VOLUME THREE

Second Edition

Handbook of Pharmaceutical Manufacturing Formulations

Liquid Products

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Handbook of Pharmaceutical Manufacturing Formulations Second Edition

Volume Series

Sarfaraz K. Niazi

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Handbook of Pharmaceutical Manufacturing Formulations: Compressed Solid Products

Volume 2
Handbook of Pharmaceutical Manufacturing Formulations: Uncompressed Solid Products

Volume 3
Handbook of Pharmaceutical Manufacturing Formulations: Liquid Products

Volume 4
Handbook of Pharmaceutical Manufacturing Formulations: Semisolid Products

Volume 5
Handbook of Pharmaceutical Manufacturing Formulations: Over-the-Counter Products

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Handbook of Pharmaceutical Manufacturing Formulations: Sterile Products

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to August P. Lemberger

Preface to the Seriesq Second Edition

The science and the art of pharmaceutical formulation keeps evolving as new materials, methods, and machines become readily available to produce more reliable, stable, and release-controlled formulations. At the same time, globalization of sourcing of raw and ~nished pharmaceuticals brings challenges to regulatory authorities and results in more frequent revisions to the current good manufacturing practices, regulatory approval dossier requirements, and the growing need for cost optimization. Since the publication of the ~rst edition of this book, a lot has changed in all of these areas of importance to pharmaceutical manufacturers. The second edition builds on the dynamic nature of the science and art of formulations and provides an evermore useful handbook that should be highly welcomed by the industry, the regulatory authorities, as well as the teaching institutions.

The ~rst edition of this book was a great success as it brought under one umbrella the myriad of choices available to formulators. The readers were very responsive and communicated with me frequently pointing out to the weaknesses as well as the strengths of the book. The second edition totally revised attempts to achieve these by making major changes to the text, some of which include:

1. Complete, revised errors corrected and subject matter reorganized for easy reference. Whereas this series has six volumes differentiated on the basis of the type of dosage form and a separate inclusion of the U.S. OTC products, ideally the entire collection is needed to bene~t from the myriad of topics relating to formulations, regulatory compliance, and dossier preparation.
2. Total number of pages is increased from 1684 to 2726.
3. Total number of formulations is expanded by about 30% with many newly approved formulations.
4. Novel formulations are now provided for a variety of drugs; these data are collected from the massive intellectual property data and suggest toward the future trend of formulations. While some of these formulations may not have been approved in the United States or Europe, these do provide additional choices, particularly for the NDA preparation. As always, it is the responsibility of the manufacturer to assure that the intellectual property rights are not violated.
5. A signi~cant change in this edition is the inclusion of commercial products; while most of this information is culled out from the open source such as the FOIA (http://www.fda.gov/foi/default.htm), I have made attempts to reconstruct the critical portions of it based on what I call the generally acceptable standards. The drug companies are advised to assure that any intellectual property rights are not violated and this applies to all information contained in this book. The freedom of information act (FOIA) is an extremely useful conduit for reliable information and manufacturers are strongly urged to make use of this information. Whereas this information is provided free of charge, the process of obtaining the information may be cumbersome, in which case, commercial sources of these databases can prove useful, particularly for the non-U.S. companies.
6. Also included are the new Good Manufacturing Guidelines (2007) with amendments (2008) for the United States and similar updates for European Union and WHO; it is strongly urged that the companies discontinue using all old documents as there are signi~cant changes in the revised form, and many of them are likely to reduce the cost of GMP compliance.
7. Details on design of clean rooms is a new entry that will be of great use to sterile product manufacturers; whereas the design and ow of personnel and material ow is of critical nature, regulatory agencies view these differently and the manufacturer is advised always to comply with most stringent requirements.
8. Addition of a self-auditing template in each volume of the series. While the cGMP compliance is a complex issue and the requirements diversi~ed across the globe, the basic compliance remains universal. I have chosen the European Union guidelines (as these are more in tune with the ICH) to prepare a self-audit module that I recommend that every manufacturer adopt as a routine to assure GMP compliance. In most instances reading the template by those responsible for compliance with keep them sensitive to the needs of GMP.
9. OTC products cross-referenced in other volumes where appropriate. This was necessary since the regulatory authorities worldwide de~ne this class of drug differently. It is important to iterate that regardless of the prescription or the OTC status of a product, the requirements for compliance with the cGMP apply equally.
10. OTC monograph status is a new section added to the OTC volume and this should allow manufacturers to chose appropriate formulations that may not require a ~ling with the regulatory agencies; it is important to iterate that an approved OTC monograph includes details of formulation including the types and quantities of active drug and excipients, labeling, and presentation. To qualify the exemption, the manufacturer must comply with the monograph in its entirety. However, subtle modi~cations that are merely cosmetic in nature and where there is an evidence that the modi~cation will not affect the safety and ef~cacy of the products can be made but require prior approval of the regulatory agencies and generally these approvals are granted.
11. Expanded discussion on critical factors in the manufacturing of formulations provided; from basic shortcuts to smart modi~cations now extend to all dosage forms. Pharmaceutical compounding is one of the oldest professions and whereas the art of formulations has been

