at least as quickly and often at a faster rate from capsules than from commercial tablets.

However, an improvement in bioavailability with this type of formulation does not always occur. Albert *et al.* (1974) found that soft capsule formulations of paracetamol and nitrofurantoin containing surfactants were only equivalent in bioavailability and not superior to commercial tablets. Gundert-Remy *et al.* (1975a) found that soft capsule formulations of diphenhydramine hydrochloride based on polyethylene glycol and surfactants were no more bioavailable than commercial sugar-coated tablets or hard capsule formulations. When the same drug was presented in soft capsule formulations in oil/wax surfactant mixtures, no reduction in bioavailability occurred. Similarly, oil/wax surfactant formulations of phenobarbitone were found to be bioequivalent to tablet formulations (Gundert-Remy *et al.*, 1975b). In these latter cases, the drugs were relatively water-soluble and the rate of drug release could be retarded by the presence of oil.

Further indications of the improved bioavailability of soft capsules come from the work of Fuccella *et al.* (1977) and Fuccella (1979), although no details of formulation are given. Comparison of commercial hard and soft capsules of temazepam in a single-dose study established that the soft capsule produced faster absorption, with earlier and higher peak plasma concentrations. However, there was no difference in the relative bioavailability as judged by the total area under the plasma concentration-time curve.

Liquid Filling of Hard Gelatin Capsules

Walker *et al.* (1980) have described a method whereby molten and thixotropic formulations can be filled into hard capsules on a conventional filling machine. Such a process allows all the advantages previously claimed for soft gelatin preparations such as the use of an accurate liquid feed, and the inclusion of polyethylene glycols and surfactants to improve the bioavailability of highly water-soluble drugs. Similarly, formulations containing waxes, which retard drug release, can be filled into hard capsules by this process, e.g. Francois *et al.* (1983). Thus the formulation techniques for both hard and soft capsules are now similar, and this widens the scope for controlling the release of drugs from capsule formulations and the range of dosage forms available.

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Bibliography of Capsules

B. E. Jones and J. M. Newton

The compilation of this bibliography was started in 1968 as a means of providing a literature source similar to that provided by Evans and Train in their 'Bibliography of the tabletting of medicinal substances' (Pharmaceutical Press, 1963). The aim was to cover the literature on hard and soft capsules, because information sources were few or non-existent. Although capsules have a long history, the number of references to them from before the 1950s is very small. This bibliography contains mainly those published since 1960 (although there are some from before that date). Earlier references will be found in Chapters 1 and 8. References have been added to the bibliography up to the second half of 1986.

A decimal classification system was devised to bring together similar references and make their information more accessible. The work is divided into four main sections:

1. Historical and General
2. Gelatin
3. Capsule Practice and Manufacture
4. Drug Availability from Capsules.

The main sections are further sub-divided into 103 smaller sets of information as shown in the Classification below.

Arrangement

The references within each subsection are arranged

1. chronologically by year of appearance,
2. alphabetically by first author within each year,
3. alphabetically by title of journal within each year for the same author,
4. numerically by volume within each year, and
5. numerically by page within each volume.

The journal (or book) reference and the title of the paper are followed, in smaller print, by a simple keyword abstract which has the information arranged in the following fashion:

1. The dosage forms described, except where the items appear in a section specific to either hard or soft gelatin capsules. This is followed by a colon.
2. A series of keywords or phrases separated by semicolons and commas and arranged in the order:
   (a) the drug name,
   (b) for *in vivo* studies the sample in which drug level was measured, i.e. plasma, urine, etc.,
   (c) the remainder of the information in alphabetical order.
3. If the reference appears in more than one subsection, the number(s) of the other subsection(s) in which it is included are listed at the end. For these entries, keywords or phrases are not repeated in each entry and only appear when relevant to the subsections.

Only the major subjects included in this bibliography have been indexed. Once the user becomes familiar with the classification headings set out below it should become a simple matter to locate the relevant references.

CLASSIFICATION

1 Historical and General

1.1 Historical

1.2 Books

1.3 Miscellaneous Applications

2 Gelatin

2.1 Official Standards

2.2 Gelatin Testing

2.3 Gelatin Manufacture and Applications

2.4 Gelatin Substitutes

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3 Capsule Practice and Manufacture

3.1 Capsule Practice

3.2 Capsules, Hard Gelatin
3.2.1 General References
3.2.2 Manufacture of Hard Capsules
3.2.2.1 Capsule Shells
3.2.2.2 Ancillary Manufacturing Processes
3.2.3 Filling Hard Capsules
3.2.3.1 Small Scale Filling
3.2.3.2 Industrial Scale Filling of Hard Capsules
3.2.3.3 Instrumented Machines, Physical Analysis
3.2.3.4 Filling Semi-solids into Hard Capsules
3.2.3.5 Self-locking Capsules
3.2.3.6 Sealing Hard Capsules
3.2.3.7 Cleaning Hard Capsules
3.2.4 Formulation of Contents of Hard Capsules
3.2.4.1 Dry Solids
3.2.4.2 Formulation of Semi-solids

3.3 Capsules, Soft Gelatin
3.3.1 General References
3.3.2 Manufacturing and Filling Soft Capsules
3.3.2.1 Seamed Capsules
3.3.2.2 Seamless Capsules
3.3.3 Formulation of Soft Capsules
3.3.3.1 Capsule Shells
3.3.3.2 Formulation of Contents of Soft Capsules
3.3.3.3 Protective Coatings for Soft Capsules

3.4 Capsules, Enteric
3.4.1 Gastric Resistant Shells
3.4.2 Coatings for Enteric Capsules
3.4.2.1 General References
3.4.2.2 Formaldehyde Treatment of Capsules
3.4.2.3 Natural Coatings for Enteric Capsules
3.4.2.4 Synthetic Coatings for Enteric Capsules

3.5 Capsules, Non-oral
3.5.1 Inhalation Capsules
3.5.2 Rectal and Vaginal Capsules

3.6 Packaging of Capsules
3.6.1 Unit-dose Packaging
3.6.2 Bulk Packaging

3.7 Capsule Standards
3.7.1 General References
3.7.2 Offical Standards

3.8 Properties of Capsules
3.8.1 General References
3.8.2 Properties of Capsule Shells
3.8.2.1 Colouring Agents
3.8.2.2 Moisture Content of Shells
3.8.2.3 Physical Properties of Shells
3.8.2.4 Physical Specifications of Shells
3.8.3 Properties of Capsule Products
3.8.3.1 Uniformity of Content
3.8.3.2 Identification of Products
3.8.3.3 Microbiology of Capsule Products
3.8.3.4 Moisture Content of Capsule Products
3.8.3.5 Physical Properties of Capsule Products
3.8.3.6 Uniformity of Weight
3.8.3.7 Storage of Capsules

4 Drug Availability from Capsules

4.1 Reviews

4.2 Drug Availability *in vitro*
4.2.1 Reviews
4.2.2 Disintegration
4.2.2.1 Standard Capsules
4.2.2.2 Disintegration of Enteric Capsules
4.2.3 Dissolution
4.2.3.1 General References
4.2.3.2 Comparative Dissolution of Dosage Forms
4.2.3.3 Comparative Dissolution of Products
4.2.3.4 Dissolution and Formulation
4.2.3.5 Dissolution of Enteric Capsules
4.2.3.6 Dissolution of Slow-release Capsules
4.2.3.7 Dissolution Methodology
4.2.3.8 Dissolution and Storage
4.2.4 Disintegration/Dissolution Correlation

4.3 Drug Availability in Animals
4.3.1 General References
4.3.2 Comparison of Dosage Forms
4.3.2.1 Comparison with Solid Preparations
4.3.2.2 Comparison with Liquid Preparations
4.3.2.3 Comparison with Injections
4.3.2.4 Comparison with Rectal Preparations
4.3.2.5 Comparison with Multiple Dosage Forms
4.3.3 Comparison of Capsule Products
4.3.4 Effect of Formulation on Absorption
4.3.5 Availability from Enteric Capsules

4.4 Drug Availability in Humans
4.4.1 Reviews
4.4.2 General References, Availability in Humans
4.4.3 Intestinal Performance
4.4.4 Comparison of Dosage Forms in Humans
4.4.4.1 Comparison with Solid Preparations

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1 Historical and General

1.1 Historical

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Gelatin Capsules

capsules, hard and soft gelatin: filling, hard gelatin, powders and pill masses, manual device; manufacture, hard and soft, history

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The manufacture of gelatin capsules

capsules, hard and soft gelatin: manufacturing method, hard gelatin capsules

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On the history of medical capsules (in German)

capsules, hard and soft gelatin: review

Griffenhagen, G., *J. Am. pharm. Ass., pract. Pharm. Edn*, 1956, *17*, 810–13

Tools of the apothecary. 10. lozenges, tablets and capsules

capsules, hard gelatin, lozenges, pastilles and tablets: filling, small scale; manufacture, small scale

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The gelatin capsule

capsules, hard gelatin: manufacture, industrial scale

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A century of commercial hard gelatin capsules

capsules, hard gelatin: enteric capsules; manufacture, industrial scale

Jones, B.E., *M & B pharm. Bull.*, 1980, *27*, 76–80

The hard gelatin capsule, a modern dosage form

capsules, hard gelatin: colorants; enteric capsules; filling, industrial scale, self-locking capsules; manufacture, industrial scale

1.2 Books

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Gelatin capsules as disposable wells for $^{14}CO_2$ absorption

capsules, hard gelatin: carbon dioxide, radioactive isotope; assays, glutamic decarboxylase; assays, reproducibility; capsule, use as container

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capsules, hard gelatin: capsule shells, perforated wall; capsule contents, soluble food extract

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Gelatin capsule for oral administration

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Capsule handling apparatus

capsules, hard gelatin: equipment, to produce capsules with holes in sides

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Flavouring (non) pharmaceutical shapes by impregnation

cachets and capsules, hard and soft gelatin: capsule shell composition, gelatin, natural or synthetic polymers; coating composition, flavouring/sweetening agent; coating method, by dipping

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An interactive drug information system

capsule, hard gelatin: imipramine hydrochloride; computer information retrieval system

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Orange plasma from tanning capsules

capsules, hard gelatin: oral tanning, cosmetic use

2 Gelatin

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Mingjiao, Gelatinum, pp. 234–5

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Gelatina, Gelatin, Eighth Fascicule, pp. 330–330-6

appearance and pH of solution; arsenic; gel strength; heavy metals; identification; loss on drying; peroxides; phenolic preservatives; sulphated ash; sulphur dioxide

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India: Pharmacopoeia of India, 3rd Edn, Delhi, Controller of Publications, 1985

Gelatin, Vol. 2, pp. 229–30

arsenic; ash; copper; heavy metals; identification; loss on drying; microbial limits; odour; solubility; water-insoluble matter; zinc

Japan: Pharmacopoeia of Japan, 10th Edn, Tokyo, Ministry of Health and Welfare, 1981

Gelatinum, Gelatin, pp. 1045–6 (English Edn)
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arsenic; heavy metals; identity; loss on drying; mercury; odour; residue on ignition; sulphite; water-insoluble substances

Jugoslavia: Pharmacopoea Jugoslavica, 4th Edn, Belgrade, Izdanje Saveznog zavoda za zdravstvenu zaštitu, 1984

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Gelatina Alba, Gelatina Animalis, Bijela Zelatina, Bela Zwotinjska gelatina, Vol. 2, pp. 437–8

acidity; arsenic; bacterial content; gel strength; heavy metals; identification; moisture content; residue on ignition; sulphur dioxide

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Gelatinum, Jelatin, pp. 261–2

acidity, alkalinity; identification; purity; residue on ignition; solubility; sulphur dioxide

USA: The United States Pharmacopeia, 21st Revision, The National Formulary, 16th Edn, Rockville, United States Pharmacopeial Convention Inc., 1985

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arsenic; heavy metals; identification; microbial limits; odour; residue on ignition; sulphur dioxide; water-insoluble substances

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acidity; arsenic; clarity; gelling properties; identification; microbiological content; moisture content; colour; purity; residue on ignition; sulphur dioxide

2.2 Gelatin Testing

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Rheology of gelatin films

capsules, soft gelatin: films, tensile relaxation modulus, effect of different gelatins

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applications, manufacture, properties, testing

Smith, H. L. and Goyan, J. E., *J. pharm. Sci.*, 1965, *54*, 545–8

Method of studying rheology of gelatin melts

capsules, soft gelatin: films, tensile relaxation modulus, effect of formulation, plasticisers

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Swelling of gelatin as a function of pH

gelatin, capsule, chemical properties

Robinson, J.A.J., Kellaway, I.W. and Marriott, C., *J. Pharm. Pharmac.*, 1975, *27*, 653–8

The effect of ageing on the rheological properties of gelatin gels

gelatin, hard capsule, manufacture; gelatin properties, gel rigidity, effect of storage

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The effect of blending on the rheological properties of gelatin solutions and gels

gelatin, hard capsule, manufacture; gelatin properties, gel rigidity, effect of blending

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gelatin, microbiological content

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The mechanical properties of gelatin films. 1. The influence of water content and preparative conditions

gelatin, hard capsule, acid and alkaline ossein; gelatin, physical properties, film strength, Young's modulus, effect of moisture content

Ludwig, A., Van Ooteghem, M. and Delva, A., *Pharm. Ind., Berl.*, 1979, *41*, 796–8

Disintegration of hard gelatin capsules. Part 1: Composition and structure of the capsule wall

gelatin, hard capsule, analysis of type, isoelectric focusing; gelatin films, hard capsule, structure, microscopy, optical, scanning electron; 3.2.1

Melia, C.D., Kellaway, I.W. and Hadgraft, J., *J. Pharm. Pharmac.*, 1981, *33*, Suppl., 20P

Varietal differences in capsule grade gelatins: mechanical properties

gelatin, hard capsules, manufacture; gelatin properties, mechanical effect of moisture content

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gelatin, hard capsule, alkaline ossein; gelatin, physical properties, gelation process, measurement by photo correlation spectrometry

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Gelatin: chemistry; manufacture; properties, testing (in German)

Hüttenrauch, R. and Fricke, S., *Naturwissenschaften*, 1984, *71*, 426–7

Importance of water structure to helical conformation and ageing of gelatin in aqueous solutions

gelatin, hard capsule, physical properties, molecular configuration, effect of water structure

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The uses of gelatin in pharmacy

capsules, soft gelatin, pastes, pastilles and suppositories: formulation, capsule shells; gelatin testing

Charles B. Knox Gelatine Company, Inc., *British Patent* 1 836 082, 1960

Method of modifying type A gelatin and product thereof

capsules, hard gelatin: gelatin films, brittleness, drying rate; gelatin modification, polycarboxylic acids

Jones, R.T., *Process Biochem.*, 1970, *5*(12), 2–8

Pharmaceutical gelatin. Manufacture

review

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Pharmaceutical gelatin. Applications

capsules, hard and soft gelatin, emulsions, lozenges, pastes, pastilles, suppositories and tablets: review

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The role of gelatin in pharmaceuticals

pharmaceutical applications, review

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gelatin, equilibrium moisture content, effect of relative humidity

Grouber, B., *Labo-Pharma Probl. Tech.*, 1983, *31*, 909–16

Gelatins, properties, standards, principal applications (in French)

applications, manufacture, properties, testing

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Murphy, H. W., assigned to Eli Lilly & Co., *U.S. Patent* 2 526 683, 1950

Methylcellulose capsules and process of manufacture

capsules, two-piece: capsule shell composition, methylcellulose; manufacturing method, dipping

Greminger, G.K. and Weaver, M.A., assigned to Dow Chemical Company, *U.S. Patent* 2 810 659, 1957

Thermoplastic compositions of water-soluble cellulose ethers

capsule, one-piece: capsule shell composition, cellulose ethers; formulation, plasticisers; manufacturing method, rotary die

Tanabe Seiyaku Co. Ltd, *Japanese Patent Application No.* 70 01277, 1970, through *Derwent Accession No.* 06531R, 1967

Polyvinyl alcohol-based soft capsules

capsules, one-piece: capsule shell composition, polyvinyl alcohol; manufacturing method, plate, rotary die; stability, bacteria, heat, light, moisture

Dow Chemical Company, *British Patent* 1 144 225, 1969

Preparation of medicinal capsule shells from hydroxyalkyl-alkylcellulose ethers

capsules, two-piece: capsule shell composition, hydroxyalkyl-alkylcellulose ethers; manufacturing method, dipping

Greminger, G.K. and Davis, L.E., assigned to Dow Chemical Company, *U.S. Patent* 3 493 407, 1970

Preparation of medicinal capsules from hydroxyalkylcellulose ethers

capsules, two-piece: capsule shell composition, hydroxyalkylcellulose ethers; aqueous and non-aqueous systems; manufacturing method, dipping

Centre de Recherches Marcel Midy and Rene Claude, *French Patent* 2 073 288, 1971, through *Derwent Accession No.* 00580T-B, 1969

Thermoplastic capsules for pharmaceutical use, administered orally, rectally or vaginally

capsules, one-piece: capsule shell composition, hydroxypropylcellulose, polyacrylic acid, polymethacrylates, polyoxyethylene, polyvinyl alcohol, vinylpyrrolidone/vinyl acetate copolymer; capsule type, oral, rectal, vaginal; manufacturing method, injection moulding, thermoforming

Langman, C.A.J., assigned to Dow Chemical Co., *U.S. Patent* 3 617 588, 1971

Dip coating for preparing cellulose ether capsules using induction heating

capsules, two-piece: capsule shell composition, hydroxyalkylcellulose ethers; manufacturing method, dipping, thermal gelation, means of heating moulds by induction

Tanabe Seiyaku Co. Ltd, *Japanese Patent Application No.* 71 10199, 1971 through *Derwent Accession No.* 19844S-B, 1967

Gelatin alkyl sulphate capsule base

capsules, one- or two-piece: capsule shell composition, gelatin alkyl sulphate or salt of; manufacturing method, standard; properties, physical strength, solubility

Röhm GmbH, *Belgian Patent* 785 702, 1972, through *Derwent Accession No.* 02444U-AB, 1971

Dissolvable pharmaceutical capsule

capsules, two-piece: capsule shell composition, polymer of vinylic monomer; capsule solubility, pH dependent; formulation of shell, aqueous dispersion; manufacturing method, dipping

Dow Chemical Co., *British Patent* 1 310 697, 1973

Dip coating process for preparing cellulose ether film products

capsules, two-piece: capsule shell composition, hydroxyalkylcellulose ethers; manufacturing method, dipping

Szymanski, C.D. and Helmstetter, G.J., assigned to National Starch and Chemical Corp., *U.S. Patent* 3 758 323, 1973

Dextrin-extended gelatin compositions

capsules, two-piece: capsule shell composition, gelatin and modified starch; method of manufacture, use; starch, liquid or thermal modification

National Starch and Chemical Corp., *Dutch Patent* 7 309 843, 1974, through *Derwent Accession No.* 08679V/05, 1972

Gelatin composition diluted with modified starch for capsule production

capsules, hard gelatin: capsule shell composition, gelatin and modified starch; manufacturing method, dipping; starch, liquid or thermal modification

Hoechst A.G., *German (BRD) Patent (Offen.)* 2 363 853, 1975, through *Derwent Accession No.* 4636W/28, 1976

Self carrying packages or capsules for medicaments

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capsules, two piece: capsule shell composition, copolymer polyethylene oxides, vinyl acetate, vinyl alcohol; formulation of coating; manufacturing method, dipping

Christen, J.D. and Cheng, W.-J., assigned to Dow Chemical Company, *U.S. Patent* 4 026 986, 1977

Capsule shell

capsules, two-piece: capsule shell composition, hydroxyalkyl starches; capsule shell properties, formulation; manufacturing method, dipping

3 Capsule Practice and Manufacture

3.1 Capsule Practice

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Gelatin capsules in dispensing pharmacy (in German)

applications; capsule products, Germany (BRD); dispensing

Kuhn, T., *Pharm. Ztg, Berl.*, 1963, *108*, 130–5, 195–8

The testing of gelatin capsules (in German)

gelatin; manufacture; pharmacopoeial standards; properties; 3.7.1

Köchel, F., *Dt. ApothZtg*, 1967, *107*, 603–7

Incompatibilities with various medicinal dosage forms (in German)

pharmaceuticals: formulation, incompatibilities

Vestfal, N.I., *Sb. Nauch. Trud., Tsent. Aptech. Nauch.-Issled. Inst.*, 1971, *11*, 158–68

Analysis of medicinal substances contained in capsules. Preliminary report (in Russian)

capsules, hard and soft gelatin: products, USSR; review

Anon., *Drugs Germ.*, 1972, *15*, 64–72

Drugs in Scherer capsules

capsules, hard and soft gelatin: applications; filling; manufacture

Thoma, K., Siemer, E. and Pfaff, G., *4th International Pharmaceutical Study Week of the German Pharmaceutical Society*, Davos, 1974, pp. 42

Manufacture and review of capsule preparations

capsules, hard and soft gelatin: applications; filling; manufacture; testing

Anon., *Mfg Chem.*, 1977, *48*(7), 19–20

The techniques of drug encapsulation

capsules, hard and soft gelatin: applications; manufacture; properties

Nerlo, H., *Pharm. Ind., Berl.*, 1977, *39*, 488–91

Effects of excipients on properties of solid oral dosage forms

capsules, hard and soft gelatin and tablets: formulation

Stephan, D., *Packung Transport*, 1978, No. 9, 416, 418, 421

Hard or soft – liquid or powder. Gelatin capsule filling (in German)

applications; capsule performance, comparison of hard and soft; capsule shells, dimensions, volume; manufacture, capsules, soft gelatin, rotary die

Jones, T.M., *Drug Cosmet. Ind.*, 1979, *124*(3), 40, 42, 44, 46, 48, 50, 53–4, 56, 103–4

The influence of excipients on the design and manufacture of tablets and capsules

formulation, contents, general; review

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Capsule technology

capsules, hard and soft gelatin: drug release, hard and soft capsules; filling, hard gelatin capsules, machines and mechanisms; formulation of contents; meeting report

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Encapsulating technology

capsule products, cleaning and inspection; filling machines, hard gelatin capsules; manufacturing methods, soft gelatin capsules

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The manufacture of hard and soft gelatin capsules (in German)

capsules, hard and soft gelatin: manufacturing methods, industrial

Fahrig, W., Chapter I in *The Capsule, Basics, Technology and Biopharmacy, a Modern Dosage Form* [in German], Fahrig, W. and Hofer, U. (Eds), Stuttgart, Wissenschaftliche Verlagsgesellschaft mbH, 1983, pp. 12–20

Introduction to capsules (in German)

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OTC capsules threatened by new Tylenol crisis

capsules, hard gelatin: product tampering, case study, USA position

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Capsules – is their fate sealed?

capsules, hard and soft gelatin: product tampering. comparison of methods to prevent, review

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The injection-moulded capsule

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An eye to the issues. Will outlawing capsules eliminate tampering?

capsules, hard gelatin: product tampering, USA position.

3.2 Capsules, Hard Gelatin

3.2.1 General References

Müller, G., *Dt. ApothZtg*, 1962, *102*, 1138–40

Hard gelatin capsules (in German)

capsules, enteric, formaldehyde treatment; filling small scale, equipment; manufacture, industrial scale; storage conditions

Childs, R.F., *Am. J. pharm. Educ.*, 1965, *29*, 119–24

Solid dosage forms: capsules

filling, small scale; identification; properties of capsules, capsule shells and products

Smith, Kline and French Laboratories, Selected Pharmaceutical Research References, Philadelphia, 1966

Manufacture of hard capsules: An annotated bibliography

capsule sealing; enteric capsules; gelatin; gelatin substitutes; manufacture

Hoffmann, A., Hoffmann, M.-A. and Meunier, A., *Bull. Soc. Pharm. Nancy*, 1968, *78*, 7–18

Hard gelatin capsules (in French)

applications; drug availability, *in vitro*, *in vivo*; enteric coating; filling, small scale, separation-resistant capsules; formulation, contents; history; manufacture; storage

Pochet, G., *Prod. Probl. Pharm.*, 1968, *23*, 313–16

Hard gelatin capsules (in French)

filling, small scale, industrial scale; manufacture; storage

Jones, B.E., *Mfg Chem.*, 1969, *40*(2), 25–8 (French translation in *Labo-Pharma Probl. Tech.*, 1969, *17*(179), 34–41)

Hard gelatin capsules: a literature review

drug availability, *in vitro*, *in vivo*; enteric coating; filling; formulation; history; manufacture; review; storage

Samková, M., *Čslká Farm.*, 1969, *18*, 262–6

The filling of drugs into gelatin capsules in pharmacies (in Czech)

capsule shells, volumes; filling, industrial, small scale; filling, capsule size determination; powder properties, bulk density

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Empty gelatin capsules (gélules). Manufacture and importance (in French)

colour; drug availability; filling machines; formulation; gelatin; manufacture; storage

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The possibilities offered by hand gelatin capsules as against other pharmaceutical forms in modern hospital pharmacy (in Italian)

applications; enteric coating; filling, small scale

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The hard gelatin capsule (in French)

filling; manufacture; requirements

Ceschel, G.C. and Fontani, F., *Boll. chim.-farm.*, 1970, *109*, 157–79

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applications; filling; testing

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A "Capsugel" factory, affiliate of Parke, Davis implanted in France (in French)

applications; capsule shells, dimensions; colour; gelatin standards; history; manufacturing method; separation-resistant capsules

Schmitt, J.-P. and Mathis, C., *Prod. Probl. Pharm.*, 1970, *25*, 752–61

Problems arising in the industrial production of hard gelatin capsules (in French)

capsule shells, colorants, dimensions, separation resistant; drug availability, *in vitro*, disintegration; filling, industrial scale; formulation, contents; powder properties, angle of repose, bulk density; product, weight uniformity; storage, product stability, effect of carbon dioxide, light, moisture, oxygen

Bovis, A., *Bull. Soc. Pharm. Marseille*, 1971, *20*, 7–18

The hard gelatin capsule (in French)

filling, small scale; history; manufacture

Van Herle, L., *Pharmacy Int.*, 1971, *1*, 12–18

Gelatin capsules (gélules)–manufacture and importance

colour; drug availability; filling, industrial scale; formulation; gelatin; manufacture; storage

Sugihara, M., *Nippon Yakuzaishi kai Zasshi*, 1972, *24*(8), 21–8

Hard capsuled medicines (in Japanese)

filling, small scale, industrial scale; manufacture; storage, products

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Hard gelatin capsules in hospital pharmacy

enteric capsules; filling, small scale; formulation, contents

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The filling and dispensing of hard gelatin capsules (in German)

capsule shells; drug availability, *in vitro*, disintegration testing, *Swiss P.* VI method; extemporaneous dispensing, equipment, official products; filling, capsule size determination; formulation, contents, official products; lubricants, Aerosil, calcium stearate, magnesium stearate; powder properties, bulk density, flow properties; product weight uniformity, comparison of filling equipment, official products; storage, stability at room temperature, official products

Newton, D.W. and Becker, C.H., *Pharmacy Times*, 1977, *43*(1), 66–70, 76–7

What's the impact of capsule and tablet formulation on product selection?

capsules, hard gelatin and tablets: dissolution; formulation of contents

Stamm, A., *Bull. Soc. Pharm. Strasb.*, 1978, *21*, 15–41

Problems posed by the choice of excipients for hard gelatin capsules, cachets and tablets (in French)

formulation, contents, general; review

Strittmatter, T., *Pharm. Ztg, Berl.*, 1978, *123*, 2238–41

The hard gelatin capsule in the dispensary

capsule shells, separation-resistant, volume and weight; filling, small scale; formulation of contents; product weight uniformity, pharmacopoeial standards; products, content weight by capsule size

Ludwig, A., Van Ooteghem, M. and Delva, A., *Pharm. Ind., Berl.*, 1979, *41*, 796–8

Disintegration of hard gelatin capsules. Part I: Composition and structure of the capsule wall

capsule shells, wall structure and thickness; 2.2

von Wattenwyl, A., *Mfg Chem.*, 1981, *52*(3), 37–8

Hard gelatin capsules – a drug form for better patient compliance

capsule colour; capsule filling, separation-resistant capsules; capsule printing, radial; market survey; patient compliance, effect of capsule

Fuhrer, C., Chapter II, in *The Capsule, Basics, Technology and Biopharmacy, a Modern Dosage Form* (in German), Fahrig, W. and Hofer, U. (Eds), Stuttgart, Wissenschaftliche Verlagsgesellschaft mbH, 1983, pp. 21–32

The capsule as a modern medical form in the pharmacy and industry (in German)

Jones, B.E., *Pharm. Technol.*, 1985, *9*, 106–8, 110, 112

Hard gelatin capsules and the pharmaceutical formulator

applications, capsule manufacture; filling machines, dosing mechanisms; formulation of contents

3.2.2 Manufacture of Hard Capsules

3.2.2.1 Capsule Shells

Colton, A., assigned to Parke, Davis & Co., *U.S. Patent* 1 787 777, 1931

Capsule machine

machine, fully automatic; manufacturing method

Dehn, F.B., *British Patent* 360 427, 1931

An improved machine for making medicinal capsules and the like

machine, fully automatic; manufacturing method

Norris, W.G., *Mfg Chem.*, 1959, *30*, 233–6

Hard gelatin capsules – how Eli Lilly make 500 million a year

filling, industrial scale; gelatin standards; manufacturing, machines, method

Norris, W.G., *Mfg Chem.*, 1961, *32*, 249–52, 258

P.D.'s new capsule plant

filling, industrial scale; gelatin standards; manufacturing, machines, method

Anon., *Pharm. J.*, 1965, *194*, 475–6

Capsule-making at Basingstoke

manufacturing, machines, method

Girombelli, A. and Michel, L., Capsules et Gélules, Symposium (Paris, Faculty of Pharmacy, University of Paris), 1970, *III*, 1–9

The production and control of the manufacture of hard gelatin capsules (in French)

manufacturing, method, quality control systems; printing; raw materials

Oglevee, H.G. and Clement, B.R., assigned to Parke, Davis & Co., *U.S. Patent* 3 632 700, 1972

Monitoring viscosity of gelatin to insure uniform walls

capsule wall thickness, automatic control by viscometry; gelatin solution, viscosity determination

Parke, Davis & Co., *British Patent* 1 297 739, 1972

Capsule production apparatus and method

capsule wall thickness, automatic control by viscometry

Parke, Davis & Co., *British Patent* 1 328 423, 1973

Apparatus suitable for use in the dip-moulding of capsules

capsule wall thickness, control by viscosity

Martyn, G.W., *Drug Devel. Comm.*, 1974–5, *1*, 39–49

The people computer interface in a capsule molding operation

manufacturing methods, computer control

Höfliger, O., *German (BRD) Patent (Offen.)* 2 557 601, 1977

Hard gelatin capsules and procedure for their manufacture

Mylan v. Qualicaps, IPR2017-00203
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capsules, two-layer; coating internal surface, hydrophobic polyelectrolyte polymer

Kupferberg-Odle, M., *German (BRD) Patent* 2 259 387, 1981

Method for making hard gelatin capsules

capsule shells, protective coatings, application by dipping; manufacturing method

Jones, B.E., *Chem. Engr, Lond.*, 1982, No. 380, 174–7

The manufacture of hard gelatin capsules

gelatin; history; manufacturing, machines, method, quality control systems; packaging; printing; storage

3.2.2.2 Ancillary Manufacturing Processes

Jones, B.E., *Annls méd. Nancy*, 1974, *13*, 191–200

The manufacture and printing of hard gelatin capsules

printing, design of logo, dimensions of print; printing equipment, industrial scale; printing ink, formulation

Su, K.S.E., Snyder, R.R. and Scott, R.R., assigned to Eli Lilly & Co., *U.S. Patent* 3 992 215, 1976

Pharmaceutical suspension for opaquing empty gelatin capsules

colorants, opacifying agents; formulation of suspension; titanium dioxide

François, D., Berneis, D.H., Cole, E.T., Pracht, I. and Schatz, B., *Mfg Chem.*, 1979, *50*(4), 48, 51, 76

Canthaxanthin to colour hard gelatin capsules

colour, stability to light; colorants, acceptability for use; colorants, natural, canthaxanthin; formulation, capsule shell; manufacture

Lykens, D. N., *Pharm. Technol.*, 1979, *3*, 57–60

Edible printing inks

printing faults, diagnosis; printing ink, formulation; printing, machines

3.2.3 Filling Hard Capsules

3.2.3.1 Small Scale Filling

Lee, J.W., *J. Am. pharm. Ass., scient. Edn.*, 1935, *24*, 469–76

Accuracy and speed factors in hand-filling capsules

capsule shells, physical specifications, weight uniformity; filling, manual methods; product weight uniformity

Matthews, D.R., *Pharm. J.*, 1948, *161*, 112

A capsule filling device

manual device, wood

Cooper, M.L., *J. Am. pharm. Ass., pract. Pharm. Edn*, 1954, *15*, 300

A capsule size selector

filling, capsule size determination

Tice, L.F. and Moore, A.W., *J. Am. pharm, Ass., pract. Pharm. Edn*, 1954, *15*, 296–7

A slide rule for selecting capsule size

filling, capsule size determination

van Nunen, J.W., *Pharm. Weekbl. Ned.*, 1962, *97*, 122–5

Capsules in the dispensary (in Dutch)

filling, capsule size determination; manual device, plastic; powder properties, bulk density; product weight uniformity

Artemev, A.I., *Aptech. Delo*, 1963, *12*(4), 58–9

An apparatus for filling gelatin capsules and starch wafers (in Russian)

cachets: manual device

Buchnev, B.P., *Aptech. Delo*, 1964, *13*(4), 80–1

Machine for filling hard gelatin capsules (in Russian)

manual device, plastic

Sandell, E., *Pharm. Ztg, Berl.*, 1964, *109*, 1099

Small scale apparatus for filling hard gelatin capsules in the dispensary (in German)

manual device, plastic

Jaspersen, H.P., *Schweiz. ApothZtg*, 1965, *103*, 747–52

A filling device for hard gelatin capsules (in German)

capsule shell, volumes, weight uniformity; filling, capsule size determination; formulation, contents; powder properties, bulk density; product weight uniformity

Ericsson, B. and Persson, H., *Svensk farm. Tidskr.*, 1966, *70*, 202–8

Hard gelatin capsules in place of pills in prescription work (in Swedish)

pills: dispensing, comparison capsules and pills

Van Ooteghem, M., *J. pharm. Belg.*, 1966, *21*, 73–85

The filling of powders in cachets and hard gelatin capsules (in French)

cachets: capsule shells, dimensions, volume; filling, capsule size determination; powder properties, bulk density, packing theory

Reuter, H., *Pharm. Prax., Berl.*, supplement to *Pharmazie*, 1968, *23*, *Suppl.* 10, 271–4

The filling of single dose medicines in the dispensary (in German)

pills, powders and tablets: extemporaneous dispensing, comparison of dosage forms; filling, dispensary equipment; product weight uniformity, comparison of dosage forms

Allart, H.H.J., *Pharm. Weekbl. Ned.*, 1971, *106*, 25–31

Capsule filling machines for use in the dispensary (in Dutch)

Thompson, G.R. and Cunningham, A., *J. pharm. Sci.*, 1975, *64*, 320–22

Versatile unit for filling gelatin capsules with drugs or chemicals

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capsule shells, physical specification; filling machine, liquid dosing; formulation of contents, liquid fill; storage, refrigerated conditions

3.2.3.2 Industrial Scale Filling of Hard Capsules

Anon., *Labo-Pharma Probl. Tech.*, 1966, *14*(145), 69–79

Why and how to fill capsules (in French)

filling machines, automatic, manual, and semi-automatic; 3.8.2.4

Pluripharm, *French Patent* 1 454 013, 1966, through *Derwent Accession No. 24 048, 1965*

Capsules

filling machine, insertion of capsules and capsule parts; incompatible medicines, separation by encapsulating; stability, incompatible medicines

Aspro-Nicholas Limited, *British Patent* 1 204 580, 1970

Encapsulated pharmaceutical dosage forms

filling machine, tablet insertion; incompatible medicines, separation by tabletting

Clement, H. and Marquardt, H.G., *Pharm. Ind., Berl.*, 1970, *32*, 169–76

Experiences with machines for filling hard gelatin capsules (in German)

filling machines, auger, dosing tube, tamping mechanisms; review

Robin, J., Capsules and Gélules, Symposium (Paris, Faculty of Pharmacy, University of Paris), 1970, *II*, 11–21

Machines for filling hard gelatin capsules (in French)

filling machines, auger, dosing tube, tamping mechanism; product sealing, banding, dot welding

Christian Brunnengräber Chemische Fabrik & Co. mbH, *German (BRD) Patent (Offen.)* 2 021 147, 1971 through *Derwent Accession No.* 72732S-B, 1970

Medicinal capsule containing separate units

filling machine, tablet insertion; incompatible medicines, separation by tabletting; stability, incompatible medicines

Gallet, M.M., *Farmaco, Ed. prat.*, 1971, *26*, 251–68

The hard gelatin capsule, filling and closing (in French)

filling machines, automatic and semi-automatic

Eli Lilly & Co., *British Patent* 1 267 304, 1972

Method for making filled capsules

filling machine, capsule body only, sealing open end with gelatin solution

Ridgway, K. and Callow, J.A.B., *Pharm. J.*, 1973, *211*, 281–5

Capsule-filling machinery

filling machines, small scale, industrial scale, semi-automatic, automatic; product weight uniformity

Perry Industries Inc., *U.S. Patent* 3 874 431, 1975, through *Derwent Accession No.* 25588 W/15, 1969

Loading medicinal powder into capsules

filling machine, air operated dosing tube mechanism

Faust, R.N., Vandervalk, W. and Warnick, R., *Chem. Engng. Prog.*, 1976, *72*(6), 84–7

Selecting a high-speed capsule machine

filling machine, comparison of automatic and semi-automatic, performance, yields; product weight uniformity, effect of filling machine

Zanasi Nigris SpA., *German (BRD) Patent (Offen.)* 2 612 472, 1976, through *Derwent Accession No.*, 81492X/44, 1975

Metering device for use in filling capsules

filling machine, dosing tube mechanism, semi-solid fill

Anon., *Mfg Chem.*, 1977, *48*(7), 26, 28, 30

Latest capsule machines on UK market

machines, automatic; machines, filled capsules, cleaning, sorting

Teague, P., *Mfg Chem.*, 1977, *48*(7), 30

Choosing your machine

machines, performance, requirements

Beckley, J.N., *Drug Cosmet. Ind.*, 1978, *123*(4), 70, 70, and 150–1

Dust control in tablet-making and capsule filling

air handling systems; cross contamination; good manufacturing practice

Manesty Machines Ltd, *German (BRD) Patent*, 2 443 466, 1978

Gelatin capsule filling machine

dosing mechanism, tablet punches and dies

Anon., *Khim.-farm. Zh.*, 1980, *14*, 100–3

mG2 filling machine for hard gelatin capsules (in Russian)

filling machine, dosing tube mechanism

Cole, G.C., *Chem. Eng, Lond.*, 1982, No. 380, 473–7

Capsule filling

capsule contents, solids and semi-solids; filling machines, instrumentation; filling machines, mechanisms; filling machines, powder plug formation, forces, effect of lubricants; formulation of contents (powders), diluents, lubricants; powder characteristics

von Doehren, P.J., Forbes, F.St. J. and Shively, C.D., *Pharm. Technol.*, 1982, *6*(9), 139–40, 143–5, 147–9, 153–4, and 156

An approach to the characterization and technology transfer of solid dosage from processes

formulation of contents, process design and optimisation; pharmaceutical processes, planning and scale-up

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Di Costanzo, F., Grandvuillemin, L., van der Mander, J. and Réaux, M., *Labo-Pharma Probl. Tech.*, 1983, *31*(337), 917–25

Filling hard gelatin capsules (in French)

fill materials, types; machines, methods of dosing, review

Hofer, U., Chapter V, in *The Capsule, Basics, Technology and Biopharmacy, a Modern Dosage Form* [in German], Fahrig, W. and Hofer, U., (Eds), Stuttgart, Wissenschaftliche Verlagsgesellschaft mbH, 1983, pp. 83–111

Dry filling (in German)

Yelvigi, M. *Pharm. Technol.*, 1984, *8*(3), 47–50, 52, 55–6

Principles of process automation for liquid and solid dosage forms

production, flow chart for automation process

3.2.3.3 Instrumented Machines, Physical Analysis

Ito, K., Hitomi, M., Kaga, S.I. and Takeya, Y., *Chem. pharm. Bull., Tokyo*, 1969, *17*, 1138–45

Studies on hard gelatin capsules II. The capsule filling of powders and effects of glidant by ring filling method-machine

filling machine, auger mechanism; filling machine, settings, speed of filling; product weight uniformity, effects of, formulation, machine settings; 3.2.4.1

Irwin, G.M., Dodson, G.J. and Ravin, L.J., *J. pharm. Sci.*, 1970, *59*, 547–50

Encapsulation of clomacran phosphate {2-chloro-9-[3-(dimethylamino)propyl]acridan phosphate} I. Effect of flowability of powder blends, lot-to-lot variability, and concentration of active ingredient on weight variation of capsules filled on an automatic capsule-filling machine

filling machine, industrial, dosing tube mechanism; powder processing, granulation, formulations, effect on product weight uniformity; powder properties, flow measurements

Cole, G.C. and May, G., *J. Pharm. Pharmac.*, 1972, *24*, *Suppl.*, 122P–3P

Instrumentation of a hard shell encapsulation machine

filling machine, dosing tube mechanism; filling machine, powder plug formation, compaction and ejection forces; formulation, diluents, lubricants; instrumented filling machine, strain gauges

Miyake, Y., Shinoda, A., Nasu, T., Furukawa, M., Uesugi, K. and Hoshi, K., *Yakuzaigaku*, 1974, *34*, 32–7

Packing properties of pharmaceutical powders into hard gelatin capsules (in Japanese)

filling machine, dosing tube mechanism; powder properties, angle of repose, density, moisture content, particle size, effect on filling; product weight uniformity, effect of machine settings and powder properties