relegated to more objective parameters, the art nevertheless remains. An experienced formulator, like an artist, would know what goes with what and why; he avoids the pitfalls and stays with conservative choices. These sections of the book present advice that is time tested, although it may appear random at times; this is intended for experienced formulators.

12. Expanded details on critical steps in the manufacturing processes provided but to keep the size of the book manageable, and these are included for prototype formulations. The reader is advised to browse through similar formulations to gain more insight. Where multiple formulations are provided for the same drug, it intended to show the variety of possibilities in formulating a drug and whereas it pertains to a single drug, the basic formulation practices can be extended to many drugs of same class or even of diversi~ed classes. Readers have often requested that more details be provided in the Manufacturing Direction sections. Whereas suf~cient details are provided, this is restricted to prototype formulations to keep the size of the book manageable and to reduce redundancy.
13. Addition of a listing of approved excipients and the level allowed by regulatory authorities. This new section allows formulators a clear choice on which excipients to choose; the excipients are reported in each volume pertaining to the formulation type covered. The listing is drawn from the FDA-approved entities. For the developers of an ANDA, it is critical that the level of excipients be kept within the range generally approved to avoid large expense in justifying any unapproved level. The only category for which the listing is not provided separately is the OTC volume since it contains many dosage forms and the reader is referred to dosage formpspeci~c title of the series. The choice of excipients forms keeps increasing with many new choices that can provide many special release characteristics to the dosage forms. Choosing correct excipients is thus a tedious exercise and requires sophisticated multivariate statistical analysis. Whereas the formulator may choose any number of novel or classical components, it is important to know the levels of excipients that are generally allowed in various formulations to reduce the cost of redundant exercises; I have therefore included, as an appendix to each volume, a list of all excipients that are currently approved by the U.S. FDA along their appropriate levels. I suggest that a formulator consult this table before deciding on which level of excipient to use; it does not mean that the excipient cannot be used outside this range but it obviates the need for a validation and lengthy justi~cation studies in the submission of NDAs.
14. Expanded section on bioequivalence submission was required to highlight the recent changes in these requirements. New entries include a comprehensive listing of bioequivalence protocols in abbreviated form as approved by the U.S. FDA; these descriptions are provided in each volume where pertinent. To receive approval for an ANDA, an applicant must generally demonstrate, among other things, equivalence of the active ingredient, dosage form, strength, route of administration and conditions of use as the listed drug, and that the proposed drug product is bioequivalent to the reference listed drug [21 USC 355(j)(2)(A); 21 CFR 314.94(a)]. Bioequivalent drug products show no signi~cant difference in the rate and extent of absorption of the therapeutic ingredient [21 U.S.C. 355(j)(8); 21 CFR 320.1(e)]. BE studies are undertaken in support of ANDA submissions with the goal of demonstrating BE between a proposed generic drug product and its reference listed drug. The regulations governing BE are provided at 21 CFR in part 320. The U.S. FDA has recently begun to promulgate individual bioequivalence requirements. To streamline the process for making guidance available to the public on how to design product-speci~c BE studies, the U.S. FDA will be issuing product-speci~c BE recommendations (www.fda.gov/cder/ogd/index.htm). To make this vital information available, an appendix to each volume includes a summary of all currently approved products by the U.S. FDA where a recommendation on conducting bioequivalence studies is made available by the U.S. FDA. When ~ling an NDA or an ANDA, the ~ler is faced with the choice of defending the methods used to justify the bioavailability or bioequivalence data. The U.S. FDA now allows application for waiver of bioequivalence requirement; a new chapter on this topic has been added along with details of the dissolution tests, where applicable, approved for various dosage forms.
15. Dissolution testing requirements are included for all dosage forms where this testing is required by the FDA. Surrogate testing to prove ef~cacy and compliance is getting more acceptance at regulatory agencies; in my experience, a well-designed dissolution test is the best measure of continuous compliance. Coupled with chapters on waivers of bioequivalence testing, this information on dissolution testing should be great value to all manufacturers; it is recommended that manufacturers develop their own in-house speci~cations, more stringent than those allowed in these listings and the USP.
16. Best-selling products (top 200 prescription products) are identi~ed with an asterisk and a brand name where applicable; in all instances, composition of these products is provided and formulation of generic equivalents. Despite the vast expansion of pharmaceutical sales and shifting of categories of blockbuster drugs, basic drugs affecting gastrointestinal tract, vascular system, and brain remain most widely prescribed.
17. Updated list of approved coloring agents in the United States, Canada, European Union, and Japan is included to allow manufactures to design products for worldwide distribution.
18. Tablet-coating formulations that meet worldwide requirements of color selection are included in the Volume 1 (compressed solids) and Volume 5 (OTC) because these represent the products often coated.
19. Guidelines on preparing regulatory ~lings are now dispersed throughout the series depending on where these guidelines are more crucial. However, the reader would, as before, need access to all volumes to bene~t from the advice and guidelines provided.

As always, comments and criticism from the readers are welcomed and these can be sent to me at Niazi@pharmsci.com or Niazi@niazi.com. I would try to respond to any inquiries requiring clari~cation of the information enclosed in these volumes.

I would like to express deep gratitude to Sherri R. Niziolek and Michelle Schmitt-DeBonis at Informa, the publisher of

this work, for seeing an immediate value to the readers in publishing the second edition of this book and allowing me enough time to prepare this work. The diligent editing and composing staff at Informa, particularly Joseph Stubenrauch, Baljinder Kaur and others are highly appreciated. Regardless, all errors and omissions remain altogether mine.

In the ~rst edition, I had dedicated each volume to one of my mentors; the second edition continues the dedication to these great teachers.

Sarfaraz K. Niazi, Ph.D.
Deer~eld, Illinois, U.S.A.

Preface to the Seriesq First Edition

No industry in the world is more highly regulated than the pharmaceutical industry because of the potential threat to a patientus life from the use of pharmaceutical products. The cost of taking a new chemical entity to ~nal regulatory approval is a staggering $800 million, making the pharmaceutical industry one of the most research-intensive industries in the world. It is anticipated that the industry will spend about $20 billion on research and development in 2004. Because patent protection on a number of drugs is expiring, the generic drug market is becoming one of the fastest growing segments of the pharmaceutical industry with every major multinational company having a signi~cant presence in this ~eld.

Many stages of new drug development are inherently constrained by time, but the formulation of drugs into desirable dosage forms remains an area where expediency can be practiced by those who have mastered the skills of pharmaceutical formulations. The *Handbook of Pharmaceutical Manufacturing Formulations* is the ~rst major attempt to consolidate the available knowledge about formulations into a comprehensive and, by nature, rather voluminous presentation.