Cole, G.C. and May, G., *J. Pharm. Pharmac.*, 1975, *27*, 353–8

The instrumentation of a Zanasi LZ/64 capsule filling machine

filling machine, dosing tube mechanism; filling machine, powder plug formation, compaction and ejection forces; formulation of contents, diluents and lubricants; instrumented filling machine, strain gauges

Kent, J.S. and Yost, M.T., *J. pharm. Sci.*, 1977, *66*, 1507–8

Strain-gauged Wheatstone bridge design for automatic capsule-filling machine

instrumented filling machine, strain gauges, design

Mony, C., Sambeat, C. and Cousin, G., *First International Conference of Pharmaceutical Technology*, (Paris, APGI, May 31–June 2, 1977), 1977, *II*, 98–108

Applications of the measure of force in the formulation and filling of hard gelatin capsules (in French)

filling machine, dosing tube mechanism; filling machine, powder plug formation, compaction and ejection forces, effects of formulation of contents; instrumented filling machine, piezoelectric capacitor; 3.2.4.1

Small, L.E. and Augsburger, L.L., *J. pharm. Sci.*, 1977, *66*, 504–9

Instrumentation of an automatic capsule-filling machine

filling machine, dosing tube mechanism; filling machine, powder plug formation, compaction and ejection forces; formulation of contents, diluents and lubricants; instrumented filling machine, strain gauges

Small, L.E. and Augsburger, L.L., *J. pharm. Sci.*, 1977, *66*, 1508

Clarification of nomenclature

instrumented machine, strain gauges, design

Kurihara, K. and Ichikawa, I., *Chem. pharm. Bull., Tokyo*, 1978, *26*, 1250–6

Effect of powder flowability on capsule-filling-weight-variation

filling machines, oscillating plate, tamping, mechanisms; powder properties, flow, angle of repose, discharge through orifice, minimum orifice diameter; product weight uniformity, effects of, filling machine mechanism, formulation of contents, powder properties; 3.2.4.1

Small, L.E. and Augsburger, L.L., *Drug Dev. ind. Pharm.*, 1978, *4*, 345–72

Aspects of the lubrication requirements for an automatic capsule filling machine

filling machine, dosing tube mechanism; filling machine, powder plug formation, compaction and ejection forces, effect of, compression force, piston height, powder bed height; formulation, machine settings; filling machine settings; 3.2.4.1

Jolliffe, I.G., Newton, J.M. and Walters, J.K., *J. Pharm. Pharmac.*, 1979, *31*, *Suppl.*, 70P

A theoretical approach to optimising capsule filling by a dosator nozzle

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filling machine, dosing tube mechanism; powder properties, relationship to machine

Woodhead, P.J., Newton, J.M., Hardy, J.G. and Jackson, S.A., *J. Pharm. Pharmac.*, 1979, *31*, *Suppl.*, 72P

A gamma-ray attenuation technique for assessing the distribution of porosity in powder beds

filling machine, dosing tube mechanism; powder properties, bulk density measurement, non-disruptive technique with gamma source

Gioia, A., *Pharm. Technol. Int.*, 1980, *3*(2), 29–32

Intrinsic flowability: a new technology for powder-flowability classification

filling machine, dosing tube mechanism; powder properties, flow, measurement, flow meter; powder properties, flow, relationship to uniformity of fill weight

Jolliffe, I.G., Newton, J.M. and Walters, J.K., *Powder Technol.*, 1980, *27*, 189–95

Theoretical considerations of the filling of pharmaceutical hard gelatin capsules

filling machine, dosing tube mechanism; filling machine, powder plug formation, theoretical analysis; powder properties, arch formation, relationship angle of powder/wall friction and machine compressive force

Mehta, A.M. and Augsburger, L.L., *Int. J. Pharmaceut.*, 1980, *4*, 347–51

Simultaneous measurement of force and displacement in an automatic capsule filling machine

capsule-filling machine, dosing tube mechanism; filling machine, powder plug formation, effects of, compression force, lubricant; formulation of contents, diluent, microcrystalline cellulose, lubricant, magnesium stearate; instrumented machine, displacement transducer, strain gauges

Chowan, Z.T. and Young, I.-C., *J. pharm. Sci.*, 1981, *70*, 927–30

Powder flow studies III: Tensile strength, consolidation ratio, flow rate and capsule-fill-weight variation relationships

capsule, uniformity of fill-weight, effect of powder properties; diluents, lactose, starch; formulation of contents, drug and excipients; lubricant, magnesium stearate; powder properties, consolidation ratio, flow rate, tensile strength, effects of, consolidation pressure, formulation

Mehta, A.M. and Augsburger, L.L., *Int. J. Pharmaceut.*, 1981, *7*, 327–34

A preliminary study of the effect of slug hardness on drug dissolution from hard gelatin capsules filled on an automatic capsule-filling machine

capsule-filling machine, dosing tube mechanism; filling machine, powder plug formation, plug hardness, effect of formulation of contents; formulation of contents, diluents, lactose, microcrystalline cellulose, lubricant, magnesium stearate; powder plugs, hardness measurement, three-point bending test; 4.2.3.4

Newton, J.M. and Bader, F., *J. Pharm. Pharmac.*, 1981, *33*, 621–6

The prediction of the bulk densities of powder mixtures, and its relationship to the filling of hard gelatin capsules

capsule filling, prediction of fill-weight, effect of powder properties; powder properties, bulk densities, effect of composition of mixtures, practical and theoretical values; powder properties, measurements of, apparent density, maximum tapped bulk density

Woodhead, P.J. and Newton, J.M., *J. Pharm. Pharmac.*, 1981, *33*, *Suppl.*, 21P

The influence of nozzle/piston clearance on the efficiency of a capsule-filling dosator

capsule filling, uniformity of weight, effects of, entrapped air, powder properties; dosing tube mechanism, powder plug formation, effects of, nozzle/piston clearance, powder properties; filling machine simulator, intermittent motion, dosing tube mechanism; instrumented dosing tube, displacement transducer, strain gauges; powder properties, particle size

Augsburger, L.L., *Pharm. Technol.*, 1982, *6*(9), 111–19

Instrumented capsule-filling machines: development and application

filling machine, dosing tube mechanism; filling machine, powder plug formation, compaction and ejection forces; formulation of contents, diluents, lubricants; instrumented filling machines, strain gauges, review of methods

Jolliffe, I.G., Newton, J.M. and Cooper, D., *J. Pharm. Pharmac.*, 1982, *34*, 230–5

The design and use of an instrumented mG2 capsule filling machine simulator

filling machine simulator, continuous motion, dosing tube mechanism; filling machine, powder plug formation, compaction and ejection forces; instrumented dosing tube, displacement transducers, strain gauges

Jolliffe, I.G. and Newton, J.M., *J. Pharm. Pharmac.*, 1982, *34*, 293–8

Practical implications of theoretical consideration of capsule filling by the dosator nozzle system

capsule filling, dosing tube mechanism; dosing tube, static assembly, measurement of nozzle surface texture; dosing tube, powder plug formation, force for arch formation, effects of, compression force, nozzle surface texture, powder properties; powder properties, measurements by Jenike shear cell, angle of internal friction, angle of wall friction; powder properties, particle size, powder flow, powder bed density

Jolliffe, I.G. and Newton, J.M., *J. Pharm. Pharmac.*, 1982, *34*, 415–19

An investigation of the relationship between particle size and compression during capsule filling with an instrumented mG2 simulator

capsule filling, uniformity of weight, effect of compression ratio; dosing tube mechanism, powder plug formation, compression and ejection forces, effect of powder properties;

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instrumented dosing tube mechanism, displacement transducers, strain gauges; machine simulator, continuous motion, dosing tube mechanism; powder properties, particle size

Jolliffe, I.G. and Newton, J.M., *J. Pharm. Pharmac.*, 1983, *35*, 7–11

The effect of dosator nozzle wall texture on capsule filling with the mG2 simulator

capsule filling, uniformity of weight, effects of, compression rates, nozzle surface texture, powder properties; dosing tube mechanism, powder plug formation, effect of powder properties; dosing tube, measurement of surface texture; instrumented dosing tube mechanism, displacement transducers, strain gauges; machine simulator, continuous motion, dosing tube mechanism; powder properties, angle of powder/wall friction, particle size

Jolliffe, I.G. and Newton, J.M., *J. Pharm. Pharmac.*, 1983, *35*, 74–8

Capsule filling studies using an mG2 production machine

capsule filling, uniformity of weight, effects of, compression ratio, nozzle surface texture, powder properties; filling machine, dosing tube mechanism; instrumented filling machine, strain gauges, comparison with machine simulator; powder properties, particle size

Jollife, I.G. and Newton, J.M., *Powder Technol.*, 1983, *35*, 151–7

Extension of theoretical considerations of the filling of pharmaceutical hard gelatin capsules to the design of dosator nozzles

filling machine, dosing tube mechanism, filling machine, powder plug formation, theoretical analysis, effect of nozzle surface texture; powder properties, arch formation and angle of powder/wall friction, relationship to nozzle surface design

Shah, K., Augsburger, L.L., Small, L.E. and Polli, G.P., *Pharm. Technol.*, 1983, *7*(4), 42, 44, 46, 48, 52–4

Instrumentation of a dosing disc automatic capsule filling machine

filling machine, tamping mechanism; filling machine, powder plug formation, compaction and ejection forces; formulation of contents, diluents and lubricants; instrumented filling machine, strain gauges

Botzolakis, J.E. and Augsburger, L.L., *J. Pharm. Pharmac.*, 1984, *36*, 77–84

The role of disintegrants in hard-gelatin capsules

filling machine, dosing tube mechanism; filling machine, powder plug formation, compaction and ejection forces; instrumented filling machine, strain gauges; powder plug hardness tester; powder plug properties, hardness, effects of, formulation of contents, machine forces; 3.2.4.1–4.2.4

Maury, M., Héraud, P., Etienne, A., Aumonier, P. and Casahoursat, L., *Fourth International Conference on Pharmaceutical Technology*, (Paris, APGI, June 3–5, 1986), 1986, *I*, 384–8

Pressure measurements during the filling of hard gelatin capsules (in French)

filling machine, dosing tube mechanism; filling machine, powder plug formation, compaction and ejection forces; instrumented filling machine, piezo-electric capacitor

Shah, K.B., Augsburger, L.L. and Marshall, K., *J. pharm. Sci.*, 1986, *75*, 291–6

An investigation of some factors influencing plug formation and fill weight in a dosing-disc type automatic capsule-filling machine

capsule-filling machine, tamping mechanism; filling machine, powder plug formation, plug hardness, effects of formulation of contents; fill weight, theoretical determination from powder properties, effects of formulation of contents, machine settings; formulation of contents, diluents, lubricant; instrumented filling machine, strain gauges; powder plugs, hardness measurement, effects of, formulation of contents, machine settings

3.2.3.4 Filling Semi-solids into Hard Capsules

Anon., *Packung & Transp. chem. Ind.*, 1978, No. 9, 421

Liquids in hard gelatin capsules

dose measurement, dosing pump; machine, automatic

Hoechst UK Ltd, *British Patent* 1 572 226, 1980

Improvements in and relating to pharmaceutical preparations in solid unit dosage forms

filling machines, detection of capsule parts, photoelectric control; filling machines, dosage of liquids; product weight uniformity; 3.2.4.2–4.2.4

Walker, S.E., Ganley, J.A., Bedford, K. and Eaves, T., *J. Pharm. Pharmac.*, 1980, *32*, 389–93

The filling of molten and thixotropic formulations into hard gelatin capsules

filling machines, detection of capsule parts, photoelectric control; filling machines, dosing of liquids; product weight uniformity, effect of liquid dosing; 3.2.4.2–4.2.3.4–4.2.3.6

François, D., *Labo-Pharma Probl. Tech.*, 1983, *31*, 944–9

Technology of pastes and oils in hard gelatin capsules (in French)

filling machines, review

François, D., Chapter VI, in *The Capsule, Basics, Technology and Biopharmacy, a Modern Dosage Form* (in German), Fahrig, W. and Hofer, U. (Eds), Stuttgart, Wissenschaftliche Verlagsgesellschaft mbH, 1983, pp. 112–26

Liquid and paste filling into hard gelatin capsules (in German)

filling machines, industrial; 3.2.4.2

McTaggart, C., Wood, R., Bedford, K. and Walker, S.E., *J. Pharm. Pharmac.*, 1984, *36*, 119–21

The evaluation of an automatic system for filling liquids into hard gelatin capsules

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filling machine, detection of capsule parts, photoelectric control; filling machine, dosing of liquids; formulation of contents; liquid properties, viscosity; product weight uniformity, effect of process conditions

Bowtle, W.J., *Br. J. pharm. Pract.*, 1986, *8*, 307–8

Semi-solid matrix capsules

thermosoftening formulation, manufacturing method, bench and industrial scale; 3.8.3.4; 4.2.3.4

3.2.3.5 Self-locking Capsules

Eli Lilly & Co., *French Patent* 1 343 698, 1963

Capsule resisting separation

Eli Lilly & Co., *British Patent* 970 761, 1964

Separation-resistant capsule

Carnaghi, A.J. and Logsdon, I., assigned to Eli Lilly & Co., *U.S. Patent* 3 285 408, 1966

Capsule with integral locking band

Eli Lilly & Co., *British Patent* 1 040 859, 1966

Capsule with integral locking band

Oglevee, H.J. and Mottin, R.E., assigned to Parke, Davis & Co., *U.S. Patent* 3 399 803, 1968

Self-locking medicament capsule

Parke, Davis & Co., *British Patent* 1 108 629, 1968

Hard shell capsule

R.P. Scherer Corporation, *British Patent* 1 133 715, 1968

Two-piece capsule

Vierna, D.S.G. and Herrera, D.L.G., *Auxiliary products for oral solid dosage forms*, Symposium (Barcelona, Faculty of Pharmacy, University of Barcelona), 1969, 153–63

Safety measures for the use of gelatin capsules (in Spanish)

manufacture; separation-resistant capsules; 3.8.3.7

Parke, Davis & Co., *British Patent* 1 302 343, 1973

Hard-shell locking capsule

Koepff, H. and Leiberich, R., *Pharm. Ind., Berl.*, 1976, *38*, 1064–72

Separation behaviour of hard gelatin capsules

capsule-filling machine, dosing tube mechanism; capsule separation force, effects, capsule type, storage; capsule separation force, measurement, Instron tester; formulation of contents

Controulis, J., *Drug Dev. ind. Pharm.*, 1985, *11*, 585–90

Hard gelatin capsules–New developments from Capsugel

capsule, shape, elongated cap; capsule, tamper resistant

3.2.3.6 Sealing Hard Capsules

Okie Inc., *U.S. Patent* 3 159 546, 1964, through *Derwent Accession No.* 14 823, 1962

Gelatin capsule sealing composition

coating composition, acetone, ethyl acetate, water; sealing, by coating at cap–body junction

Centre de Recherches Marcel Midy., *French Patent* 1 587 915, 1970

Radiation welding of gelatin capsules for medicines

contents, powders; sealing spot heat welding

Sankyo Co. Ltd, *Japanese Patent Application No.* 7 250 367, 1972, through *Derwent Accession No.* 00985U-AB, 1969

Gelatin capsule sealing

band sealing, composition of solution; coating material, hydroxypropyl cellulose, polyvinyl acetal diethylaminoacetate

Wittwer, F., *Pharm. Technol.*, 1985, *9*(6), 24, 26, 28–29

New developments on hermetic sealing of hard gelatin capsules

capsule sealing, by immersion; sealing solution, gelatin solvent

Cadé, D., Cole, E.T., Mayer, J.P. and Wittwer, F., *Fourth International Conference on Pharmaceutical Technology*, (Paris, APGI, June 3–5, 1986), 1986, *I*, 389–97

Liquid filled and sealed hard gelatin capsules

capsule sealing, method using liquid immersion and drying; formulation of contents, liquids; sealed capsules, applications

3.2.3.7 Cleaning Hard Capsules

Parke, Davis & Co., *German (BRD) Patent* 2 152 778, 1974

Capsule cleaning rig

apparatus, vibratory bowl; cleaning material, sodium chloride; filled capsules, cleaning

Parke, Davis & Co., *German (BRD) Patent* 2 152 807, 1974

Pharmaceutical capsule machine

cleaning machine; dust removal by airflow; empty capsule removal by suction

Taisho Pharmaceutical Co., *Japanese Patent Application No.* 5 004 727, 1975, through *Derwent Accession No.* 20244W/12, 1970

Polishing washing agents for the production of hard capsules

cleaning machine, coating pan; dust removal by sugar coated with non-toxic surfactant

Perry Industries Inc., *U.S. Patent* 4 058 868, 1977, through *Derwent Accession No.* 86280Y/48, 1976

Cleaning and polishing of capsules; by impact against electrically charged screen followed by tumbling in a napped fabric lined drum

3.2.4 Formulation of Contents of Hard Capsules

3.2.4.1 Dry Solids

Husa, W.J. and Becker, C.H., *J. Am. pharm. Ass.*,

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scient. Edn, 1940, *29*, 78–86

Incompatibilities in prescriptions III. The use of inert powders in capsules to prevent liquefaction due to formation of a eutectic mixture

camphor, salol; diluents, various; storage trials

Husa, W.J. and Becker, C.H., *J. Am. pharm. Ass., scient. Edn*, 1940, *29*, 136–41

Incompatibilities in prescriptions IV. The use of inert powders in capsules to prevent liquefaction due to deliquescence

deliquescent drug mixtures; diluents, various; storage trials

Husa, W.J. and Macek, T.J., *J. Am. pharm. Ass., scient. Edn*, 1942, *31*, 213–16

Incompatibilities in prescriptions V. The use of tribasic calcium phosphate and silica gel in capsules to prevent liquefaction

deliquescent drug mixtures; diluents, calcium phosphate, silica gel; storage trials

Bellafiore, I.J., *J. Am. pharm. Ass., pract. Pharm. Edn*, 1953, *14*, 580–2

Stabilization of capsules of eutectic mixtures against liquefaction

aspirin, caffeine citrate, camphor, phenazone; diluent, kaolin; eutectic mixtures; storage

Boger, W.P. and Gavin, J.J., *New Engl. J. Med.*, 1959, *261*, 827–32

An evaluation of tetracycline preparations

tetracyclines; diluents, citric acid, dicalcium phosphate, glucosamine and lactose; 4.4.6.1

Jacobs, P., *Pharm. Weekbl. Ned.*, 1964, *99*, 719–21

Filling of capsules with voluminous substances (in Dutch)

powder compression devices; powder properties, bulk density

Czetsch-Lindenwald, H.V. and Tawashi, R., *Pharm. Ind., Berl.*, 1965, *27*, 146–51

Tests with hard gelatin capsules (in German)

glidant, fumed silica; nomogram, fill-weight, capsule size determination; 3.8.2.4; 3.8.3.6

Czetsch-Lindenwald, H.V. and Asker, A.F., *Pharm. Ind., Berl.*, 1966, *28*, 614–16

Lubricants for filling hard gelatin capsules (in German)

lubricants, various; powder properties, flow measurements; product weight uniformity

Zoglio, M.A., Maulding, H.V., Haller, R.M. and Briggen, S., *J. pharm. Sci.*, 1968, *57*, 1877–80

Pharmaceutical heterogeneous systems III. Inhibition of stearate lubricant induced degradation of aspirin by the use of certain organic acids

acetylsalicylic acid; lubricant, magnesium stearate; stability, effect of formulation

Czetsch-Lindenwald, H.V., *Auxilary products for oral solid dosage forms*, Symposium (Barcelona, Faculty of Pharmacy, University of Barcelona), 1969, 143–9

Influence of lubricants on the accuracy of fill of capsules (in Spanish)

lubricants, aluminium stearate, magnesium stearate, polyethylene glycol, silicon dioxide, talc; powder properties, flow, effect of lubricants; product weight uniformity, effect of lubricants; storage, high humidity, effect of lubricant

Delonca, H., Puech, A., Segura, G. and Youakim, Y., *J. Pharm. Belg.*, 1969, *24*, 317–31

Influence of excipients and conditions of storage on the stability of medicines. II. Capsules of acetylsalicylic acid (in French)

aspirin; diluents, calcium phosphate, calcium sulphate, maize starch, polyvinylpyrrolidone, sodium alginate; lubricant, talc; 3.8.3.7

Ito, K., Hitomi, M., Kaga, S.-I. and Takeya, Y., *Chem. pharm. Bull., Tokyo*, 1969, *17*, 1138–45

Studies on hard gelatin capsules II. The capsule filling on powders and effects of glidant by ring filling method-machine

diluents, lactose, starch; glidants, colloidal silicon dioxide, product weight uniformity, effect of formulation; 3.2.3.2

Fonner, D.E., Buck, J.R. and Banker, G.S., *J. pharm. Sci.*, 1970, *59*, 1587–96

Mathematical optimization techniques in drug product design and process analysis

formulation, processing, mathematical optimisation technique, Lagrangian analysis

Prista, L.N., Morgado, R.R., Fonseca, A. and Pinho, A.A., *Anais Fac. Farm. Porto*, 1970, *30*, 19–34

Studies on hard gelatin capsules I. Ease of filling with powders (in Portuguese)

filling materials, powder types, calcium carbonate, lactose, quinine hydrochloride, sodium chloride; lubricants, polyethylene glycol 4000, silicon dioxide, stearates, aluminium, magnesium, zinc; powder properties, flow, angles of repose, effect of lubricants

Samyn, J.C. and Jung, W.Y., *J. pharm. Sci.*, 1970, *59*, 169–75.

In vitro dissolution from several experimental capsule formulations

diluents, dibasic calcium phosphate, lactose, disintegrants, starch; lubricants, magnesium stearate, talc; 4.2.4

Caldwell, H.C. and Westlake, W.J., *J. pharm. Sci.*, 1972, *61*, 984–5

Magnesium lauryl sulfate, soluble lubricant

lithium carbonate; diluent, spray-dried lactose; lubricants, magnesium lauryl sulphate, magnesium stearate

Khalil, S.A. and Ali, L.M.M., *Acta pharm. suec.*, 1972, *9*, 563–72

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Some formulation factors affecting disintegration and dissolution of chloramphenicol capsules

chloramphenicol; diluents, calcium phosphate, lactose; lubricants, magnesium stearate, talc; 4.2.4

Caldwell, H.C. and Westlake, W.J., *Can. J. pharm. Sci.*, 1973, *8*, 50–3

Magnesium lauryl sulfate–soluble lubricant

lithium carbonate; diluent, lactose; lubricants, magnesium lauryl sulphate, magnesium stearate, sodium lauryl sulphate; powder properties, particle size determination, Coulter counter; 3.8.3.6; 4.2.4

Goodhart, F.W., McCoy, R.H. and Ninger, F.C., *J. pharm. Sci.*, 1973, *62*, 304–10

New *in vitro* disintegration and dissolution test method for tablets and capsules

diluents, microcrystalline cellulose, starch; lubricants, magnesium stearate, stearic acid; wetting agents, sodium lauryl sulphate; 4.2.4

Caldwell, H.C., *J. pharm. Sci.*, 1974, *63*, 770–3

Dissolution of lithium and magnesium from lithium carbonate capsules containing magnesium stearate

lithium carbonate; diluent, lactose; lubricants, magnesium lauryl sulphate, magnesium stearate, sodium stearate, stearic acid; product weight uniformity, comparison and effect of lubricants; wetting agent, sodium lauryl sulphate; 4.2.3.4

Newton, J.M. and Razzo, F.N., *J. Pharm. Pharmac.*, 1974, *26*, *Suppl.*, 30P–36P

The influence of additives on the *in vitro* release of drugs from hard gelatin capsules

nitrofurantoin, nitrofurazone, oxytetracycline dihydrate, tetracycline hydrochloride; diluents, lactose, sodium starch glycolate, starch; lubricant, magnesium stearate; wetting agent, sodium lauryl sulphate; 4.2.3.4

Varthalis, S. and Pilpel, N., *J. Pharm. Pharmac.*, 1976, *28*, 415–9

Anomalies in some properties of powder mixtures

paracetamol, oxytetracycline; diluent, lactose; powder properties, bulk density

Mony, C., Sambeat, C. and Cousin, G., *First International Conference of Pharmaceutical Technology*, (Paris, APGI, May 31–June 2, 1977), 1977, *II*, 98–108

Applications of the measure of force in the formulation and filling of hard gelatin capsules (in French)

diluents, celluloses, microcrystalline and granular, lactose, powder and microcrystalline, starches, maize, potato and rice, starch modified, sodium carboxymethyl starch; lubricants, magnesium stearate, talc; product weight uniformity, effect of diluents, lubricants; 3.2.3.3

Ryder, J. and Thomas, A., *J. Pharm. Pharmac.*, 1977, *29*, *Suppl.*, 63p

A comparison of the effectiveness of several disintegrants in capsules of 4-ethoxycarbonylphenoxy-2′-pyridylmethane (BRL 10614)

4-ethoxycarbonylphenoxy-2′-pyridylmethane; disintegrants, polyvinylpyrrolidone, cross-linked (Polyclar AT), sodium carboxymethylcellulose, low substituted (Nymcel ZSB16), sodium starch glycolate (Primojel), starch (maize); 4.2.3.4

Seager, H., *Mfg Chem.*, 1977, *48*(4), 25–35

Spray-coating bulk drugs aids dosage form production

drug availability, *in vivo*, human, serum levels, comparisons of dosage forms and formulations; powder properties, modification by spray-coating techniques

Kurihara, K. and Ichikawa, I., *Chem. pharm. Bull., Tokyo*, 1978, *26*, 1250–6

Effect of powder flowability on capsule-filling-weight-variation

diluents, microcrystalline cellulose, lactose, potato starch; lubricant, magnesium stearate; product weight uniformity, effect of formulation; 3.2.3.3

Liedtke, R., *German (BRD) Patent (offen.)* 2719156, 1978

Two compartment medical capsules

capsule, hard gelatin, two compartment; formulation, incompatible ingredients

Mendes, R.W., Masih, S.Z. and Kanumuri, R.R., *J. pharm. Sci.*, 1978, *67*, 1613–16

Effect of formulation and process variables on bioequivalency of nitrofurantoin I: Preliminary studies

nitrofurantoin; diluents, compressible sugar, lactose, mannitol; lubricant, magnesium stearate; 4.2.3.4

Small, L.E. and Augsburger, L.L., *Drug Dev. ind. Pharm.*, 1978, *4*, 345–72

Aspects of the lubrication requirements for an automatic capsule filling machine

diluents, microcrystalline cellulose, lactose, compressible starch; formulation of contents, effect on filling machine; lubricants, magnesium lauryl sulphate, magnesium stearate, stearic acid; 3.2.3.3

Beecham Group Limited, *French Patent* 2320731, 1979

Oral antibiotic–polyvinylpyrrolidone capsules, with short disintegration times and which are rapidly soluble

disintegrant, crospovidone

Kassem, A.A., Zaki, S.A., Mursi, N.M. and Tayel, S.A., *Pharmazie*, 1979, *34*, 86–91

Effect of certain additives on the dissolution rate of chloramphenicol

adsorbents, colloidal silicon dioxide, various grades; diluents, dextrose, lactose, sucrose; solid dispersions, method of manufacture, fusion; surface-active agents, natural, dehydrocholic acid, sodium deoxycholate; surface-active agents, synthetic, macrogol esters, macrogol ethers, sodium lauryl sulphate; 4.2.3.4

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Merle, C., Artaud, M. and Guyot-Hermann, A.M., *Farmaco, Edn prat.*, 1979, *34*, 210–19

Influence of glidants on the dissolution rate of acetylsalicylic acid in hard gelatin capsules (in French)

lubricants, hydrophilic, colloidal silicon dioxide (Aerosil, Levilite), hydrophobic, talc, magnesium stearate; powder properties, porosity, effects of lubricants, mechanism of action; 4.2.3.4

Stewart, A.G., Grant, D.J.W. and Newton, J.M., *J. Pharm. Pharmac.*, 1979, *31*, 1–6

The release of a model low-dose drug (riboflavine) from hard gelatin capsule formulations

diluents, dicalcium phosphate, kaolin, lactose, microcrystalline cellulose, modified starch, sodium bicarbonate, sodium carboxymethyl starch, starch; lubricant, magnesium stearate; 4.5.5

Shek, E., Ghani, M. and Jones, R.E., *J. pharm. Sci.*, 1980, *69*, 1135–42

Simplex search in optimisation of capsule formulation

diluent, lactose; formulation, mathematical optimisation technique, simplex method, level of disintegrant; disintegrant, maize starch; lubricant, stearic acid; powder properties, tapped bulk density, rate of consolidation; 4.2.3.4

Botzolakis, J.E., Small, L.E., and Augsburger, L.L., *Int. J. Pharmaceut.*, 1982, *12*, 341–9

Effect of disintegrants on drug dissolution from capsules filled on a dosator-type automatic capsule-filling machine

hydrochlorothiazide, paracetamol; diluent, dicalcium phosphate dihydrate; disintegrants, maize starch, sodium carboxymethylcellulose, sodium carboxymethyl starch, crospovidone; glidant, sodium silicoaluminate; 4.2.4.

Botzolakis, J.E. and Augsburger, L.L., *J. Pharm. Pharmac.*, 1984, *36*, 77–84

The role of disintegrants in hard-gelatin capsules

hydrochlorothiazide; diluents, dicalcium phosphate, lactose; disintegrants, croscarmellose types A and B, sodium carboxymethyl starch; lubricant, magnesium stearate; 3.2.3.3; 4.2.4

Stamm, A., Boymond, C. and Mathis, C., *Drug Dev. ind. Pharm.*, 1984, *10*, 355–80

Some aspects of the formulation of hard gelatin capsules

diluents, granulating materials, glycerol palmitostearate, hydrogenated castor oil, hydroxypropylmethylcellulose, methacrylic acid polymers, polyethylene glycol, polyvinylpyrrolidone; diluents, powders, lactose, microcrystalline cellulose, pregelatinised starch; glidant, colloidal silicon dioxide; lubricant, magnesium stearate; 4.2.3.4

Chowhan, Z.T. and Chi, L.-H., *Pharm. Technol.*, 1985, *9*(3), 84, 86, 90, 92, 94–97

Drug-excipient interactions resulting from powder mixing, I: Possible mechanisms of interaction with starch and its effect on drug dissolution

ketorolac tromethamine; diluents, lactose, starch, maize and pregelatinised; disintegrants, starch, maize and pregelatinised; drug, content uniformity, effect of lubricant mixing; lubricant, magnesium stearate; 4.2.2.1; 4.2.3.4

Chowhan, Z.T., and Chi, L.-H., *Pharm. Technol.*, 1985, *9*(4), 30, 32–33, 36, 38–41

Drug-excipient interactions resulting from powder mixing. II: Possible mechanisms of interactions with crospovidone and its effect on in vitro dissolution

ketorolac tromethamine; diluent, lactose; disintegrant, crospovidone; drug, content uniformity, effect of lubricant mixing; lubricant, magnesium searate; 4.2.2.1; 4.2.3.4

Mehta, A.M. and Jones, D.M., *Pharm. Technol.*, 1985, *9*(6), 52, 54–55, 58–60

Coated pellets under the microscope

coating machines, tablet pan, conventional and modified, fluidised bed; coating materials, ethyl cellulose, hydroxypropylmethyl cellulose; pellets, coated, method of manufacture; pellets, physical properties, surface characteristics by scanning electron microscopy, effects of, coating device, position of spray

O'Connor, R.E. and Schwartz, J.B., *Drug. Dev. ind. Pharm.*, 1985, *11*, 1837–57

Spheronisation II: Drug release from drug-diluent mixtures

chlorothiazide, chlorpheniramine maleate, quinidine sulphate, theophylline; diluents, microcrystalline cellulose, microcrystalline cellulose/carmellose sodium; drug availability, dissolution rate of pellets, effect of formulation; pellets, method of manufacture, wet granulation, extrusion, spheronisation; pellets, physical properties, density, friability, particle size

Anno, E. M. and Rees, J. E., *Fourth International Conference on Pharmaceutical Technology*, (Paris, APGI, June 3–5, 1986), 1986, *V*, 61–69

Release of phenytoin sodium from capsules containing two- and three-component mixes

phenytoin sodium; diluents, calcium sulphate dihydrate, lactose; lubricant, magnesium stearate; powder properties, state of mixture, scanning electron microscopy, X-ray microanalysis; 4.2.3.4

Ari-Ulubelen, A., Akbuğa, J., Bayraktar-Alpmen, G. and Gülhan, S., *Pharm. Ind., Berl.*, 1986, *48*, 393–395

Effect of formulation factors on the in vitro dissolution characteristics of phenytoin sodium capsules

phenytoin sodium; diluents, calcium sulphate dihydrate, lactose, maize starch, sodium sulphate; lubricants, colloidal silicon dioxide, magnesium stearate, talc; 4.2.3.4

Chowhan, Z.T. and Chi, L.-H., *J. pharm. Sci.*, 1986, *75*, 534–541

Drug-excipient interactions resulting from powder mixing, III: Solid state properties and their effect on drug dissolution

prednisone; diluents, calcium hydrogen phosphate, pregelatinised starch; disintegrants, pregelatinised starch, sodium starch glycolate; drug, content uniformity, effects of, formulation of contents, lubricant mixing; lubricant, magnesium stearate; 4.2.2.1; 4.2.3.4

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Chowhan, Z.T. and Chi, L.-H., *J. pharm. Sci.*, 1986, *75*, 542–545

Drug-excipient interactions resulting from powder mixing, IV: Role of lubricants and their effect on in vitro dissolution

ketorolac tromethamine; diluent, lactose; disintegrant, crospovidone; lubricants, magnesium stearate, sodium stearyl fumarate; 4.2.2.1.; 4.2.3.4

Kohri, N., Mori, K.-I., Miyazaki, K. and Arita, T., *J. pharm. Sci.*, 1986, *75*, 57–61

Sustained release of nifedipine from granules

binders, ethylcellulose, hydroxypropylmethylcellulose, hydroxypropylmethylcellulose phthalate; diluents, maize starch, microcrystalline cellulose; formulation, pH-dependent and pH-independent granules; 4.5.6.2

3.2.4.2 Formulation of Semi-solids

Centre de Recherches Marcel Midy, *Swiss Patent* 510550, 1971, through *Derwent Accession No.* 648585-BJ, 1969

Encapsulation process

diluents, fatty substances, non oxidisable, melting point 30–40°; filling machine, volumetric dosing

Broer, J., *Verpack.-Rdsch., Frankf.*, 1978, *28*, 706–7

The filling of liquids into hard gelatin capsules (in German)

capsules, comparison of hard and soft; filling, liquids and semi-solids, industrial scale; formulation, contents, liquid and semi-solid

Cuiné, A., Mathis, C., Stamm, A. and François, D., *Labo-Pharma Probl. Tech.*, 1978, *26*(274), 222–7

Filling hard gelatin capsules with viscous solutions of active principles. I – Preliminary studies – Excipients (in French)

capsule, sealing; excipients, oils and thickening agents; formulation properties, melting point, surface tension, viscosity; stability, effect of temperature and time

Cuiné, A., Mathis, C., Stamm, A. and François, D., *Labo-Pharma Probl. Tech.*, 1978, *26*(276), 421–30

Filling hard gelatin capsules with viscous solutions of active principles. II – Rheological study of fatty excipients (in French)

excipients, thixotropic mixtures; formulation properties, viscosity, thixotropic mixtures

Cuiné, A., Mathis, C., Stamm, A. and François, D., *Pharm. Ind., Berl.*, 1978, *40*, 654–7

The filling of viscous solutions of active materials into hard gelatin capsules (in German)

clofibrate, vitamin A; applications; capsule, sealing; excipients, oils and thickening agents; formulation properties, viscosity

Cuiné, A., Mathis, C., Stamm, A. and François, D., *Labo-Pharma Probl. Tech.*, 1979, No. 292, 863–8

Filling of hard gelatin capsules with viscous solutions (or suspensions) of active ingredients III. Formulation of active ingredients (in French)

active ingredients, powders and semi-solid materials; excipients, oils; filling machine, cold and hot filling; formulation properties, viscosity, effect of formulation; stability testing; thickening agents, colloidal silicon dioxide, waxes

François, D. and Jones, B.E., *Mfg Chem.*, 1979, *50*(3), 37, 38, and 41

Making the hard capsules with the soft centre

capsules, comparison of hard and soft; filling, liquids and semi-solids, small scale, industrial scale; formulation, contents, liquids and semi-solids, adjuvants and diluents; history; review

Boymond, C. and Mathis, C., *Second International Conference on Pharmaceutical Technology*, (Paris, APGI, June 3–5, 1980), 1980, IV, 93–103

A study of the influence of formulation on the release of ephedrine hydrochloride from hard gelatin capsules (in French)

excipients, hydrophobic, glycerides; formulation, delayed release; 4.2.3.4

Cuiné, A., Mathis, C. and Stamm, A., *Second International Conference on Pharmaceutical Technology*, (Paris, APGI, June 3–5, 1980), 1980, I, 66–76

Hard gelatin capsules with paste contents: study of the rheological properties and *in vitro* release of active principles (in French)

capsule, sealing; excipients, oils; formulation properties, viscosity, effect of formulation; thickening agents, colloidal silicon dioxide, waxes; 4.2.3.4

Hoechst UK Ltd, *British Patent* 1 572 226, 1980

Improvements in and relating to pharmaceutical preparations in solid unit dosage forms

diluents, polyethylene glycols, polyvinyl acetate; formulation of contents, prolonged release; thickeners, colloidol silicon dioxide, hydrogenated castor oil; 3.2.3.4; 4.2.4

Kreuter, J., Speiser, P.P. and Prasad, N.K., *Second International Conference on Pharmaceutical Technology*, (Paris, APGI, June 3–5, 1980), 1980, II, 103–8

In vitro release of different dosage forms of 8-methoxypsoralen

excipients, solvents, oleyl oleate, polysorbate 80; 4.2.3.2

Walker, S.E., Ganley, J.A., Bedford, K. and Eaves, T., *J. Pharm. Pharmac.*, 1980, *32*, 389–93

The filling of molten and thixotropic formulations into hard gelatin capsules

content uniformity, comparison of liquid and powder formulations; filling machine performance, effect of formulation; formulation, effect on dissolution rate, controlled-release and standard products; formulation, thermosetting and thixotropic mixtures, method of manufacture; product weight uniformity, comparison of liquid and powder formulations; 3.2.3.4; 4.3.3.4; 4.2.3.6

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Lilly Industries Ltd, *British Patent* 1 590 864, 1981

Thixotropic filling medium for hard gelatin capsules

diluents, review of; physical properties, of contents, surface tension, viscosity, effect of formulation

François, D., Denmat, A., Waugh, A. and Woodage, T., *Pharm. Ind., Berl.*, 1982, *44*, 86–9

The *in vitro* and *in vivo* availability of phenylpropanolamine from oil/paste formulations in hard gelatin capsules

phenylpropanolamine; diluents, powders, lactose; diluents, semi-solids, hydrophilic, Labrafil M 2130 BS, lipophilic, arachis oil/beeswax; formulation of contents, semi-solids, prolonged release; 4.5.6.2

Hunter, E., Fell, J.T., Sharma, H. and McNeilly, A. -M., *Pharm. Ind., Berl.*, 1982, *44*, 90–1

The "in vivo" behaviour of hard gelatin capsules filled with thixotropic liquids

diluent, polyethylene glycol 1000; physical properties, viscosity of contents, effect of thickener; thickener, colloidal silicon dioxide; 4.4.3

Mathis, C. and Cuiné, A., *Labo-Pharma Probl. Tech.*, 1983, *31*, 935–43

Formulation, stability and *in vitro* availability of active principles as solutions or viscous suspensions filled in hard gelatin capsules (in French)

capsule sealing; excipients, natural and synthetic, physical properties; formulation, physical properties, effect of formulation, addition of colloidal silicon dioxide; 4.2.3.4

François, D., Chapter VI, in *The Capsule, Basics, Technology and Biopharmacy*, a *Modern Dosage Form* (in German), Fahrig, W. and Hofer, U. (Eds), Stuttgart, Wissenschaftliche Verlagsgesellschaft mbH, 1983, pp. 112–26

Liquid and paste filling into hard gelatin capsules (in German)

clofibrate, phenylpropanolamine, vitamin E, examples; 3.2.3.4

Bauer, K.H. and Dortunc, B., *Drug Dev. ind. Pharm.*, 1984, *10*, 699–712

Non-aqueous emulsions as vehicles for capsule fillings

caffeine, chloramphenicol, salicylic acid, sodium salicylate; diluents, polyethylene glycol, propylene glycol, rape seed oil, semi-solid triglyceride/wax mixtures; formulation, non-aqueous emulsions; 4.5.5

Djimbo, M. and Moës, A.J., *J. Pharm. Belg.*, 1984, *39*, 36–42

Release of drugs formulated as hard pastes filled into hard gelatin capsules. Part 1. Physical properties and *in vitro* testing

acetylsalicylic acid, theophylline; diluents, pastes, polyethylene glycols, suppository bases; paste properties, rheology, effect of formulation; disintegrants, Ac-Di-Sol, polyplasdone, sodium carboxymethyl starch; 4.2.3.4

Bowtle, W.J., Lucas, R.A. and Barker, N.J., *Fourth International Conference on Pharmaceutical Technology*, (Paris, APGI, June 3–5, 1986), 1986, *V*, 80–89

Formulation and process studies in semi-solid matrix capsule technology

fenoprofen, vancomycin; excipients, polyethylene glycols; excipients, physical properties, heating/cooling characteristics, rheology; fill materials, physical properties; semi-solid filling, process characteristics; 3.8.3.7; 4.5.5

Chatham, S.M., Newton, J.M. and Walker, S.E., *Fourth International Conference on Pharmaceutical Technology*, (Paris, APGI, June 3–5, 1986). 1986, *II*, 213–20

The influence of thermal history on the morphology of PEG 4000

polyethylene glycol 4000, structure, measurement by differential scanning calorimetry and X-ray crystallography, effect of thermal history

Hagenlocher, M., Hannula, A.M., Wittwer, F., Soliva, M. and Speiser P., *Fourth International Conference on Pharmaceutical Technology*, (Paris, APGI, June 3–5, 1986), 1986, *I*, 398–405