The book is divided into six volumes based strictly on the type of formulation science involved in the development of these dosage forms: sterile products, compressed solids, uncompressed solids, liquid products, semisolid products, and over-the-counter (OTC) products. Although they may easily fall into one of the other ~ve categories, OTC products are considered separately to comply with the industry norms of separate research divisions for OTC products. Sterile products require skills related to sterilization of the product, and of less importance is the bioavailability issue, which is an inherent problem of compressed dosage forms. These types of considerations have led to the classi~cation of pharmaceutical products into these six categories. Each volume includes a description of regulatory ~ling techniques for the formulations described. Also included are regulatory guidelines on complying with current good manufacturing practices (cGMPs) speci~c to the dosage form and advice is offered on how to scale up the production batches.

It is expected that formulation scientists will use this information to benchmark their internal development protocols and reduce the time required to ~le by adopting formulae that have survived the test of time. Many of us who have worked in the pharmaceutical industry suffer from a ~xed paradigm when it comes to selecting formulations: r Not invented heres perhaps is kept in the back of the minds of many seasoned formulations scientists when they prefer certain platforms for development. It is expected that with a quick review of the formulation possibilities that are made available in this book such scientists would bene~t from the experience of others. For teachers of formulation sciences, this series offers a wealth of information. Whether it is selection of a preservative system or the choice of a disintegrant, the series offers many choices to study and consider.

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Preface to the Volumeq First Edition

Liquid products, for the purpose of inclusion in this volume, include nonsterile drugs administered by any route in the form of solutions (monomeric and multimeric), suspensions (powder and liquid), drops, extracts, elixirs, tinctures, paints, sprays, colloidons, emulsions, aerosols, and other uid preparations. Sterile liquid products are presented in another volume. Whereas liquid drugs do not share the compression problems of solid dosage forms, the ~lling problems of powder dosage forms, and the consistency problems of semisolid dosage forms, they do have their own set of considerations in the formulation and manufacturing stages. The considerations of prime importance for liquid drugs include solubility of active drugs, preservation, taste masking, viscosity, avoring, appearance, and stability (chemical, physical, and microbiological), raw materials, equipment, the compounding procedures (often the order of mixing), and ~nally the packaging (to allow a stable product to reach patients). Suspensions present a special situation in which even the powder for reconstitution needs to be formulated such that it can be stable after reconstitution; therefore, limited examples are included here.

Chapter 1 in section I (Regulatory and Manufacturing Guidance) describes the practical details in complying with the current good manufacturing practice (cGMP) requirements in liquid manufacturing. This chapter does not address the speci~c cGMP parameters but deals with the practical aspects as may arise during a U.S. Food and Drug Administration (FDA) inspection. This includes what an FDA inspector would be looking into when auditing a liquid manufacturing facility.

Chapter 2 describes the stability testing of new drugs and dosage forms. Drawn from the most current international conference on harmonization (ICH) guidelines, this chapter describes in detail the protocols used for stability testing not only for new drugs but also for new dosage forms. The chapter is placed in this volume because stability studies are of greater concern in liquid dosage forms; however, keeping in mind the overall perspective of the series of this title, this chapter would apply to all dosage forms. Again, emphasis is placed on the practical aspects, and the reader is referred to of~cial guidelines for the development of complete testing protocols. It is noteworthy that the ICH guidelines divide the world into four zones; the discussion given in this chapter mainly refers to the U.S. and European regions, and again the formulator is referred to the original guideline for full guidance. Stability studies constitute one of the most expensive phases of product development because of their essential time investment. As a result, formulators often prepare a matrix of formulations to condense the development phase, particularly where there are known issues in compatibility, drug interactions, and packaging interactions. The FDA is always very helpful in this phase of study protocols, particularly where a generic drug is involved. It is also a good idea to benchmark the product against the innovator product. However, one should understand clearly that the FDA is not bound to accept stability data even though it might match that of the innovator product. The reason for this may lie in the improvements made since the innovator product was approved. For example, if a better packaging material that imparts greater safety and shelf life is available, the FDA would like this to be used (not for the purpose of shelf life, but for the safety factors). In recent years, the FDA has placed greater emphasis on the control of active pharmaceutical ingredient (API), particularly if it is sourced from a new manufacturer with a fresh DMF. Obviously, this is one way how the innovator controls the proliferation of generic equivalents. The original patents that pertain to synthesis or manufacturing of the active raw material may have been superseded by improved processes that are not likely to be a part of a later patent application (to protect the trade secret because of double-patenting issues). The innovator often goes on to revise the speci~cations of the active pharmaceutical ingredient to the detriment of the generic manufacturer. However, my experience tells me that such changes are not necessarily binding on the generic manufacturer, and as long as cGMP compliance in the API is demonstrated and the impurities do not exceed the reference standard (if one is available), there is no need to be concerned about this aspect. However, manufacturers are advised to seek a conference with the FDA should this be a serious concern. At times, the manufacturer changes the ~nished product speci~cation as the patents expire or reformulates the product under a new patent. A good example of this practice was the reformulation of calcitriol injection by Abbott as its patent came to expiry. The new speci~cations include a tighter level of heavy metals, but a generic manufacturer should have no problem if the original speci~cations are met because the product was approvable with those speci~cations.

Chapter 3 describes the container closure systems; again, this discussion would apply to all dosage forms. It is noteworthy that the regulatory agencies consider containers and packaging systems, all those components that come in contact with the product, protect the product from environment, or are instrumental in the delivery of the product as part of the product de~nition. Whereas the industry is much attuned to studies of the effects of the API and dosage formulation components, the study of container or closure systems is often left to the end of the study trials. This is an imprudent practice, as it might result in loss of valuable time. The packaging industry generally undergoes faster changes than do the chemical or pharmaceutical industries. New materials, better tolerances, more environmentally friendly materials, and now, with the use of mechanical devices in many dosage forms, appropriate dosing systems emerge routinely. As a rule of thumb, the closure system for a product should be the ~rst criterion selected before development of the dosage form. Switching between a glass and a plastic bottle at a later stage can be a very expensive exercise. Because many of these considerations are drawn by marketing teams, who may change their product positioning, the formulation team must be

appropriately represented in marketing decision conferences. Once a decision has been made about the presentation of a product, the product development team should prepare several alternatives, based on the ease of formulation and the cost of the ~nished product involved. It should be emphasized at all stages of development that packaging scale-ups require just as much work as does a formulation scale-up or changes. As a result, the FDA provides the scale-up and postapproval change (SUPAC) guidelines for packaging components. Changes in the dimensions of a bottle may expose a large surface of liquid to the gaseous phase in the bottle and thus require a new stability testing exercise. This chapter forms an important reminder to formulators on the need to give consideration to every aspect of the container closure system as part of routine development.

Chapter 4 introduces the area of Preapproval Inspections, a process initiated by the FDA in the wake of the grand scandals in the generic pharmaceutical industry a few years ago. The FDA guidelines now allow rpro~lings of companies and list the requirements of Preapproval Inspections when an application has been ~led. Whereas the emphasis in this chapter is on rpreapproval,s the advice provided here applies to all regulatory inspections. A regulatory inspection can be an arduous exercise if the company has not prepared for it continuously. Preparedness for inspection is not something that can be achieved through a last-minute crash program. This chapter goes into considerable detail on how to create a cGMP culture, how to examine the documentary needs, assignment of responsibility, preparation of validation plan, and above all, the art of presenting the data to the FDA. Also discussed are the analyses of the outcome of inspection. Advice is provided on how to respond to Form 483 issued by the FDA, and the manufacturer is warned of the consequences of failing an inspection. Insight is also provided for foreign manufacturers, for whom a different set of rules may be applied because of the physical constraints of inspection. The inspection guidelines provided apply to both the manufacturers of API as well as to the ~nished products.

Chapter 5 includes highlights of topics of importance in the formulation of liquid products. However, this chapter is not an all-inclusive guide to formulation. Only highlights of points of concern are presented here, and the formulator is referred to several excellent treatises available on the subject.