Hard gelatin capsules for rectal drug delivery

paracetamol; diluents, Labrafil M2130 BS, M2735 BS, Miglyol 812, Witepsol H15; 3.5.2; 4.5.3.4

Mathis, C. and Heimendinger, J., *Fourth International Conference on Pharmaceutical Technology*, (Paris, APGI, June 3–5, 1986), 1986, *V*, 90–98

Test of programming the release of active principles from pasty excipients in hard gelatin capsules (in French)

aspirin; excipients, Gelucires, Labrafils, Precirol, Simulsols; 4.2.3.4

3.3 Capsules, Soft Gelatin

3.3.1 General References

Baum, E., *Chemikerzeitung*, 1952, *76*, 847–50

The gelatin capsule, an economic packaging form (in German)

applications; manufacture

Kipphan, K., *Chemie-Ingr.-Tech.*, 1952, *24*, 299–301

The gelatin capsule, its manufacture and its use (in German)

applications; manufacture

Brass, H., *Pharm. Ind., Berl.*, 1954, *16*, 421–4

The gelatin capsule, its manufacture and pharmaceutical significance (in German)

applications; manufacture

Kipphan, K., *Dt. ApothZtg*, 1955, *95*, 1032–6

Gelatin capsules (in German)

applications; manufacture

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Clemow, J., *Mfg Chem.*, 1957, *28*, 170–2
Gelatin capsules – 50 million a week
applications; manufacturing method, rotary die

Müller, G., *Fette Seifen Anstr-Mittel*, 1960, *62*, 395–9
The manufacture of gelatin capsules (in German)
applications; capsule properties; formulation of shell; manufacture, seamed capsules, automatic and semi-automatic machines

Müller, G., *Mfg Chem.*, 1961, *32*, 63–6
Methods and machines for making gelatin capsules
formulation, shell; manufacture, seamed and seamless capsules

Widmann, A., *Pharm. Weekbl. Ned.*, 1961, *96*, 669–71
The manufacture of gelatin capsules (in Dutch)
applications; manufacture

Clemow, J., *Labo-Pharma.*, 1962, *10*(104), 63–7
Soft gelatin capsules (in French)
applications; history; manufacture

Müller, G., *Pharm. Ztg, Berl.*, 1962, *107*, 444–6
Soft gelatin capsule – machines (in German)
manufacture, industrial scale, seamed and seamless capsules

Genet, H., *Capsules et Gélules*, Symposium (Paris, Faculty of Pharmacy, University of Paris), 1970, *I*, 1–28
The soft gelatin capsule (in French)
capsules, enteric; filling; history; manufacture, seamed and seamless; pharmacopoeial standards; raw materials, standards; requirements

Torrado Valeiras, J.J., *Monitor Farm. Terap.*, 1970, *76*, 181–4
Soft gelatin capsules (in Spanish)
applications; manufacture

Widmann, A., *Pharma Int.*, 1970, No. 1, 5–10
Soft gelatin capsules
applications, oral, rectal, vaginal, veterinary; manufacturing method, rotary die; pharmacopoeial standards; properties; storage, packaging, stability

Stephan, D., *Packung Transp. chem. Ind.*, 1975, No. 12, 2–4
Soft gelatin capsules: Convenience and optimum form for bitter medicines (in German)
applications; manufacturing method, rotary die

Hellberg, N., *Farmaceutisk Revy*, 1977, *76*, 30–1
Soft capsules – not only easy to swallow . . . (in Swedish)
applications; drug availability; manufacture

Maconachie, S., *Mfg Chem.*, 1977, *48*(8), 33, 35–6, 39
Soft gelatin capsules in product development
drug availability, *in vivo*; formulation, contents; stability

Stephan, D., *Packung Transp. chem. Ind.*, 1979, No. 4, 188
Soft gelatin capsules not only for medicines (in German)
applications, chemical and cosmetic; manufacturing method, rotary die

Baes, E. A., *Mfg Chem.*, 1981, *52*(3), 33–4
Soft shell capsules
applications; drug availability; manufacture; market analysis

Berry, I.R., *Drug Cosmet. Ind.*, 1982, *131*, 40
One-piece, sealed soft gelatin capsules—why tamper resistant
applications; packaging

Seager, H. *Pharm. Technol.*, 1985, *9*, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104
Soft gelatin capsules: a solution to many tabletting problems
applications; drug availability, *in vivo*, comparison with other dosage forms; manufacturing method, rotary die; physical properties, comparison with drugs and tablets; stability, effects of storage

3.3.2 Manufacturing and Filling Soft Capsules

3.3.2.1 Seamed Capsules

Scherer, R.P., *British Patent* 395 546, 1933
Method of and apparatus for making capsules
manufacturing method, rotary die

Ravenscroft, E.A. and Young, F.H., assigned to Abbott Laboratories, *U.S. Patent* 2 205 837, 1940
Capsule making machine
capsule identification, by embossing; manufacturing method, rotary die

Scherer, R.P., *U.S. Patent* 2 199 210, 1940
Method and apparatus for making capsules by needle injection
capsule fill, liquid; capsule filling, needle injection; manufacturing method, rotary die

Waring, O.I., assigned in part to Rothberg, P., *U.S. Patent* 2 199 425, 1940
Method and means for making capsules
capsule fill, solid, semi-solid, liquid; manufacturing method, rotary die

Ravenscroft, E.A., assigned to Abbott Laboratories, *U.S. Patent* 2 279 505, 1942
Capsule making machine
capsule fill, liquids; manufacturing method, rotary die

Anon., *Mfg Chem.*, 1955, *26*, 56–8
Pharmaceutical processing of aureomycin
tetracyclines; capsule fill, powder; manufacturing method

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Cooke, C.H., assigned to Upjohn Company, *U.S. Patent* 3 081 234, 1963

Elimination of entrapped air in elastic capsules

capsule fill, granules and powders; manufacturing method, rotary die; processing conditions

Anon., *Mfg Chem.*, 1965, *36*(9), 65

Encapsulating machine for soft shell products

manufacturing method, rotary die

Kath, A.W., assigned to R.P. Scherer Corp., *U.S. Patent* 3 269 088, 1966

Opposed gelatin sheets pressed together after filling

manufacturing method, rotary die; processing conditions

Berry, I.R., *Drug Cosmet. Ind.*, 1984, *134*(4), 26–8, 30, 84–5

Process validation for soft gelatin capsules

capsule properties, seam thickness, wall thickness, weight uniformity; manufacturing method, rotary die, process conditions; product weight uniformity

3.3.2.2 Seamless Capsules

Merrill, E.C., Reddie, J.W. and Anderson, J.M., assigned to United Drug Company, *U.S. Patent* 2 275 154, 1942

Method for making capsules

manufacturing method, extrusion

Plourde, N.N., assigned to Gunnell Capsulations, Inc., *U.S. Patent* 2 692 404, 1954

Seamless moulded capsule

capsule shell composition, gelatin and gelatin substitute; manufacturing method, injection moulding; processing conditions

Briess, P., *Mfg Chem.*, 1961, *32*, 275

The "drop" method of capsule manufacture

manufacturing method, drop

Moreland, S.T., *U.S. Patent* 4 028 024, 1977

Manufacture of filled capsules or the like

capsule shell composition, moisture content; machine; manufacturing method, extrusion, gelatin low moisture content

3.3.3 Formulation of Soft Capsules

3.3.3.1 Capsule Shells

Patterson, S.J. and Lerrigo, A.F., *Q. J. Pharm. Pharmac.*, 1947, *20*, 83–6

Betanaphthol in gelatin capsules – its use as a preservative, with a method for its determination

preservative, betanaphthol, effect of storage on concentration

Scherer, J.O., assigned to R.P. Scherer Corporation, *U.S. Patent* 2 628 916, 1953

Process of preparing molten gelatin solution

manufacture, preparation bubble-free gelatin solution; manufacture, process for applying vacuum

Weidenheimer, J.F. and Callahan, F.M., assigned to American Cyanamid Company, *U.S. Patent* 2 770 553, 1956

Soft gelatin encapsulation

plasticisers, acetamide, formamide

Stanley, J.P. and Bradley, C.W., assigned to R.P. Scherer Corporation, *U.S. Patent* 2 870 062, 1959

Acid treated high Bloom gelatin

gelatin, manufacture, acid-treated bone; gelatin, properties, high Bloom, low viscosity; plasticisers

American Cyanamid Company, *British Patent* 1 037 463, 1966

Surface dyeing and pigment marking of gelatin capsules

colour, surface dyeing; formulation, printing inks; identification, colour, imprinting

Mima, H., Noda, E. and Banba, H., assigned to Takeda Chemical Industries, Limited, Japan, *U.S. Patent* 3 456 051, 1969

Protection against humidity by addition of buffer

gelatin film composition, inclusion of buffer; stability, protection of contents

R.P. Scherer Corporation, *British Patent* 1 252 200, 1971

Improved gelatine capsules

capsule shell properties, mechanical strength, moisture resistance; gelatin film composition, additives, glycerol, silicone fluid; 3.4.2.2

Rolle, F.J., assigned to R.P. Scherer Corporation, *U.S. Patent* 3 653 934, 1972

Gastro-resistant capsules

gelatin film composition (non-enteric), additives, glycerol, silicone fluid; 3.4.2.2

Hom, F.S., Veresh, S.A. and Miskel, J.J., *J., pharm. Sci.*, 1973, *62*, 1001–6

Soft gelatin capsules I: factors affecting capsule shell dissolution rate

gelatin, Bloom strength, type; plasticisers, glycerol, hexaglycerol, sorbitol; solution enhancers, lysine hydrochloride, urea; 4.2.3.1

Tanabe Seiyaku Company Limited, *Japanese Patent* 7 310 522, 1973, through *Derwent Accession No.* 19506U-AB,1969

Soft capsules

capsule properties, mechanical strength, solubility, stability; drug release, enteric and non-enteric capsules; gelatin film, composition

Hom, F.S., Veresh, S.A. and Ebert, W.R., *J. pharm. Sci.*, 1975, *64*, 851–7

Soft gelatin capsules II: oxygen permeability study of capsule shells

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pigments, titanium dioxide; plasticisers, decaglycerol, glycerol, hexaglycerol, sorbitol; 3.8.2.3

Hom, F.S., *Drug Dev. ind. Pharm.*, 1984, *10*, 275–87

Soft gelatin capsules III: an accelerated method for evaluating the dissolution stability of various gel formulations

plasticisers, glycerol, sorbitol; solution enhancers, 1-histidine, semicarbazide; 4.2.3.1

Armstrong, N.A., James, K.C., Collet, D. and Thomas, M., *Drug Dev. ind. Pharm.*, 1985, *11*, 1859–68

Solute migration from oily solutions into glycerol-gelatin mixtures

gelatin film composition, additives, glycerol; solute migration, measurement into glycerogelatin column from oily solution; solute migration, effect of composition of glycerogelatin base, nature of solutes

3.3.3.2 Formulation of Contents of Soft Capsules

Kreuger, P., assigned to N.V. Moutsuikerindustrie and Extractiebedrijf Maltostase, *U.S. Patent* 2 580 683, 1951

Aqueous fills of sugar syrup

contents, syrup vehicles; gelatin film composition, additives, glycerol, sugar; stability, protection of contents

Kurtz, W.M., assigned to Upjohn Company, *U.S. Patent* 3 126 321, 1964

Soft gelatin capsules

oleaginous vehicle, formulation, oil and purified cellulose; stability, protection of contents

Hom, F.S. and Miskel, J.J., *J. pharm. Sci.*, 1970, *59*, 827–30

Oral dosage form design and its influence on dissolution rates for a series of drugs

diluents, polyethylene glycol 400, polyol-surfactants, non-ionic; 4.2.3.2

Hom, F.S. and Miskel, J.J., *Lex & Sci.*, 1971, *8*(1), 18–26

Enhanced dissolution rates for a series of drugs as a function of dosage form design

diluents, polyethylene glycol 400, polyol-surfactant, non-ionic; 4.2.3.2

Cardini, C. and Stacchini, A., *Boll. chim.-farm.*, 1973, *112*, 104–9

Studies of availability of certain drugs in oral pharmaceutical dosage forms (in Italian)

diluents, beeswax, hydrogenated vegetable oils, polyethylene glycol 400 and 4000, polysorbate 81, soya lecithin, vegetable oils; 4.2.3.2

R.P. Scherer Corporation, *British Patent* 1 341 121, 1973

Soft gelatin capsule containing a fill of high water content

capsule fill, liquid, gel-lattice vehicles, high water content; manufacturing method, rotary die

R.P. Scherer Ltd, *German (BRD) Patent (Offen.)* 2 513 601, 1975, through *Derwent Accession No.* 67705W/41, 1974

Gelatin capsules containing cardiac glycosides

cardiotonic glycosides; contents, solutions in dimethylacetamide, dimethylformamide, polyethylene glycol

Wellcome Foundation Ltd, *German (BRD) Patent (Offen.)* 2 507 635, 1975, through *Derwent Accession No.* 59151W/36, 1974

Digoxin solutions in capsule forms

capsules: digoxin; drug availability *in vivo*, comparison of dosage forms; formulation of contents, organic solvent solution; formulation of shell, plasticisers; manufacturing method, rotary die

Bobbé, D., Mathis, C., Stamm, A., Metziger, P. and Gabler, W., *Labo-Pharma Probl. Tech.*, 1976, *24*(258), 879–85

Study of the stability of oily suspensions in soft gelatin capsules (in French)

capsule fill, physical properties, effect of formulation; diluents, vegetable oils and waxes; powder properties, particle size distribution, specific surface area; stability of suspensions, sedimentation rate, effect of formulation; suspension, dicalcium phosphate; 3.8.3.7

Bobbé, D., Mathis, C., Stamm, A., Metziger, P. and Widmann, A., *First International Conference on Pharmaceutical Technology*, (Paris, APGI, May 31–June 2, 1977), 1977, *V*, 109–19

Study of the influence of several excipients and adjuvants on the dissolution rate of amidopyrine from soft gelatin capsules (in French)

amidopyrine; diluents, arachis oil, beeswax, dimethicones, Labrafils, Miglyol, polyethylene glycols; formulation of shell; surfactants, soya lecithin, Tweens; 4.2.3.4

Eckert, T. and Kemper, F., assigned to Kali-Chemie Pharma GmbH, *German (BRD) Patent (Offen.)* 2 631 214, 1978

Increasing the solubility of poorly soluble pharmaceuticals for their application in gelatin capsules

diluents, glycerol mono-oleate, monoglycerides of C_{12-18} fatty acids

Springolo, V., *Boll. chim.-farm.*, 1978, *117*, 113–21

The bioavailability of formulations of erythromycin base and stearate in gastric-resistant soft gelatin capsules (in Italian)

erythromycin, base, stearate; diluents, beeswax, fractionated coconut oil, hydrogenated vegetable oil, liquid paraffin, vegetable oil; surfactants, sodium lauryl sulphate, soya lecithin; 3.4.2.2; 4.4.7.1

Stelle, V., Haslam, J., Yata, N., Okada, H., Lindenbaum, S. and Higuchi, T., *J. pharm. Sci.*, 1978, *67*, 1375–7

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Enhancement of bioavailability of a hydrophobic amine antimalarial by formulation with oleic acid in a soft gelatin capsule

diluents, oleic acid; 4.4.4.1

D'Onofrio, G.P., Oppenheim, R.C., and Bateman, N.E., *Int. J. Pharmaceut.*, 1979, *2*, 91–9

Encapsulated microcapsules

diluents, ethyl acetate, light liquid paraffin; formulation, controlled-release granules; manufacture, microencapsulation with ethyl cellulose; 4.2.3.6

R.P. Scherer Corporation, *German (BRD) Patent* 2 135 801, 1979

Soft gelatin capsules with aqueous filling in moisture equilibrium with shell

capsule shell, composition; contents, water-soluble polypeptides, polysaccharides, edible synthetic polymers; formulation of contents, high moisture content; manufacturing method, rotary die

Laboratories Negma, *French Patent* 2 500 302, 1982

Novel pharmaceutical compositions of indomethacin (in French)

indomethacin; diluents, hydrophilic, polyethylene glycols, lipophilic arachis oil, beeswax, hydrogenated soya oil, partially hydrogenated vegetable oils; surfactants, Tween 80; 4.5.5

Richard, J. and Andermann, G., *Pharm. Acta Helv.*, 1982, *57*, 116–21

A study of the stability of cyclandelate in soft gelatin capsules (in French)

diluents, polyethylene glycol 400; 3.8.3.7

Aiache, J.-M., Roca, R., Bastide, J., Bastide, M. and Kantelip, J.-P., *J. Pharm. Belg.*, 1983, *38*, 5–21

Biopharmaceutical study of indomethacin new drug dosage forms (in French)

indomethacin; diluents, hydrophilic, polyethylene glycols, lipophilic, arachis oil, beeswax, partially hydrogenated vegetable oils, soya oil; 4.5.5

Bateman, N.E. and Uccellini, D.A., *J. Pharm. Pharmac.*, 1984, *36*, 461–4

Effect of formulation on the bioavailability of retinol, D-α-tocopherol and riboflavine

retinol, D-α-tocopherol, riboflavine, diluents, Aqua-Biosorb, soya oil; 4.4.4.1

Schmidt, P.C. and Stockebrand, B., *Pharm. Res.*, 1986, *3*, 230–34

Capsules with prolonged action, II. Capsule filling by a gelation process

codeine, theophylline; excipients, triethyl citrate, ethylcellulose, polyethylene glycol 400, sesame oil; formulation of contents, physical properties, phase diagram, rheology; formulation of contents, prolonged release, formation of matrix by gelatin; 4.2.3.6

Serujuddin, A.T.M., Sheen, P-C. and Augustine, M.A., *J. pharm. Sci.*, 1986, *75*, 62–4

Water migration from soft gelatin capsule shell to fill material and its effect on drug solubility

drug, water insoluble; diluents, polyethylene glycol 400, Gelucine 44/14; drug solubility, determination, effects of encapsulation, comparison of hard and soft gelatin capsules; encapsulation, method, rotary die; formulation, physical properties, melting point

3.3.3.3 Protective Coatings for Soft Capsules

Yen, E.C. and Stirn, F. E., assigned to American Cyanamid Co., *U.S. Patent* 2 727 833, 1955

Washing and coating composition

coating compositions, moisture resistant, non-tacky; coating formulation; coating method, dipping

Vance, J.J. and Yen, E.C., assigned to American Cyanamid Company, *U.S. Patent* 2 770 571, 1956

Barrier layer of beta pinene polymer

coating compositions, protection of contents; coating formulation, β-pinene polymer; coating method, inside surface gelatin film

A. Nattermann & Co., *French Patent* 1 559 913, 1969, through *Derwent Accession No.* 37 929, 1967

Gelatin capsules coated with methacrylic acid/methyl methacrylate copolymer

coating compositions, heat resistant, sticking prevention; coating formulation, copolymer methacrylic acid/methyl methacrylate, plasticiser; coating method, by spraying

Ciba S.A., *Belgian Patent* 757 715, 1971, through *Derwent Accession No.* 283865-AB, 1969

Hydroxypropylmethyl cellulose coated gelatin capsules

coating materials, ethyl cellulose, hydroxypropylmethylcellulose, polyalkalene glycol, shellac; coating method, spray application; storage, tropical conditions

Engelking, C., assigned to A. Nattermann & Cie, GmbH, *U.S. Patent* 3 592 945, 1971

Increasing heat resistance by coating with copolymer

coating compositions, heat and moisture resistant; coating formulation, anionic copolymer and plasticiser; coating method, spraying

Ciba-Geigy, A. G., *British Patent* 1 324 242, 1973

Coated gelatine capsules and a process for their manufacture

capsule properties, moisture resistance; coating, formulation; coating method, coating pan, fluidised-bed spray technique

3.4 Capsules, Enteric

3.4.1 Gastric Resistant Shells

Bogin, H.H., assigned to Parke, Davis & Co., *U.S. Patent* 2 575 789, 1951

Process and apparatus for manufacturing capsules

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capsules, hard gelatin: capsule shell composition, gelatin, metal salt partial ester polycarboxylic acid and cellulose ester; manufacturing method, dipping

Parke, Davis & Co., *British Patent* 672 814, 1952

Process and apparatus for manufacturing of capsules

capsules, hard gelatin: capsule shell composition, cellulose acetate phthalate, gelatin; manufacturing method, dipping

Golovkin, V.A. and Skorik, V.M., *Farmatsiya, Mosk.*, 1972, *21*, 20–2

On the formulation of entero-soluble gelatin capsules (in Russian)

capsules, soft gelatin: chloramphenicol; capsule shell composition, ammonium cellulose acetate phthalate, gelatin; drug availability, *in vitro*, disintegration testing; manufacture, small scale, seamless capsules

Parke, Davis & Co., *Belgian Patent* 802 585, 1973, through *Derwent Accession No.* 03496V-AB, 1972

Keratinised pharmaceutical capsules

capsules, hard gelatin: capsule shell composition, gelatin, hydroxypropylmethylcellulose phthalates; formulation of capsule film; manufacturing method, dipping

Hirai, M. and Shimizu, T., assigned to Parke, Davis & Co., *U.S. Patent* 3 826 666, 1974

Enteric capsules

capsules, hard gelatin: capsule shell composition, gelatin, hydroxypropylmethylcellulose phthalate; manufacturing method, dipping

Lilly Industries Ltd, *Dutch Patent* 7 401 812, 1974, through *Derwent Accession No.* 62413V/35

Capsules insoluble at low pH

capsules, hard gelatin: applications, catalysts, pharmaceuticals, textiles, water softeners; capsule shells, two-layer; capsule shell composition, gelatin layer, enteric layer; manufacturing method, dipping

Susai, M., *Japanese Patent Application No.* 9 116 219, 1974, through *Derwent Accession No.* 15108W/09, 1973

Enteric capsule preparations

capsules, soft gelatin: capsule shell composition, casein, cellulose acetate phthalate, gelatin, hydroxypropylmethylcellulose phthalate, latex

Lilly Industries Ltd, *British Patent* 1 455 884, 1976

Improvements in the production of capsules

capsules, hard gelatin: capsule shells, two-layer; capsule shell composition, gelatin layer, enteric layer; manufacturing method, dipping

Okajima, Y., *German (BRD) Patent (Offen.)* 2 616 748, 1976

Capsules soluble in the intestinal fluids

capsules, two-piece: formulation of shell, gelatin or hydroxypropylmethylcellulose and cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, methacrylate polymers; manufacturing method

3.4.2 Coatings for Enteric Capsules

3.4.2.1 General References

Dumez, A.G., *J. Am. pharm. Ass.*, 1921, *10*, 372–6

A contribution to the history of the development of the enteric capsule

capsules, hard and soft gelatin and pills: enteric coating, materials, methods; history

Lesser, M.A., *Drug Cosmet. Ind.*, 1941, *49*, 151–5, 161

Enteric coatings

capsules and tablets: coating, methods and materials, review; disintegration testing, *in vitro*, *in vivo*, review

Keefer, C.S., *J. Am. pharm. Ass., pract. Pharm. Edn*, 1945, *6*, 210–15

Status of oral penicillin

capsules, hard gelatin: penicillin; enteric, materials and methods

Kanig, J.L., *Drug Stand.*, 1954, *22*, 113–21

Production and testing of enteric coatings

capsules and tablets: disintegration testing, *in vitro*, *in vivo*, critical review

Parrott, E.L., *J. Am. pharm. Ass.*, 1961, *NS1*, 158–9

An extemporaneous enteric coating

capsules, hard gelatin: acetylsalicylic acid, potassium iodide; coating materials, *n*-butyl stearate/carnauba wax/stearic acid and cellulose acetate phthalate; coating method, small scale, hand dipping; 4.5.6.1

Smith, G. and Cox, P.H., *Pharm. J.*, 1963, *190*, 245–6

Enteric-coated capsules of cobalt chloride

capsules, hard gelatin: cobalt chloride; coating materials, cellulose acetate phthalate, salol, shellac; coating method, hand dipping; disintegration testing, modified *B.P.* method; formulation, coating

Morgado, R.R., Pinho, A.A. and Prista, L.N., *Anais Fac. Farm. Porto*, 1970, *30*, 47–53

Studies on gelatin capsules III – The treatment of capsules to make them gastric resistant (in Portuguese)

capsules, hard gelatin: coating materials, cellulose acetate phthalate, formaldehyde; coating methods, dipping; disintegration method, *U.S.P.* XVII; disintegration testing, comparison of coating methods; formulation, coating, plasticisers, solvents

Gumma, A. and Mirimanoff, A., *Pharm. Acta Helv.*, 1971, *46*, 278–89

Study of several pharmaceutical procedures applied to therapeutics of substitution by *Lactobacillus acidophilus* (in French)

capsules, hard gelatin and tablets, film-coated: *Lactobacillus acidophilus*; coating materials, cellulose acetate phthalate, formaldehyde, methacrylic polymers; coating method; disintegration testing, oscillating tube apparatus, comparison of methods

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Cognyl, G., *Labo-Pharma Probl. Tech.*, 1974, No. 230, 249–51

Hard gelatin capsules and gastric resistance (in French)

capsules, hard gelatin: coating, materials, methods, testing; formulation of contents, gastric resistance; review

3.4.2.2 Formaldehyde Treatment of Capsules

Weyland, J., *Apothekerzeitung, Berl.*, 1931, *46*, 470–3

Hardened gelatin capsules (in German)

capsules, hard and soft gelatin: drug availability, *in vitro*, disintegration; gelatin, reaction with formaldehyde; history; manufacturing methods

Glassman, J.A., *U.S. Patent* 3 186 910, 1965

Method for producing peroral capsules

capsules, hard gelatin: drug release, variable, enteric, non-enteric parts; filling machine, multiple joining of capsules; formaldehyde treatment by spraying

Glassman, J.A., *U.S. Patent* 3 228 789, 1966

Peroral capsules and tablets and the method for making same

capsules, hard gelatin: drug release, variable, enteric and non-enteric parts; formaldehyde solutions, alcoholic, aqueous; formaldehyde treatment by dipping

Biorex Laboratories Ltd, *British Patent* 1 093 286, 1967

Improvements in or relating to dosage unit forms for the administration of medicaments and diagnostic agents

capsules, hard gelatin: capsules, insoluble shells; coating method, immersion; drug release, by pressure from pyloric sphincter; formulation of contents

Boymond, P., Sfiris, J. and Amacker, P., *Pharm. Ind., Berl.*, 1966, *28*, 836–42 and *Drugs Germ.*, 1967, *10*, 7–19

The manufacture and testing of enterosoluble capsules (in German; English translation in *Drugs Germ.*)

capsules, hard gelatin: coating method, formaldehyde vapour, heat treatment, dipping in silicone resin and shellac; stability testing, effect of relative humidity; 4.2.2.2; 4.4.7.1

R.P. Scherer Corporation, *British Patent* 1 252 200, 1971

Improved gelatine capsules

capsules, hard and soft gelatin: formulation of shell; manufacturing method; 3.3.3.1

Rolle, F.J., assigned to R.P. Scherer Corporation, *U.S. Patent* 3 653 934, 1972

Gastro-resistant capsules

capsules, soft gelatin: coating method, coating pan; formulation, formaldehyde solution; 3.3.3.1

Springolo, V., *Boll. chim.-farm.*, 1978, *117*, 113–21

The bioavailability of formulations of erythromycin base and stearate in gastric-resistant soft gelatin capsules (in Italian)

capsules, soft gelatin: coating method, immersion; 3.3.3.2; 4.4.7.1

3.4.2.3 Natural Coatings for Enteric Capsules

Stoklosa, M.J. and Ohmart, L.M., *J. Am. pharm. Ass., pract. Pharm. Edn*, 1953, *14*, 507, 514–15

Enteric coatings in dispensing pharmacy. 2. A practical method of extemporaneous enteric coating

capsules, hard gelatin and pills: sodium salicylate; coating materials, *n*-butyl stearate-carnauba wax; coating method, hot dipping; enteric coat, stability on storage, effects of plasticisers, thickness of coat; formulation; coating, plasticisers; 4.4.7.1

Mercer, W.G., *Australas J. Pharm.*, 1955, *36*, 1169

Enteric coated capsules of cobalt chloride

capsules, hard gelatin: cobalt chloride; coating materials, beeswax, salol; coating method, hand dipping; disintegration testing

3.4.2.4 Synthetic Coatings for Enteric Capsules

Volwiler, E.H., assigned to Abbott Laboratories, *U.S. Patent* 1 690 760, 1928

Enteric coated capsules

capsules, hard gelatin: coating materials, cellulose ester, nitrocellulose; coating method, dip coating

Caldwell, H.C. and Rosen, E., *J. pharm. Sci.*, 1964, *53*, 1387–91

New air suspension apparatus for coating discrete solids

capsules, hard gelatin, granules and tablets: coating material, cellulose acetate phthalate; coating method, fluidised-bed spray technique, capsule presealing with coat applied in coating pan

Cook, C.H. and Webber, M.G., *Am. J. Hosp. Pharm.*, 1965, *22*, 95–9

An extemporaneous method of preparing enteric-coated capsules

capsules, hard gelatin: coating materials, cellulose acetate phthalate, polyvinyl acetate resins; coating method, immersion; formulation, coating, plasticisers, solvents; 4.5.6.1

Rothgang, G., *Pharm. Ind., Berl.*, 1967, *29*, 869–70

The coating of hard gelatin capsules with Eudragit L and S for preparations resistant to gastric juice (in German)

capsules, hard gelatin: coating materials, methylacrylic polymers; coating method, coating pan, spray application; disintegration testing, *Ger. P.* (DAB 7); formulation, coating, plasticisers, solvents; product sealing, banding

Wolkoff, H.N., Pinchuk, G. and Shapiro, P.H., *J. pharm. Sci.*, 1968, *57*, 317–21

Design and evaluation of a miniature air-suspension coating apparatus

capsules, hard gelatin and tablets: coating material, cellulose acetate phthalate; coating method, fluidised-bed spray technique

Jones, B. E., *Mfg Chem.*, 1970, *41*(5), 53–4, 57

Production of enteric coated capsules

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capsules, hard gelatin: coating materials, cellulose acetate phthalate, methacrylic polymers; coating method, fluidised-bed spray technique; manufacturing methods, review; pharmacopoeial standards; physical stability testing

Sanol-Arzneimittel Dr. Schwarz GmbH, *Belgian Patent* 750379, 1970, through *Derwent Accession No.* 84509R-AB, 1969

Gelatin capsules resistant to gastric juice which dissolve when in small intestine

capsules, hard gelatin: coating materials, carboxyvinyl polymer, hydroxymethylpropylcellulose, polyvinylpyrrolidone; coating method, coating pan

Eckert, T., Cordes, G. and Seidel, R., *Arzneimittel-Forsch.*, 1971, *21*, 1403–6

Release of active substances from enteric-coated gelatin capsules *in vivo* and *in vitro*. Part 4. Study with the pH radiotransmitter in man (in German)

capsules, hard gelatin: coating film, measurement of thickness; coating material, cellulose acetate phthalate; coating method, fluidised-bed spray technique; formulation, coating; 4.5.2

Dedukh, N.G., Khanina, G.I., Pospelova, V.V., Kryazher, V.N., Shniger, N.U., Marko, O.P. and Bronshtein, A.S., *Farmatsiva, Mosk.*, 1972, *21*, 16–19

Characteristics of acid-proof gelatin capsules (in Russian)

capsules, hard gelatin: coating materials, cellulose acetate phthalate; enteric coating, comparison coating materials, storage

Ekberg, L. and Källstrand, G., *Svensk farm. Tidskr.*, 1972, *76*, 375–8

The enteric coating of hard gelatin capsules on a dispensary scale (in Swedish)

capsules, hard gelatin: coating materials, cellulose acetate phthalate; coating method, modified air-suspension technique; formulation, coating, plasticisers, solvents; 4.5.6.1

Festa, B., *French Patent* 2137170, 1972, through *Derwent Accession No.* 14835U-B, 1971

Coating process with gastric juice-resistant solution for gelatin capsules

capsules, hard gelatin: coating materials, cellulose acetate phthalate; coating method, coating pan under reduced pressure

Green Cross Corporation, *French Patent* 2118883, 1972, through *Derwent Accession No.* 74600T-B, 1970

Enteric coating of hard capsules – after pre-sealing with aqueous organic solvent mixtures

capsules, hard gelatin: capsule sealing, spraying with volatile organic solvent/water; coating materials, cellulose acetate phthalate; coating method, spraying

Aiache, J.-M., Vidal, J.L., Aiache, S., Jeanneret, A. and Cornat, F., *Labo-Pharma Probl. Tech.*, 1974, *22*(232), 457–63

Methods for the biopharmaceutical testing of enteric capsules: Test with "enterocaps" capsules (in French)

capsules, hard gelatin: coating material, cellulose acetate phthalate; coating method, coating pan, airless spray; enteric coating, materials, methods, review; 4.4.7.1; 4.5.6.1

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Gelatin capsules soluble in small intestines

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Eckert, T., Cordes, G. and Ollenschläger, G., *Pharm. Ind., Berl.*, 1976, *38*, 836–41

Release of active substances from enteric-coated gelatin capsules *in vitro* and *in vivo*. Part 5. Study with films of cellulose acetate phthalate (CAP) and hydroxypropylmethylcellulose phthalate (HP-50) (in German)

capsules, hard gelatin: coating materials, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate; coating method, fluidised-bed spray technique; coating quantities and thickness; formulations, coating, plasticisers, solvents; 4.5.2

Evans, B.K., Fenton-May, V.G. and Lee, M.G., *J. clin. Pharm.*, 1979, *4*, 173–7

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capsules, hard gelatin: coating material, cellulose acetate phthalate; coating method, coating tower; formulation, coating

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New small scale apparatus for enteric coating of hard gelatin capsules

capsules, hard gelatin: coating materials, cellulose acetate phthalate, methyl acrylic polymers; coating method, dipping, mechanical device, bench-scale; formulation, coating, plasticiser, triacetin, solvents, acetone, ethyl acetate/isopropyl alcohol; 4.2.2.2

Rhodes, J. and Evans, B.K., *International Patent* WO 83/00435, 1983

Orally administrable pharmaceutical compositions

capsules, hard gelatin: coating materials, methacrylic acid polymers; coating method, modified air-suspension technique; formulation, coating, plasticisers, solvents; 4.4.3; 4.4.7.2

Werchan, D., *Pharmazie*, 1984, *39*, 275–6

Film coating of gelatin capsules in the dispensary (in German)

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capsules, hard gelatin: coating materials, cellulose acetate phthalate, polyvinyl acetate phthalate; coating method, coating pan, bench-scale; formulation, coating, plasticiser, propylene glycol, solvents, acetone, dichloromethane; 4.2.2.2

3.5 Capsules, Non-oral

3.5.1 Inhalation Capsules

Fisons Pharmaceuticals Ltd, *British Patent* 1 182 779, 1970

Inhaler for finely powdered medicaments

capsules, hard gelatin: inhalation device

Fisons Pharmaceuticals Limited, *U.S. Patent* 3 507 277, 1970

Oral inhalation powdered medicament device for pierceable capsule

capsules, hard gelatin: inhalation device

Bell, J.H., Hartley, P.S. and Cox, J.S.G., *J. pharm. Sci.*, 1971, *60*, 1559–64

Dry powder aerosols 1: a new powder inhalation device

capsules, hard gelatin: aerosol powder, generating system; powder properties, particle size

ISF S.P.A., *Belgian Patent* 821 152, 1975, through *Derwent Accession No.* 29075W/18, 1974

Portable inhaler for powdered medicaments

capsules, hard gelatin: inhalation device

Chowhan, Z.T. and Amaro, A.A., *J. pharm. Sci.*, 1977, *66*, 1254–8

Powder inhalation aerosol studies I: selection of a suitable drug entity for bronchial delivery of new drugs

capsules, hard gelatin: 7-methylsulphinyl-2-xanthone carboxylic acid and sodium salt; drug availability, *in vitro*, air sampling device; drug availability, *in vitro*, effects of, formulation, moisture content, particle size; powder properties, cohesiveness, particle size; 3.8.3.4

Hallworth, G.W., *Br. J. clin. Pharmac.*, 1977, *4*, 689–90

An improved design of powder inhaler

capsules, hard gelatin and inhaler, aerosol: salbutamol sulphate; drug availability, *in vitro*, multi-stage liquid impinger, comparison of devices

Chowhan, Z.T. and Linn, E.E., *Int. J. Pharmaceut.*, 1979, *3*, 117–26

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capsules, hard gelatin: 7-methylsulphinyl-2-xanthone carboxylic acid, labelled, unlabelled; drug availability, *in vitro*, comparison of methods, air sampling device, rat lung model; drug availability, *in vitro*, effects of, dose, formulation, inhalation pattern; formulation of contents

Crompton, G.K., *Eur. J. respir. Dis.*, 1982, *63*, 96–9

Clinical use of dry powder systems

capsules, hard gelatin: inhalation device; comparison of products

Pover, G.M., Browning, A.K., Mullinger, B.M., Butler, A.G. and Dash, C.H., *Practitioner*, 1982, *226*, 565–7

A new dry powder inhaler

capsules, hard gelatin: inhalation device, patient preference study

3.5.2 Rectal and Vaginal Capsules

Widmann, A., *Pharm. Ind., Berl.*, 1960, *22*, 348–52

Rectal gelatin capsules (in German)

capsules, soft gelatin: paracetamol; formulation of contents, excipients; rectal use; 4.4.4.4

Fichsel, H., *Kinderärztl. Prax.*, 1963, *31*, 245–50

Experiences with a new antipyretic and analgesic in a new rectal capsule form (in German).

capsules, soft gelatin: phenacetin; salicylamide; rectal use; 4.4.4.4

Widmann, A. and Bauer, K.H., assigned to R.P. Scherer GmbH, Germany, *U.S. Patent* 3 197 369, 1965

Rectal capsule-coating from homogeneous melt of emulsifying agent and lubricating substance

capsules, soft gelatin: coating compositions, lubrication for rectal insertion; coating formulation, emulsifying agent and lubricant; coating method, coating pan; rectal use

Bauer, K., assigned to Ciba Corp., *U.S. Patent* 3 432 594, 1969

Rectal capsule-coating of 1:1 methylcellulose and acrylic acid polymer

capsules, soft gelatin: coating compositions, hydrophilic, non-tacky; coating formulations, gel forming; coating method, pill coating machine; rectal and vaginal use

Widmann, A., assigned to R.P. Scherer GmbH, Germany, *U.S. Patent* 3 467 748, 1969

Rectal capsule-coating of polyethylene glycol and polyvinyl acetate

capsules, soft gelatin: coating compositions, lubrication for rectal insertion; coating formulation, polyethylene glycol or emulsifiable substance and polyvinyl acetate; coating method, coating pan, revolving drum; rectal use

Akzo, N.V., *Dutch Patent* 7 302 521, 1974, through *Derwent Accession No.* 65689V/37

Foaming effervescent capsules

capsules, hard gelatin: capsule shell composition, gelatin, polyethylene oxides, carbohydrate; formulation, contents, effervescent mixture, foaming agent; rectal and vaginal use

Hunger, G., assigned to E.R. Squibb & Sons, Inc., *U.S. Patent* 3 886 940, 1975

Capsule

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Feprazone. Bioavailability in a new suppository preparation

capsules, soft gelatin: rectal use; 4.4.4.4

Carp, G.B., Chemtob, C. and Chaumeil, J.C., *Second International Conference on Pharmaceutical Technology*, (Paris, APGI, June 3–5, 1980), 1980, V, 68–80

Availability from rectally administered solid dosage forms: use of rectal soft gelatin capsules (in French)

capsules, soft gelatin: capsule shape; formulation, contents, shell; rectal use; 4.2.4

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Formulation of highly available theophylline rectal suppositories

capsules, soft gelatin: theophylline, anhydrous, monohydrate; rectal use; 4.5.3.4

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A three-day study with miconazole gelatin capsules in vaginal candidosis

capsules, soft gelatin: miconazole; drug, clinical effects; vaginal use

Möller, H., *Pharm. Ind., Berl.*, 1984, *46*, 514–20

In vitro and in vivo dissolution of rectal indomethacin dosage forms (in German)

capsules, soft gelatin: formulation, contents; rectal use; 4.5.3.4

Hagenlocher, M., Hannula, A.M., Wittwer, F., Soliva, M. and Speiser, P., *Fourth International Conference on Pharmaceutical Technology,* (Paris, APGI, June 3–5, 1986), 1986, *I*, 398–405

Hard gelatin capsules for rectal drug delivery

capsules, hard gelatin; coating compositions, lubrication for rectal insertion; coating formulation, sealing coat, Eudragit, gliding coat, macrogols; coating method; fluidised bed spray coater; rectal use; 3.2.4.2; 4.5.3.4

3.6 Packaging of Capsules

3.6.1 Unit-dose Packaging

Samuels, T.M. and Guthrie, D.L., *Am. J. Hosp. Pharm.*, 1966, *23*, 5–11

Unit dose packaging. A new machine for strip packaging tablets and capsules

capsules and tablets: packaging materials, moisture permeability; strip packaging machine, swell scale

Angele, M.M., *Chem. Rdsch.*, 1972, *25*, 125–6, 128

The blister packing and strip packing of Parke-Davis pure gelatin capsules (in German)

capsules, hard gelatin: blister packaging machines; packaging materials, permeability, moisture and gases; strip packaging machines

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The presentation of dispensed tablets and capsules

capsules, hard and soft gelatin and tablets: dispensing containers; safety

Dean, D.A., *Pharm. J.*, 1972, *209*, 238–41

Unit packaging of tablets and capsules

capsules, hard and soft gelatin and tablets: blister packaging, machines, materials; strip packaging, machines, materials

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Part II. Hermetic packaging of drugs: optimized sealing of foil pouches

capsules, hard gelatin: blister packaging machine operating conditions; packaging materials, foil laminate specifications; strip packaging, sealing efficiency, effect of sealing temparature

Reamer, J.T. and Grady, L.T., *Am. J. Hosp. Pharm.*, 1978, *35*, 787–93

Moisture permeation of newer unit dose repackaging materials

capsules and tablets: unit-dose systems, comparison of products, American market; storage testing, moisture permeation rate determinations

Gupta, V.D., Stewart, K.R. and Gupta, A., *Am. J. Hosp. Pharm.*, 1980, *37*, 165, 169

Stability of oral solid drugs after repackaging in single-unit containers

capsules and tablets: packaging materials; strip packaging machine, small scale; 3.8.3.7

3.6.2 Bulk Packaging

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A new high in packaging efficiency. A striking improvement in the automatic packaging of tablets, coated tablets, and gelatin capsules

capsules, gelatin and tablets, plain and sugar-coated: packaging equipment, automatic machinery

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pharmaceutical products: containers, high density polyethylene; official products, United States; seals, metal screw caps; 3.8.3.4; 3.8.3.7

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Automation in pharmaceutical packaging with reference to tablets, sugar coated tablets and capsules

capsules and tablets: packaging materials, review

Li Wan Po, A., Morland, I. and Robins, L., *J. clin. Pharm.*, 1977, *2*, 131–5

Chemical cross-contamination in the pharmacy

capsules, hard gelatin: cross-contamination, identification and quantification, thin-layer chromatography; dispensing, automatic counting machines, cross-contamination; tablet friability, effect on cross-contamination

3.7 Capsule Standards

3.7.1 General References

Kern, W., *Pharm. Ind., Berl.*, 1956, *18*, 474–93

The importance of the gelatin capsule as a dosage form in different countries. The appropriate pharmacopoeia or codex for the manufacturing of these medicines (in German)

capsules, hard and soft gelatin: manufacture, industrial scale; pharmacopoeial products; pharmacopoeial standards

Kuhn, T., *Pharm. Ztg, Berl.*, 1963, *108*, 130–5, 195–8

The testing of gelatin capsules (in German)

capsules, hard and soft gelatin: gelatin; manufacture; pharmacopoeial standards; 3.1

Jones, B.E. and Törnblom, J.-F.V., *Pharm. Acta Helv.*, 1975, *50*, 33–45

Gelatin capsules in the pharmacopoeiae

capsules, hard and soft gelatin: review, official compendia, worldwide

3.7.2 Official Standards

Europe: European Pharmacopoeia, 2nd Edn, Part II, 57160 Sainte-Ruffine, France, Maisonneuve S.A., 1984

Capsulae, Capsules, First Fascicule pp. 16–16-3

disintegration; uniformity of mass

Countries that have adopted the standards of the European Pharmacopoeia include Austria, Belgium, Britain, Denmark, Eire, Finland, France, Germany (West), Greece, Iceland, Italy, Luxembourg, Netherlands, Norway, Spain, Sweden, Switzerland

India: Pharmacopoeia of India, 3rd Edn, Delhi, Controller of Publications, 1985

Capsules, Vol. 2, pp. 91–2

content of active ingredient; disintegration; uniformity of weight

Japan: Pharmacopoeia of Japan, 10th Edn, Tokyo, Ministry of Health and Welfare, 1981

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disintegration test; weight variation

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odour; solubility; acidity or alkalinity

Jugoslavia: Pharmacopoea Jugoslavica, 4th Edn, Belgrade, Izdanje Saveznog zavoda za zdravstvenu zaštitu, 1984

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content uniformity; disintegration; weight uniformity

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Capsulae, Capsule, pp. 161–2

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disintegration; weight uniformity

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Capsules, p. 1335

acid neutralising capacity (pp. 1192–3); disintegration (pp. 1242–3); dissolution (pp. 1243–4); packaging (pp. 1240–1); uniformity of dosage units (*Suppl.* 1, pp. 1909–1910)

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dimensions; disintegration; solubility; solution, clarity; weight uniformity

3.8 Properties of Capsules

3.8.1 General References

U.S. Government Printing Office, Federal Specification, U-C-115b. Capsule, Gelatin, 1958

capsules, hard gelatin: definition; inspection, procedures; packaging, requirements; tests, acid solubility, appearance, colour, water resistance

Anon., *Fr.-Pharm.*, 1967, *20*, 27–31

Capsules of pure gelatin. Tests on hard gelatin capsules (in French)

capsules, hard gelatin: capsule shell permeability, gases, moisture; capsule volumes

Marquardt, H.-G., *Fr.-Pharm.*, 1970, *23*, 13–15

Influence of chemical components, light, temperature and moisture on Parke, Davis hard gelatin capsules (in French)

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The determination of ampicillin and penicillin G as contaminants in tetracycline and erythromycin solid dosage forms

capsules and tablets: erythromycin, estolate, ethylsuccinate, stearate, tetracycline hydrochloride (capsules); identification, contamination by ampicillin, penicillin G

Kammerl, E., Chapter X in *The Capsule, Basics, Technology and Biopharmacy, a Modern Dosage Form* (in German), Fahrig, W. and Hofer, U. (Eds), Stuttgart, Wissenschaftliche Verlagsgesellschaft mbH, 1983, pp. 181–95.