Section II contains formulations of liquid products and lists a wide range of products that fall under this classi~cation, as interpreted in the volume. There are three levels at which these formulations are described. First, the Bill of Materials is accompanied by detailed manufacturing directions; second, the manufacturing directions are abbreviated because they are already described in another product of similar nature; and third, only the composition is provided as supplied by the manufacturer. With the wide range of formulations included in this volume, it should be a simple matter for an experienced formulator to convert these formulations into quantitative Bills of Materials and then to benchmark it against similar formulations to come up with a working formula. The problems incumbent in the formulation of liquid products are highlighted in chapter 5, but these are generic problems, and the formulator should be aware of any speci~c situations or problems that may arise from time to time. I would like to hear from the formulators about these problems so that they could be included in future editions of this book. Again, the emphasis in this series is on a practical resolution of problems; the theoretical teachings are left to other, more comprehensive works on this topic. The key application of the data provided herein is to allow the formulator to select the ingredients that are reportedly compatible, avoiding need for long-term studies to establish compatibilities.

I am grateful to CRC Press for taking this lead in publishing what is possibility the largest such work in the ~eld of pharmaceutical products. It has been a distinct privilege to know Mr. Stephen Zollo, senior editor at CRC Press. Stephen has done more than any editor can do to encourage an author into completing this work on a timely basis. The editorial assistance provided by CRC Press staff was indeed exemplary, particularly the help given by Erika Dery, Amy Rodriguez, and others. Although much care has gone into correcting errors, any errors remaining are altogether mine. I shall appreciate the readers bringing these to my attention for correction in future editions of this volume (niazi@pharmsci.com).

This volume is dedicated to one of the great educators and a leader in the pharmaceutical profession, August P. Lemberger, who is truly a Wisconsin man. At the University of Wisconsin in Madison, he was an undergraduate and graduate student. He was then a professor, and twice Dean of the School of Pharmacy (1943p44, 1946p52, 1953p69, 1980p91). During the period between 1969 and 1980, he assumed the responsibility of deanship at the University of Illinois, where I was a graduate student. In 1972, he offered me my ~rst teaching job, as an instructor of pharmacy at the University of Illinois, while I was still in graduate school. I was one of the greatest bene~ciaries of his kindness and attention. Gus has an unusual ability to put everyone at ease, respect everyone around him, and in the end, come out as a group leader. Whatever little I have accomplished in my life is mostly because of Gus. Many awards, recognitions, and salutations were offered to Gus during his celebrated career. His research contributions included stability studies, suspension, emulsion stabilization, and later in his career, the various aspects of pharmaceutical education. I wish him many years of happy retirement and shuttling back and forth between his homes in Arizona and Wisconsin. Thanks, Gus.

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About the Author

Sarfaraz K. Niazi has been teaching and conducting research in the pharmaceutical industry for over 35 years. He has authored hundreds of scienti~c papers, textbooks, and presentations on the topics of pharmaceutical formulation, biopharmaceutics, and pharmacokinetics of drugs. He is also an inventor with scores of patents in the ~eld of drug and dosage form delivery systems; he is also licensed to practice law before the U.S. Patent and Trademark Of~ce. Having formulated hundreds of products from the most popular consumer entries to complex biotechnology-derived products, he has accumulated a wealth of knowledge in the science and art of formulating and regulatory ~lings of investigational new drugs (INDs) and new drug applications (NDAs). Dr. Niazi advises the pharmaceutical industry internationally on issues related to formulations, cGMP compliance, pharmacokinetics and bioequivalence evaluation, and intellectual property issues (http://www.pharmsci.com). He can be contacted at Niazi@pharmsci.com.

Part II

Manufacturing Formulations

Cefpodoxime Proxetil for Oral Suspension

Each 5 mL of Vantin oral suspension contains cefpodoxime proxetil equivalent to 50 or 100 mg of cefpodoxime activity after constitution and the following inactive ingredients: arti~cial avorings, butylated hydroxyanisole, carboxymethylcellulose sodium, microcrystalline cellulose, carrageenan, citric acid, colloidal silicon dioxide, croscarmellose sodium, hydroxypropylcellulose, lactose, maltodextrin, natural avorings, propylene glycol alginate, sodium citrate, sodium benzoate, starch, sucrose, and vegetable oil.

Ceftin for oral suspension, when reconstituted with water, provides the equivalent of 125 or 250 mg of cefuroxime (as cefuroxime axetil) per 5 mL of suspension. Ceftin for oral suspension contains the inactive ingredients polyvinyl pyrrolidone K30, stearic acid, sucrose, and tutti-frutti avoring.