Quality control in the manufacture of capsule preparations (in German)

capsules: industrial methods and systems

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Process validation for hard gelatin capsules

capsules, hard gelatin: industrial scale filling, process control methods, validation

3.8.2 Properties of Capsule Shells

3.8.2.1 Colouring Agents

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Identification in pharmaceutical preparations of authorised synthetic organic colorants (in French)

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capsules, hard gelatin, granules and syrups: dyes, extraction, predigestion with trypsin, formation quaternary ammonium complexes; dyes, identification, chromatography, thin-layer

Alary, J., Luu Duc, C. and Coeur, A., *Bull. Trav. Soc. Pharm. Lyon*, 1966, *10*, 78–86

Identification of synthetic colouring materials in several pharmaceutical preparations (in French)

capsules, hard and soft gelatin and tablets, film- and sugar-coated: dyes, extraction, solvent; dyes, identification, chromatography, paper, thin-layer; products, France

Brustier, V., Bourbon, P., Amselem, A., Achor, G., Casabonne, M. and Ferrand, J.C., *Annls pharm. Fr.*, 1966, *24*, 51–6

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capsules, hard and soft gelatin, granules, ointments, solutions, suppositories, syrups and tablets, coated and plain: dyes, extraction, formation quaternary ammonium complexes; dyes, identification, chromatography, thin-layer, silica gel

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Rapid isolation of synthetic colorants for their identification from gelatin capsules. Applications to other pharmaceutical forms (in French)

capsules, hard gelatin, granules, powders and tablets, sugar-coated: dyes, extraction, ion-exchange paper; dyes, identification, chromatography, thin-layer, cellulose

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capsules, hard and soft gelatin and tablets, sugar-coated: dyes, extraction, powder adsorption; dyes, identification, chromatography, thin-layer; products, Germany (BRD)

Smith, H.L., *J. pharm. Sci.*, 1974, *63*, 639–41

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capsules, soft gelatin: capsules, surface dyeing process; dyes, water-soluble, sorption rates on capsules; formulation of shell

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pharmaceuticals: colorant properties, review

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capules: dye extraction, adsorption on activated charcoal; dyes, identification, chromatography, high pressure liquid

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3.8.2.2 Moisture Content of Shells

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Humidity in flexible gelatin capsules

capsules, soft gelatin: capsule deformation test, apparatus; capsule pliability, relationship to moisture content, effect of storage

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Water vapour sorption and diffusion through hard gelatin capsules

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capsules, hard gelatin: capsule shells, dimensions, effect of relative humidity on; moisture content, effect of relative humidity on; storage conditions

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Investigation of hard gelatin capsules, part II: Measurement of the moisture content by continuous increase of the humidity (in German)

capsules, hard gelatin: capsule shells, formulation, colorants, titanium dioxide; gelatin properties, sol/gel transformation, effect of humidity; moisture content, effect of relative humidity on, relationship to capsule shell formulation

3.8.2.3 Physical Properties of Shells

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An apparatus for determination of breaking strength of packaging materials

ampoules, capsules, hard and soft gelatin: impact tester; hard gelatin capsules, breaking force; soft gelatin capsules, pliability, effect of plasticiser concentration

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Gas permeability of hard gelatin capsules (in German)

capsules, hard gelatin: gas permeability measurements, carbon dioxide, ethylene oxide, effects of, capsule coating, pressure, temperature; capsule coating, methacrylic acid polymer; sterilisation, gaseous, ethylene oxide/carbon dioxide mixture; 3.8.3.3

3.8.2.4 Physical Specifications of Shells

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Determination of thickness of walls of hard gelatin capsules by radioisotopic means

capsules, hard gelatin: capsule shells, wall thickness; manufacture, industrial scale; thickness measurements, radioactive tracers

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Tests with hard gelatin capsules (in German)

capules, hard gelatin: capsule volumes, weights; 3.2.4.1; 3.8.3.6

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Why and how to fill capsules (in French)

capsules, hard gelatin: capacity, dimensions, weight; 3.2.3.2

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Objective visual evaluation of the relative content of major and minor defects in tablets and capsules

capsules and tablets: product appearance defects; visual assessment, sampling methods, viewing procedure

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Automated capsule inspection method

capsules, hard gelatin: visual faults, classification; visual faults, inspection, automatic by light projection, T.V. cameras

3.8.3 Properties of Capsule Products

3.8.3.1 Uniformity of Content

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Selection, evaluation, and control of the assay of the pharmaceutical product I. Reproducibilities of assay and drug recovery from dosage forms

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Comparison of criteria for content uniformity

capsules, hard and soft gelatin and tablets: comparison of criteria, statistical evaluation, computer simulation

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The consequences of content-uniformity requirements for production (in German)

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Analytical studies in the stability of medicines packed in gelatin capsules (in Roumanian)

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The shelf life of some antibiotic preparations stored under tropical conditions

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A comparison of the stability of commercial cephradine and cephalexin capsules

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Study on the influence of light and colorants on the stability of nifedipine capsules (in Italian)

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A study of the stability of cyclandelate in soft gelatin capsules (in French)

cyclandelate; comparison of batches, effects of storage; 3.3.3.2

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4.2.1 Reviews

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capsules and tablets: disintegration testing, apparatus; dissolution testing, apparatus

4.2.2 Disintegration

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A study of the disintegration of pharmaceutical preparations for oral administration (in Italian)

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Preliminary norms for the disintegration, solubility and other characteristics of solid dosage forms as well as the manufacturing of the official preparations (in German)

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Czetsch-Lindenwald, H.V., *Pharm. Ind., Berl.*, 1962, *24*, 110–14

The disintegration of gelatin capsules (in German)

capsules, hard and soft gelatin: disintegration testing, effects of, apparatus, capsule contents, capsule type, test media, test temperature; disintegration testing, enteric-coated products; disintegration testing, pharmacopoeial standards

Anon., *Med. Lett. Drug. Ther.*, 1963, *5*(24) 94–5

Tests of chloral hydrate

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4.2.3 Dissolution

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capsules, soft gelatin: dissolution method, *U.S.P.* XX basket; dissolution testing, effects of, formulation of capsule shell, moisture content of shell, storage; storage conditions, low humidity, elevated temperatures; 3.3.3.1

4.2.3.2 Comparative Dissolution of Dosage Forms

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capsules, hard gelatin and tablets: chloramphenicol, sulphathiazole, tetracycline hydrochloride; dissolution method, stirred flask; dissolution testing, effect of storage conditions; 3.8.3.7

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In vitro release of different dosage forms of 8-methoxypsoralen

capsules, hard gelatin and tablets: 8-methoxypsoralen; dissolution method, stirred flask; dissolution testing, effect of formulation; formulation of contents, adsorbates, solid dispersions, solutions; 3.2.4.2

4.2.3.3 Comparative Dissolution of Products

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Dissolution characteristics of capsule shells and drug release from commercial tetracycline-HCl capsules

capsules, hard gelatin: tetracycline hydrochloride; disintegration method, stirred flask; disintegration testing, measurement of shell rupture; dissolution method, *U.S.P.* XIX; dissolution testing, determination of dissolution rate constant, effects of, ionic strength and pH of dissolution medium, stirrer depth

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Further studies on the effect of additives on the release of drug from hard gelatin capsules

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The release of drugs from hard gelatin capsules

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The influence of starch and lactose on the release rates of drugs from hard gelatin capsules

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The effect of starch concentration on the release of phenobarbitone from hard gelatin capsules

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Dissolution of lithium and magnesium from lithium carbonate capsules containing magnesium stearate

capsules, hard gelatin: lithium carbonate; dissolution method, *U.S.N.F.* XIII; dissolution testing, effects of, formulation, magnesium dissolution rate, surface tension of test media; product weight uniformity, comparison and effect of lubricants; 3.2.4.1

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The influence of additives on the *in vitro* release of drugs from hard gelatin capsules

capsules, hard gelatin: nitrofurantoin, nitrofurazone, oxytetracycline dihydrate, tetracycline hydrochloride; dissolution method, beaker; dissolution testing, effect of formulation; 3.2.4.1

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Drug formulations

dissolution testing, effect of formulation; formulation of contents, diluent, sodium starch glycolate

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capsules, soft gelatin: amidopyrine; dissolution method, Sartorius apparatus; dissolution testing, comparison of formulations; 3.3.3.2

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Study using the apparatus of Stricker on the influence of several excipients and adjuvants on the dissolution rate of iron salts from soft gelatin capsules (in French)

capsules, hard and soft gelatin and tablets, sugar-coated: ferrous fumarate, sulphate; dissolution method, Stricker; dissolution testing, comparison of dosage forms, effect of formulation

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The dissolution rate of medicines from gelatin capsules (in Spanish)

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Extemporaneous reduction of commercial capsule dosage – Macrodantin

capsules, hard gelatin: nitrofurantoin; dissolution method, modified *U.S.P.* rotating basket; dissolution testing, effects of, capsule fill, capsule shell, formulation, test media; formulation of contents, diluents, lactose, starch

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A study of the dissolution and bioavailability of a hydrophobic drug

capsules, hard gelatin: griseofulvin; dissolution method, beaker, modified; dissolution testing, effect of hydrophilic coating; formulation of contents, hydrophilic treatment, particle coating by granulation, hydroxypropylcellulose; powder properties, intrinsic dissolution rate, measurement by non-disintegrating disk

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Effect of shear mixing on *in vitro* drug release of capsule formulations containing lubricants

capsules, hard gelatin: nitrofurantoin, procainamide hydrochloride; dissolution method, beaker; dissolution testing, effect of, processing conditions, mixer shear rates; formulation of contents, diluent, lactose, lubricants, magnesium lauryl sulphate, magnesium stearate

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The *in vitro* bioavailability of various drugs formulated as hard gelatin capsules

capsules, hard gelatin: imipramine, nitrofurantoin, nitrofurazone, oxytetracycline dihydrate, phenylbutazone, tetracycline hydrochloride; dissolution method, beaker; dissolution testing, effect of formulation; formulation of contents, diluents, lactose, sodium starch glycolate, starch, lubricant, magnesium stearate, wetting agent, sodium lauryl sulphate

Newton, J.M. and Razzo, F.N., *J. Pharm. Pharmac.*, 1977, *29*, 294–7

The influence of additives on the presentation of a drug in hard gelatin capsules

capsules, hard gelatin: nitrofurazone; dissolution method, modified beaker; dissolution testing, effect of formulation, statistical evaluation; formulation of contents, diluents, lactose, starch, lubricant, magnesium stearate, wetting agent, sodium lauryl sulphate

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A comparison of the effectiveness of several disintegrants in capsules of 4-ethoxycarbonylphenoxy-2′-pyridyl methane (BRL 10614)

capsules, hard gelatin: 4-ethoxycarbonylphenoxy-2′-pyridyl methane; dissolution method, stirred flask; dissolution testing, effects of, formulation, storage; filling machine, dosing tube mechanism; 3.2.4.1

Bastami, S.M. and Groves, M.J., *Int. J. Pharmaceut.*, 1978, *1*, 151–64

Some factors influencing the in vitro release of phenytoin from formulations

capsules, hard gelatin and tablets: phenytoin, phenytoin sodium; dissolution method, stirred flask; dissolution testing, effects of, drug particle size, formulation, pH test medium; formulation of contents, diluents, lactose, starch; powder properties, particle size

Geneidi, A.S., Ali, A.A. and Salama, R.B., *J. pharm, Sci.*, 1978, *67*, 114–16

Solid dispersions of nitrofurantoin, ethotoin, and coumarin with polyethylene glycol 6000 and their coprecipitates with povidone 25 000

capsules, hard gelatin: coumarin, ethotoin, nitrofurantoin; dissolution method, beaker; formulation of contents; solid dispersions, method of manufacture

Gurny, R., Boymond-Genoud, M. and Guitard, P., *J. Pharm. Belg.*, 1978, *33*, 6–10

Study of the influence of particle size and lactose on the dissolution of phenacetin and acetanilide capsules using a multiple regression method

capsules, hard gelatin: acetanilide, phenacetin; dissolution method, continuous flow; dissolution testing, effects of, drug particle size, formulation; formulation of contents, diluent, lactose; powder properties, particle size

Lerk, C.F., Lagas, M., Fell, J.T. and Nauta, P., *J. pharm. Sci.*, 1978, *67*, 935–9

Effect of hydrophilization of hydrophobic drugs on release rate from capsules

capsules, hard gelatin: hexobarbitone; coating materials, hydroxyethylcellulose, methycellulose; coating method, granulation; dissolution method, beaker; dissolution testing, effects of, hydrophilic coating of hydrophobic drug, surface tension of test medium; formulation of contents, hydrophilic coating; powder properties, contact angle, density, particle size

Mendes, R.W., Masih, S.Z. and Kanumuri, R.R., *J. pharm. Sci.*, 1978, *67*, 1613–16

Effect of formulation and process variables on bioequivalency of nitrofurantoin I: Preliminary studies

capsules, hard gelatin and tablets, chewable and standard: nitrofurantoin; dissolution method, beaker; dissolution testing, effects of, drug particle size, formulation of contents; 3.2.4.1

Kassem, A.A., Zaki, S.A., Mursi, N.M. and Tayel, S.A., *Pharmazie*, 1979, *34*, 86–91

Effect of certain additives on the dissolution rate of chloramphenicol

capsules, hard gelatin: chloramphenicol; dissolution method, beaker; dissolution testing, effect of formulation; formulation of contents, solid dispersions; 3.2.4.1

Kassem, A.A., Zaki, S.A., Mursi, N.M. and Tayel, S.A., *Pharm. Ind., Berl.*, 1979, *41*, 390–3

Chloramphenicol solid dispersion system I

capsules, hard gelatin: chloramphenicol; dissolution method, beaker; dissolution testing, effect of formulation; formulation of contents, solid dispersions, carbowaxes, polyvinylpyrrolidones; solid dispersions, method of manufacture

Merle, C., Artaud, M. and Guyot-Hermann, A.M., *Farmaco, Edn prat.*, 1979, *34*, 210–19

Influence of glidants on the dissolution rate of acetylsalicylic acid in hard gelatin capsules (in French)

capsules, hard gelatin: acetylsalicylic acid; dissolution method, continuous flow; dissolution testing, effects of formulation; 3.2.4.1

Ammar, H.O., Kassem, M.A., Salama, H.A. and El-Ridy, M.S., *Pharm. Ind., Berl.*, 1980, *42*, 757–60

On the dissolution of digoxin

capsules, hard gelatin, powders and tablets: digoxin; dissolution method, beaker, rotating basket; dissolution testing, capsule filled with solid dispersion, powders, effect of particle size, solid dispersions, effect of formulation; dissolution testing, comparison of capsules and tablets; formulation of solid dispersions, polyethylene glycols, polyvinylpyrrolidones

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Boymond, C. and Mathis, C., *Second International Conference on Pharmaceutical Technology*, (Paris, APGI, June 3–5, 1980), 1980, *IV*, 93–103

A study of the influence of the formulation on the release of ephedrine hydrochloride from hard gelatin capsules (in French)

capsules, hard gelatin: ephedrine hydrochloride; dissolution method, stirred flask; dissolution testing, effects of, capsule preparation, size, formulation, powder properties; stability, effect of formulation; 3.2.4.2

Cuine, A., Mathis, C. and Stamm, A., *Second International Conference on Pharmaceutical Technology*, (Paris, APGI, June 3–5, 1980), 1980, *I*, 66–76

Hard gelatin capsules with paste contents: study of the rheological properties and *in vitro* release of active principles (in French)

capsules, hard gelatin: acetylsalicylic acid, clofibrate, sodium salicylate; dissolution method, Sartorius apparatus, *U.S.P.* XVII modified; dissolution testing, effect of formulation; 3.2.4.2

Shek, E., Ghani, M., and Jones, R.E., *J. pharm. Sci.*, 1980, *69*, 1135–42

Simplex search on optimisation of capsule formulation

capsules, hard gelatin: dissolution method, stirred flask; dissolution testing, T_8 and T_{30} effects of formulation of contents; formulation, mathematical optimisation technique, simplex method, dissolution rate; 3.2.4.1

Walker, S.E., Ganley, J.A., Bedford, K. and Eaves, T., *J. Pharm. Pharmac.*, 1980, *32*, 389–93

The filling of molten and thixotropic formulations into hard gelatin capsules

capsules, hard gelatin: triamterene; dissolution method, *U.S.P.*; dissolution testing, comparison of liquid and powder formulations; formulation of contents, solid dispersion and solid solution; 3.2.3.4; 3.2.4.2; 4.2.3.6

York, P., *Drug Dev. ind. Pharm.*, 1980, *6*, 605–27

Studies of the effect of powder moisture content on drug release from hard gelatin capsules

capsules, hard gelatin: barbitone, sodium salt; dissolution method, modified beaker; dissolution testing, effect of powder properties; formulation of contents, diluents, lactose, maize starch; powder properties, contact angle, powder bed, liquid penetration and permeability; 3.8.3.4

Bremecker, K.-D. and List, P.H., *Pharm. Ind., Berl.*, 1981, *43*, 1026–8

The influence of relative humidity on drug release from hard gelatin capsules in vitro (in German)

capsules, hard gelatin: chlordiazepoxide, nortriptyline hydrochloride, pericyazine, procaine hydrochloride; capsule, contents and shells, moisture content, effect of relative humidity of storage; capsule shells, diffusion of contents, effects of hydrophilic/hydrophobic materials, moisture content; dissolution method, flow through cell; dissolution testing, effect of moisture content of capsule contents and shells

Doelker, E., Doelker, C. and Mordier, D., *J. Pharm. Belg.*, 1981, *36*, 404–11

The role of wetting on the release of hydrophobic drugs from hard gelatin capsules. I. Liquid diffusion through the wall and capillary penetration into the powder bed (in French)

capsules, hard gelatin: phenacetin; dissolution testing, effects of, powder wetting, test medium; formulation of contents; powder properties, particle size, wetting characteristics; 4.2.2.1

Mehta, A.M. and Augsburger, L.L., *Int. J. Pharmaceut.*, 1981, *7*, 327–34

A preliminary study of the effect of slug hardness on drug dissolution from hard gelatin capsules filled on an automatic capsule-filling machine

capsules, hard gelatin: hydrochlorothiazide; dissolution method, stirred flask; dissolution testing, effects of, formulation of contents, powder slug hardness; formulation of contents, diluents, lactose, microcrystalline cellulose, lubricant, magnesium stearate; 3.2.3.3

Miyazaki, S., Inoue, H. and Nadai, T., *Pharmazie*, 1981, *36*, 482–4

Effects of antacids on the dissolution of minocycline and demethylchlortetracycline from capsules

capsules, hard gelatin: demeclocycline, minocycline, antacids, adsorption and elution properties; antacids, aluminium silicate, magnesium aluminosilicate, magnesium trisilicate; dissolution method, rotating basket; dissolution testing, effect of antacids

Shah, K.A., Warren, J.W., Onwuelezi, G., Benmaman, J.D. and Monk, C.M., *Drug Dev. ind. Pharm.*, 1981, *7*, 683–91

In vitro release of hydrochlorothiazide from capsule formulations

capsules, hard gelatin: hydrochlorothiazide; dissolution method, rotating basket; dissolution testing, effect of formulation; formulation of contents, diluents, calcium hydrogen phosphate, lactose, maize starch, microcrystalline cellulose; product, content and weight uniformity

Akbuğa, J., Gülhan, S. and Bayraktar-Alpmen, G., *Pharmazie*, 1983, *38*, 478–80

Studies on flufenamic acid capsules and tablets

capsules, hard gelatin and tablets: flufenamic acid; disintegration testing, comparison of products (capsules); dissolution method, rotating basket; dissolution testing, comparisons of, dosage forms, products (capsules); formulation of contents, diluents, lactose, maize starch, lubricant, magnesium stearate, surfactant, sodium lauryl sulphate

Mathis, C. and Cuiné, A., *Labo-Pharma Probl. Tech.*, 1983, *31*(337) 935–43

Formulation, stability and *in vitro* availability of active principles as solutions or viscous suspensions filled in hard gelatin capsules (in French)

capsules, hard gelatin: acetylsalicylic acid, ferrous sulphate, sodium salicylate; dissolution method, modified disintegration

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apparatus; dissolution testing, effects of formulation, comparison of excipients; 3.2.4.2

Muhammad, N.A.H. and Newton, J.M., *J. Pharm. Pharmac.*, 1983, *35*, 345–9

The influence of pH of dissolution fluid and particle size of drug on the in-vitro release of drug from hard gelatin capsules

capsules, hard gelatin: acetysalicylic acid; dissolution method, modified beaker; dissolution testing, effects of pH test media, powder properties; powder properties, particle size

Armstrong, N.A., James, K.C. and Pugh, W.K.L., *J. Pharm. Pharmac.*, 1984, *36*, 357–60

An in-vitro investigation of drug availability from lipophilic solutions

capsules, soft gelatin: 4-hydroxybenzoic acid; dissolution method, partition/permeation apparatus; dissolution testing, comparison of encapsulated and free solutions, effects of, capsule shell, formulation of contents; formulation of contents, solvents, isopropyl myristate, 1-octanol

Armstrong, N.A., James, K.C. and Pugh, W.K.L., *J. Pharm. Pharmac.*, 1984, *36*, 361–5

Drug migration into soft gelatin capsule shells and its effect on in-vitro availability

capsules, soft gelatin: acetomenaphthone, ephedrine, 4-hydroxybenzoic acid, phenobarbitone; dissolution method, partition/permeation apparatus; dissolution testing, effects of, capsule shell, drug, partition coefficient and solubility, formulation of contents; drug migration in capsule shell, effect of manufacturing process; formulation of contents, solvents, isopropyl myristate, 1-octanol

Djimbo, M. and Möes, A.J., *J. Pharm. Belg.*, 1984, *39*, 36–42

Release of drugs formulated as hard pastes filled into hard gelatin capsules. Part 1. Physical properties and *in vitro* testing

capsules, hard gelatin and tablets: acetylsalicylic acid, theophylline; dissolution method, paddle; dissolution method, intrinsic value, theophylline products, rotating disk; dissolution testing, comparison of dosage forms, effect of formulation; formulation of contents, semi-solids; 3.2.4.2

Elbary, A.A., Fadel, H.M. and Nour, S.A., *Pharmazie*, 1984, *39*, 110–12

Dissolution rate of chloramphenicol from hard gelatin capsules as a function of type of adjuvants and methods of granulation

capsules, hard gelatin: chloramphenicol; dissolution method, rotating basket; dissolution testing, comparison of excipients, effects of, content type, formulation; formulation of contents, granules, by dry and wet granulation

Newton, J.M. and Muhammad, N.A.H., *J. Pharm. Pharmac.*, 1984, *36*, 42–4

The influence of agitation intensity, particle size and pH of dissolution fluid on the in-vitro release of drug from hard gelatin capsules

capsules, hard gelatin: acetylsalicylic acid; dissolution method, modified beaker; dissolution testing, effects of, agitation intensity, pH test media, powder properties; powder properties, particle size

Stamm, A., Boymond, C. and Mathis, C., *Drug Dev. ind. Pharm.*, 1984, *10*, 355–80

Some aspects of the formulation of hard gelatin capsules

capsules, hard gelatin and tablets: griseofulvin, tetracycline hydrochloride; dissolution method, paddle; dissolution testing, comparison of dosage forms; effects of, formulation of contents, porosity of fill; 3.2.4.1

Chowhan, Z.T. and Chi, L.-H., *Pharm. Technol.*, 1985, *9*(3), 84, 86, 90, 92, 94–97

Drug-excipient interactions resulting from powder mixing, I; Possible mechanisms of interaction with starch and its effect on drug dissolution

capsules, hard gelatin: ketorolac tromethamine; dissolution method, paddle; dissolution testing, effects of, formulation of contents, lubricant mixing; powder properties, particle interactions, scanning electron microscopy; 3.2.4.1; 4.2.2.1

Chowhan, Z.T. and Chi, L.-H., *Pharm. Technol.* 1985, *9*(4), 30, 32–33, 36, 38–41

Drug-excipient interactions resulting from powder mixing, II: Possible mechanisms of interaction with crospovidone and its effect on in vitro dissolution

capsules, hard gelatin: ketorolac tromethamine; dissolution method, paddle; dissolution testing, effects of, drug particle size, lubricant mixing; powder properties, particle interactions, scanning electron microscopy; 3.2.4.1; 4.2.2.1

Combes, A., Bonnet, L. and Rouffiac, R., *Pharm. Acta Helv.*, 1985, *60*, 203–8

The influence of excipients on the rate of release of two non-steroidal anti-inflammatory drugs from capsules (in French)

capsules, hard gelatin: acetylsalicylic acid, indomethacin; dissolution method, continuous flow; dissolution testing, effects of formulation of contents, excipient salt type; formulation of contents, diluents, calcium and sodium salts of glucuronic, lactic and sulphuric acid, lactose; results, factorial analysis

De Beukelaer, P. and Van Ooteghem, M., *s.t.p. Pharma*, 1985, *1*, 956–61

Influence of powder bed porosity and wettability on liquid penetration and on drug release of powder mixtures filled into hard gelatin capsules

capsules, hard gelatin: dissolution method, beaker; drug availability, effects of, capsule content properties, liquid penetration, porosity, wettability, formulation of contents; formulation of contents, diluent, lactose; powder properties, liquid penetration, application of Washburn equation

Anno, E.M. and Rees, J.E., *Fourth International Conference on Pharmaceutical Technology*, (Paris, APGI, June 3–5, 1986), 1986, *V*, 61–69

Release of phenytoin sodium from capsules containing two- and three-component mixes

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capsules, hard gelatin: phenytoin sodium; dissolution method, paddle; dissolution testing, effect of, formulation of contents, method of mixing of contents; drug, solubility and swelling; 3.2.4.1

Ari-Ulubelen, A., Akbuğa, J., Bayraktar-Alpmen, G. and Gülhan, *Pharm. Ind., Berl.*, 1986, *48*, 393–395

Effect of formulation factors on the in vitro dissolution characteristics of phenytoin sodium capsules

capsules, hard gelatin: phenytoin sodium; dissolution method, rotating basket; dissolution testing, effects of, formulation of contents, method of preparation, powder mixing, slugging; formulation of contents, comparison of excipients and lubricants; 3.2.4.1

Bowtle, W.J., *Br. J. pharm. Pract.*, 1986, *8*, 307–8

Semi-solid matrix capsules

capsules, hard gelatin: indomethacin; dissolution testing, effect of formulation; formulation of contents, semi-solid, excipients differing HLB values; 3.2.3.4; 3.8.3.4

Chowhan, Z.T. and Chi, L.-H., *J. pharm. Sci.*, 1986, *75*, 534–541

Drug-excipient interactions resulting from powder mixing. III: Solid state properties and their effect on drug dissolution

capsules, hard gelatin: prednisone; dissolution method, paddle; dissolution testing, effects of, formulation of contents, lubricant mixing; powder properties, particle interactions, scanning electron microscopy; 3.2.4.1; 4.2.2.1

Chowhan, Z.T. and Chi, L.-H., *J. pharm. Sci.*, 1986, *75*, 542–545

Drug-excipient interactions resulting from powder mixing, IV: Role of lubricants and their effect on in vitro dissolution

capsules, hard gelatin: ketorolac tromethamine; dissolution method, paddle; dissolution testing, comparison of lubricants, effect of lubricant mixing; powder properties, particle interactions, scanning electron microscopy; 3.2.4.1; 4.2.2.1

Mathis, C. and Heimendinger, J., *Fourth International Conference on Pharmaceuticl Technology*, (Paris, APGI, June 3–5, 1986), 1986, *V*, 90–98

Test of programming the release of active principles from pasty excipients in hard gelatin capsules (in French)

capsules, hard gelatin: aspirin; dissolution method, paddle; dissolution testing, effects of formulation; 3.2.4.2

Matthieu, A.M., van Ooteghem, M. and Ludwig, A., *Fourth International Conference on Pharmaceutical Technology*, (Paris, APGI, June 3–5, 1986), 1986, *V*, 55–60

The influence of the solubility of adjuvants on the release of hydrophobic medicaments in hard gelatin capsules (in French)

capsules, hard gelatin: phenacetin; disintegration and dissolution method, beaker: disintegration and dissolution testing, effects of, composition, pH and viscosity of test medium, formulation of contents; diluent and drug solubility, effect of pH; formulation of contents, diluents, dicalcium phosphate, lactose, saccharose, sodium chloride

4.2.3.5 Dissolution of Enteric Capsules

Jacob, M., Duru, C. and Puech, A., *Sciences Tech. pharm.*, 1979, *8*, 93–7

Preparation of fluoride dosage forms. In vitro control of the release of the active principle (in French)

capsules, hard gelatin and tablets, sugar-coated: sodium fluoride; capsule enteric coating, cellulose acetate phthalate; capsule, fill-weight and uniformity of fill; disintegration testing; dissolution method, Erweka; dissolution testing, comparison of dosage form, effect of enteric coating

4.2.3.6 Dissolution of Slow-release Capsules

Souder, J.C. and Ellenbogen, W.C., *Drug Stand.*, 1958, *26*, 77–83

Laboratory control of dextro amphetamine sulfate sustained release capsules

capsules, hard gelatin: dexamphetamine sulphate; dissolution method, rotating bottle

Royal, J., *Drug Stand.*, 1959, *27*, 1–6

A comparison of *in vitro* rates of release of several brands of dextro amphetamine sulfate sustained release capsules

capsules, hard gelatin: dexamphetamine sulphate; dissolution method, modified *U.S.P.* XV disintegration apparatus

Vliet, E.B., *Drug Stand.*, 1959, *27*, 97–9

A suggested *in vitro* procedure for measuring the rate of drug release from timed release tablets and capsules

capsules, hard gelatin and tablets: dissolution method, modified *U.S.P.* disintegration apparatus

Krueger, E.O. and Vliet, E.B., *J. pharm. Sci.*, 1962, *51*, 181–4

In vitro testing of timed release tablets and capsules

capsules, hard gelatin and tablets: dissolution method, rotating bottle; dissolution testing, collaborative study, sustained-release preparations

Chiaramonti, D., Giana, C., Innocenti, F. and Segre, A.D., *Farmaco, Edn prat.*, 1970, *25*, 257–62

Proposed method for the analysis of prolonged release medicines (in Italian)

capsules, hard gelatin: dissolution method, rotating flask; dissolution testing, effect of change in pH test medium; product, sustained-release granules

Goldman, R., *Drug Cosmet. Ind.*, 1970, *107*(3), 52–64, 151–6

Sustained release capsules

capsules, hard gelatin: review

Widmann, A., Eiden, F. and Tenczer, J., *Arzneimittel-Forsch.*, 1970, *20*, 283–9

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Release of drugs from Depot soft gel capsules (in German)

capsules, soft gelatin: chlorpheniramine maleate, codeine; capsules shell, non-disintegrating; dissolution method, beaker; dissolution testing, effect of change in pH test medium, prolonged-release preparations; 4.4.3

Berkowitz, R.D., *Hosp. Pharm.*, 1971, *6*, 8–16

A study of in vitro release rates of sustained-release dextro amphetamine sulfate capsules

capsules, hard gelatin: dexamphetamine sulphate; dissolution method, *U.S.N.F.* XII; formulation of contents, sustained-release preparation

Schwarz, R., *ZentBl. Pharm.*, 1971, *110*, 1127–36

On the testing of sustained-release preparations (in German)

capsules, hard and soft gelatin: dissolution method, continuous flow, rotating bottle; dissolution testing, comparison of methods

Baichwal, M.R. and Yelvigi, M.S., *Indian J. Pharm.*, 1973, *35*, 146–50

Sustained release capsules using polyglycerol esters

capsules, hard gelatin: acetylsalicylic acid; dissolution method, modified disintegration apparatus; formulation of contents, polyethylene glycol esters

Bloch, R., Loebel, E. and Loschever, M., *German (BRD) Patent (Offen.)* 2 627 113, 1977

Capsule for controlled release of drugs

capsules, hard gelatin: capsule shell solubility, reduction with cross-linking agent; capsule sealing, epoxy resins

Steinbach, D. and Möller, H., *Int. J. Pharmaceut.*, 1978, *1*, 197–204

Investigations into the accuracy of dosage and release of active drug from sustained release preparations of isosorbide dinitrate

capsules, hard gelatin and tablets, coated and plain: isosorbide dinitrate; content uniformity, DAB 7, *U.S.P.* XIX; dissolution method, Diffutest and *U.S.N.F.* XIV; dissolution testing, prolonged-release preparations; product weight uniformity, DAB 7, *U.S.P.* XIX

Matheson, L.E., *Drug Dev. ind. Pharm.*, 1979, *5*, 459–71

Comparison of in vitro release rates of multisource sustained-release papaverine hydrochloride products

capsules, hard gelatin: papaverine hydrochloride; dissolution method, rotating bottle; dissolution testing, comparison between lots and manufacturers

D'Onofrio, G.P., Oppenheim, R.C. and Bateman, N.E., *Int. J. Pharmaceut.*, 1979, *2*, 91–9

Encapsulated microcapsules

capsules, soft gelatin: acetylsalicylic acid; dissolution method, continuous flow; dissolution testing, effects of, coating, drug dose; 3.3.3.2

Baggesen, S. and Bechgaard, H., *Pharm. Acta Helv.*, 1980, *55*, 312–15

In vitro evaluation of two controlled release propoxyphene hydrochloride formulations. Influence of the composition of dissolution media on drug release.

capsules, hard gelatin: dextropropoxyphene hydrochloride; dissolution method, modified rotating bottle; dissolution testing, effects of dissolution medium, buffer composition, ionic strength, pH, surface tension; experimental procedure, factorial experiment, statistical analysis; formulation of contents, pellets

Walker, S.E., Ganley, J.A., Bedford, K. and Eaves, T., *J. Pharm. Pharmac.*, 1980, *32*, 389–93

The filling of molten and thixotropic formulations into hard gelatin capsules

capsules, hard gelatin: nomifensine hydrogen maleate; dissolution method, *U.S.P.*; dissolution testing, effect of formulation; 3.2.3.4; 3.2.4.2; 4.2.3.4

Yalabik-Kaş, H.S., *Drug Dev. ind. Pharm.*, 1983, *9*, 1047–60

Microencapsulation and in vitro dissolution of oxazepam from ethyl cellulose microcapsules

capsules, hard gelatin: oxazepam; dissolution method, stirred flask; dissolution testing, effects of, formulation, test media, kinetic analysis; formulation of contents, controlled release, microencapsulation, ethylcellulose

Simons, K.J., Plett, K.D. and Simons, F.E.R., *Pharm. Acta Helv.*, 1984, *59*, 145–8

Dissolution studies of some regular and sustained-release dyphylline dosage forms

capsules, hard gelatin and tablets, standard and sustained-release: diprophylline; dissolution method, rotating basket; dissolution testing, effect of test media, simulated gastric and intestinal fluids

Paris, L. and Stamm, A., *s.t.p. Pharma*, 1985, *1*, 412–18

Study of the influence of pH on the in vitro dissolution of prolonged-release theophylline preparations (in French)

capsules, hard gelatin and tablets: theophylline; dissolution method, paddle; dissolution testing, comparison of dosage forms, effect pH test media; test media, pH change with time

Schmidt, P.C. and Stockebrand, B., *Pharm. Res.*, 1986, *3*, 230–34

Capsules with prolonged action, II. Capsule filling by a gelation process

capsules, soft gelatin: codeine, theophylline; dissolution method, paddle; dissolution testing, comparison of drugs, effects of; formulation; nature of matrix; 3.3.3.2

Schmidt, P.C. and Stockebrand, B., *Pharm. Res.*, 1986, *3*, 235–39

Capsules with prolonged action, III. Release of active ingredients from cast films

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capsules, soft gelatin: indomethacin, nifedipine, theophylline; dissolution method, paddle; dissolution testing, comparison with model systems; drug release, model systems, cast films, partition and permeation studies; drug release from membranes, effects of, film thickness, formulation, test conditions; formulation of membranes

4.2.3.7 Dissolution Methodology

Needham, T.E. and Luzzi, L.A., *J. pharm. Sci.*, 1974, *63*, 925–8

Comparison of dissolution profiles of tablets and capsules from the U.S.P., Levy, and magnetic basket methods

capsules, hard gelatin and tablets: butobarbitone sodium; dissolution methods, beaker, magnetic basket, *U.S.P.* XVIII

Cakiryildiz, C., Mehta, P.J., Rahmen, W. and Schoenleber, D., *J. pharm. Sci.*, 1975, *64*, 1692–7

Dissolution studies with a multichannel continuous-flow apparatus

capsules, hard gelatin: powders and tablets: tetracycline hydrochloride; dissolution methods, continuous flow, rotating basket

Brossard, D., Massoum, R., Poelman, M.C. and Chaumeil, J.C., *First International Conference on Pharmaceutical Technology*, (Paris, APGI, May 31–June 2, 1977). 1977, *V*, 182–93

Dissolution of solid oral dosage forms: critical study of two apparatus (in French)

capsules, hard gelatin, granules, powders and tablets: nitrofurantoin; dissolution methods, continuous flow, stirred flask; dissolution testing, comparison of dosage forms, effect of apparatus, speed of flow and stirring

Carstensen, J.T., Lai, T.Y.-F. and Prasad, V.K., *J. pharm. Sci.*, 1978, *67*, 1303–7

U.S.P. dissolution IV: Comparison of methods

capsules, hard gelatin and tablets: nitrofurantoin; dissolution methods, rotating filter, *U.S.P.*, rotating basket, disintegration apparatus, paddle; dissolution testing, comparison of dosage forms, effect of apparatus variables

Pharmaceutical Manufacturers' Association of Tokyo, *Iyakuhin kenkyu*, 1978, *9*, 573–80

Studies on dissolution method for tablets and capsules (in Japanese)

capsules, hard gelatin and tablets: indomethacin; dissolution methods, *U.S.P.* XIX methods I and II, modified disintegration apparatus (Jpn); dissolution testing, effect of inter-laboratory variations

Cartwright, A.C., *Drug Dev. ind. Pharm.*, 1979, *5*, 277–91

Practical aspects of dissolution testing

capsules and tablets: dissolution method, rotating basket; dissolution method, automatic sampling system, use of dissolution calibrators; dissolution testing, identification and review of test variables

Brossard, D., Massoum, R., Poelman, M.C. and Chaumeil, J.C., *Second International Conference on Pharmaceutical Technology*, (Paris, APGI, June 3–5, 1980), 1980, *II*, 119–33

Applications of the technique of continuous flux and of Poole's flask to different oral dosage forms: Study of hard gelatin capsules (in French)

capsules, hard gelatin: nitrofurantoin; dissolution methods, continuous flow, stirred flask; dissolution testing, effect of capsule holder, formulation of contents; dissolution testing, results, dissolution efficiency, reproducibility, sensitivity; formulation of contents, diluents, lubricants

Langenbucher, F. and Moeller, H., *Drugs Germ.*, 1981, *24*, 131–5

Possible improvements of the U.S.P. XX dissolution test standards

capsules and tablets: dissolution method, *U.S.P.* XX; dissolution testing, effects of, equipment variation, sampling techniques; dissolution testing, floating products, metal sinker (capsules)

Koch, H.P., Alcorn, G. and Ritschell, W.A., *Pharmazie*, 1983, *38*, 233–5

Comparison of two-dissolution apparatuses: Rotating basket versus rotating flask. Correlation of data from four commercial theophylline prolonged release dosage forms.

capsules, hard gelatin and tablets: theophylline; dissolution method, rotating basket, rotating flask; dissolution testing, comparisons of, method, products

Möller, H., *Pharm. Ind., Berl.*, 1983, *45*, 617–22

Dissolution testing of different dosage forms using the flow-through method

capsules, hard and soft gelatin, powders, suppositories and tablets: benzobromarone, isosorbide dinitrate, tetracycline; dissolution method, continuous flow, paddle; dissolution testing, comparison of methods, effects of formulation

Herzfeldt, C.D., *Pharm. Technol.*, 1984, *8*(9), 70–6

Automated dissolution testing of indomethacin capsules and tablets

capsules, hard gelatin and tablets: indomethacin; dissolution method, paddle, rotating basket, dissolution standards, *U.S.P.* XX, acceptance criteria; dissolution testing, automation, comparison of dosage forms, products, test methods

Baichwal, M.R., Deshpande, S.G. and Shetty, U.C., *Drug Dev. ind. Pharm.*, 1985, *11*, 1639–56

Comparative evaluation of four dissolution apparatus

capsules, hard gelatin: dissolution methods, basket and paddle, paddle, rotating basket, rotating basket with paddle; dissolution testing, comparison of methods, effect of agitation intensity; formulation of contents, pellets

Gander, B., Ventouras, K., Gurny, R. and Doelker, E., *Int. J. Pharmaceut.*, 1985, *27*, 117–24

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In vitro dissolution medium with supramicellar surfactant concentration and its relevance for in vivo absorption

capsules, hard gelatin and tablets: palmitoylcatechin; disintegration method, *U.S.P.*; disintegration testing, comparison of dosage forms, effect of test media; dissolution method, paddle; dissolution testing, comparison of dosage forms, effect of test media

Pandit, N.K., Strykowski, J.M., McNally, E.J. and Waldbillig, A.M., *Drug Dev. ind. Pharm.*, 1985, *11*, 1797–1818

Surfactant solutions as media for dissolution testing of a poorly water-soluble drug

capsules, hard gelatin: 4-(4-biphenylyl-butanol); dissolution method, beaker; dissolution testing, effects of test media; drug solubility, effects of surfactants; surfactants, polyoxyethylene lauryl ether, sodium dodecyl sulphate; test media, addition of surfactants

Machida, Y., Tokumura, T., Komuro, S., Tsushima, Y., Tatsuishi, K., Kayano, M. and Nagai, T., *Chem. pharm. Bull., Tokyo*, 1986, *34*, 2637–41

A new method of dissolution testing for oily drug preparations using an improved apparatus

capsules, soft gelatin and tablets: d-α-tocopherol; dissolution method, modified paddle; dissolution testing, effects of, apparatus configuration, test media; dissolution testing, lipophilic materials

4.2.3.8 Dissolution and Storage

Akbufa, J., Ari-Ulubelen, A. and Bayraktar-Alpmen, G., *Pharmazie*, 1984, *39*, 695–6

Effect of relative humidity and ageing on drug release. Part 2: Experimental phenytoin sodium capsules

capsules, hard gelatin: phenytoin sodium; dissolution method, rotating basket; dissolution testing, effects of, formulation of contents, storage conditions; formulation of contents, lactose and magnesium stearate; storage conditions, humidity, RH 75% and 95%, time 2, 4 and 8 weeks

Martin, E.D., Frazer, R.J.L. and Camens, I., *Med. J. Aust.*, 1985, *143*, 634–5

Storage of phenytoin capsules

capsules, hard gelatin: phenytoin sodium; dissolution method, rotating basket; dissolution testing, effect of storage, comparison with standard capsules; drug clinical effect, effect of product storage; storage conditions, tropical

Rubino, J.T., Halterlein, L.M. and Blanchard, J., *Int. J. Pharmaceut.*, 1985, *26*, 165–74

The effects of ageing on the dissolution of phenytoin sodium capsule formulations

capsules, hard gelatin: phenytoin sodium; dissolution method, rotating basket; dissolution testing, effects of, formulation of contents, storage conditions; formulation of contents, excipients, diluents and diluent/drug ratio; pharmacokinetic analysis; storage conditions, humidity, RH, 11% and 67%, time 2 and 8 weeks

4.2.4 Disintegration/Dissolution Correlation

Sandell, E. and Eckemark, K.-E., *Acta pharm. suec.*, 1966, *3*, 235–9

Release of potassium chloride from hard gelatin capsules

capsules, hard gelatin: potassium bicarbonate, potassium chloride; disintegration testing, Paikoff and Drumm; dissolution method, beaker

Newton, J.M. and Rowley, G., *J. Pharm. Pharmac.*, 1970, *22*, *Suppl.*, 163S–8S

On the release of drug from hard gelatin capsules

capsules, hard gelatin: ethinamate; disintegration testing, effect of filling, particle size; dissolution method, beaker; powder properties, capsule powder bed permeability measurement

Samyn, J.C. and Jung, W.Y., *J. pharm. Sci.*, 1970, *59*, 169–75

In vitro dissolution from several experimental capsule formulations

capsules, hard gelatin: disintegration method, *U.S.P.* tablet test; disintegration testing, effect of formulation, diluents, disintegrants, lubricants; dissolution method, modified *U.S.P.* disintegration apparatus; dissolution testing, effects of, formulation, powder properties; powder properties, packing density, liquid penetration measurement, viscosity of powder blends, determination; 3.2.4.1

Sandell, E., Eriksson, K. and Mellström, G., *Acta pharm. suec.*, 1970, *7*, 559–66

A disintegration test for evaluation of drug availability from tablets and capsules

capsules, hard gelatin and tablets: chloramphenicol, indomethacin, tetracycline; disintegration method, oscillating tube with sieves; dissolution method, beaker

Siegfried, B., *Schweiz. ApothZtg*, 1970, *108*, 178–80

Comparative estimation of the oral dosage forms, capsule and pill, an example of a standard sedative capsule and pill (in German)

capsules, hard gelatin and pills: methylphenobarbitone; disintegration method, *Swiss P.* VI; dissolution method, beaker; dissolution testing, effect of storage; formulation, contents; product weight uniformity

Khalil, S.A. and Ali, L.M.M., *Acta pharm. suec.*, 1972, *9*, 563–72

Some formulation factors affecting disintegration and dissolution of chloramphenicol capsules

capsules, hard gelatin: chloramphenicol; disintegration method, *B.P.*; dissolution method, modified *B.P.* disintegration apparatus; powder properties, powder beds, liquid penetration measurements; 3.2.4.1

Caldwell, H.C. and Westlake, W.J., *Can. J. pharm. Sci.*, 1973, *8*, 50–3

Magnesium lauryl sulfate: soluble lubricant

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capsules, hard gelatin and tablets: lithium carbonate; disintegration method, *U.S.N.F.* XIII Method II; disintegration testing, effect of formulation, comparison of lubricants; dissolution method, modified *U.S.N.F.* XIII disintegration; dissolution testing, effect of formulation, comparison of lubricants; 3.2.4.1; 3.8.3.6

Goodhart, F.W., McCoy, R.H. and Ninger, F.C., *J. pharm. Sci.*, 1973, *62*, 304–10

New *in vitro* disintegration and dissolution test method for tablets and capsules

capsules, hard gelatin and tablets: disintegration method, modified beaker, *U.S.P.*; dissolution method, modified beaker, *U.S.P.* XVIII disintegration apparatus; dissolution testing, effect of variation in test conditions; 3.2.4.1

Khalil, S.A.H. and Ali, L.M.M., *Indian J. Pharm.*, 1973, *35*, 59–62

Effect of dissolution medium and moisture content of the powder on the dissolution of chloramphenicol capsules

capsules, hard gelatin: chloramphenicol; disintegration method, *B.P.*; dissolution method, *B.P.* disintegration apparatus; dissolution testing, effects of, capsule contents, moisture content, test media

Cox, H.L.M., Breimer, D.D. and Freeke, G., *Pharm. Weekbl. Ned.*, 1974, *109*, 1018–26

In vitro testing of the release of chloral hydrate from soft gelatin capsules (in Dutch)

capsules, soft gelatin: chloral hydrate; disintegration testing, enteric-coated and untreated capsules; dissolution method, beaker; dissolution testing, comparison, enteric-coated and untreated capsules; dissolution testing, simulation of intestinal pH changes

Weyers, W. and Gebhart, U., *Pharm. Acta Helv.*, 1976, *51*, 233–7

Comparative examination of gastrointestinal absorption of tetracycline preparations (in German)

capsules, hard and soft gelatin and tablets, film- and sugar-coated: tetracycline hydrochloride; disintegration method, *Swiss P.* VI; dissolution method, Dibbern; dissolution testing, effect of pH on absorption

Merle, C., Mangin, C. and Guyot-Hermann, A.M., *Bull. Soc. Pharm. Lille*, 1977, *33*, 87–94

Trials with a continuous flow dissolution apparatus. Application to the study of the influence of powder packing in hard gelatin capsules (in French)

capsules, hard gelatin: acetylsalicylic acid, sodium salicylate; disintegration method, *U.S.P.* XVIII; disintegration testing, effect of capsule size/powder packing; dissolution method, continuous flow; dissolution testing, effects of, capsule size, powder packing

Grakovskaya, L.K., Nesterova, L.Y., Okhotnikova, V.F., Zak, A.F., Ermolova, O.B. and Batuashvili, T.A., *Antibiotiki*, 1978, *23*, 215–19 per *Chem. Abstr.*, 1978, *88*, 197546d

Effects of adjuvants on the bioavailability of tetracycline hydrochloride from capsules (*in vitro* studies) (in Russian)

capsules, hard gelatin: tetracycline hydrochloride; disintegration testing, effect of formulation; dissolution testing, effect of formulation; formulation of contents, diluents, magnesium carbonate, calcium phosphate, lactose, lubricant, calcium stearate

Saito, T., Suzuki, S., Nambu, N. and Nagai, T., *Yakuzaigaku*, 1978, *38*, 29–34

Test of the physical stability regarding dissolution property of solid preparations (in Japanese)

capsules, hard gelatin and tablets: indomethacin (capsules); disintegration method, oscillating tube; disintegration testing, effect of storage; dissolution method, rotating basket; dissolution testing, effect of storage; storage conditions, humidity (52%, 92%), temperature (5°, 30°); 3.8.3.7

Carp, G.B., Chemtob, C. and Chaumeil, J.C., *Second International Conference on Pharmaceutical Technology*, (Paris, APGI, June 3–5, 1980), 1980, *V*, 68–80

Availability from rectally administered solid dosage forms: use of rectal soft gelatin capsules (in French)

capsules, soft gelatin: phenobarbitone, free acid and sodium salt; disintegration method, *Fr.P.* 9th Edn, modified, *Pol.P.*, modified, *Swiss P.*, Widmann's (polythene bags); disintegration testing, comparison of methods; dissolution method, partitioning; dissolution testing, effect of formulation; 3.5.2

Hoechst UK Ltd, *British Patent* 1 572 226, 1980

Improvements in and relating to pharmaceutical preparations in solid unit dosage forms

capsules, hard gelatin: triamterene; disintegration method, *B.P.*; disintegration testing, effect of formulation of contents; dissolution method, *U.S.P.*; dissolution testing, effect of formulation of contents; formulation of contents, powder fill, semi-solid fill; 3.2.3.4; 3.2.4.2

Newton, J.M. and Bader, F., *J. Pharm. Pharmac.*, 1980, *32*, 167–71

The influence of drug and diluent particle size on the in vitro release of drug from hard gelatin capsules

capsules, hard gelatin: acetylsalicylic acid; disintegration method, *B.P.*; dissolution method, beaker; dissolution testing, effects of, formulation, powder properties; dissolution testing, results, analysis of variance of T50; formulation of contents, diluent, lactose; powder properties, particle size, porosity of powder bed

Grakovskaia, L.K., Garsheva, G.B., Dedukh, N.G., Khlystova, Z.I. and Koyal'chenko, N.D., *Antibiotiki*, 1981, *26*, 592–4

Effect of antibiotic granulation procedure on quality of capsules with semi-synthetic penicillins (with special reference to sodium dicloxacillin) (in Russian)

capsules, hard gelatin: sodium dicloxacillin; disintegration method, oscillating tube; disintegration testing, effect of powder properties; dissolution method, rotating basket; dissolution testing, effect of powder properties; formulation of

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contents; powder properties, method of preparation, dry compaction, wet granulation

Botzolakis, J.E., Small, L.E, and Augsburger, L.L., *Int. J. Pharmaceut.*, 1982, *12*, 341–9

Effect of disintegrants on drug dissolution from capsules filled on a dosator-type automatic capsule-filling machine

capsules, hard gelatin: hydrochlorothiazide, paracetamol; disintegration method, *U.S.P.*; disintegration testing, effects of, filling conditions, formulation of contents; dissolution method, stirred flask; dissolution testing, effects of, filling conditions, formulation of contents; disintegration/dissolution correlation, effect of drug type; 3.2.4.1

Botzolakis, J.E. and Augsburger, L.L., *J. Pharm. Pharmac.*, 1984, *36*, 77–84

The role of disintegrants in hard-gelatin capsules

capsules, hard gelatin: disintegration method, *U.S.P.* XX; disintegration testing, effects of, filling forces, formulation of contents; dissolution method, paddle; dissolution testing, effects of, filling forces, formulation of contents; 3.2.3.3; 3.2.4.1

Ritschel, W.P. and Parab, P., *Drug Dev. ind. Pharm.*, 1985, *11*(1), 147–67

Dissolution of some lithium dosage forms and correlation with Enslin number

capsules, hard gelatin and tablets: disintegration method, *U.S.P.*; disintegration testing, comparison of dosage forms; dissolution method, rotating basket; dissolution testing, comparison of dosage forms, correlation with powder properties; kinetic analysis, dissolution rate constants, correlation with powder properties; powder properties, water uptake measurement

4.3 Drug Availability in Animals

4.3.1 General References

Poole, J.W., *Revue can. Biol.*, 1973, *32*, *Suppl.*, 43–51

Penicillins: use of an animal model to predict bioavailability

capsules, hard gelatin and suspensions: ampicillin anhydrous, trihydrate, dicloxacillin, levels, serum (dog); drug availability, dog serum levels, correlation with human

Maeda, T., Takenaka, H., Yamahira, Y. and Noguchi, T., *J. pharm. Sci.*, 1977, *66*, 69–73

Use of rabbits for GI drug absorption studies

capsules, hard gelatin and tablets: griseofulvin, indomethacin, levels, plasma (rabbit); gastric emptying rate

4.3.2 Comparison of Dosage Forms

4.3.2.1 Comparison with Solid Preparations

Kagawa, C.M., Bouska, D.J. and Anderson, M.L., *J. pharm. Sci.*, 1964, *53*, 450–1

Oral absorption with various preparations of spironolactone in dogs

capsules, hard gelatin and tablets, uncoated and sugar-coated: spironolactone, levels, plasma (dogs); drug clinical effects, urine levels, sodium, potassium

Williams, J.F. and Trejos, A., *Res. vet. Sci.*, 1970, *11*, 392–4

The influence of gelatin capsules upon the activity of bunamidine hydrochloride against Echinococcus granulosus in dogs

capsules, hard gelatin and tablets: bunamidine hydrochloride, drug effects, parasite numbers (dogs); drug administration, tablet inside capsule; drug availability, effect of encapsulated tablet

Stella, V., Haslam, J., Yata, N., Okada, H., Lindenbaum, S. and Higuchi, T., *J. pharm. Sci.*, 1978, *67*, 1375–7

Enhancement of bioavailability of a hydrophobic amine antimalarial by formulation with oleic acid in a soft gelatin capsule

capsules, hard and soft gelatin: α-(dibutylaminomethyl)-6,8-dichloro-2-(3′,4′-dichlorophenyl)-4-quinolinemethanol, levels, serum (dogs); drug availability, effect of formulation; drug solubility, determination aqueous solubility; pharmacokinetic analysis, area under curve comparisons; 3.3.3.2

4.3.2.2 Comparison with Liquid Preparations

Andermann, G., Dietz, M. and Mergel, D., *Pharm. Acta Helv.*, 1979, *54*, 366–9

Bioavailability of medicines based on cyclandelate (in French)

capsules, hard and soft gelatin and suspensions: cyclandelate, levels, serum (rabbits); formulation of contents; pharmacokinetic analysis, relative bioavailability

4.3.2.3 Comparison with Injections

Helmi, R., Elian, A., Moustafa, M. and Sharaf, E., *J. Egypt. med. Ass.*, 1968, *51*, 70–7

A study of the serum concentrations of oxytetracycline after administration of different pharmaceutical preparations

capsules, hard gelatin and injections, intramuscular and intravenous: oxytetracycline hydrochloride, levels, serum (dogs)

Cabana, B.E., Willhite, L.E. and Bierwagen, M.E., *Antimicrob. Ag. Chemother.*, 1969, 35–41

Pharmacokinetic evaluation of the oral absorption of different ampicillin preparations in beagle dogs

capsules, soft gelatin and injections, intravenous: ampicillin, potassium, sodium and trihydrate, levels, serum, urine (dogs); pharmacokinetic analysis

Cotler, S., Holazo, A., Boxenbaum, H.G. and Kaplan, S.A., *J. pharm. Sci.*, 1976, *65*, 822–7

Influence of route of administration on physiological availability of levodopa in dogs

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boluses, intravenous and capsules, hard gelatin: levodopa, levels, plasma (dogs); pharmacokinetic analysis

4.3.2.4 Comparison with Rectal Preparations

Lambelin, G., Roncucci, R., Simon, M.-J., Orloff, S., Mortier, G., Veys, E. and Buu-Hoï, N.P., *Arzneimittel-Forsch.*, 1968, *18*, 56–60

Absorption and excretion of ^{14}C-p-butoxyphenylacethydroxamic acid in man and animals

capsules, hard gelatin, suppositories and tablets, enteric-coated: *p*-butoxyphenylacethydroxamic acid, levels, blood, serum, urine (rabbits, rats); radioactive isotope technique; 4.4.4.4

Anger-Braun, F., Sado, P.A., Le Verge, R. and Devissaguet, J.P., *Second International Conference on Pharmaceutical Technology*, (Paris, APGI, June 3–5, 1980), 1980, *III*, 145–54

Bioavailability of quinidine in soft gelatin capsules after oral and rectal administration to rabbits (in French)

capsules, soft gelatin and solutions: quinidine sulphate and metabolites, levels, serum (rabbits); formulation of contents; pharmacokinetic analysis

4.3.2.5 Comparison with Multiple Dosage Forms

Walkenstein, S.S., Wiser, R., Gudmundsen, C.H., Kimmel, H.B. and Corradino, R.A., *J. pharm. Sci.*, 1964, *53*, 1181–6

Absorption, metabolism, and excretion of oxazepam and its succinate half-ester

capsules, hard gelatin, injections, intramuscular and suspensions: oxazepam, succinate half-ester, levels, faeces, plasma, urine (dogs); radioactive isotope technique; 4.4.4.3

Conklin, J.D., Sobers, R.J. and Wagner, D.L., *J. pharm. Sci.*, 1969, *58*, 1365–8

Urinary drug excretion in dogs during therapeutic doses of different nitrofurantoin dosage forms

capsules, hard gelatin, injections, intramuscular and tablets: nitrofurantoin, levels, serum, urine (dogs)

Mercer, H.D., Garg, R.C. Powers, J.D. and Powers, T.E., *Am. J. vet. Res.*, 1977, *38*, 1353–9

Bioavailability and pharmacokinetics of several dosage forms of ampicillin in the cat

capsules, hard gelatin, injections, intramuscular, intravenous and subcutaneous and suspensions: ampicillin, anhydrous, sodium, trihydrate, levels, serum (cats); pharmacokinetic analysis, dosage/route relationship

4.3.3 Comparison of Capsule Products

Agarwal, S.L., Tayal, J.N. and Deshmankar, B.S., *J. Indian med. Ass.*, 1966, *46*, 13–14

Studies on the oral absorption of antibiotics. Part 1. Chloramphenicol

capsules, hard gelatin: chloramphenicol, levels, serum (dogs)

Ogata, H., Aoyagi, N., Kaniwa, N., Ejima, A., Kitaura, T., Ohki, T. and Kitamura, K., *Int. J. Pharmaceut.*, 1986, *29*, 121–6

Evaluation of beagle dogs as an animal model for bioavailability testing of cinnarizine capsules

capsules, hard gelatin: cinnarizine, levels, plasma (dogs); drug availability, comparison with human data, effect of gastric pH; gastric pH measurement, comparison with human

4.3.4 Effect of Formulation on Absorption

Fincher, J.H., Adams, J.G. and Beal, H.M., *J. pharm. Sci.*, 1965, *54*, 704–8

Effect of particle size on gastrointestinal absorption of sulfisoxazole in dogs

capsules, hard gelatin: sulphafurazole, levels, blood (dogs); drug availability, effect of particle size

Paul, H.E., Hayes, K.J., Paul, M.F. and Borgmann, A.R., *J. pharm. Sci.*, 1967, *56*, 882–5

Laboratory studies with nitrofurantoin. Relationship between crystal size, urinary excretion in the rat and man, and emesis in dogs

capsules, hard gelatin: nitrofurantoin, levels, urine (rats); drug availability, effect of drug particle size; drug clinical effects, emesis (dogs); 4.4.4.1

Ljungberg, S. and Otto, G., *Acta pharm. suec.*, 1970, *7*, 449–56

Particle size and intestinal absorption of acetylsalicylic acid in dogs

capsules, hard gelatin: acetylsalicylic acid, levels, serum (dogs); drug availability, effect of particle size; powder properties, particle size, effect of granulation

Newmark, H.L. and Berger, J., *J. pharm. Sci.*, 1970, *59*, 1246–8

Coumermycin A_1 – Biopharmaceutical studies I

capsules, hard gelatin, injections, intravenous and solutions: coumermycin, soluble salts, sugar amines, complexing agents, levels, blood (dogs); drug availability, effect of formulation, drug chemical form; formulation of contents, *N*-methylglucamine gels

Hansford, D.T., Newton, J.M. and Wilson, C.G., *Pharm. Ind., Berl.*, 1980, *42*, 646–50

The influence of formulation on the absorption of orally administered griseofulvin preparations in rabbits

capsules, hard gelatin, solutions and suspensions: griseofulvin, levels, plasma (rabbits); drug availability, comparison of dosage forms, percentage of drug absorption

4.3.5 Availability from Enteric Capsules

Nash, J.F. and Crabtree, R.E., *J. pharm. Sci.*, 1961, *50*, 134–7

Absorption of tritiated *d*-desoxyephedrine in sustained-release dosage forms

capsules, hard gelatin: methylamphetamine hydrochloride, resinates, levels, blood, urine (dogs); enteric coating, cellulose acetate phthalate

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4.4 Drug Availability in Humans

4.4.1 Reviews

Wagner, J. G., *J. pharm. Sci.*, 1961, *50*, 359–87

Biopharmaceutics: absorption aspects

Wagner, J.G., *Can. J. pharm. Sci.*, 1966, *1*, 55–68

Design and data analysis of biopharmaceutical studies in man

Riegelman, S., *The physiological equivalence of drug dosage forms*, Symposium (Food and Drug Directorate, Ottawa), 1969, 13–22

Pharmacokinetic analysis of drug dosage forms

capsules, hard gelatin and suspensions: griseofulvin, levels, plasma

Schneller, G.H., *J. Am. pharm. Ass.*, 1969, *NS9*, 455–9

Hazard of therapeutic nonequivalency of drug products

Wagner, J.G., *J. pharm. Sci.*, 1969, *58*, 1253–7

Interpretation of percent dissolved–time plots derived from *in vitro* testing of conventional tablets and capsules

capsules and tablets: presentation of results

Florence, A.T., *Pharm. J.*, 1972, *208*, 456–63

Generic equivalence: A look at the literature

Blanchard, J., *Am. J. Pharm.*, 1978, *150*, 132–51

Gastrointestinal absorption II. Formulation factors affecting drug availability

Ganderton, D., *Acta pharm. suec.*, 1978, *15*, 314–15

Effect of production variables on the properties of tablets and capsules related to bioavailability

Garcia, C.R., Siqueiros, A. and Benet, L.Z., *Pharm. Acta Helv.*, 1978, *53*, 99–109

Oral controlled release preparations

capsules and tablets: controlled-release products, capsules of coated granules

4.4.2 General References, Availability in Humans

Stelmach, H., Robinson, J.R. and Eriksen, S.P., *J. pharm. Sci.*, 1965, *54*, 1453–8

Release of a drug from a dosage form

capsules, hard gelatin, solutions and tablets: aspirin; drug availability, *in vivo*, computer (analog) simulation

Martin, C.M., *J. Am. med. Ass.*, 1968, *205*(9), 23–4, 30

Brand, generic drugs differ in man

capsules: chloramphenicol, phenytoin sodium, levels, serum; sulphafurazole, crushed tablets administered in capsules

Wheeler, L.M., *Drug Cosmet. Ind.*, 1972, *110*(2), 64, 66, 124–7

The standard dose form for pharmaceutical research

capsules, hard gelatin: clinical trials, double-blind; formulation of contents

Baars, R. E., Rapp, R.P., Young, B. and Canafax, D., *Drug Intell. & clin. Pharm.*, 1978, *12*, 584–8

Phenytoin 300 mg daily; not a dose for everyone. A comparison of a 300 mg capsule with three 100 mg capsules

capsules, hard gelatin: phenytoin, levels, serum; drug availability, effect of dosage levels

Cloyd, J.C., Gumnit, R.J. and Lesar, T.S., *Ann. Neurol.*, 1980, *7*, 191–3

Reduced seizure control due to spoiled phenytoin capsules

capsules, hard gelatin: phenytoin, levels, serum; drug availability, effect of capsule storage

Evens, R. P., Frazer, D. G., Ludden, T. M. and Sutherland, E.W., *Am. J. Hosp. Pharm.*, 1980, *37*, 232–5

Phenytoin toxicity and blood levels after a large oral dose

capsules, hard gelatin: phenytoin, levels, plasma; drug availability, effect of high dosage

Aiache, J.-M., Aiache, S., Renoux, R. and Mohamed, H., *Labo-Pharma Probl. Tech.*, 1983, *31*, 926–34

The place of the hard gelatin capsule: biopharmaceutical aspects (in French)

capsules, hard gelatin: disintegration; dissolution; drug availability, *in vivo*, effects of formulation, physiological factors; formulation of contents

Anon, *Med. Lett. Drug. Ther.*, 1983, *25*, 11–12

Digoxin solution in capsules (Lanoxicaps)

capsules, soft gelatin: digoxin, drug availability, review

Berry, I.R., *Mfg Chem.*, 1984, *55*(4), 54–5

Bioavailability and soft gelatin capsules

capsules, soft gelatin: drug availability, comparison with other dosage forms; review

4.4.3 Intestinal Performance

Oser, B.L., Melnick, D. and Hochberg, M., *Ind. Engng Chem. analyt. Edn*, 1945, *17*, 405–11

Physiological availability of the vitamins. Study of methods for determining availability of vitamins in pharmaceutical products

capsules, soft gelatin, solutions and tablets: thiamine, levels, urine; disintegration method, X-ray, radio-opaque contents; formulation of contents, adsorbents, acid clays and fuller's earth

Feinblatt, T.M. and Ferguson, E.A., *New Engl. J. Med.*, 1956, *254*, 940–3

Timed-disintegration capsules. An in vivo roentgenographic study

capsules, hard gelatin: barium sulphate; disintegration method, X-ray, radio-opaque contents; formulation of contents, granules, controlled release

Eckert, T., *Arzneimittel-Forsch.*, 1967, *17*, 645–6

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The pH-endoradio probe: a method for determining the in vivo disintegration of oral dosage forms. Part I. The disintegration of hard gelatin capsules in vivo (in German)

capsules, hard gelatin: disintegration method, pH radiotransmitter; disintegration testing, capsule shell, release of contents

Widmann, A., Eiden, F. and Tenczer, J., *Arzneimittel-Forsch.*, 1970, *20*, 283–9

Release of drugs from Depot soft gel capsules (in German)

capsules, soft gelatin: chlorpheniramine maleate, codeine; capsule shell, non-disintegrating; disintegration method, X-ray, radio-opaque contents; drug availability, prolonged release; formulation of contents; 4.2.3.6

Casey, D.L., Beihn, R.M., Digenis, G.A. and Shambhu, M.B., *J. pharm. Sci.*, 1976, *65*, 1412–13

Method for monitoring hard gelatin capsule disintegration times in humans using external scintigraphy

capsules, hard gelatin: gastric behaviour, visualisation method, gamma scintigraphy, technetium–99 m; gastric behaviour, testing, effects of, formulation of contents, patient's fasting state

Evans, K.T. and Roberts, G.M., *Lancet*, 1976, *2*, 1237–9

Where do all the tablets go?

capsules, hard gelatin and tablets: gastric behaviour, clinical effects, disintegration in oesophagus, patient problems; visualisation method, X-ray, radio-opaque contents; disintegration testing, location of site

Carlborg, B., Kumlien, A. and Olsson, H., *Läkartidningen*, 1978, *75*, 4609–11

Oesophageal strictures caused by oral drug therapy (in Swedish)

capsules and tablets: oesophageal behaviour, effects of, physiological factors, products, review

Hunter, E., Fell, J.T., Calvert, R.T. and Sharma, H., *Int. J. Pharmaceut.*, 1980, *4*, 175–83

"In vivo" disintegration of hard gelatin capsules in fasting and non-fasting subjects

capsules, hard gelatin: disintegration method, *B.P.*; formulation of contents, ion-exchange resin, fast and slow disintegration; gastric behaviour, visualisation method, gamma scintigraphy, technetium-99 m; gastric behaviour, testing, dispersion of contents, gastric emptying, effect of patient's fasting state

Anon., *Drug & Ther. Bull.*, 1981, *19*(9), 33–4

Tablets and capsules that stick in the oesophagus

capsules and tablets: gastric and oesophageal behaviour, comparison of dosage forms, review

Evans, K.T. and Roberts, G.M., *J. clin. Hosp. Pharm.*, 1981, *6*, 207–8

The ability of patients to swallow capsules

capsules, hard and soft gelatin: barium sulphate; gastric and oesophageal behaviour, visualisation method, X-ray, radio-opaque contents; gastric and oesophageal behaviour, testing, comparison of dosage forms, effects of co-administration of water, condition of patient's oesophagus

Hunter, E., Fell, J.T. and Sharma, H., *J. Pharm. Pharmac.*, 1981, *33*, 617–18

A comparison of the behaviour of tablet and capsule formulations in vivo

capsules, hard gelatin and tablets: formulation of contents, ion-exchange resin; gastric behaviour, visualisation method, gamma scintigraphy, technetium-99 m; gastric behaviour, testing, comparison of, dosage form, effect of patient's fasting state

McCloy, E.C. and Kane, S., *Br. med. J.*, 1981, *282*, 1703

Drug-induced oesophageal ulceration

capsules, hard gelatin: oesophageal behaviour, adverse clinical effects, letter

Channer, K.S. and Virjee, J. *Br. med. J.*, 1982, *285*, 1702

Effect of posture and drink volume on the swallowing of capsules

capsules, hard gelatin: barium sulphate; gastric and oesophageal behaviour, visualisation method, X-ray, radio-opaque contents; oesophageal behaviour, effects of, co-administration of water, patient's posture, erect, supine

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An oral preparation to release drugs in the human colon

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Oesophageal transit of six commonly used tablets and capsules

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The gastric emptying of pellets contained in hard gelatin capsules

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A study of the fluid intake with tablets and capsules in geriatric patients

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The effect of hyoscine butylbromide on the swallowing of capsules

capsules, hard gelatin: gastric and oesophageal behaviour, visualisation method, X-ray, radio-opaque contents; gastric and oesophageal behaviour, testing, effects of, co-administration of hyoscine butylbromide and water, patient's posture, erect or supine, site of capsule disintegration

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The gastric emptying of hard gelatin capsules

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The in vivo behaviour of hard gelatin capsules filled with thixotropic liquids: Part 2: Quantitative aspects

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Orally administerable pharmaceutical compositions

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A comparative study of the gastrointestinal transit of a pellet and tablet formulation

capsules, hard gelatin and tablet: capsule contents, pellets; gastric behaviour, visualisation method, gamma scintigraphy, indium-111 (tablet), technetium-99 m (capsule); gastric behaviour, gastric emptying, time to colon, comparison of dosage forms, effect of calorific value of meal

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Release of drugs formulated as hard pastes filled into hard gelatin capsules. Part 2. *In vivo* studies

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Effect of stress on the gastric emptying of capsules

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On the intestinal transit of a single non-disintegrating object

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Simultaneous measurement of gastric emptying of the soluble and insoluble components of a formulation using a dual isotope, gamma scintigraphic technique

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The effect of formulation on oesophageal transit

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Drug delivery to the proximal colon

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Where do all the tablets go in 1986?

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4.4.4 Comparison of Dosage Forms in Humans

4.4.4.1 Comparison with Solid Preparations

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Gastrointestinal absorption of spironolactone

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Indomethacin and peptic ulcer

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Bioavailability of digoxin

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Pharmacokinetics of orally administered acetaminophen in man

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On the absorption of phenobarbitone from various dosage forms (in German)

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Absorption of diphenhydramin-HCl of different dosage forms

capsules, hard and soft gelatin and tablets, sugar-coated: diphenhydramine hydrochloride, levels, plasma; formulation of contents, soft gelatin capsules, excipients

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Bioavailability of digoxin improved by pharmaceutical manufacturing process

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Evaluation of digoxin capsules in outpatients

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Tetracycline, another example of generic bioinequivalence

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Bioavailability of spironolactone in two different pharmaceutical forms (in German)

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Comparative study of relative bioavailability of several spironolactone formulations in a steady-state test (in German)

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Single-dose pharmacokinetics of macrocrystalline nitrofurantoin formulations

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Comparative bioavailability of two forms of spironolactone. Rationalisation applied to dosage (in French)

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Gibberd, F.B., Spencer, K.M., Webley, M. and Berry, D., *Br. J. clin. Pharmac.*, 1982, *13*, 455–6

A comparison of the bioavailability of 2 brands of phenytoin

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Phenytoin toxicity when tablets substituted for capsules

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Sustained release disopyramide compared to plain capsules after change-over from intravenous infusion

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Malini, P.L., Strocchi, E., Negroni, S., Ambrosioni, E. and Magnani, B., *Curr. ther. Res.*, 1983, *33*, 646–50

Greater bioavailability of digoxin in a new capsule preparation

capsules, soft gelatin and tablets: digoxin, levels, plasma, urine; drug availability, comparison of dose, 100 μg in capsules and 125 μg in tablets; pharmacokinetic analysis

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Pharmacokinetic evaluation of osmotically controlled indomethacin delivery systems in man

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Bateman, N.E. and Uccellini, D.A., *J. Pharm. Pharmac.*, 1984, *36*, 461–4

Effect of formulation on the bioavailability of retinol, D-α-tocopherol and riboflavine

capsules, hard and soft gelatin and tablets: vitamins A, B_2, E, levels, plasma; drug availability, comparison of formulations, capsules, soft gelatin; pharmacokinetic analysis; 3.3.3.2

Doherty, J.E., Marcus, F.I. and Binnion, P.F., *Curr. ther. Res.*, 1984, *35*, 301–6

A multicenter evaluation of the absolute bioavailability of digoxin dosage forms

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Comparative bioavailability of several phenytoin preparations marketed in Austria

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Reynier, J.P., Bovis, A. and Bertocchio, M.-H., *Pharm. Acta Helv.*, 1984, *59*, 191–99

Bioavailability of clorazepate dipotassium from different oral dosage forms (in French)

capsules, hard gelatin, injections, intravenous and tablets: clorazepate dipotassium, metabolites, levels, serum; drug availability, comparison of standard release capsules and tablets with sustained release tablets; pharmacokinetic analysis

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Evaluation of the bioavailability of sarpicillin, the methoxymethyl ester of hetacillin, in humans

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Serum levels of different formulations of oxytetracycline in adult healthy volunteers

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Bioinequivalence of erythromycin ethylsuccinate and enteric-coated pellets following multiple oral doses

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4.4.4.2 Comparison with Liquid Preparations

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Studies on the absorption rate of barbiturates in man

capsules, hard gelatin, solutions, suspensions and tablets: amylobarbitone, butobarbitone, cyclobarbitone calcium, cyclopentobarbitone and sodium salt, hexobarbitone and sodium salt, pentobarbitone and sodium salt, quinalbarbitone and sodium salt, levels, plasma; formulation of contents, wetting agent, sodium lauryl sulphate

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Bioavailability of ampicillin measured after repeated oral doses

capsules, hard gelatin: ampicillin, levels, serum; drug availability, effect of dosage regimen, multiple doses

Chow, M., Quintiliani, R., Cunha, B.A., Thompson, M., Finkelstein, E. and Nightingale, C.H., *J. clin. Pharmac.*, 1979, *19*, 185–94

Pharmacokinetics of high-dose oral cephalosporins

capsules, hard gelatin: cephalexin, cephradine, levels, serum, urine; pharmacokinetic analysis

Erking, W., Lücker, P.W., Stöcker, K.-P. and Wetzelsberger, K., *Arzneimittel-Forsch.*, 1979, *29*, 1184–9

Relative bioavailability of a new spironolactone preparation (in German)

capsules, hard gelatin: spironolactone, metabolites, levels, serum, urine; pharmacokinetic analysis

Hamilton-Miller, J.M.T. and Brumfitt, W., *J. antimicrob. Chemother.*, 1979, *5*, 699–704

The bioavailability for four different commercially available brands of ampicillin compared with that of talampicillin

capsules, hard gelatin and tablets: ampicillin (capsules), levels, serum

Sorel, R.H.A. and Roseboom, H., *Int. J. Pharmaceut.*, 1979, *3*, 93–9

Rapid in vitro and in vivo conversion of hydroxymethylnitrofurantoin into nitrofurantoin as measured by HPLC

capsules, hard gelatin and tablets: nitrofurantoin, hydroxymethylnitrofurantoin, levels, urine

Welling, P.G., Elliott, R.L., Pitterle, M.E., Corrick-West, H.P. and Lyons, L.L., *J. pharm. Sci.*, 1979, *68*, 150–5

Plasma levels following single and repeated doses of erythromycin estolate and erythromycin stearate

capsules, hard gelatin, suspensions and tablets: erythromycin estolate and stearate, levels, plasma

Cid, E., Henriquez, A., Andrade, A., Olguin, R., Firmani, E. and Fuentes, B., *J. Pharm. Belg.*, 1980, *35*, 273–6

Relationship between bioavailability and clinical effect of chloramphenicol

capsules, hard gelatin: chloramphenicol, levels, urine; drug clinical effect, healthy volunteers and patients

Ali, H.M., *Int. J. Pharmaceut.*, 1981, *7*, 301–6

Comparative bioavailability of eight brands of ampicillin

capsules, hard gelatin: ampicillin, levels, urine; pharmacokinetic analysis

Ali, A.A. and Farouk, A., *Int. J. Pharmaceut.*, 1981, *9*, 239–43

Comparative studies on the bioavailability of ampicillin anhydrate and trihydrate

capsules, hard gelatin: ampicillin, anhydrous, trihydrate, levels, urine

Buniva, G., Pagani, V. and Carozzi, A., *Int. J. clin. Pharmac. Ther. Toxic.*, 1983, *21*, 404–9

Bioavailability of rifampicin capsules

capsules, hard gelatin: rifampicin, levels, serum; drug availability, comparison of experimental formulations with standard formulation, effect of manufacturing method; formulation of contents, excipients, particle size

Chaudhari, G.N., Tipnis, H.P., Doshi, B.S. and Kulkarni, R.D., *Eur. J. clin. Pharmac.*, 1984, *26*, 261–4

Bioequivalence studies in humans of indomethacin capsules marketed in India

capsules, hard gelatin: indomethacin, levels, plasma; pharmacokinetic analysis

Khalil, S. A., Mortada, L.M. and Ismail, F.A., *Drug Dev. ind. Pharm.*, 1984, *10*, 929–48