Cefuroxime Axetil Suspension

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
25.00	1	R-Cefuroxime axetil	25.00
0.40 mL	2	Sorbitol solution 70%	0.40 L
20.00	3	Saccharin	20.00
QS	4	Water puri~ed	QS to 1 L

Manufacturing Directions

1. Charge the sorbitol solution and 20% of item 5 in a mixing vessel.
2. Add item 1 and mix vigorously to form a suspension.
3. Add items 3 and any avors, if needed, and mix.
4. Bring to volume.
5. Fill.

Cetirizine Hydrochloride Syrup

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
5.00	1	Cetirizine hydrochloride	1.03
1750.00	2	Lycosin 80/55	350.00
600.00	3	Sorbitol 70%	120.00
5.00	4	Sodium citrate	1.00
300.00	5	Propylene glycol	60.00
4.50	6	Methyl paraben	0.90
0.50	7	Propyl paraben	0.10
3.75	8	Saccharin sodium	0.75
10.00	9	Flavor raspberry	2.00
QS	10	Water puri~ed	QS to 1 L

Manufacturing Directions

1. Charge 30% of item 10 in a stainless steel jacketed kettle and heat to 90°C to 95°C.
2. Add and dissolve items 6 and 7; cool to 40°C.
3. Add to step above item 4 and item 8 and mix to dissolve.
4. Add items 2, 3, and 5 and mix to dissolve.
5. In a separate vessel, charge 30% of item 10 and add to it item 1, mix to dissolve, and then add to step 4.
6. Add avor(s) and bring to volume with item 10.

Chlophedianol, Ipecac, Ephedrine, Ammonium Chloride, Carbinoxamine, and Balsam Tolu Syrup

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/L (g)
0.001 mL	1	Ipecac uid extract	1.00 mL
5.00	2	Chlophedianol hydrochloride	5.00
1.32	3	Ephedrine hydrochloride (powder)	1.32
8.80	4	Ammonium chloride (reagent-grade granules)	8.80
0.80	5	Carbinoxamine maleate	0.80
0.90	6	Methyl paraben	0.90
0.10	7	Propyl paraben	0.10
6.25	8	Balsam of Tolu (eq. aqueous extract)	6.25
2.66	9	Saccharin sodium (dihydrate powder)	2.66
319.22	10	Sucrose (granulated sugar)	319.22
238.33	11	Glucose liquid (corn syrup)	238.33
83.93	12	Sorbitol solution (calculate as 70% sorbitol crystals)	83.93
40.00	13	Alcohol	40.00
166.67	14	FD&C red dye (Amaranth E123)	166.67 mg
0.80	15	Raspberry avor	0.80
100.00	16	Propylene glycol	100.00
QS	17	HyFlo ~lter aid	0.50
QS	18	Water puri~ed	~450.00 mL

Manufacturing Directions

1. Charge balsam of Tolu and 25 mL of water in a steam bath.
2. Raise the temperature, stirring continuously to mix water with the balsam.
3. Boil for half an hour and allow to decant while cooling.
4. Discard extracted balsam of Tolu.
5. Filter the supernatant liquid through ~lter paper and store apart.
6. Charge 150 mL water in a jacketed mixing tank and heat to boiling.
7. Add and dissolve parabens with mixing.
8. Add and dissolve sugar with constant mixing.
9. Heat to 70°C to 75°C.
10. Once sugar is dissolved, add glucose, sorbitol, and saccharin sodium. Mix well until dissolved.
11. Dissolve ammonium chloride in 28 mL water.
12. Add to mixing tank.
13. Add extract balsam of Tolu from ~rst step with mixing. Mix well and cool to 25°C to 30°C.
14. Add and dissolve ephedrine and carbinoxamine in 20 mL water and add to mixing tank. Mix well.
15. Add and dissolve chlophedianol in 50 g of propylene glycol and add to mixing tank.
16. Add balance of propylene glycol to mixing tank.
17. Add and dissolve Ipecac uid extract and raspberry avor in alcohol.
18. Add to mixing tank.
19. Dissolve dye in 5 mL water and add to tank with continuous mixing.
20. Rinse container with 5 mL of water and add rinsing.
21. Adjust to volume with puri~ed water.
22. Add HyFlo ~lter aid to syrup and mix well.
23. Recirculate through ~lter press or equivalent until sparkling clear.