Bioavailability of eight brands of ampicillin capsules

capsules, hard gelatin: ampicillin, levels, urine; pharmacokinetic analysis

Dahmen, W., Pabst, G., Molz, K.-H., Lutz, D. and Jaeger, H., *Arzneimittel-Forsch.*, 1985, *35*, 1842–4

Bioavailability of new Nifedipine preparations in man. 2. Bio-equivalence of Nifedipine in form of soft gelatin capsules (in German)

capsules, soft gelatin: nifedipine levels, plasma; pharmacokinetic analysis

Del Arno, E., Cordoba, M. and Torrado, J.J., *Ann. Real Acad. Farm.*, 1985, *51*, 471–6

Bioavailability of rifampicin (in Spanish)

capsules, hard gelatin: rifampicin, levels, plasma; pharmacokinetic analysis

Ogunbona, F.A. and Akanni, A.O., *Pharmazie*, 1985, *40*, 479

Comparative bioavailability studies on some brands of ampicillin capsules

capsules, hard gelatin: ampicillin, levels, urine

Rossi, S.S., Clayton, L.M. and Hofmann, A.F., *J. pharm. Sci.*, 1986, *75*, 288–90

Determination of chenodiol bioequivalence using an unmobilized multi-enzyme bioluminescence technique

capsules: chenodiol, 7α-hydroxy bile acids, levels, serum; pharmacokinetic analysis

4.4.6 Effect of Formulation on Absorption

4.4.6.1 Solid Preparations

Boger, W.P. and Gavin, J.J., *New Engl. J. Med.*, 1959, *261*, 827–32

An evaluation of tetracycline preparations

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capsules, hard gelatin and powders: tetracyclines, levels, serum, urine; drug availability, effect of formulation, diluents; 3.2.4.1

Kraml, M., Dubuc, J. and Gaudry, R., *Antibiotics Chemother.*, 1962, *12*, 239–42

Gastrointestinal absorption of griseofulvin: II. Influence of particle size in man

capsules, hard gelatin: griseofulvin, levels, serum; drug availability, effect of particle size; powder properties, particle size determination

Avery, G.S., Adams, E.F. and Samson, K.L., *N.Z. med. J.* 1968, *68*, 408–9

Phenytoin capsules

capsules, hard gelatin: phenytoin, adverse drug interactions, intoxications, review

McQueen, E.G., *N.Z. med. J.*, 1968, *68*, 332

Phenytoin capsules

capsules, hard gelatin: phenytoin; drug availability, effect of formulation; formulation of contents, diluent, identification method

Arnold, K., Gerber, N. and Levy, G., *Can. J. pharm. Sci.*, 1970, *5*, 89–92

Absorption and dissolution studies on sodium diphenylhydantoin capsules

capsules, hard gelatin: phenytoin sodium, levels, plasma; drug availability, comparison of dosage regimens, single and multiple doses, effect of co-administration of sodium bicarbonate solution; 4.2.3.1

Tyrer, J.H., Eadie, M.J., Sutherland, J.M. and Hooper, W.D., *Br. med. J.*, 1970, *4*, 271–3

Outbreak of anticonvulsant intoxication in an Australian city

capsules, hard gelatin: phenytoin, levels, blood, faeces; drug availability, effect of formulation, diluents; formulation of contents, diluents, calcium sulphate, lactose

Bochner, F., Hooper, W., Tyrer, J. and Eadie, M., *Proc. Aust. Ass. Neurol.*, 1973, *9*, 165–70

The explanation of the 1968 Australian outbreak of diphenylhydantoin intoxication

capsules, hard gelatin: phenytoin, levels, blood; formulation of contents, diluents, calcium sulphate, lactose

Taylor, T. and Chasseaud, L.F., *J. pharm. Sci.*, 1977, *66*, 1638–9

Plasma concentrations and bioavailability of clofibric acid from its calcium salt in humans

capsules, soft gelatin: clofibrate, calcium salt, clofibric acid, levels, plasma; drug effect, antilipaemic action calcium salts; formulation of contents, combination with calcium carbonate

O'Grady, J., Johnson, B.F., Bye, C. and French, J., *Eur. J. clin. Pharmac.*, 1978, *14*, 357–60

The comparative bioavailability of Lanoxin tablets and Lanoxicaps with and without sorbitol

capsules, soft gelatin and tablets: digoxin, levels, urine; drug availability, comparison of dosage forms; drug availability, effects of formulation; formulation of contents, diluent, sorbitol; pharmacokinetic analysis, comparative bioavailability

Neuvonen, P.J., *Clin. Pharmacokinet.*, 1979, *4*, 91–103

Bioavailability of phenytoin: clinical pharmacokinetic and therapeutic implications

capsules, hard gelatin: phenytoin, free acid, sodium salt; drug availability, comparison of products, effect of formulation, review; 4.5.1

Wolen, R.L., Carmichael, R.H., Ridolfo, A.S., Thompkins, L. and Ziege, E.A., *Biomed. mass Spectrom.*, 1979, *6*, 173–8

The effect of crystal size on the bioavailability of benoxaprofen: Studies utilizing deuterium labelled drug

capsules, hard gelatin and solutions: benoxaprofen, levels, plasma; drug availability, effect of drug particle size; radioactive isotope technique

4.4.6.2 Semi-solid Preparations

Calvert, R.T., Barker, M., Ganley, J.A. and McEwen, J., *J. Pharm. Pharmac.*, 1983, *35*, *Suppl.*, 58P

In-vivo evaluation of a rapidly dissolving glibenclamide formulation

capsules, hard gelatin: glibenclamide, levels, blood; drug availability, effect of formulation; drug levels, radioimmunoassay technique; formulation of contents, semi-solid fill, diluent, polyethylene glycols 400/3000; gastric behaviour, visualisation method, gamma scintigraphy, technetium-99m

Ganley, J.A., McEwen, J., Calvert, R.T. and Barker, M.C.J., *J. Pharm. Pharmac.*, 1984, *36*, 734–39

The effect of in-vivo dispersion and gastric emptying on glibenclamide absorption from a novel, rapidly dissolving capsule formulation

capsules, hard gelatin: glibenclamide, levels, plasma; formulation of contents, polyethylene glycol matrix; gastric behaviour, visualisation method, gamma scintigraphy, technetium-99 m; gastric behaviour, capsule disintegration, gastric emptying, correlation with plasma levels, effect of patient's fasting state; pharmacokinetic analysis

4.4.7 Availability from Controlled Release Products

4.4.7.1 Enteric Capsules

Bukey, F.S. and Rhodes, P., *J. Am. pharm. Ass.*, 1935, *24*, 567–70

A comparative study of enteric coatings

capsules, hard gelatin and tablets: coating materials, keratin, shellac; disintegration method, X-ray, radio-opaque contents

Goorley, J.T. and Lee, C.O., *J. Am. pharm. Ass.*, 1938, *27*, 379–84

A study of enteric coating

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capsules, hard gelatin: coating material, shellac/castor oil; disintegration method, fluoroscopic examination, X-ray, radio-opaque contents

Lark-Horovitz, K. and Leng, H.R., *Nature*, 1941, *147*, 580–1

Radioactive indicators, enteric coatings and intestinal absorption

capsules, hard gelatin: coating material, castor oil/shellac; disintegration method, radioactive isotope technique

Hodge, H.C., Forsyth, H.H. and Ramsey, G.H., *J. Pharmac. exp. Ther.*, 1944, *80*, 241–9

Clinical trials of cellulose acetate phthalate as an enteric coating

capsules, soft gelatin and tablets: barium sulphate; coating material, cellulose acetate phthalate; disintegration method, fluoroscopic examination, X-ray, radio-opaque contents

Stoklosa, M.J. and Ohmart, L.M., *J. Am. pharm. Ass., pract. Pharm. Edn*, 1953, *14*, 507 and 514–5

Enteric coatings in dispensing pharmacy. 2. A practical method of extemporaneous enteric coating

capsules, hard gelatin and pills: sodium salicylate, levels, urine (human); disintegration method, fluoroscopic examination; 3.4.2.3

Boymond, P., Sfiris, J. and Amacker, P., *Pharm. Ind., Berl.*, 1966, *28*, 836–42 and *Drugs Germ.*, 1967, *10*, 7–19

The manufacture and testing of enterosoluble capsules (in German; English translation in *Drugs Germ.*)

capsules, hard gelatin: disintegration method, model system, stomach and urine marker; 3.4.2.2; 4.2.2.2

Mascoli, C.C., Leagus, M.B., Weibel, R.E., Stokes, J., Reinhart, H. and Hilleman, M.R., *Proc. Soc. exp. Biol. Med.*, 1966, *121*, 1264–8

Attempt at immunization by oral feeding live Rhinoviruses in enteric-coated capsules

capsules, hard gelatin: rhinoviruses; coating material, cellulose acetate phthalate; disintegration method, X-ray, radio-opaque contents

Eckert, T., Rothgang, G. and Seidel, R., *Arzneimittel-Forsch.*, 1968, *18*, 372–3

The pH-endoradio probe: a method for investigating the disintegration of medicinal preparations with gastric juice resistant coatings in the intestines. Part 2. The disintegration of gelatin capsules with gastric juice resistant coatings (in German)

capsules, hard gelatin: coating material, methacrylates; disintegration method, pH radiotransmitter

Lindup, W.E., Parke, D.V. and Colin-Jones, D., *Gut*, 1970, *11*, 555–8

The absorption of carbenoxolone administered orally as a positioned-release capsule

capsules, hard gelatin: carbenoxolone sodium, levels, serum; capsules, formaldehyde treatment, position release; disintegration method, X-ray, radio-opaque contents; disintegration testing, site of disintegration

Aiache, J.-M., Vidal, J.L., Aiache, S., Jeanneret, A. and Cornat, F., *Labo-Pharma Probl. Tech.*, 1974, *22*(232), 457–63

Methods for the biopharmaceutical testing of enteric capsules: Tests with "enterocaps" capsules (in French)

capsules, hard gelatin: disintegration method, X-ray, radio-opaque contents; 3.4.2.4; 4.5.6.1

Aiache, J.M., Aiache, S., Jeanneret, A., Cornat, F. and Vidal, J.L., *Boll. chim.-farm.*, 1975, *114*, 636–50

Methods for the biopharmaceutical testing of enteric capsules: Tests with "enterocaps" capsules (in French)

capsules, hard gelatin: disintegration method, X-ray, radio-opaque contents; 3.4.2.4; 4.5.6.1

Springolo, V., *Boll. chim.-farm.*, 1978, *177*, 113–21

The bioavailability of formulations of erythromycin base and stearate in gastric resistant soft gelatin capsules (in Italian)

capsules, soft gelatin: erythromycin, base and stearate, levels, plasma; enteric coating, formaldehyde treatment; 3.3.3.2; 3.4.2.2

Rees, W.D.W., Evans, B.K. and Rhodes, J., *Br. med. J.*, 1979, *2*, 835–6

Treating irritable bowel syndrome with peppermint oil

capsules, hard gelatin: peppermint oil; coating material, cellulose acetate phthalate; drug, clinical effect, comparison with placebo

Nassif, E.G., Younoszai, M.K., Weinberger, M.M. and Nassif, C.M., *J. Pediat.*, 1981, *98*, 320–3

Comparative effects of antacids, enteric coating and bile salts on the efficacy of oral pancreatic enzyme therapy in cystic fibrosis

capsules, hard gelatin: pancrelipase; drug, clinical effects, comparison of dosage forms, enteric-coated pellets in capsules, standard capsules, effects of co-administration of, antacids, bile salts; drug, clinical effects, fat absorption, nitrogen excretion; treatment costs, comparison of products

Dew, M.J., Hughes, P.J., Lee, M.G., Evans, B.K. and Rhodes, J., *Br. J. clin. Pharmac.*, 1982, *14*, 405–8

An oral preparation to release drugs in the human colon

capsules, hard gelatin: sulphapyridine, levels, plasma; coating material, methacrylic acid polymers; drug availability, correlation of plasma levels and site of disintegration; gastric behaviour, visualisation method, X-ray, radio-opaque contents; 4.4.3

Taylor, R.H., Mee, A.S., Misiewicz, J.J., Bernardo, D.E. and Polanska, N., *Br. med. J.*, 1982, *285*, 1392–3

Decrease in pancreatic steatorrhoea by positioned-release enzyme capsules

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capsules, hard gelatin and powders: tetracyclines, levels, serum, urine; drug availability, effect of formulation, diluents; 3.2.4.1

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In-vivo evaluation of a rapidly dissolving glibenclamide formulation

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The effect of in-vivo dispersion and gastric emptying on glibenclamide absorption from a novel, rapidly dissolving capsule formulation

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4.4.7 Availability from Controlled Release Products

4.4.7.1 Enteric Capsules

Bukey, F.S. and Rhodes, P., *J. Am. pharm. Ass.*, 1935, *24*, 567–70

A comparative study of enteric coatings

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Goorley, J.T. and Lee, C.O., *J. Am. pharm. Ass.*, 1938, *27*, 379–84

A study of enteric coating

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capsules, hard gelatin: pancreatin, drug, clinical effect, faecal fat levels; drug availability, comparison of standard and formaledehyde-treated capsule

Bell, G.D., Richmond, C.R. and Somerville, K.W., *Br. J. clin. Pharmac.*, 1983, *16*, 228-9P

Peppermint oil capsules (Colpermin) for the irritable bowel syndrome: a pharmacokinetic study

capsules, hard and soft gelatin: peppermint oil, menthol, levels, urine; drug availability, comparison of enteric-coated hard gelatin capsule and standard soft gelatin capsule; drug release, site of capsule disintegration

Boymond, C., Chanliau, J., Minck, R. and Stamm, A., *Pharm. Acta Helv.*, 1983, *58*, 266–9

The enteric coating of hard gelatin capsules with acrylic resins: coating technique and in vivo trial (in French)

ampoules and capsules, hard gelatin: bacteriophages; capsules, enteric-coated; drug, clinical effects, effect on urinary bacterial levels, comparison of dosage forms and effect of administration by fibroscope; 3.4.2.4

Thomas, P., Richards, D., Richards, A., Rogers, A., Evans, B.K., Dew, M.J. and Rhodes, J., *J. Pharm. Pharmac.*, 1985, *37*, 757–8

Absorption of delayed-release prednisolone in ulcerative colitis and Crohn's disease

capsules, hard gelatin; [^{3}H] prednisolone, levels, urine; coating material, methacrylates; drug availability, comparison of standard and coated capsules, effect of patient's disease state

Petroski, D., *Am. J. Gastroenterol.*, 1986, *81*, 26–8

A comparison of enteric-coated aspirin granules with plain and buffered aspirin; a report of two studies

capsules, hard gelatin and tablets: acetylsalicylic acid, levels, serum; drug availability, comparison of standard release tablets and enteric product in capsules; drug, side-effects, gastrointestinal damage measured by endoscopy, patient's subject record, comparison of dosage forms

4.4.7.2 Slow-release Capsules

Cass, L.J. and Frederik, W.S., *Curr. ther. Res.*, 1962, *4*, 263–9

Clinical evaluation of long-release and capsule forms of pentobarbital sodium

capsules, hard gelatin and tablets: pentobarbitone sodium; drug, clinical evaluation; drug availability, comparison of dosage regimens, single and multiple dose

Hollister, L.E., Kanter, S.L. and Clyde, D.J., *Clin. Pharmac. Ther.*, 1963, *4*, 612–8

Studies of prolonged-action medication. III. Pentobarbital sodium in prolonged-action form compared with conventional capsules: Serum levels of drug and clinical effects following acute doses

capsules, hard gelatin and tablets: pentobarbitone sodium, levels, serum; drug, clinical effect, Clyde mood scale

Beckett, A.H. and Tucker, G.T., *J. Pharm. Pharmac.*, 1966, *18*, *Suppl.*, 72–5S

A method for the evaluation of some oral prolonged-release forms of dexamphetamine in man, using urinary excretion data

capsules, hard gelatin, granules and solutions: dexamphetamine sulphate, levels, urine, acid pH; drug availability, comparisons of, dosage forms, dosage regimens

Allen, E.S., *Curr. ther. Res.*, 1969, *11*, 745–9

Effect of timed release on the bioavailability of ascorbic acid: Ascorbicap vs. non-timed dosage forms

capsules, hard gelatin: ascorbic acid, levels, blood, urine; drug availability, comparison of dosage regimens; formulation of contents

Beckett, A.H. and Brookes, L.G., *J. Pharm. Pharmac.*, 1971, *23*, 837–41

Administration of two or more related drugs to investigate the effect of molecular modification and formulation on drug absorption, metabolism and excretion

capsules, hard gelatin and tablets: amphetamines, metabolites, levels, urine, acid pH; drug availability, comparison of dosage forms; formulation of contents, slow-release product

Testa, B. and Beckett, A.H., *Pharm. Acta Helv.*, 1974, *49*, 21–7

The metabolism of diethylpropion in man; influence of changes in drug formulation and urinary pH

capsules, hard gelatin: diethylpropion hydrochloride, metabolites, levels, urine, acid pH; formulation of contents, slow-release product

Maneksha, S., *Br. J. clin. Pract.*, 1975, *29*, 12–13

Prolonged action fenfluramine capsules versus fenfluramine tablets in general practice

capsules, hard gelatin and tablets: fenfluramine, clinical effect, mean weight loss; drug availability, comparison of dosage forms, slow-release forms

Soeterboek, A.M. and Van Thiel, M., *J. int. med. Res.*, 1976, *4*, 393–401

Serum quinidine levels after chronic administration of four different quinidine formulations

capsules, hard gelatin and tablets: quinidine bisulphate, levels, serum; drug availability, comparison of dosage forms, standard and controlled-release forms

Frigo, G.M., Perucca, E., Teggia-Droghi, M., Gatti, G., Mussini, A. and Salerno, J., *Br. J. clin. Pharmac.*, 1977, *4*, 449–54

Comparison of quinidine plasma concentration curves following oral administration of short- and long-acting formulations

capsules, hard gelatin and tablets, standard and soluble: quinidine, arabogalactane sulphate (capsules), bisulphate, polygalacturonate, sulphate, levels, plasma; drug availability, comparisons of, salt of drug, products, slow-release preparations; pharmacokinetic analysis

Jørgensen, A., *Eur. J. clin. Pharmac.*, 1977, *12*, 187–90

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Comparative bioavailability of a sustained release preparation of amitriptyline and conventional tablets

capsules, hard gelatin and tablets: amitriptyline, levels, serum; drug availability, comparison of dosage forms, standard and controlled-release forms; formulation of contents (capsule), slow-release pellets; pharmacokinetic analysis

Manion, C.V., Lalka, D., Baer, D.T. and Meyer, M.B., *J. pharm. Sci.*, 1977, *66*, 981–4

Absorption kinetics of procainamide in humans

capsules, hard gelatin, infusions, intravenous and tablets, sustained-release: procainamide hydrochloride, levels, plasma, urine; drug availability, comparison of dosage forms, standard and slow-release forms; pharmacokinetic analysis

Bateman, N.E., Finnin, B.C., Jordan, G.J. and Reed, B.L., *Aust. J. pharm. Sci.*, 1978, *7*, 93–5

Bioavailability of theophylline from a prolonged-release soft gelatin capsule using HPLC assay of saliva samples

capsules, soft gelatin and elixirs: theophylline, levels, saliva; drug availability, comparison of dosage forms

Weinberger, M., Hendeles, L. and Bighley, L., *New Engl. J. Med.*, 1978, *299*, 852–7

The relation of product formulation to absorption of oral theophylline

capsules, hard gelatin, solutions and tablets: theophylline, levels, serum; drug availability, comparison of dosage forms

Campbell, D.B., Hopkins, V., Richards, R. and Taylor, D., *Curr. med. Res. Opinion*, 1979, *6*, *Suppl.* 1, 160–8

Fenfluramine plasma concentrations after administration of a sustained-release capsule formulation and rapid-release tablets

capsules, hard gelatin and tablets: fenfluramine, levels, plasma; drug availability, comparison of, dosage forms, dosage regimen; formulation of contents, slow release

Chubb, J.M., MacFarlane, M.D. and Woosley, R.L., *Fedn Proc.*, 1979, *38*, 585, No. 1887

Bioavailability of Theobid Duracap: sustained-release anhydrous theophylline

capsules, hard gelatin and elixirs: theophylline, levels, serum; drug availability, comparison of dosage forms

Douglas-Jones, A.P., *J. int. med. Res.*, 1979, *7*, 221–3

Comparison of a once daily long-acting formulation of propranolol with conventional propranolol given twice daily in patients with mild to moderate hypertension

capsules, hard gelatin: propranolol; drug availability, comparison of standard and slow-release products; drug, clinical effects

Falliers, C.J., *Int. J. clin. Pharmac. Biopharm.*, 1979, *17*, 125–30

Pharmacodynamic and spirometric responses to a sustained-release theophylline capsule

capsules, hard gelatin and elixirs: theophylline, levels, serum; drug, clinical effects; drug availability, comparison of dosage forms

Fleming, T.E., *Ann. Allergy*, 1979, *42*, 341

Re: Aerolate SR-JR-III capsules of theophylline

capsules, hard gelatin: theophylline; drug availability, controlled release, effect on side-effects; drug availability, serum levels for prophylaxis

Halkin, H., Almog, S. and Friedman, E., *Israel J. med. Scis*, 1979, *15*, 448–50

Serum concentrations of isosorbide dinitrate produced by a sustained-release capsule

capsules, hard gelatin and tablets: isosorbide dinitrate, levels, serum; drug availability, comparison slow-release capsules with standard tablets

Halkin, H., Vered, I., Saginer, A. and Rabinowitz, B., *Eur. J. clin. Pharmac.*, 1979, *16*, 387–91

Once daily administration of sustained release propranolol capsules in the treatment of angina pectoris

capsules, hard gelatin and tablets: propranolol, levels, serum; drug availability, comparison of slow-release capsule and standard tablet; drug, clinical effects

Meyer, M.C., Gollamudi, R. and Straughn, A.B., *J. clin. Pharmac.*, 1979, *19*, 435–44

The influence of dosage form on papaverine bioavailability

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Peristaltic dissolution apparatus: Utility in new dosage form design

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Plasma levels and renal excretion of [^{3}H]-codeine phosphate in humans receiving tablets or depot capsules (in German)

capsules, hard gelatin and tablets: codeine phosphate, levels, plasma; drug availability, comparison slow-release capsules and standard tablets; radioactive isotope technique

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Absorption characteristics of sustained release theophylline capsules administered in apple sauce

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A multicenter trial of microencapsulated potassium chloride

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Saletu, B., Grünberger, J., Amrein, R. and Skreta, M., *J. int. med. Res.*, 1981, *9*, 408–33

Assessment of pharmacodynamics of a new "controlled-release" form of diazepam (Valium CR Roche) by quantitative EEG and psychometric analysis in neurotic subjects

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A clinical and pharmacokinetic study of indomethacin in standard and slow release formulations

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Clinical assessment of theophylline absorption from Theolair-SR and two other sustained-release formulations relative to a conventional formulation

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Geigenberger, A., Degen, J. and Maier-Lenz, H., *Arzneimittel-Forsch.*, 1982, *32*, 1138–40

Comparative pharmacokinetics and bioavailability of isosorbide dinitrate and its metabolite 5-isosorbide mononitrate from two prolonged release formulations

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Investigations into gastric tolerance of a sustained release theophylline formulation

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Comparison at steady state of sustained-release theophylline tablets and capsules

capsules, hard gelatin and tablets: theophylline, levels, serum; drug availability, comparison of controlled-release capsules and tablets; pharmacokinetic analysis

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A comparison of the physiological actions of propranolol tablets and capsules (Inderal and Inderal Retard)

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Comparative oral bioavailability of conventional propranolol tablets and a new controlled-absorption propranolol capsule

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Preparation and characterisation of therapeutic hydrogels as dosage forms

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Use of isosorbide dinitrate saliva concentrations for biopharmaceutical investigations

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Absorption of theophylline from enteric coated and sustained release formulations in fasted and non-fasted subjects

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Orally administrable pharmaceutical compositions

capsules, hard gelatin: sulphapyridine, levels, plasma; capsules, enteric-coated; drug availability, correlation of plasma levels and site of disintegration; gastric behaviour, visualisation method, X-ray, radio-opaque contents; 3.4.2.4; 4.4.3

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Forty-eight-hour absorption pharmacokinetic profiles of two sustained-release theophylline preparations

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Houghton, G.W., Dennis, M.J., Templeton, R., Calvert, R.M. and Cresswell, D.G., *Int. J. clin. Pharmac. Ther. Toxic.*, 1984, *22*, 131–3

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Relative bioavailability of Etofibrate. A comparison of an acute and a new sustained release formulation

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Morley, K.D., Bernstein, R.M., Hughes, G.R.V., Black, C.M., Rajapakse, C.N.A. and Wilson, L., *Curr. med. Res. Opinion*, 1984, *9*, 28–34

A comparative trial of a controlled-release formulation of ketoprofen ('Oruvail') and a conventional capsule formulation of ketoprofen ('Orudis') in patients with osteoarthritis of the hip

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Comparison of inter- and intra-subject variation in oral absorption of theophylline from sustained-release products

capsules, hard gelatin, solutions and tablets: theophylline, levels, serum; drug availability, comparison of dosage forms, effect of subject variation; pharmacokinetic analysis, comparison with solution

Soubeyra, J., Cornet, F., Gillet, A., Georges, D. and Brazier, J.L., *Eur. J. clin. Pharmac.*, 1984, *27*, 325–28

A 'once a day administration' sustained-release theophylline formulation: Disposition and pharmacokinetics

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Timing optimizes sustained-release indomethacin treatment of osteoarthritis

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Comparative study of the bioavailability and pharmacokinetics of slow-release formulations of isosorbide dinitrate against standard drugs and determination of isosorbide-5-mononitrate

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Sado, P.A., Gibassier, D., Le Verge, R., Acerbi, D. and Schiantarelli, P., *J. Pharm. Belg.*, 1985, *40*, 308–22

Relative bioavailability of vinburnine in man (microgranules/hard gelatin capsules) (in French)

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Pharmakinetic overview of indomethacin and sustained-release indomethacin

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4.4.8 Effect of Physiological Factors on Availability

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Oxytetracycline (oxycyclin) serum concentration after oral administration (in Danish)

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Absorption, excretion and half-life of clinimycin in normal adult males

capsules, hard gelatin and tablets: clinimycin, levels, serum, urine; drug availability, comparison of dosage forms, effect of patient's fasting state

Barr, W.H., Adir, J. and Garrettson, L., *Clin. Pharmac. Ther.*, 1971, *12*, 779–84

Decrease of tetracycline absorption in man by sodium bicarbonate

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Pharmacokinetics of pentobarbital after intravenous and oral administration

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Influence of magnesium and aluminium hydroxide mixture on chlordiazepoxide absorption

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Effect of food and liquid on the pharmacokinetics of propoxyphene

capsules, hard gelatin and solutions: dextropropoxyphene hydrochloride, levels, plasma; drug availability, comparison of dosage forms, effects of, fluid intake, food type, carbohydrate, fat, protein, patient's fasting state; pharmacokinetic analysis

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The influence of food on nitrofurantoin bioavailability

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Propoxyphene and norpropoxyphene: Influence of diet and fluid on plasma level

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The effect of an antacid on the bioavailability of indomethacin

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Bioavailability of talampicillin

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Lindenbaum, J., *Clin. Pharmac. Ther.*, 1977, *21*, 278–82

Greater bioavailability of digoxin solution in capsules. Studies in the postprandial state

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Plasma level of chlormethiazole and two metabolites after oral administration to young and aged human subjects

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Absolute availability of lithium

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Raghuram, T.C. and Krishnaswamy, K., *Eur. J. clin. Pharmac.*, 1977, *12*, 281–4

Influence of nutritional status on plasma levels and relative bioavailability of tetracycline

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Bioavailability of ampicillin and amoxicillin in fasted and nonfasted subjects

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Bioavailability of tetracycline and doxycycline in fasted and nonfasted subjects

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Adir, J. and Barr, W.H., *J. Pharmacokinet. Biopharm.*, 1978, *6*, 99–110

Dose-dependent bioavailability of tetracycline in man

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Decreased tetracycline bioavailability caused by a bismuth subsalicylate antidiarrhoeal mixture

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Effect of Maalox and Kaopectate on absorption of digoxin from tablets and capsules

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Effect of calcium and antacids on phenytoin bioavailability

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The effect of sodium on the bioavailability of lithium

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Oral phenytoin loading in adults: rapid achievement of therapeutic plasma levels

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Absorption and bioavailability of oral erythromycin

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Bioavailability and pharmacokinetics in man of acipimox, a new antilipolytic and hypolipemic agent

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Influence of food on the bioavailability of Trental (Pentoxifylline) in man

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Chan, K., Tse, J., Orme, M. and Sibeon, R.G., *J. clin. Hosp. Pharm.*, 1982, *7*, 155–60

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The effects of food and posture on the pharmacokinetics of a novel formulation of nifedipine

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Accumulation of nifedipine after multiple doses

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Ogata, H., Aoyagi, N., Kaniwa, N., Ejima, A., Sekme, N., Kitamura, M. and Inoue, Y., *Int. J. Pharmaceut.*, 1986, *29*, 113–120

Gastric acidity dependant bioavailability of cinnarizine from two commercial capsules in healthy volunteers

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4.4.9 Effect of Psychological Factors on Availability

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An interesting American consumption test (in German)

capsules, soft gelatin and tablets, plain and sugar-coated: patient preference, comparison of dosage forms, ease of swallowing

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Sedative effects of placebo treatment

capsules, hard gelatin: placebo, clinical effects, sleep, onset and duration; clinical response, effects of, capsule colour, order of administration, patient's sex

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Tablet colour in anxiety states

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Demonstration to medical students of placebo responses and non-drug factors

capsules, hard gelatin: placebo, clinical effects, sedative, stimulant; clinical effects, effects of, capsule colour; dose

Masheter, H.C., *Br. med. J.*, 1977, *1*, 973–4

Keep on taking the tablets

capsules, hard gelatin: flufenamic acid, phenylbutazone; patient compliance, effect of dosage form

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Effect of capsule colour and order of administration of hypnotic treatments

capsules, hard gelatin: heptabarbitone; drug, clinical effects, sleep, onset and duration; drug, clinical response, effects of, capsule colour, order of administration, patient's sex, placebo

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Effect of obtrusive measures on antibiotic compliance

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Patient preference: Lithium pills versus capsules

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Better acceptance through colour (in German)

capsules: patient compliance, effect of colour

Blaustein, M., *Am. J. Psychiat.*, 1986, *143*, 1066

Patients taking drug capsules may fear Tylenol-like poisoning

capsules, hard gelatin: patient compliance, effect of media reporting of tampering

4.5. Drug Availability, *in vitro/in vivo* Correlation

4.5.1 General References

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Evaluation of physical and pharmaceutical factors involved in drug release and availability from chloramphenicol capsules

capsules, hard gelatin: chloramphenicol, levels, plasma; deaggregation rate testing; dissolution method, modified *U.S.P.* disintegration apparatus; drug availability, *in vitro*, drug permeation, rat intestine; powder properties, particle size

Mattila, M.J., Koskinen, R. and Takki, S., *Annls Med. intern. Fenn.*, 1968, *57*, 75–9

Absorption of ethionamide and prothionamide *in vitro* and *in vivo*

capsules, hard gelatin and tablets, film- and sugar-coated: ethionamide, prothionamide, level, serum; drug availability, *in vitro*, rat intestinal perfusion studies; drug availability, *in vivo*, ethionamide, effect of co-administration of antacids

Poole, J.W., *Drug Inf. Bull.*, 1969, *3*, 8–16

Some experiences in the evaluation of formulation variables on drug availability

capsules, hard gelatin and tablets: drug, levels, serum (dogs, human); dissolution method, beaker

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Absorption and dissolution characteristics of 14 different oral chloramphenicol preparations tested on healthy human male subjects

capsules, suspensions and tablets: chloramphenicol, palmitate, stearate, levels, serum; dissolution method, beaker, sink and non-sink conditions; drug availability, comparisons of, dosage forms, products

Kaplan, S.A. and Cotler, S., *J. pharm. Sci.*, 1972, *61*, 1361–5

Use of cannulated everted intestinal sac for serial sampling as a drug absorbability (permeability) screen

capsules, injections, intravenous and solutions: drug levels, blood (dog); drug testing, *in vitro*, permeability through everted rat intestinal sac; drug availability, *in vitro-in vivo* correlation, comparison of dissolution, permeability data, effect of drug pK_a

Jusko, W.J. and Lewis, G.P., *J. pharm. Sci.*, 1973, *62*, 69–76

Comparison of ampicillin and hetacillin pharmacokinetics in man

capsules, hard gelatin and injections, intravenous: ampicillin, hetacillin, levels, plasma, urine; dissolution method, beaker; pharmacokinetic analysis

Neuvonen, P.J., *Clin. Pharmacokinet.*, 1979, *4*, 91–103

Bioavailability of phenytoin: clinical pharmacokinetic and therapeutic implications

capsules, hard gelatin and tablets: phenytoin, comparison of dosage forms and products; drug, chemical properties; drug,

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clinical effects, effects of, drugs, physiological factors; review; 4.4.2

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Tests and standards for capsule preparations with consideration to *in vivo* conditions (in German)

capsules, hard and soft gelatin and tablets: doxycycline, tetracycline, levels, plasma; dissolution methods, flow-through cell, paddle, rotating basket; dissolution testing, comparison of methods; drug availability, comparison of dosage forms; literature review

Möller, H., *Pharm. Ind., Berl.*, 1986, *48*, 514–9

Biopharmaceutical assessment of modified release oral dosage forms

capsules, hard gelatin and tablets: indomethacin, propranolol, theophylline, percentage release; dissolution method, flow through cell, paddle; dissolution testing, comparison of methods, pharmacopoeial requirements; drug availability, physiological factors, comparison of drugs; pharmacokinetic analysis

4.5.2 Disintegration and Performance

Eckert, T., Cordes, G. and Seidel, R., *Arzneimittel-Forsch.*, 1971, *21*, 1403–6

Release of active substances from enteric-coated gelatin capsules *in vivo* and *in vitro*. Part 4. Study with the pH radiotransmitter in man (in German)

capsules, hard gelatin: disintegration method, *in vitro*, *Ger. P.* (DAB 7); disintegration method, *in vivo*, pH radiotransmitter; disintegration testing, effect of coat thickness; 3.4.2.4

Eckert, T., Cordes, G. and Ollenschläger, G., *Pharm. Ind., Berl.*, 1976, *38*, 836–41

Release of active substances from enteric-coated gelatin capsules *in vitro* and *in vivo*. Part 5. Study with films of cellulose acetate phthalate (CAP) and hydroxypropylmethylcellulose phthalate (HP–50) (in German)

capsules, hard gelatin: capsule contents, glutamic acid hydrochloride; disintegration method, *in vitro*, *Ger. P.* (DAB 7) with pH electrode; disintegration method, *in vivo*, pH radiotransmitter; disintegration testing, comparison of polymers, effect of coating thickness; 3.4.2.4

Hey, H., Matzen, P., Andersen, J.T., Didriksen, E. and Nielsen, B., *Br. J. clin. Pharmac.*, 1979, *8*, 237–42

A gastroscopic and pharmacological study of the disintegration time and absorption of pivampicillin capsules and tablets

capsules, hard gelatin and tablets: pivampicillin, disintegration method, *U.S.P.* XIX; disintegration, *in vivo*, gastroscopy; dissolution method, *U.S.P.* XIX; drug availability, comparison of dosage forms, effect of gastroscopy

4.5.3 Comparison of Dosage Forms, *in vitro*/*in vivo*

4.5.3.1 Comparison with Solid Preparations

Graffner, C. and Sjögren, J., *Acta pharm. suec.*, 1971, *8*, 19–26

Side-effects of potassium chloride in products with different dissolution rates

capsules, hard gelatin and tablets: potassium chloride; dissolution method, beaker; drug availability, side-effects, comparison of dosage forms; formulation of contents

Davis, C.M., Vandersarl, J.V. and Kraus, E.W., *Am. J. med. Sci.*, 1973, *265*, 69–74

Tetracycline inequivalence: the importance of 96-hour testing

capsules and tablets, film-coated: tetracycline hydrochloride, levels, serum, urine; dissolution method, rocking cylinder; drug availability, comparison of products

Davis, S.S., Poxon, R., Mitchard, M. and Williams, M.E., *Lancet*, 1973, *1*, 667–8

Biological availability of methaqualone

capsules, hard gelatin and tablets: methaqualone, levels, plasma; dissolution method, not stated; drug availability, comparison of products

Meyer, M.C., Slywka, G.W.A., Dann, R.E. and Whyatt, P.L., *J. pharm. Sci.*, 1974, *63*, 1693–8

Bioavailability of 14 nitrofurantoin products

capsules, hard gelatin and tablets: nitrofurantoin, levels, urine; content uniformity; disintegration method, *U.S.P.* XVIII; dissolution method, *U.S.P.*XVIII; drug availability, comparison of products

Okhotnikova, V.F., Geitman, I.Y., Yakhyaev, V.D., Grakovskaya, L.K. and Kivman, G.Y., *Antibiotiki*, 1974, *19*, 843–7

Correlation between disintegration and solubility of tablets and capsules of tetracycline and its blood level in humans (in Russian)

capsules, hard gelatin and tablets: tetracycline, levels, blood; disintegration testing; dissolution method, rotating basket

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Availability of methaqualone from commercial preparations: *in vitro* and *in vivo* studies in man

capsules, hard gelatin and tablets: methaqualone, levels, plasma; dissolution method, rotating basket; drug availability, comparison of products

Cartwright, A.C., Hatfield, H.L., Yeadon, A. and London, E., *J. antimicrob. Chemother.*, 1975, *1*, 317–22

A comparison of the bioavailability of minocycline capsules and film-coated tablets

capsules, hard gelatin and tablets, film-coated: minocycline, levels, serum; dissolution method, *U.S.P.* XVIII

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Bioavailability and dissolution of different formulations of oxytetracycline preparations

capsules, hard gelatin and tablets, film-coated: oxytetracycline, dihydrate and hydrochloride, levels, plasma; dissolution method, *U.S.N.F.* XIII; drug availability, comparison of products

Angelucci, L., Petrangeli, B., Celletti, P. and Favilli, S., *J. pharm. Sci.*, 1976, *65*, 455–6

Bioavailability of flufenamic acid in hard and soft gelatin capsules

capsules, hard and soft gelatin: flufenamic acid, levels, plasma (dogs); dissolution method, *U.S.P.* XVIII; formulation of contents

Chemburkar, P.B., Smyth, R.D., Buehler, J.D., Shah, P.B., Joslin, R.S., Polk, A. and Reavey-Cantwell, N.H., *J. pharm. Sci.*, 1976, *65*, 529–33

Correlation between dissolution characteristics and absorption of methaqualone from solid dosage forms

capsules, hard gelatin and tablets: methaqualone hydrochloride, levels, serum; dissolution method, resin flask, rotating flask; drug availability, comparison of products

Morris, J.G.L., Parsons, R.L., Trounce, J.R. and Groves, M.J., *Br. J. clin. Pharmac.*, 1976, *3*, 983–90

Plasma dopa concentrations after different preparations of levodopa in normal subjects

capsules, hard gelatin and tablets, standard and slow-release: levodopa, levels, plasma; disintegration method, *B.P.*; disintegration testing, effect of pH test media; dissolution method, beaker; dissolution testing, effect of pH test media; drug availability, comparison of products, effects of, co-administration of carbidopa, metoclopramide, slow-release preparations; drug metabolism, effect of intestinal absorption site

Okhotnikova, V.F., Grakovskaya, L.K., Koroleva, V.G., Minasova, G.S. and Zak, I.R., *Antibiotiki*, 1976, *21*, 719–21

Rate of tetracycline dissolution from tablets and capsules and biological availability of the antibiotic (in Russian)

capsules, hard gelatin and tablets: tetracycline, levels, blood; dissolution method, rotating basket

Mendes, R.W., Masih, S. Z. and Kanumuri, R.R., *J. pharm. Sci.*, 1978, *67*, 1616–19

Effect of formulation and process variables on bioequivalency of nitrofurantoin II: *In vivo – in vitro* correlation

capsules, hard gelatin and tablets, chewable and standard: nitrofurantoin, levels, urine; disintegration; dissolution method, *U.S.P.*; drug availability, effects of, drug particle size, formulation

Needham, T.E., Shah, K., Kotzan, J. and Zia, H., *J. pharm. Sci.*, 1978, *67*, 1070–3

Correlation of aspirin excretion with parameters from different dissolution methods

capsules, hard gelatin and tablets: aspirin, levels, urine; dissolution method, basket, magnetic basket, modified beaker, *U.S.P.*; dissolution testing, comparison of methods; drug availability, comparison of products, controlled-release tablets and standard capsules

Papadimitriou, D.C. and Sheth, B.B., *Drug Dev. ind. Pharm.*, 1978, *4*, 373–87

Correlation of dissolution – dialysis rates with bioavailability of nitrofurantoin solid dosage forms

capsules, hard gelatin and tablets: nitrofurantoin, levels, urine; dissolution method, modified *U.S.P.* plus dialysis chamber; *in vivo–in vitro* correlation, correlation of apparent dialytic rate constant with biological parameters

Alvisi, V., Longhini, C., Bagni, B., Portaluppi, F., Ruina, M. and Fersini, C., *Arzneimittel-Forsch.*, 1979, *29*, 1047–50

An improvement in digoxin bioavailability. Studies with soft gelatin capsules containing a solution of digoxin

capsules, soft gelatin and tablets: digoxin, levels, plasma, urine; dissolution method, paddle; drug clinical effect, cardiac functions

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Bioavailability and related heart function index of digoxin capsules and tablets in cardiac patients

capsules, soft gelatin and tablets: digoxin, levels, serum; dissolution method, beaker; dissolution testing, effect of dissolution media; drug availability, chemical effects, heart function index; pharmacokinetic analysis, comparative bioavailability

Brandau, R. and Wehnert, H.-U., *Arzneimittel-Forsch.*, 1979, *29*, 552–5

Dissolution rates and bioavailability of phenytoin preparations (in German)

capsules, hard gelatin, suspensions and tablets: phenytoin, calcium, sodium salts, levels, plasma (human); dissolution method, *U.S.P.* XIX; drug availability, comparison of products; 4.5.3.2

Leonard, G.S., Tovey, G.D. and Lee, R.M., *Drug Dev. ind. Pharm.*, 1979, *5*, 217–26

The pharmaceutical development and bioavailability of cimetidine capsule and tablet formulations

capsules, hard gelatin and tablets: cimetidine, levels, blood; disintegration method, *B.P.* 1973; dissolution method, *U.S.P.* XIX

Needham, T.E., Javid, P. and Brown, W., *J. pharm. Sci.*, 1979, *68*, 952–4

Bioavailability and dissolution paramaters of seven lithium carbonate products

capsules, hard gelatin and tablets: lithium carbonate, levels, saliva, urine (human); dissolution method, modified beaker, *U.S.P.* XIX

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Alam, A.S., Hagerman, L.M. and Imondi, A.R., *Int. J. Pharmacodyn.*, 1980, *247*, 180–9

Bioavailability of sulpiride tablet and capsule in dogs

capsules, hard gelatin and tablets: sulpiride, levels, urine, (dogs); dissolution method, rotating basket; dissolution testing, effect of test media; pharmacokinetic analysis; test media, simulated gastric and intestinal juice

Gröning, R., *Drug Dev. ind. Pharm.*, 1980, *6*, 475–91

Development and evaluation of dissolution tests using clinical data

capsules, hard gelatin and tablets: nitrofurantoin, levels, urine; dissolution methods, flow-through two-compartment cell, paddle, rotating basket; dissolution testing, comparison of, methods, products

Zak, A.F., Batuashvili, T.A. and Shchedrin, V.I., *Antibiotiki*, 1980, *25*, 24–8

Bioavailability of oral ampicillin (in Russian)

capsules, hard gelatin and tablets: ampicillin, anhydrous and trihydrate, levels, serum (human); dissolution method, basket

Cid, E., Morán, I., Monaris, M., Lasserre, C. and Vidal, V., *Biopharm. Drug Disp.*, 1981, *2*, 391–4

Bioavailability of four brands of phenytoin

capsules, hard gelatin and tablets: phenytoin sodium, levels, plasma; dissolution method, rotating basket; drug availability, comparison of products; pharmacokinetic analysis

El-Yazigi, A. and Sanchuk, R.J., *J. pharm. Sci.*, 1985, *74*, 161–4

In vitro–in vivo correlation and dissolution studies with oral theophylline dosage forms

capsule, hard gelatin and tablets: theophylline; dissolution methods, basket, rotating filter; dissolution testing, comparison of dosage forms, formulations, slow and standard release, effects of, pH test media, stirring rate; pharmacokinetic analysis, correlation with *in vivo*, blood levels (rabbit)

Neisingh, S.E., Sam, A.P. and de Nijs, H., *Drug Dev. ind. Pharm.*, 1986, *12*, 651–63

A dissolution method for hard and soft gelatin capsules containing testosterone undecanoate in oleic acid

capsules, hard and soft gelatin: testosterone undecanoate levels, plasma; dissolution method, flow-through cell; dissolution testing, comparison of dosage forms, effect of formulation; drug availability, comparison of dosage forms, effect of formulation

Sournac, M., Ducroux, P., Aiache, J. M., Renoux, R., Kantelip, J.P. and Ducros, M., *Fourth International Conference on Pharmaceutical Technology*, (Paris, APGI, June 3–5, 1986), 1986, II, 108–17

Studies in the comparative bioavailability of aspirin from four pharmaceutical forms. Application of statistical moments to the interpretation of the results and the establishment of *in vitro/in vivo* correlations (in French)

capsules, hard gelatin and tablets: acetylsalicylic acid, levels, plasma; dissolution method, rotating paddle; dissolution testing, comparison of dosage forms; drug availability, comparison of dosage forms; pharmacokinetic analysis

4.5.3.2 Comparison with Liquid Preparations

Baun, D.C., Bowen, B.M. and Wood, D.E., *Am. J. Hosp. Pharm.*, 1975, *32*, 1047–9

Comparison of the bioavailability of Cyanocobalamin from capsule and liquid dosage forms

capsules, hard gelatin and solutions: cyanocobalamin, levels, urine; dissolution method, continuous flow apparatus; radioactive isotope technique

Pandit, J.K., Jagadeesh, G., Nagabooshanam, M. and Tripathi, M.K., *Drug Dev. ind. Pharm.*, 1984, *10*, 85–99

Effect of some formulation additives on the oral absorption of indomethacin

capsules, hard gelatin and suspensions: indomethacin, levels, plasma (dog); dissolution method, modified beaker; dissolution testing, comparisons of, capsule products, dosage forms, effect of, drug treatment; drug availability, comparisons of, capsule products, dosage forms, effect of formulation; drug treatment, surface coating by co-precipitation with sodium taurocholate

4.5.3.3 Comparison with Injections

Flasch, H., Asmussen, B. and Heinz, N., *Arzneimittel-Forsch.*, 1978, *28*, 326–30

Enhanced bioavailability of digoxin from silica matrix formulations (in German)

capsules, hard gelatin, injections, intravenous and tablets, enteric, sugar-coated and uncoated: digoxin, levels, urine; disintegration method, DAB; dissolution method, continuous flow cell; drug availability, effect of formulation; formulation of contents, diluent, silicic acid; pharmacokinetic analysis

4.5.3.4. Comparison with Rectal Preparations

Wellauer, J., del Buono, M., Ory, A.M. and Steiger-Trippi, K., *Pharm. Acta Helv.*, 1960, *35*, 619–30

Gelatin-rectal-capsule, a new dosage form for rectal treatment

capsules, soft gelatin and suppositories: disintegration method, *in vitro*, Erweka apparatus; disintegration method, *in vivo*, X-ray, radio-opaque contents; rectal capsule

Parrott, E.L. and Matheson, L.E., *J. pharm. Sci.*, 1977, *66*, 955–8

Rectal absorption of nitrofurantoin

capsules, hard gelatin and suppositories: nitrofurantoin, levels, urine; dissolution method, *U.S.P.* disintegration apparatus

Moës, A.J., *Pharm. Acta Helv.*, 1981, *56*, 21–5

Formulation of highly available theophylline rectal suppositories

capsules, soft gelatin and suppositories: theophylline, anhydrous, monohydrate, levels, serum; dissolution method, suppositories, flow-through cell; drug properties, partition coefficient, solubility, measurements; intrinsic dissolution method, beaker; 3.5.2

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Möller, H., *Pharm. Ind., Berl.*, 1984, *46*, 514–20

In vitro and *in vivo* dissolution of rectal indomethacin dosage forms (in German)

capsules, soft gelatin and suppositories: indomethacin; disintegration testing; dissolution method, flow-through cell; dissolution testing, effect of formulation; product properties, melting point, viscosity, effect of storage; 3.5.2

Hagenlocher, M., Hannula, A.M., Wittwer, F., Soliva, M. and Speiser, P., *Fourth International Conference on Pharmaceutical Technology*, (Paris, APGI, June 3–5, 1986), 1986, *I*, 398–405

Hard gelatin capsules for rectal drug delivery

capsules, hard gelatin, enema, solutions, oral and suppositories: paracetamol, levels, saliva; disintegration method DAB 8; disintegration testing, effect of capsule coating; dissolution testing, modified beaker; dissolution testing, comparisons of dosage forms, formulation of contents; pharmacokinetic analysis; 3.2.4.2; 3.5.2

4.5.3.5 Comparison with Multiple Dosage Forms

Calesnick, B., Katchen, B. and Black, J., *J. pharm. Sci.*, 1965, *54*, 1277–80

Importance of dissolution rates in producing effective diazoxide blood levels in man

capsules, hard gelatin, injections, intravenous, solutions and tablets: diazoxide, levels, blood; drug clinical effects, blood glucose levels, blood pressure; dissolution method, Stoll Gershberg

Flanagan, T.H., Broad, R.D., Rubinstein, M.H. and Longworth, A.R., *J. Pharm. Pharmac.*, 1969, *21, Suppl.*, 129S–34S

Dissolution and absorption of ICI 49,455

capsules, hard gelatin, solutions and tablets, film-coated and plain: ICI 49,455, levels, blood (dogs); dissolution method, beaker; drug availability, *in vitro*, goldfish death time

Chiou, W.L. and Riegelman, S., *J. pharm. Sci.*, 1970, *59*, 937–42

Oral absorption of griseofulvin in dogs: increased absorption via solid dispersion in polyethylene glycol 6000

capsules, hard gelatin, solutions and tablets: griseofulvin, levels, plasma, urine (dogs); dissolution method, modified *U.S.P.* disintegration apparatus; drug availability, effect of formulation; formulation of contents, solid dispersions in polyethylene glycol

Nash, J.F., Scholz, N.E. and Maxwell, S.B., *Toxic. appl. Pharmac.*, 1971, *19*, 537–45

A study of propoxyphene and salicylate concentrations in human plasma following the administration of propoxyphene napsylate and aspirin

capsules, hard gelatin, suspensions and tablets: aspirin, dextropropoxyphene hydrochloride and napsylate, caffeine, phenacetin, levels, plasma; disintegration method, *U.S.P.*; dissolution method, *U.S.P*; drug availability, effect of, capsule formulation, drug combination

Stricker, H., *Pharm. Ind., Berl.*, 1971, *33*, 446–54 and *Drugs Germ.*, 1971, *14*, 126–40

On the relationship between drug absorption and dissolution in the gastrointestinal tract (1) (in German, English translation in *Drugs Germ.*)

capsules, hard gelatin, solutions and tablets: aspirin, phenoxymethylpenicillin potassium, sulphapyrimidine, levels, plasma (human); dissolution method, Sartorius apparatus, *U.S.P.* XVIII; dissolution testing, comparison of methods

Fischler, M., Frisch, E.P. and Örtengren, B., *Acta pharm. suec.*, 1973, *10*, 483–92

Plasma concentrations after oral administration of different pharmaceutical preparations of clomethiazole

capsules, soft gelatin, solutions and tablets: clomethiazole, levels, plasma; disintegration method, *Nord.P.* apparatus

Wiseman, E.H., McIlhenny, H.M. and Bettis, J.W., *J. pharm. Sci.*, 1975, *64*, 1469–75

Flumizole, a new nonsteroidal anti-inflammatory agent

capsules, hard gelatin, infusions, intravenous, injections, intravenous and solutions: flumizole, levels, faeces, serum, urine (dogs, humans); dissolution method, *U.S.N.F.* XIII apparatus; pharmacokinetic analysis

Bergan, T., Berdal, B.P. and Holm, V., *Acta pharmac. tox.*, 1976, *38*, 308–20

Relative bioavailability of phenoxymethylpenicillin preparations in a cross-over study

capsules, hard gelatin, solutions, suspensions and tablets: phenoxymethylpenicillin, levels, serum; dissolution method, *U.S.P.*XVIII

Garrett, E.R., Roseboom, H., Green, J.R. and Schuermann, W., *Int. J. clin. Pharmac. Biopharm.*, 1978, *16*, 193–208

Pharmacokinetics of papaverine hydrochloride and the biopharmaceutics of its oral dosage forms

capsules, hard gelatin, injections, intravenous, solutions and tablets: papaverine hydrochloride, levels, serum; dissolution method, shaken flask; drug availability, comparison of dosage regimen, standard and slow-release preparation (capsule); pharmacokinetic analysis

Brandau, R. and Wehnert, H.-U., *Arzneimittel-Forsch.*, 1979, *29*, 552–5

Dissolution rates and bioavailability of phenytoin prepartions (in German)

capsules, hard gelatin, suspensions and tablets: phenytoin, calcium and sodium salts, levels, plasma; dissolution method, *U.S.P.* XIX; 4.5.3.1

Sved, S., Hossie, R.D., McGilveray, I.J., Beaudoin, N. and Brien, R., *Can.. J. pharm. Sci.*, 1979, *14*, 67–71

Bioavailability, absorption and dissolution kinetics of phenytoin formulations

capsules, hard gelatin, suspensions and tablets: phenytoin sodium, levels, plasma (human); dissolution method, modified beaker; drug availability, comparison of products; pharmacokinetic analysis

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4.5.4 Comparison of Capsule Products

Bartelloni, P.J., Calia, F.M., Minchew, B.H., Beisel, W.R. and Ley, H.L., *Am. J. med. Sci.*, 1969, *258*, 203–8

Absorption and excretion of two chloramphenicol products in humans after oral administration

capsules, hard gelatin: chloramphenicol, levels, serum, urine; dissolution method, modified *U.S.P.* disintegration apparatus; drug availability, comparison of dosage regimens

Macdonald, H., Pisano, F., Burger, J., Dornbush, A. and Pelcak, E., *Clin. Med.*, 1969, *76*, 30–3

Physiologic availability of various tetracyclines

capsules: tetracyclines, levels, serum, urine; content uniformity; disintegration method, *U.S.P.*; dissolution method, rocking cylinder; drug availability, comparison of dosage regimens, single and multiple doses

Macdonald, H., Pisano, F., Burger, J., Dornbush, A. and Pelcak, E., *Drug Inf. Bull.*, 1969, *3*, 76–81

Physiological availability of various tetracyclines

capsules: tetracyclines, levels, serum, urine; content uniformity; disintegration method, *U.S.P.*; dissolution method, rocking cylinder; drug availability, comparison of dosage regimens, single and multiple doses

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Effectiveness of oxytetracyclines

capsules: oxytetracyclines; FDA certification

MacLeod, C., Rabin, H., Ruedy, J., Caron, M., Zarowny, D. and Davies, R.O., *Can. med. Ass. J.*, 1972, *107*, 203–9

Comparative bioavailability of three brands of ampicillin

capsules, hard gelatin: ampicillin trihydrate, levels, serum; dissolution method, *U.S.P.* XVIII; product, content uniformity

Butler, K., *Revue Can. Biol.*, 1973, *32, Suppl.*, 53–67

Biological availability of oxytetracycline HCl capsules

capsules, hard gelatin: oxytetracycline hydrochloride, levels, serum; dissolution method, Stoll-Gershberg apparatus; pharmacokinetic analysis

Andrade, L., Ortiz, S., Firmani, F. and Cid, E., *Annls pharm. fr.*, 1978, *36*, 639–44

Bioavailability of three brands of commercial ampicillin (in French)

capsules, hard gelatin: ampicillin, levels, urine (human); dissolution method, rotating basket

Berezovskaia, L.N., Koroleva, V.G., Granatova, E.K. and Grakovskais, L.K., *Antibiotiki*, 1979, *24*, 821–4

Bioavailability of doxycycline capsules (in Russian)

capsules, hard gelatin: doxycycline, levels, serum; dissolution testing, *U.S.P.* method; drug availability, comparison with American products

Bron, J., Vree, T.B., Damsma, J.E., Hekster, Y.A. and van der Kleijn, E., *Arzneimittel-Forsch.*, 1979, *29*, 1614–20

Dissolution, bioavailability and pharmacokinetics of three nitrofurantoin preparations in man

capsules, hard gelatin and tablets: nitrofurantoin, levels, plasma, urine; disintegration method, *U.S.P.* XIX; dissolution method, rotating basket; drug availability, formulation of contents, effect of particle size

Quay, J.F., Childers, R.F., Johnson, D.W., Nash, J.F. and Stucky, J.F., *J. pharm. Sci.*, 1979, *68*, 227–32

Cinoxacin in female mongrel dogs: effect of urine pH on urinary excretion and correlation of *in vitro* characteristics of oral dosage forms with bioavailability

capsules, hard gelatin, injections, intravenous and solutions: cinoxacin, levels, plasma, urine (dogs); dissolution method, modified basket; drug availability, formulation of contents, effect of powder properties, urinary pH; powder properties, particle size, surface area

Trivedi, B.M. and Patel, P.R., *Indian J. pharm. Sci.*, 1979, *41*, 66–8

Bioavailability of ampicillin in dogs

capsules, hard gelatin: ampicillin, levels, serum (dogs); dissolution method, rotating basket

Zak, A.F., Batuashvili, T.A. and Shchedrin, V.I., *Antibiotiki*, 1981, *26*, 728–31

Rifampicin drugs for oral use and their bioavailability (in Russian)

capsules, hard gelatin: rifampicin, levels, plasma; dissolution method, rotating basket; dissolution testing, comparison of products; drug availability, comparison of products

Kaniwa, N., Ogata, H., Aoyagi, N., Shibazaki, T., Ejima, A., Watanabe, Y., Motahashi, K., Sasahara, K., Nakajima, E., Morioka, T. and Nikanai, T., *Int. J. clin. Pharmac. Ther. Toxic.*, 1983, *21*, 56–63

The bioavailability of flufenamic acid and its dissolution rate from capsules

capsules, hard gelatin: flufenamic acid, levels, serum (dogs and humans); dissolution method, disintegration apparatus (*Jpn P.*), paddle, rotating basket, solubility simulator; dissolution testing, effects of, pH test medium, surfactant; pharmacokinetic analysis, comparison of dogs and humans

Shah, V.P., Prasad, V.K., Alston, T., Cabana, B.E., Gural, R.P. and Meyer, M.C., *J. pharm. Sci.*, 1983, *72*, 306–8

Phenytoin I: *In vitro–in vivo* correlation for 100-mg phenytoin sodium capsules

capsules, hard gelatin: phenytoin sodium, levels, plasma; dissolution method, paddle, rotating basket; dissolution testing, comparison of products; drug availability, comparison of products; pharmacokinetic analysis

Shah, V.P., Prasad, V.K., Freeman, C., Skelly, J.P. and Cabana, B.E., *J. pharm. Sci.*, 1983, *72*, 309–10

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Phenytoin II: *In vitro–in vivo* bioequivalence standard for 100-mg phenytoin sodium capsules

capsules, hard gelatin: phenytoin sodium, levels, plasma; dissolution method, rotating basket; dissolution testing, comparison of products, fast and slow dissolving, proposed pharmacopoeial limit; drug availability, comparison of products; pharmacokinetic analysis

Shinozavva, S., Yoshimura, A. and Araki, Y., *Res. Commun. chem. Path. Pharmac.*, 1983, *42*, 161–4

The dissolution and bioavailability of Rifampicin products in healthy subjects and tubercular patients

capsules, hard gelatin: rifampicin, levels, plasma; dissolution method, rotating basket; dissolution testing, effect of test media; drug availability, effect of patient's disease state; pharmacokinetic analysis

Gouda, H.W., Moustafa, M.A. and Al-Shora, H.I., *Int. J. Pharmaceut.*, 1984, *18*, 213

Effect of storage on nitrofurantoin solid dosage forms

capsules, hard gelatin and tablets: nitrofurantoin, levels, urine; dissolution method, *U.S.P.*; dissolution testing, effects of, drug particle size in capsules, storage; 3.8.3.7

Aoyagi, N., Ogata, H., Kaniwa, N., Ejime, A., Nakata, H., Tsutsumi, J., Fujita, T. and Amada, I., *Int. J. clin. Pharmac. Ther. Toxic.*, 1985, *23*, 578–84

Bioavailability of indomethacin capsules in humans (III): correlation with bioavailability in beagle dogs

capsules, hard gelatin: indomethacin, levels, plasma (dogs); drug availability, effects of, formulation; gastric acidity; pharmacokinetic analysis, correlation with dissolution results

Kahr, R.K., Urumov, A. and Minkov, E., *Pharmazie*, 1985, *40*, 734–735

Comparative bioavailability studies of some oral amoxycillin products in rabbits

capsules, hard gelatin: amoxycillin, levels, serum (rabbit); dissolution methods, paddle, rotating basket, Sartorius; pharmacokinetic analysis

Mortada, L.M., Ismail, F.A. and Khalil, S.A., *Drug Dev. ind. Pharm.*, 1985, *11*(1), 101–30

Correlation of urinary excretion with *in vitro* dissolution using four dissolution methods for ampicillin capsules

capsules, hard gelatin: ampicillin, levels, urine; dissolution methods, disintegration apparatus modified, paddle, rotating basket, spiral stirrer method; dissolution testing, comparisons of, dissolution method, products, effect of stirrer speed

4.5.5 Effect of Formulation

Nelson, E. and Yuzuriha, Y., *J. Am. pharm. Ass., scient. Edn*, 1959, *48*, 96–103

Influence of dissolution rate and surface on tetracycline absorption

capsules, hard gelatin: tetracycline, hydrochloride phenolsulphonphthalein salt, sodium hexametaphosphate complex, levels, urine (human); dissolution method, solution rate of compressed disks; drug availability, effects of, diluent, sodium bicarbonate, particle size of active drug; formulation of contents, compressed disks, granules prepared by compression

Roland, M., *J. Pharm. Belg.*, 1967, *22*, 67–94

Formulation and availability of pharmaceutical tablets: applications to triamterene (in France)

capsules, hard gelatin and tablets: triamterene, levels, urine; disintegration method, Erweka apparatus; dissolution method, Souder and Ellenbogen; drug availability, comparison of dosage forms, effect of drug particle size

McGee, B.J., Kennedy, D.R. and Walker, G.C., *J. pharm. Sci.*, 1970, *59*, 1430–3

Some factors affecting release and availability of drugs from hard gelatin capsules

capsules, hard gelatin: acetylsalicylic acid, levels, plasma (rabbit); dissolution method, beaker; dissolution testing, effect of excipients

Koeleman, H.A. and van Oudtshoorn, M.C.B., *S. Afr. med. J.*, 1973, *47*, 94–9

An evaluation of the biological availability of chloramphenicol

capsules, hard gelatin: chloramphenicol, levels, urine; disintegration method, *B.P.*; dissolution method, beaker, modified *B.P.* disintegration apparatus; drug availability, effect of powder properties; powder properties, deaggregation rate determination, particle size determination; pharmacokinetic analysis

Dugal, R., Brodeur, J. and Caillé, G., *J. clin. Pharmac.*, 1974, *14*, 513–9

Ampicillin systemic bioavailability: the influence of dosage form

capsules, hard gelatin: ampicillin trihydrate, levels, serum; dissolution method, *U.S.P.* XVIII; formulation of contents, dry granulation, powder fill

Nash, J.F., Bechtel, L.D., Lowary, L.R., Rodda, B.E. and Rose, H.A., *Drug Devel. Comm.*, 1974–5, *1*, 443–57

The relationship between the particle size of dicumarol and its bioavailability in dogs. Part I. Capsules

capsules, hard gelatin: dicoumarol, levels, plasma, prothrombin time (dogs); dissolution method, *U.S.P.* XVIII; drug availability, effect of drug particle size

Nash, J.F., Childers, R.F., Lowary, L.R. and Rose, H.A., *Drug Devel. Comm.*, 1974–5, *1*, 459–70

The relationship between the particle size of dicumarol and its bioavailability in dogs. Part II. Drug substance

capsules, hard gelatin: dicoumarol, levels, plasma, prothrombin time (dogs); dissolution method, *U.S.P.* XVIII; drug availability, effect of drug particle size; powder properties, crystal structure

Allen, J.G. and Davies, C.A., *J. Pharm. Pharmac.*, 1975, *27*, 50–1

The effect of addition of lactose on the oral absorption of a highly lipid soluble drug

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capsules, hard gelatin and solutions: narcotic analgesic, levels, blood (dogs); dissolution method, modified beaker; drug availability, effect of drug particle size; formulation of contents, diluents, lactose, starch

Hill, S.A., Jones, K.H., Seager, H. and Taskis, C.B., *J. Pharm. Pharmac.*, 1975, *27*, 594–8

Dissolution and bioavailability of the anhydrate and trihydrate forms of ampicillin

capsules, hard gelatin: ampicillin anhydrous and trihydrate, levels, serum; dissolution method, flask apparatus

Johnson, B.F., Mcauley, P.V., Smith, P.M. and French, J.A.G., *J. Pharm. Pharmac.*, 1977, *29*, 576–8

The effects of storage upon *in vitro* and *in vivo* characteristics of soft gelatin capsules containing digoxin

capsules, soft gelatin: digoxin, levels, plasma; dissolution method, beaker; drug availability, effect of storage

Kassem, M.A., Salama, H.A., Ammar, H.O. and El-Ridy, M.S., *Pharm. Ind., Berl.*, 1977, *39*, 396–9

On the dissolution and bioavailability of phenindione. III. Dissolution and bioavailability of phenindione capsules

capsules, hard gelatin and powders: phenindione, levels, from blood clotting times (rabbit); dissolution method, beaker, *U.S.P.* XVIII; dissolution testing, effects of, capsule shell, drug particle size, formulation; formulation of contents, solid dispersions

Kent, J.S., Mroszczak, E. and Yost, M., *Drug Dev. ind. Pharm.*, 1977, *3*, 507–22

The use of radio-labelled drug in early dosage form development to provide a relation between physical dosage form characteristics and bioavailability

capsules, hard gelatin: dibenzthiepin, acetic acid derivative, ^{14}C-labelled, levels, serum, urine (monkey); dissolution method, *U.S.P.* type; formulation of contents; powder properties, particle shape, specific area; radioactive isotope technique

Kranz, O., Soliva, M. and Speiser, P.P., *Pharm. Ind., Berl.*, 1977, *39*, 712–5

The bioavailability of paracetamol from formulated hard gelatin capsules (in German)

capsules, hard gelatin and solutions: paracetamol, levels, saliva; dissolution method, column; drug availability, effect of formulation of capsule shells and contents; formulation of contents, lubricant, magnesium stearate

Kranz, O. and Speiser, P., *First International Conference on Pharmaceutical Technology*, Paris, APGI, 1977, IV, 209–13

The biopharmacy of capsules (in French)

capsules, hard gelatin: paracetamol, levels, saliva, urine ; dissolution method, flow-through cell; dissolution testing, effects of, formulation of capsule contents and shells; drug availability, effects of, formulation of capsule contents and shells; formulation of capsule shells, bone gelatin, skin gelatin, mixed gelatins; formulation of contents, hydrophilic, granules coated with polyvinylpyrrolidone, hydrophobic, mixed with magnesium stearate

Fell, J.T., Calvert, R.T. and Riley-Bentham, P., *J. Pharm. Pharmac.*, 1978, *30*, 479–82

Bioavailability of griseofulvin from a novel capsule formulation

capsules, hard gelatin: griseofulvin, levels, urine; coating materials, hydroxypropylcellulose; coating method, granulation; dissolution method, beaker; dissolution testing, effect of hydrophilic coating of hydrophobic drug; formulation, hydrophilic coatings; pharmacokinetic analysis

Lerk, C.F., Lagas, M., Lie-A-Huen, L., Broersma, P. and Zuurman, K., *J. pharm. Sci.*, 1979, *68*, 634–8

In vitro and *in vivo* availability of hydrophilized phenytoin from capsules

capsules, hard gelatin: phenytoin, levels, plasma; disintegration method, *B.P.* 1973; dissolution method, beaker; formulation of contents, drug particle coating, methylcellulose

Nash, J.F., Bechtol, L.D., Bunde, C.A., Bopp, R.J., Farid, K.Z. and Spradlin, C.T., *J. pharm. Sci.*, 1979, *68*, 1087–90

Linear pharmacokinetics of orally administered fenoprofen calcium

capsules, hard gelatin: fenoprofen calcium, levels, plasma, urine; dissolution method, rotating basket

Ridolfo, A.S., Thompkins, L., Bechtol, L.D. and Carmichael, R.H., *J. pharm. Sci.*, 1979, *68*, 850–2

Benoxaprofen, a new anti-inflammatory agent: particle-size effect of dissolution rate and oral absorption in humans

capsules, hard gelatin: benoxaprofen, levels, plasma, urine; dissolution method, rotating basket; formulation of contents, particle size

Stewart, A.G., Grant, D.J.W. and Newton, J.M., *J. Pharm. Pharmac.*, 1979, *31*, 1–6

The release of a model low-dose drug (riboflavine) from hard gelatin capsule formulations

capsules, hard gelatin: riboflavine, levels, urine; dissolution method, beaker; 3.2.4.1

Wagner, J.G., Stoll, R.G., Weidler, D.J., Ayres, J.W., Hallmark, M.R., Sakmar, E. and Yacobi, A., *J. Pharmacokinet. Biopharm.*, 1979, *7*, 147–58

Comparison of the *in vitro* and *in vivo* release of digoxin from four different soft gelatin capsule formulations

capsules, soft gelatin: digoxin, levels, serum, urine; disintegration, capsule bursting time; dissolution method, *U.S.P.* XVIII; drug availability, effects of capsule disintegration

Bowtle, W., Woodage, T. and Waugh, A., *Int. J. Pharmaceut.*, 1981, *9*, 305–13

Bromhexine: *in vitro* and *in vivo* studies of release from mono- and bi-component preparations

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capsules, hard gelatin: bromhexine, base, hydrochloride, levels, plasma; cefaclor, levels, plasma; dissolution method, rotating basket; dissolution testing, effect of cefaclor presence; drug availability, effect of cefaclor presence; formulation of contents, bromhexine with or without cefaclor; pharmacokinetic analysis

Rosenberg, J.M., *N.Y. St. J. Med.*, 1981, *81*, 759

Please provide information concerning the differences between prompt phenytoin sodium capsules and extended phenytoin sodium capsules

capsules, hard gelatin: phenytoin; drug availability, comparison with *in vitro* dissolution standards, effect of fast and slow release forms

Boymond-Genoud, M., Eide-Jurgensen, G., Mordier, D., Doelker, E. and Buri, P., *J. Pharm. Belg.*, 1982, *37*, 135–40

The role of wetting in the release of hydrophobic drugs from hard gelatin capsules. II Deaggregation, dissolution and bioavailability in man (in French)

capsules, hard gelatin: phenacetin, levels, plasma; dissolution methods, continuous flow, paddle, rotating basket; dissolution testing, effects of, formulation of contents, powder properties, test media; powder properties, deaggregation, particle size; test media, inclusion of surfactants, polysorbate 80, dioctyl sodium sulphosuccinate

Laboratoires Negma, *French Patent* 2 500 302, 1982

Novel pharmaceutical compositions of indomethacin (in French)

capsules, soft gelatin: indomethacin, levels, plasma (rabbit); dissolution method, *U.S.P.*; dissolution testing, effect of formulation of contents; drug side-effects, gastric intolerance, effect of formulation of contents; 3.3.3.2

Aiache, J.-M., Roca, R., Bastide, J., Bastide, M. and Kantelip, J.-P., *J. Pharm. Belg.*, 1983, *38*, 5–21

Biopharmaceutical study of indomethacin new drug dosage forms (in French)

capsules, soft gelatin: indomethacin, levels, plasma (human); dissolution method, paddle; dissolution testing, effect of lipophilic contents; drug availability, animal, comparison of formulations and drug substance by LD50 in mice and rats; drug clinical effects (rat), anti-inflammatory activity on paw swelling, comparison of drug, excipients and products; drug side-effects (rat), effect on gastro-intestinal tract, comparison of drug, excipients and products; pharmacokinetic analysis; 3.3.3.2

Bauer, K.H. and Dortunc, B., *Drug Dev. ind. Pharm.*, 1984, *10*, 699–712

Non-aqueous emulsions as vehicles for capsule fillings

capsules, hard gelatin: riboflavine, salicylic acid, levels, urine; dissolution method, flow-through cell; 3.2.4.2

Shinkuma, D., Hamaguchi, T., Yamanaka, Y. and Mizuno, N., *Int. J. Pharmaceut.*, 1984, *21*, 187–200

Correlation between dissolution method and bioavailability of different commercial mefenamic acid capsules

capsules, hard gelatin: mefenamic acid, levels, plasma; disintegration method, *Jpn. P.* X; disintegration testing, comparison of products, effect of encapsulation; dissolution method, paddle; dissolution testing, comparison of products, fast and slow dissolving; drug availability, comparison of capsule contents, encapsulated, free; pharmacokinetic analysis

Aoyagi, N., Ogata, H., Kaniwa, N. and Ejima, A., *Int. J. clin. Pharmac. Ther. Toxic.*, 1985, *23*, 529–34

Bioavailability of indomethacin capsules in humans (II): correlation with dissolution rate

capsules, hard gelatin: indomethacin; disintegration method, *Jpn. P.* X; disintegration testing, effects of, formulation of contents, pH test media; dissolution methods, paddle, oscillating basket, rotating basket, solubility simulator; dissolution testing, effects of, pH of test media, stirrer speed; pharmacokinetic analysis, correlation with *in vivo* results

Aoyagi, N., Ogata, H., Kaniwa, N. and Ejima, A., *Int. J. clin. Pharmac. Ther. Toxic.*, 1985, *23*, 469–74

Bioavailability of indomethacin capsules in humans (1): bioavailability and effects of gastric acidity

capsules, hard gelatin: indomethacin, levels, serum; dissolution method, paddle; dissolution testing, effects of formulation of contents; drug availability, effects of, formulation of contents, patient's gastric acidity; pharmacokinetic analysis

Bowtle, W.J.., Lucas, R.A. and Barker, N.J., *Fourth International Conference on Pharmaceutical Technology*, (Paris, APGI, June 3–5, 1986), 1986, *V*, 80–89

Formulation and process studies in semi-solid matrix capsule technology

capsules, hard gelatin: fenoprofen, levels, serum; dissolution method, flow through cell; dissolution testing, effect of formulation; drug availability, effect of formulation; 3.2.4.2.; 3.8.3.7

Tossounian, J.L., Mergens, W.J. and Sheth, P.R., *Drug Dev. ind. Pharm.*, 1985, *11*, 1019–1050

Bioefficient products. A novel delivery system

capsules, hard gelatin and tablets: riboflavine, levels, urine; capsules, floating dosage form; dissolution method, beaker; dissolution testing, comparison of dosage forms and formulations; 4.4.3

Mohamad, H., Renoux, R., Aïache, S., Aïache, J.-M. and Kantelip, J.-P., *Sciences tech. pharm.*, 1986, *2*(18), 630–635

Study on the biopharmaceutical stability of medicines: application to tetracycline hydrochloride capsules: II *in vivo* study

capsules, hard gelatin: tetracycline hydrochloride, levels, plasma, urine; dissolution testing, comparison of batches, effect of storge; drug availability, comparison of batches, effect of storage; pharmacokinetic analysis; pharmacokinetic parameters, comparison of formulas, effect of storage

4.5.6 Controlled Release Products

4.5.6.1 Enteric Capsules

Bauer, C.W. and Geraughty, R.J., *J. Am. pharm. Ass., pract. Pharm. Edn*, 1953, *14*, 504–7 and 512

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Enteric coatings in dispensing pharmacy. I. The preliminary investigation

capsules, hard gelatin and tablets: sodium salicylate, levels, urine; coating materials, carnauba wax, *n*-butyl stearate; coating method, hot dipping; disintegration method, *in vitro*, *U.S.P.*, disintegration method, *in vivo*, timed urine analysis; disintegration testing, *in vitro*, effect of solvents; formulation of coating, stability

Parrott, E.L., *J. Am. pharm. Ass.*, 1961, *NS1*, 158–9

An extemporaneous enteric coating

capsules, hard gelatin: acetylsalicylic acid, levels, urine; potassium iodide, levels, saliva; disintegration method, *in vitro*, *U.S.P.* apparatus; drug availability, *in vivo*, comparison of coating materials; 3.4.2.1

Cook, C.H. and Webber, M.G., *Am. J. Hosp. Pharm.*, 1965, *22*, 95–9

An extemporaneous method of preparing enteric-coated capsules

capsules, hard gelatin: disintegration method, *in vitro*, modified *U.S.P.* XVI; disintegration method, *in vivo* (dogs), X-ray, radio-opaque contents; 3.4.2.4

Cordes, G., *Pharm. Ind., Berl.*, 1969, *31*, 328–31 and *Drugs Germ.*, 1969, *12*, 111–7

Enteric-coated hard gelatin capsules as a dosage form for enzyme preparations (in German: English translation in *Drugs Germ.*)

capsules, hard gelatin and tablets: pancreatin; disintegration method, *in vitro, Ger. P.* (DAB 7); disintegration method, *in vivo*, radiotransmitter; disintegration testing, effects of, enteric film thickness, filling method; dissolution method, beaker; dissolution testing, measurement of lipase activity

Ekberg, L. and Källstrand, G., *Svensk farm. Tidskr.*, 1972, *76*, 375–8

The enteric coating of hard gelatin capsules on a dispensary scale (in Swedish)

capsules, hard gelatin: capsules, enteric coated; disintegration method, *in vitro, Nord. P.*; disintegration method, *in vivo*, gamma scintigraphy, technetium-99m; disintegration testing, *in vitro*, effect of film thickness; disintegration testing, *in vivo*, comparison of coated and uncoated capsules; 3.4.2.4

Aiache, J.-M., Vidal, J.L., Aiache, S., Jeanneret, A. and Cornat, F., *Labo-Pharma Probl. Tech.*, 1974, *22*(232), 457–63

Methods for the biopharmaceutical testing of enteric capsules: Tests with 'enterocaps' capsules (in French)

capsules, hard gelatin: doxapram base, levels, blood (human); 3.4.2.4; 4.4.7.1

Aiache, J.-M., Aiache, S., Jeanneret, A., Cornat, F. and Vidal, J.L., *Boll. chim.-farm.*, 1975, *114*, 636–50

Methods for the biopharmaceutical testing of enteric capsules: Tests with 'enterocaps' capsules (in French)

capsules, hard gelatin: doxapram base, methylenecycline, levels, blood; 3.4.2.4; 4.4.7.1

Jain, N.K. and Naik, S.U., *J. pharm. Sci.*, 1984, *73*, 1806–11

Design of a slow-release capsule using laser drilling

capsules, hard gelatin: tetracycline hydrochloride; capsule shells, perforated walls, laser drilling; capsules, enteric, formaldehyde treatment; disintegration method, rotating basket, gastric and intestinal fluids; disintegration testing, effect of formaldehyde; dissolution method, rotating basket; dissolution testing, effects of, formulation of contents, hole, size and number; gastric behaviour, visualisation method, X-ray, radio-opaque contents; formulation of contents, diluents, drug particle size, surfactants; gastric behaviour, transit times

4.5.6.2 Slow-release Capsules

Rosen, E. and Swintosky, J.V., *J. Pharm. Pharmac.*, 1960, *12*, *Suppl.*, 237–44T

Preparation of a ^{35}S labelled trimeprazine tartrate sustained action product for its evaluation in man

capsules, hard gelatin: trimeprazine tartrate, levels, blood, urine; dissolution method, Souder and Ellenbogen; formulation of contents; radioactive isotope technique

Heimlich, K.R., MacDonnell, D.R., Flanagan, T.L. and O'Brien, P.D., *J. pharm. Sci.*, 1961, *50*, 232–7

Evaluation of a sustained release form of phenylpropanolamine hydrochloride by urinary excretion studies

capsules, hard gelatin: phenylpropanolamine hydrochloride, levels, urine; dissolution method, Souder and Ellenbogen; formulation of contents

Rosen, E., *J. pharm. Sci.*, 1963, *52*, 98–100

Relationship of *in vitro* release to urinary recovery in man of a sustained-release preparation of ^{35}S prochlorperazine

capsules, hard gelatin: prochlorperazine maleate, levels, urine; dissolution method, Souder and Ellenbogen; drug availability, comparison of formulation, normal and slow-release; product form, sustained-release pellets; radioactive isotope technique

Rosen, E., Ellison, T., Tannenbaum, B., Free, S.M. and Crosley, A.P., *J. pharm. Sci.*, 1967, *56*, 365–9

Comparative study in man and dog of the absorption and excretion of dextroamphetamine-^{14}C sulphate in sustained-release and nonsustained-release dosage forms

capsules, hard gelatin: dexamphetamine sulphate, levels, urine (dogs, humans); dissolution method, Souder and Ellenbogen; dissolution testing, effect of formulations; radioactive isotope technique

Rosen, E., Polk, A., Free, S.M., Tannenbaum, P.J. and Crosley, A.P., *J. pharm. Sci.*, 1967, *56*, 1285–7

Comparative study in man of the absorption and excretion of amobarbital-^{14}C from sustained-release and non-sustained-release dosage forms

capsules, hard gelatin: amylobarbitone sodium, levels, plasma, urine; dissolution method, Souder and Ellenbogen

Beckett, A.H. and Tucker, G.T., *J. Pharm. Pharmac.*, 1968, *20*, 174–93

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Application of the analogue computer to pharmacokinetic and biopharmaceutical studies with amphetamine-type compounds

capsules, hard gelatin, granules and solutions: amphetamines, levels, urine, acid pH; dissolution method, modified *B.P.* disintegration apparatus, rolling bottle, rotating bottle; drug availability, comparison of dosage forms, normal and slow-release forms; pharmacokinetic analysis, computer simulation

Simmons, D.L., Legore, A.A., Klapka, M. and Joshi, N.N., *Can. J. pharm. Sci.*, 1973, *8*, 139–41

An *in vitro–in vivo* evaluation of phenformin formulations

capsules, hard gelatin: phenformin, clinical effect, blood glucose level (guinea pig); dissolution method, rotating disk; drug administration by duodenal implantation; drug availability, comparison of normal and slow-release forms; formulation of contents, prolonged release

Bauguess, C.T., Fincher, J.H., Sadik, F. and Hartman, C.W., *J. pharm. Sci.*, 1975, *64*, 1489–92

Blood concentration profiles of acetaminophen following oral administration of fatty acid esters of acetaminophen with pancreatic lipase to dogs

capsules, hard gelatin: paracetamol, acetate and decanoate, levels, blood (dogs); drug availability, effect of co-administration of lipase; formulation of contents, slow release; pharmacokinetic analysis

Bauer, K.H., Otten, H. and Weuta, H., *Pharm. Ind., Berl.*, 1976, *38*, 823–7

Serum concentrations and urinary excretion quotient obtained from coated and uncoated oral ampicillin preparations (in German)

capsules, hard gelatin and tablets, film-coated: ampicillin, anhydrous, trihydrate, levels, serum, urine; dissolution method, beaker; drug availability, comparison of dosage forms, standard and slow-release forms; formulation of contents, controlled-release pellets

Schneider, H., Nightingale, C.H., Quintiliani, R. and Flanagan, D.R., *J. pharm. Sci.*, 1978, *67*, 1620–2

Evaluation of an oral prolonged-release antibiotic formulation

capsules, hard gelatin, injections, intravenous and tablets, prolonged-release: cephalexin, levels, serum, urine; dissolution method, *U.S.P.*; drug availability, comparison of commercial capsule product and slow-release tablet

Schoenwald, R.D., Garabedian, M.E. and Yakatan, G.J., *Drug Dev. ind. Pharm.*, 1978, *4*, 599–609

Decreased bioavailability of sustained release acetazolamide dosage forms

capsules, hard gelatin and tablets: acetazolamide, levels, plasma; dissolution method, paddle; drug availability, comparison of slow-release capsule and standard tablets

Gröning, R., *Pharm. Ind., Berl.*, 1979, *41*, 369–75

An *in vitro* and *in vivo* study of the release of nitrofurantoin from dosage forms (in German)

capsules, hard gelatin and tablets: nitrofurantoin, levels, urine; dissolution method, flow-through cell, paddle; drug availability, comparison of dosage forms; drug availability, slow-release capsule

Möller, H., Ali, S. L. and Steinbach, D., *Int. J. Pharmaceut.*, 1980, *7*, 157–67

Pharmaceutical and biological availability of sustained release preparations of potassium chloride

capsules, hard gelatin and tablets: potassium chloride, levels, K^+ in urine; dissolution method, rotating basket, paddle; dissolution testing, comparison of dosage forms; drug availability, comparison of slow-release pellets in capsules and coated tablets; patient's state, control of K^+ intake by diet

Chambliss, W.G., Cleary, R.W., Fischer, R., Jones, A.B., Skierkowski, P., Nicholes, W. and Kibbe, A.H., *J. pharm. Sci.*, 1981, *70*, 1248–51

Effect of docusate sodium on drug release from a controlled-release dosage form

capsules, hard gelatin: chlorpheniramine, levels, plasma; dissolution method, rotating basket; dissolution testing, effect of surfactant, docusate sodium; drug availability, effect of co-administration of 2 × 100 mg capsules of docusate sodium; drug availability, *in vitro*, measurement of micellar entrapment of chlorpheniramine in docusate sodium solutions; formulation of contents, controlled-release pellets; pharmacokinetic analysis

Laven, R. and Schäfer, E.-A., *Arzneimittel-Forsch.*, 1981, *31*, 353–6

Release of norfenefrine from sustained-release formulations by an *in vitro* dissolution model/simulation of 'drug levels' by calculation using pharmacokinetic constants and comparison with *in vivo* course of action

capsules, hard gelatin: norfenefrine hydrochloride; dissolution method, Stricker; dissolution testing, comparison of delayed-release and prolonged-release formulations; drug availability, *in vitro* simulation, calculation of blood levels; drug, clinical effects (cat), effect on blood pressure, comparison of formulations; pharmacokinetic analysis

Row, J.S. and Carless, J.E., *J. Pharm. Pharmac.*, 1981, *33*, 561–4

Comparison of the in vitro dissolution behaviour of various indomethacin formulations with their in vivo bioavailability

capsules, hard gelatin: indomethacin, levels, plasma; dissolution method, modified beaker; dissolution testing, comparison of standard and controlled-release products, effects of formulation of microcapsules; drug availability, comparisons of, standard and microencapsulated drug, controlled-release and microencapsulated drug; drug side-effects, comparison of formulations; formulation of contents, controlled-release pellets and powders; formulation of drug microcapsules, gelatin/acacia coacervates, various drug/colloid ratios; pharmacokinetic analysis

Schneider, G.F., Heese, G.U., Huber, H.J., Janzen, N., Jünger, H., Moser, C. and Stanislaus, F., *Arzneimittel-Forsch.*, 1981, *31*, 1489–97

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Bioavailability of theophylline in a new oral sustained-release preparation (in German)

capsules, hard gelatin, solutions and tablets: theophylline, levels, plasma; dissolution method, paddle; dissolution testing, comparison of slow-release capsules and tablets; drug availability, comparison of dosage forms, effect of dose (capsules); formulation of contents, controlled-release pellets; pellet properties, density, friability, stability, uniformity of content; pharmacokinetic analysis

Yau, M.K.T. and Meyer, M.C., *J. pharm. Sci.*, 1981, *70*, 1017–24

In vivo – in vitro correlations with a commercial dissolution simulator I: Methenamine, nitrofurantoin and chlorothiazide

capsules, hard gelatin and tablets: nitrofurantoin, levels, urine, literature; dissolution method, rotating basket, Sartorius apparatus; dissolution testing, comparisons of, dosage forms, products; drug availability, correlation, *in vitro* simulator, Sartorius apparatus and *in vivo* data

Bechgaard, H., Brodie, R.R., Chasseaud, L.F., Houmoller, P., Hunter, J.O., Siklos, P. and Taylor, T., *Eur. J. clin. Pharmac.*, 1982, *21*, 511–5

Bioavailability of indomethacin from 2 multiple-units controlled-release formulations

capsule, hard gelatin: indomethacin, levels, plasma; dissolution method, rotating flask; dissolution testing, effects of, formulation, pH test media; drug availability, comparison of standards and slow-release formulations; formulation of contents, enteric-coated pellets; pharmacokinetic analysis

El-Egakey, M.A. and Speiser, P.P., *Acta pharm. Tech.*, 1982, *28*, 169–75

The *in vitro* and *in vivo* release studies of slow release phenylpropanolamine; polymethylcyanoacrylate entrapment products

capsules, hard gelatin: phenylpropanolamine, levels, urine; dissolution method, stirred flask; dissolution testing, contents, effect of formulation of pellets; drug availability, effect of formulation of pellets; formulation of contents, pellets, drug entrapment in methyl cyanoacrylate polymers; pellets, physical properties, particle size, effect of varying drug/monomer ratio

François, D., Denmat, A., Waugh, A. and Woodage, T., *Pharm. Ind., Berl.*, 1982, *44*, 86–9

The *in vitro* and *in vivo* availability of phenylpropanolamine from oil/paste formulations in hard gelatin capsules

capsules, hard gelatin: phenylpropanolamine hydrochloride, levels, plasma; dissolution method, Poole's apparatus; dissolution methodology, effect of lipophilic contents, correction for solvent evaporation; dissolution testing, comparison of formulations, powder and semi-solid fills; drug availability, comparison of formulations, powder and semi-solid fills; formulation of contents, semi-solid, hydrophilic, standard release, hydrophobic, slow release; pharmacokinetic analysis; 3.2.4.2

Yau, M.K.T. and Meyer, M.C., *J. pharm. Sci.*, 1983, *72*, 681–6

In vivo – in vitro correlations with a commercial dissolution simulator II: papaverine, phenytoin and sulfisoxazole

capsules, hard gelatin, elixirs and tablets: phenytoin sodium, papaverine hydrochloride, levels, plasma, literature; dissolution method, rotating basket, Sartorius apparatus; dissolution testing, comparison of dosage forms, papaverine hydrochloride, comparison of products, phenytoin sodium; drug availability correlation, *in vitro* simulator, Sartorius apparatus and *in vivo* data

Suryakusuma, H. and Jun, H.W., *J. Pharm. Pharmac.*, 1984, *36*, 497–501

Encapsulated hydrophilic polymer beads containing indomethacin as controlled release drug delivery systems

capsules, hard gelatin: indomethacin, levels, serum (dog); dissolution method, rotating basket; drug availability, comparison of formulations, standard powder and slow-release beads, effects of, bead coating polymers and thickness; formulation of bead coatings; production of hydrophilic polymer beads

Kohri, N., K.-I., Miyazaki, K. and Arita, T., *J. pharm. Sci.*, 1986, *75*, 57–61

Sustained release of nifedipine from granules

capsules, hard gelatin: nifedipine levels, serum (rabbits); dissolution method, rotating paddle; dissolution testing, comparison of formulations, effects of, binder type, drug content, pH of test media; drug availability, comparisons of, formulations, products; 3.2.4.1

Magbi, M., Beukaddour, N., Rodriguez, F., Michaud, P. and Rouffiac, R., *Fourth International Conference on Pharmaceutical Technology*, (Paris, APGI, June 3–5, 1986), 1986, *II*, 118–127

Comparison of controlled release formulations of theophylline, in vitro correlations (in French)

Capsules, hard gelatin, solutions and tablets: theophylline levels, saliva; dissolution method, rotating paddle; dissolution testing, comparisons of dosage forms, effect of pH test medium; drug availability, comparison of dosage forms; pharmacokinetic analysis

Morimoto, M., Yamashita, K., Koyama, H., Fujimoto, H., Toguchi, H. and Kitamori, N., *Chem. pharm. Bull., Tokyo*, 1986, *34*, 1257–63

Evaluation of sustained-release capsules of molsidomine (SIN-10) in dogs and monkeys

capsules, hard gelatin and tablets: molsidomine, levels, plasma (dog, monkey); dissolution method, rotating basket; dissolution testing, effects of, formulation of contents, pH of test medium; drug availability, comparison of dosage form, controlled release capsule, standard release tablet; formulation of contents, controlled release pellets; pharmacodynamic study; pharmacokinetic analysis

Steinijans, V.W., Schulz, H.-U., Beier, W. and Radtke, H.W., *Int. J. Clin. Pharmac. Ther. Toxic.*, 1986, *24*, 438–47

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Once daily theophylline: multiple-dose comparison of an encapsulated micro-osmotic system (Euphylong) with a tablet (Uniphyllin)

capsules, hard gelatin and tablets: theophylline, levels, serum; dissolution method, paddle; drug availability, comparison of dosage forms; pharmacokinetic analysis

4.6 Investigational Drug Administration

4.6.1 Comparison of Drugs

White, W.F. and Gisvold, O., *J. Am. pharm. Ass., scient. Edn*, 1952, *41*, 42–6

Absorption rate studies of orally administered cardiac glycosides in cats

capsules, hard gelatin, solutions and tablets: acetyldigoxin (capsules), digitoxin, digoxin, lanatoside C; drug clinical effect, survival time (cats)

Weikel, J.H., *J. Am. pharm. Ass., scient. Edn*, 1958, *47*, 477–9

A comparison of human serum levels of acetylsalicylic acid, salicylamide and N-acetyl-*p*-aminophenol following oral administration

capsules, hard gelatin: aspirin, paracetamol, salicylamide, levels, serum

Steigbigel, N.H., Reed, C.W. and Finland, M., *Am. J. med. Sci.*, 1968, *255*, 296–312

Absorption and excretion of five tetracycline analogues in normal young men

capsules: tetracycline, demeclocycline, doxycycline, methacycline, minocycline, levels, serum, urine

Speirs, C.F., Stenhouse, D., Stephen, K.W. and Wallace, E.T., *Br. J. Pharmac.*, 1971, *43*, 242–7

Comparison of human serum, parotid and mixed saliva levels of phenoxymethylpenicillin, ampicillin, cloxacillin and cephalexin

capsules, hard gelatin and tablets: phenoxymethylpenicillin, levels, saliva (human); drug availability, effect of tablets in capsule

Nauta, E.H. and Mattie, H., *Br. J. clin. Pharmac.*, 1975, *2*, 111–21

Pharmacokinetics of flucloxacillin and cloxacillin in healthy subjects and patients on chronic intermittent haemodialysis

capsules, hard gelatin and infusions, intravenous: cloxacillin sodium, flucloxacillin sodium, levels, urine (human); drug availability, effect of patient's health, kidney performance; pharmacokinetic analysis

Harvengt, C. and Desager, J.-P., *Curr. ther. Res.*, 1976, *19*, 145–51

Pharmacokinetics and bioavailability of simfibrate, a clofibric acid derivative

capsules, soft gelatin: clofibric acid and derivatives, levels, plasma

Risberg, A.-M., Henricsson, S. and Ingvar, D.H., *Eur. J. clin. Pharmac.*, 1977, *12*, 105–9

Evaluation of the effect of fosazepam (a new benzodiazepine), nitrazepam and placebo on sleep patterns in normal subjects

capsules, hard gelatin: fosazepam, nitrazepam, clinical effects, sleep

Frithz, G. and Gröppi, W., *J. int. med. Res.*, 1981, *9*, 338–42

Temazepam versus nitrazepam: A comparative trial in the treatment of sleep disturbances

capsules, soft gelatin and tablets: nitrazepam (tablets), temazepam (capsules); drug clinical effects, sleep, duration, onset, quality, comparison of drugs

4.6.2 Drug, Clinical Effects

Sandell, E., *Acta pharm. suec.*, 1967, *4*, 223–5

Tolerance to ammonium, potassium and sodium chloride in hard gelatin capsules

capsules, hard gelatin: ammonium chloride, potassium chloride, sodium chloride; formulation, effect on emesis (human)

Sterner, W., Voss, B. and Widmann, A., *Arzneimittel-Forsch.*, 1968, *18*, 1056–8

On the gastro-intestinal compatibility of orally applied drugs (in German)

capsules, soft gelatin and powders: capsicum oleoresin, podophyllin; drug, clinical effect, gastro-intestinal irritation (rats)

Husain, S.L., *Lancet*, 1969, *1*, 1069–71

Oral zinc sulphate in leg ulcers

capsules, hard gelatin: zinc sulphate, clinical effect, wound healing

Wilson, D.E., Quertermus, J., Raiser, M., Curran, J. and Robért, A., *Ann. intern. Med.*, 1976, *84*, 688–91

Inhibition of stimulated gastric secretion by an orally administered prostaglandin capsule

capsules, hard gelatin and solutions: 16,16-dimethylprostaglandin, clinical effect, gastric acid secretion

Baugh, R. and Calvert, R.T., *Eur. J. clin. Pharmac.*, 1977, *12*, 201–4

The effect of diphenhydramine alone and in combination with ethanol on histamine skin response and mental performance

capsules, hard gelatin: diphenhydramine hydrochloride, clinical effects, histamine skin response, serial seven subtraction, digit symbol substitution, tracking clinical effects, effect of co-administration of ethanol

Lithell, H., Boberg, J., Hedstrand, H., Hellsing, K., Ljunghall, S. and Vessby, B., *Eur. J. clin. Pharmac.*, 1977, *12*, 51–7

Effects of clofibrate on glucose tolerance, serum insulin, serum lipoproteins and plasma fibrinogen

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capsules, soft gelatin: clofibrate, biochemical effects, blood glucose, glucose intolerance, plasma fibrinogen, serum insulin; drug, clinical effects, body-weight, serum lipoprotein

Phillips, B.M. and Palermo, B.T., *J. pharm. Sci.*, 1977, *66*, 124–7

Physical form as a determinant of effect of buffered acetylsalicylate formulations on G.I. microbleeding

capsules, hard gelatin, powders, suspensions and tablets: aspirin, drug effects, gastro-intestinal bleeding (dogs); powder properties, particle size

Sutton, D.R. and Gosnold, J.K., *Br. med. J.*, 1977, *1*, 1598

Oesophageal ulceration due to clindamycin

capsules, hard gelatin: clindamycin, side-effects, oesophageal ulceration

Baars, R., Rapp, R., Young, B. and Canafax, D., *Ann. Neurol.*, 1978, *4*, 90

Phenytoin therapy – a comparison of one 300 mg capsule with three 100 mg capsules

capsules, hard gelatin: phenytoin; drug clinical effects, comparison of products, dosage regimen

Francis, M.E., Marshall, A.B. and Turner, W.T., *Vet. Rec.*, 1978, *102*, 377–80

Amoxycillin: clinical trial in dogs and cats

capsules, hard gelatin, injections and suspensions: amoxycillin, trihydrate; drug availability, comparison of dosage forms

Hennies, O.L., *J. int. med. Res.*, 1981, *9*, 62–8

A new skeletal muscle relaxant (DS 103–282) compared to diazepam in the treatment of muscle spasm of local origin

capsules, hard gelatin: diazepam, 5-chloro-4-(2-imidazolin-2-ylamino)-2,1,3-benzothiadiazole hydrochloride; drug, clinical effects, back pain reduction

Russell, A.S. and Le Morvan, P., *Curr. ther. Res.*, 1985, *38*, 599–605

Double-blind comparison between ketoprofen capsules four times daily and enteric-coated tablets twice daily in patients with osteoarthritis

capsules, hard gelatin and tablets, enteric coated: ketoprofen; drug, clinical effects, comparison of standard release capsule with delayed release tablets; drug, side-effects, comparisons of, dosage forms, dosage regimens

Wittig, R., Zorick, F., Roehrs, T., Paxton, C., Lamphere, J. and Roth, T., *Curr. ther. Res.*, 1985, *38*, 15–22

Effects of temazepam soft gelatin capsules on the sleep of subjects with insomnia

capsules, soft gelatin: temazepam; drug, clinical effects, polysomnographic measuring technique; drug, clinical trial, comparison with placebo

4.6.3 Drug, Formulation Effects

Aguiar, A.J. and Zelmer, J.E., *J. pharm. Sci.*, 1969, *58*, 983–7

Dissolution behaviour of polymorphs of chloramphenicol palmitate and mefenamic acid

capsules, hard gelatin: mefenamic acid, levels, blood; dissolution method, modified beaker; drug availability, effect of drug form, comparison of polymorphs

Khalafallah, N., Gouda, M.W. and Khalil, S.A., *J. pharm. Sci.*, 1975, *64*, 991–4

Effect of surfactants on absorption through membranes IV: effects of dioctyl sodium sulfosuccinate on absorption of a poorly absorbable drug, phenolsulfonphthalein, in humans

capsules and solutions: phenolsulphonphthalein (solution), levels, urine; drug availability, effect of co-administration of surfactant, dioctyl sodium sulphosuccinate (capsules or solution); drug trial, side-effects, effect of dosage form; surfactants, effect on biological membranes

Allen, P.V., Rahn, P.D., Sarapu, A.C. and Vanderwielen, A.J., *J. pharm. Sci.*, 1978, *67*, 1087–93

Physical characterization of erythromycin: anhydrate, monohydrate and dihydrate crystalline solids

capsules, hard gelatin: erythromycin, anhydrous, mono- and dihydrate; dissolution method, modified *U.S.P.*; dissolution testing, comparison of drug forms, effect of powder properties; powder properties, thermal analysis, surface area measurements

Kreuter, J. and Higuchi, T., *J. pharm. Sci.*, 1979, *68*, 451–4

Improved delivery of methoxsalen

capsules, hard gelatin and solutions: methoxsalen, levels, blood (dogs and rats); formulation of contents, liquid filling

Coronelli, M., Zuzolo, V., Tonti, M., Carosi, M. and Teggia, L., *Curr. ther. Res.*, 1983, *33*, 639–45

Antianginal activity of nifedipine in 5 mg capsules for acute administration

capsules, hard gelatin: nifedipine; drug, clinical effects, antianginal activity, measurements, cardiac performance

4.6.4 Drug Metabolism

Rubin, A., Rodda, B.E., Warrick, P., Ridolfo, A.S. and Gruber, C.M., *J. pharm. Sci.*, 1972, *61*, 739–45

Physiological disposition of fenoprofen in man II. Plasma and urine pharmacokinetics after oral and intravenous administration

capsules, hard gelatin and injections, intravenous: fenoprofen, calcium and sodium salts, metabolites, levels, plasma, urine; fenoprofen-^{14}C, calcium, metabolites, levels, faeces, plasma, urine; formulation of contents; radioactive isotope technique

Martin, L.E., Tanner, R.J.N., Clark, T.J.H. and Cochrane, G.M., *Clin. Pharmac. Ther.*, 1974, *15*, 267–75

Absorption and metabolism of orally administered beclomethasone dipropionate

capsules, hard gelatin and solutions: beclomethasone dipropionate, levels, faecal, plasma, urine; radioactive isotope technique

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Verebely, K. and Inturrisi, C.E., *Clin. Pharmac. Ther.*, 1974, *15*, 302–9

Disposition of propoxyphene and norpropoxyphene in man after a single oral dose

capsules, hard gelatin: dextropropoxyphene hydrochloride, metabolite (norpropoxyphene), levels, plasma, urine

Cotler, S., Holazo, A., Boxenbaum, H.G. and Kaplan, S.A., *J. pharm. Sci.*, 1976, *65*, 822–7

Influence of route of administration on physiological availability of levodopa in dogs

capsules, hard gelatin, catheter, hepatoportal and injections, intravenous: levodopa, levels, serum, urine (dogs); drug metabolism, gastro-intestinal tract

Farid, N.A., Born, G.S., Kessler, W.V., Russell, H.T., Shaw, S.M. and Lange, W.E., *J. pharm. Sci.*, 1977, *66*, 536–8

Synthesis of ^{14}C-meglumine salicylate and its disposition in humans after oral administration

capsules, hard gelatin: meglumine salicylate, metabolites, levels, blood, faeces, urine; radioactive isotope technique

Sasahara, K., Nitanai, T., Habara, T., Kojima, T., Kawahara, Y., Morioka, T. and Nakajima, E., *J. pharm. Sci.*, 1981, *70*, 730–3

Dosage form design for improvement of bioavailability of levodopa IV: Possible causes of low bioavailability of oral levodopa in dogs

capsules, hard gelatin: levodopa, levels, serum (dogs); drug availability, comparison of route of administration; drug metabolism, effects of, gut position, intestinal flora; intestinal flora, effect of antibiotics; pharmacokinetic analysis

4.6.5 Pharmacokinetic Analysis

Nelson, E. and Schaldemose, I., *J. Am. pharm. Ass., scient. Edn*, 1959, *48*, 489–95

Urinary excretion kinetics for evaluation of drug absorption I. Solution rate limited and nonsolution rate limited absorption of aspirin and benzyl penicillin; absorption rate of sulfaethylthiadiazole

capsules, hard gelatin, suspensions and tablets: aspirin (tablets), benzylpenicillin, potassium and procaine, sulphaethidole (suspensions), levels, urine; drug form, compressed disks; drug availability, effect of formulation; formulation of contents, diluent, sodium bicarbonate

Nelson, E., *J. Am. pharm. Ass., scient. Edn*, 1960, *49*, 54–6

Urinary excretion kinetics for evaluation of drug absorption II. Constant, rate-limited release of tetracycline after ingestion by humans

capsules, hard gelatin and suspensions: tetracycline, disodium mucate and hydrochloride, levels, urine; drug availability, comparison of dosage forms, effect of formulation; drug form, compressed disks; formulation of contents, diluent, sodium bicarbonate

Nelson, E., *J. Am. pharm. Ass., scient. Edn*, 1960, *49*, 437–40

Urinary excretion kinetics for evaluation of drug absorption III. Method for calculation of absorption rate and application to tetracycline absorption in humans

capsules, hard gelatin: tetracycline, disodium mucate and hydrochloride, levels, urine; drug availability, effect of formulation; drug form, pellets; formulation of contents, diluents, sodium bicarbonate; pharmacokinetic analysis, absorption rate determination

Nelson, E., Long, S. and Wagner, J.G., *J. pharm. Sci.*, 1964, *53*, 1224–7

Correlation of amount of metabolite excreted and its excretion rate with available surface area of tolbutamide in dosage forms

capsules, hard gelatin: tolbutamide, metabolites, levels, urine; drug form, coated granules, compressed disks; drug availability, correlation surface area of drug form with urinary excretion; powder properties, surface area determination

Newmark, H.L., Berger, J. and Carstensen, J.T., *J. pharm. Sci.*, 1970, *59*, 1249–51

Coumermycin A_7 — Biopharmaceutical studies II

capsules, hard gelatin and injections, intravenous: coumermycin, and *N*-methylglucamine salt, levels, blood (dogs and humans)

Coutinho, C.B., Spiegel, H.E., Kaplan, S.A., Yu, M., Christian, R.P., Carbone, J.J., Symington, J., Cheripko, J.A., Lewis, M., Tonchen, A. and Crews, T., *J. pharm. Sci.*, 1971, *60*, 1014–19

Kinetics of absorption and excretion of levodopa in dogs

capsules, hard gelatin and injections, intravenous: levodopa, 2-^{14}C-levodopa, levels, serum, urine (dogs); drug availability, comparison acute and chronic dosage; radioactive isotope technique

Rubin, A., Rodda, B.E., Warrick, P., Ridolfo, A. and Gruber, C.M., *J. pharm. Sci.*, 1971, *60*, 1797–1801

Physiological disposition of fenoprofen in man I: pharmacokinetic comparison of calcium and sodium salts administered orally

capsules, hard gelatin: fenoprofen, calcium and sodium salts, levels, plasma

DiSanto, A.R. and Wagner, J.G., *J. pharm. Sci.*, 1972, *61*, 1086–90

Pharmacokinetics of highly ionised drugs II: Methylene blue – absorption, metabolism and excretion in man and dog after oral administration

capsules, hard gelatin: methylene blue, levels, urine (dogs, humans)

Macdonald, H., Kelly, R.G., Allen, E.S., Noble, J.F. and Kanegis, L.A., *Clin. Pharmac. Ther.*, 1973, *14*, 852–61

Pharmacokinetic studies on minocycline in man

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capsules, hard gelatin and injections, intravenous: demeclocycline, doxycycline, methacycline, minocycline, levels, faeces, serum, urine; drug availability, comparison of dosage regimens, single and multiple dose; pharmacokinetic analysis, comparison of drugs; tissue distribution, minocycline

Kaplan, S.A., Alexander, K., Jack, M.L., Puglisi, J.C.V., de Silva, J.A.F., Lee, T.L. and Weinfeld, R.E., *J. pharm. Sci.*, 1974, *63*, 527–35

Pharmacokinetic profiles of clonazepam in dog and humans and of flunitrazepam in dogs

capsules, hard gelatin, injections, intravenous, solutions, and tablets: clonazepam, flunitrazepam, metabolites, levels, blood (dogs, humans); drug availability, effect of drug particle size

Loo, J.C.K., Foltz, E.L., Wallick, H. and Kwan, K.C., *Clin. Pharmac. Ther.*, 1974, *16*, 35–43

Pharmacokinetics of pivampicillin and ampicillin in man

capsules, hard gelatin, injections, intramuscular and intravenous and tablets: ampicillin, anhydrous, trihydrate, pivampicillin, levels, serum, urine; drug availability, comparison of dosage regimen, single and multiple dose

Lund, L., Alvan, G., Berlin, A. and Alexanderson, B., *Eur. J. clin. Pharmac.*, 1974, *7*, 81–6

Pharmacokinetics of single and multiple doses of phenytoin in man

capsules, hard gelatin and injections, intravenous: phenytoin, levels, plasma; drug availability, comparison of dosage regimens, single and multiple dose

Albert, K.S., Hallmark, M.R., Sakmar, E., Weidler, D.J. and Wagner, J.G., *J. Pharmacokinet. Biopharm.*, 1975, *3*, 159–70

Pharmacokinetics of diphenhydramine in man

capsules, hard gelatin, infusions, intravenous and solutions: diphenhydramine hydrochloride, levels, plasma, urine

Nauta, E.H. and Mattie, H., *Br. J. clin. Pharmac.*, 1975, *2*, 111–21

Pharmacokinetics of flucloxacillin and cloxacillin in healthy subjects and patients on chronic intermittent haemodialysis

capsules, hard gelatin, infusions, intravenous and suspensions: cloxacillin, flucloxacillin, levels, serum, urine; drug availability, comparison of dosage forms; pharmacokinetic analysis, comparison of parameters, absorption, elimination process, effect of patient's state of health

Greenblatt, D.J., Schillings, R.T., Kyriakopoulos, A.A., Shader, R.I., Sisenwine, S.F., Knowles, J.A. and Ruelius, H.W., *Clin. Pharmac. Ther.*, 1976, *20*, 329–41

Clinical pharmacokinetics of lorazepam 1. Absorption and disposition of oral ^{14}C-lorazepam

capsules, soft gelatin: lorazepam, metabolites, levels, faeces, plasma; radioactive isotope technique

Gugler, R., Manion, C.V. and Azarnoff, D.L., *Clin. Pharmac. Ther.*, 1976, *19*, 135–42

Phenytoin: pharmacokinetics and bioavailability

capsules, hard gelatin and infusions, intravenous: phenytoin, levels, plasma; drug availability, comparison of dosage regimens, single and multiple dose

Johnson, B.F., Bye, C.E., Jones, G.E. and Sabey, G.A., *Eur. J. clin. Pharmac.*, 1976, *10*, 231–6

The pharmacokinetics of beta-methyl digoxin compared with digoxin tablets and capsules

capsules, soft gelatin, injections, intravenous and tablets: digoxin, beta-methyl digoxin, levels, serum, urine; drug availability, comparison of dosage regimens, single and multiple dose

Jusko, W.J., Koup, J.R. and Alván, G., *J. Pharmacokinet. Biopharm.*, 1976, *4*, 327–36

Nonlinear assessment of phenytoin bioavailability

capsules, hard gelatin and injections, intravenous: phenytoin, levels, serum

Lesne, M., Sturbois, X. and Mercier, M., *Pharm. Acta Helv.*, 1976, *51*, 367–70

Comparative pharmacokinetic study of two pharmaceutical forms of nicotinic acid (in French)

capsules, hard gelatin: nicotinic acid, levels, plasma; drug availability, comparison, standard and slow-release forms

Altamura, A.C., Gomeni, R., Sacchetti, E. and Smeraldi, E., *Eur. J. clin. Pharmac.*, 1977, *12*, 59–63

Plasma and intracellular kinetics of lithium after oral administration of various lithium salts

capsules, hard gelatin: lithium, carbonate, chloride, sulphate, levels, plasma; drug availability, effect of salt type

Alván, G., Siwers, B. and Vessman, J., *Acta pharmac. tox.*, 1977, *40, Suppl.*, 1, 40–51

Pharmacokinetics of oxazepam in healthy volunteers

capsules, hard gelatin: oxazepam, metabolites, levels, faeces, plasma, urine; drug availability, comparison of dosage regimens, single and multiple doses

Boxenbaum, H.G., Geitner, K.A., Jack, M.L., Dixon, W.R., Spiegel, H.E., Symington, J., Christian, R., Moore, J.D., Weissman, L. and Kaplan, S.A., *J. Pharmacokinet. Biopharm.*, 1977, *5*, 3–23

Pharmacokinetic and biopharmaceutic profile of chlordiazepoxide hydrochloride in healthy subjects: single-dose studies by the intravenous, intramuscular and oral routes

capsules, hard gelatin and injections, intramuscular and intravenous: chlordiazepoxide hydrochloride, levels, plasma

Boxenbaum, H.G., Geitner, K.A., Jack, M.L., Dixon, W.R. and Kaplan, S.A., *J. Pharmacokinet. Biopharm.*, 1977, *5*, 25–39

Pharmacokinetic and biopharmaceutic profile of chlordiazepoxide hydrochloride in healthy subjects: multiple-dose oral administration

capsules, hard gelatin: chlordiazepoxide hydrochloride, metabolites, levels, plasma; drug availability, comparison of dosage regimens

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Luders, R.C., Maggio-Cavaliere, M.B., Egger, H., Gum, O.B., Resnick, O., Bartlett, F., Gaito, M.J., Soo, A. and Li, C., *Clin. Pharmac. Ther.*, 1977, *21*, 721–30

Disposition of pirprofen, a new anti-inflammatory drug

capsules, hard gelatin: pirprofen, levels, plasma, urine; drug availability, comparison of dosage regimens, chronic dosing; drug metabolism; radioactive isotope technique

Stenbaek, Ø., Myhre, E., Rugstad, H.E., Arnold, E. and Hansen, T., *Eur. J. clin. Pharmac.*, 1977, *12*, 117–23

Pharmacokinetics of methyldopa in healthy man

capsules, hard gelatin: methyldopa, levels, serum, urine; radioactive isotope technique

Swaisland, A.J., Franklin, R.A., Southgate, P.J. and Coleman, A.J., *Br. J. clin. Pharmac.*, 1977, *4*, 61–5

The pharmacokinetics of ciclazindol (Wy 23409) in human volunteers

capsules, hard gelatin: ciclazindol, levels, plasma, urine; radioactive isotope technique

Finkelstein, E., Quintiliani, R., Lee, R., Bracci, A. and Nightingale, C.H., *J. pharm. Sci.*, 1978, *67*, 1447–50

Pharmacokinetics of oral cephalosporins: cephradine and cephalexin

capsules, hard gelatin and tablets: cephalexin, cephradine, levels, serum, urine; drug availability, comparisons of, dosage form, drug, effect of dosage regimen; pharmacokinetic parameters, serum, urine

Rodenstein, D., De Coster, A. and Gazzaniga, A., *Clin. Pharmacokinet.*, 1978, *3*, 247–54

Pharmacokinetics of oral acetylcysteine: absorption, binding and metabolism in patients with respiratory disorders

capsules, hard gelatin: ^{35}S-acetylcysteine, metabolites, levels, endobronchial mucus, lung tissue, serum, urine; radioactive isotope technique

Friis, M.L., Grøn, U., Larsen, N.-E., Pakkenberg, H. and Hvidberg, E.F., *Eur. J. clin. Pharmac.*, 1979, *15*, 275–80

Pharmacokinetics of bromocriptine during continuous oral treatment of Parkinson's disease

capsules: bromocriptine, levels, plasma

Palmieri, A., *Am. J. pharm. Educ.*, 1979, *43*, 21–3

An undergraduate experiment in biopharmaceutics: serum and urine bioavailability of ampicillin

capsules, hard gelatin: ampicillin, levels, urine; drug availability, effect of co-administration of probenecid; urine excretion data

Sasahara, K., Nitanai, T., Habara, T., Morioka, T. and Nakajima, E., *J. pharm. Sci.*, 1980, *69*, 1374–8

Dosage form design for improvement of bioavailability of levodopa III: influence of dose on pharmacokinetic behaviour of levodopa in dogs and parkinsonian patients

capsules, hard gelatin and injections, intravenous: levodopa, metabolites, blood, urine (dogs, humans); drug availability, effect of dose

Tanigawara, Y., Yamaoka, K., Nakagawa, T. and Uno, T., *J. pharm. Sci.*, 1982, *71*, 1129–33

Moment analysis for the separation of mean *in vivo* disintegration, dissolution, absorption, and disposition time of ampicillin products

capsules, hard gelatin, injections, intravenous and powders: ampicillin, anhydrous, trihydrate, levels, urine; drug availability, comparisons of, drug and product form; pharmacokinetic analysis, calculation of mean absorption, disintegration, dissolution, residence times and urinary recovery

Park, G.B., Kershner, R.P., Angellotti, J., Williams, R.L., Benet, L.Z. and Edelson, J., *J. pharm. Sci.*, 1983, *72*, 817–9

Oral bioavailability and intravenous pharmacokinetics of amrinone in humans

capsules, hard gelatin and injections, intravenous: amrinone, levels, plasma; drug availability, comparison of routes of administration

Groning, R., *Pharm. Ind., Berl.*, 1984, *46*, 88–96

Gastrointestinal passage and bioavailability of oral dosage forms. Application of statistics to description of limited absorption (in German)

capsules and tablets: drug availability, comparisons of, dosage forms and products; pharmacokinetic analysis, statistical evaluation; pharmacokinetic rate constant, absorption probability, relationship to gastrointestinal tract position

4.6.6 Methods of Administration to Animals

Jurgelsky, W. and Morison, R., *Am. J. vet. Res.*, 1964, *25*, 563–64

A method for administering capsules to rabbits

capsules, hard gelatin: dosage administration, rabbits; stomach tube

Brunk, R., *Berl. Münch. tierärztl. Wschr*, 1968, *81*, 203–4

The technique of administering capsules to dogs by means of an applicator (in German)

capsules, hard and soft gelatin: dosage administration, dogs; hand applicator

Conzelman, G.M., *Lab. Anim. Care*, 1970, *20*, 280–2

A stomach tube for the administration of gelatin capsules to nonhuman primates

capsules, hard gelatin: carcinogens; dosage administration, primates; stomach tube

Shani, J., Givant, Y. and Sulman, F.G., *Lab. Anim. Care*, 1970, *20*, 1154–5

A capsule-feeder for small laboratory animals

capsules, hard gelatin: dosage administration, mice, rats, capsule-feeder device

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Fisk, S.K. and Soave, O.A., *Lab. Anim. Sci.*, 1971, *21*, 752–3

A device for the administration of capsules and tablets to cats

capsules, hard and soft gelatin and tablets: dosage administration, cats; stomach tube

Stanislaus, F., Schneider, G.F. and Hofrichter, G., *Arzneimittel-Forsch.*, 1979, *29*, 186–7

The technique of administration of medicines in solid forms to rats (in German)

capsules, hard gelatin: capsules, special small sizes; dosage administration, rats, anaesthetised; stomach tube

Lax, E.R., Militzer, K. and Trauschel, A., *Lab. Anim.*, 1983, *17*, 50–4

A simple method for oral administration of drugs in solid form to fully conscious rats

capsules, hard gelatin: capsules, special small sizes; dosage administration, rats; stomach tube

4.6.7 Diagnostic Tests

Beal, C.B. and Brown, J.W., *Am. J. dig. Dis.*, 1968, *13*, 113–22

A rapid screening test for gastric achlorhydria

capsules, hard gelatin: congo red, thread impregnated; gastric pH determination, *in vivo*

Kleeberg, J.J., *Israel J. med. Scis.*, 1968, *4*, 149–52

Estimation of gastric acidity by X-ray

capsules, hard gelatin: barium sulphate; disintegration, *in vivo*, X-ray testing; drug availability, *in vitro*, disintegration; gastric pH determination; protective coating, acid sensitive

Haas, S., *Ann. intern. Med.*, 1970, *72*, 549–52

Contamination of protein-bound iodine by pink gelatin capsules colored with erythrosine

capsules, hard gelatin: capsule colorants, erythrosine; dye levels, serum-bound iodine

Beal, C.B., *U.S. Patent* 3 683 890, 1972, through *Derwent Accession No.* 558437-B, 1970

Duodenum sample collecting device

capsules, hard gelatin: capsule, double unit, small capsule inside larger capsule; capsule solubility, outer one soluble, inner one insoluble; diagnostic sampling device, containing radio-opaque flexible yarn with sampling tube, weighted capsule

Farbwerke Hoechst A.G., *Dutch Patent* 7 210 728, 1973, through *Derwent Accession No.* 11868U-BK, 1971

Radioactive iodine capsules–for thyroid function tests

capsules, hard gelatin: capsule filling, low melting point solid; formulation of contents, diluent, suppository base

Babb, R.R. and Beal, C.B., *Gut*, 1974, *15*, 492–3

Use of a duodenal capsule for localisation of upper gastro-intestinal haemorrhage

capsules, hard gelatin: blood detection, upper gastro-intestinal tract; capsule, size 00, filled, silicone rubber bag, yarn

McDonald, J.W.D., Barr, R.M. and Barton, W.B., *Ann. intern. Med.*, 1975, *83*, 827–9

Spurious Schilling test result obtained with intrinsic factor enclosed in capsules

capsules, hard gelatin: cyanocobalamin; ^{57}Co, levels, urine; radioactive isotope technique

Hoffman, N.E., LaRusso, N.F. and Hofmann, A.F., *Mayo Clin. Proc.*, 1976, *51*, 171–5

Sampling intestinal content with a sequestering capsule. A noninvasive technique for determining bile acid kinetics in man

capsules, hard gelatin: capsule contents, dialysis tube, identification system, X-ray marker; *in vivo* sampling, radioactive labelled bile acids

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Directory of Manufacturers

The names and addresses of the manufacturers (or agents) of products mentioned in the text are listed below in alphabetical order.

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C.I. Electronics Ltd, Brunel Rd, Churchfields, Salisbury, Wilts, England.

Davcaps, P.O. Box 11, Monmouth, Gwent NP5 3NX, Wales.

Elanco Qualicaps (a division of Eli Lilly Company), Lilly Corporate Center, IN 46285–9400, U.S.A.
U.K. office: Elanco Qualicaps, Lilly Industries Ltd, Kingsclere Rd, Baskingstoke, Hants RG21 2XA, England

Farmatic s.r.l., Via Progresso 2/C, 40064 Ozzano Emilia, Bologna, Italy.
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Feton, 799 Chaussée de Louvain, Brussels 1140, Belgium.
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Harro Höfliger, Helmholtzstrasse 4, 7151 Allmersback, Im Ta., W. Germany.
U.K. agent: Raupack Ltd, 131 High Street, Old Woking, Surrey GU22 9LD, England.

R.W. Hartnett Company, 1021–27 Cherry St, Philadelphia 7, U.S.A.

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U.K. office: Robert Bosch Packaging Machinery (U.K.) Limited, Invincible Road, Farnborough, Hants GU17 7QU, England

IMA Group (agents for Farmatic s.r.l. and Nuova Zanasi s.p.a.), Via Emilia 281, 40064 Ozzano Emilia, Bologna, Italy.
U.K. office: Imapak UK Ltd, Coworth Park, Ascot, Berks SL5 7SF, England.

Kruger, Willi KG, Preussenstr. 56, 4030 Ratingen 6, W. Germany.

Leidsche Apparatenfabriek N.V. (LAF), OS-en Paardenlaan 41–43, Leiden, Holland.

Macofar s.a.s., Via Bellini 6, Sesto di Rastignano, Bologna, Italy.
U.K. agent: B.S.A.L. Agencies Ltd, 2 Portsmouth Rd, Kingston-on-Thames, KT1 2LU, England.

Manesty Machines Ltd, Evans Rd, Speke, Liverpool L24 9LQ, England.
Agents for: Osaka Automatic Machine Mfg Co. Ltd, 7–9–4 Nishigatanda, Shinagawa-Ku, Tokyo 141, Japan.

Markem Machines Ltd, Ladywell Trading Estate, Eccles New Rd, Salford, Lancs, England.

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U.K. agent: Imapak UK Ltd, Coworth Park, Ascot, Berks SL5 7SF, England.

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R.P. Scherer Ltd, Frankland Rd, Blagrove, Swindon, Wilts SN5 8YS, England.

Tevopharm-Schiedam N.V., 13 Rubenslaan, Schiedam, Netherlands.

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Handbook of Pharmaceutical Excipients

A joint publication of The Pharmaceutical Society of Great Britain and the American Pharmaceutical Association

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