Chlophedianol, Ipecac, Ephedrine, Ammonium Chloride, Carbinoxamine, and Balsam Tolu Syrup

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/L (g)
0.001 mL	1	Ipecac uid extract	1.000 mL
5.000	2	Chlophedianol hydrochloride	5.000
1.320	3	Ephedrine hydrochloride	1.320
8.800	4	Ammonium chloride	8.800
0.800	5	Carbinoxamine maleate	0.800
0.900	6	Methyl paraben	0.900
0.100	7	Propyl paraben	0.100
6.250	8	Balsam, tolu (aqueous extract)	6.250
2.660	9	Saccharin sodium powder dihydrate	2.660
319.220	10	Sucrose (sugar, granulated)	0.320
238.330	11	Glucose liquid (corn syrup)	0.240
83.933	12	Sorbitol solution 70%	0.084
40.000	13	Alcohol (ethanol)	40.000
166.670	14	Dye red	0.160
0.800	15	Flavor	0.800
100.000	16	Propylene glycol	100.000
QS	17	Filter aid HyFlo	0.500
QS	18	Water puri~ed	~450.000 mL

Manufacturing Directions

1. Charge balsam tolu and 25 mL of water in a steam bath.
2. Raise the temperature, stirring continuously, to mix water with balsam. Boil for half an hour and allow decanting while cooling. Discard extracted balsam tolu. Filter the supernatant liquid through ~lter paper and store apart.
3. Charge 150 mL water in a jacketed mixing tank; heat to boiling.
4. Add and dissolve parabens with mixing. Add and dissolve sugar with constant mixing. Heat to 70°C to 75°C.
5. Once sugar is dissolved, add glucose, sorbitol, and saccharin sodium.
6. Mix well until dissolved.
7. Dissolve ammonium chloride in 28 mL water. Add to mixing tank.
8. Add extract balsam tolu with mixing.
9. Mix well and cool to 25°C to 30°C. Add and dissolve ephedrine, carbinoxamine in 20 mL water and add to mixing tank. Mix well.
10. Add and dissolve chlophedianol in 50 g of propylene glycol and add to mixing tank. Add balance of propylene glycol to mixing tank.
11. Add and dissolve Ipecac uid extract and avor raspberry in alcohol. Add to mixing tank. Dissolve dye in 5 mL water; add to tank with continuous mixing.
12. Rinse container with 5 mL of water and add rinsing.
13. Adjust to volume with puri~ed water.
14. Add ~lter aid HyFlo to syrup and mix well.
15. Recirculate through ~lter press or equivalent until sparkling clear.

Cisapride Suspension

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
5.00	1	Cisapride USE: cisapride monohydrate	1.04
9.00	2	Methyl paraben	1.80
1.00	3	Propyl paraben	0.20
1000.00	4	Sucrose	200.00
50.00	5	Microcrystalline cellulose (Avicel RC 591)	10.00
12.50	6	Methylcellulose 4000	2.50
5.00	7	Sodium chloride	1.00
2.50	8	Polysorbate 80 (Tween 80)	0.50
2.50	9	All fruit avor	0.50
q	10	Water puri~ed	QS to 1 L

Manufacturing Directions

Cisapride dispersion should be uniformity mixed or levigated. Avicel RC-591 and methylcellulose dispersion should be uniform and smooth.

1. Mix item 8 in 100 g of item 10 (35p40°C) in a stainless steel vessel, using stirrer. Add item 1 and mix to make smooth dispersion and keep aside. Check the smoothness of dispersion.
2. Add 185 g of item 10 to a suitable mixer and heat to 90°C to 95°C. Dissolve items 2 and 3 while mixing. Add and dissolve item 4 while mixing.
3. Cool down to approximately 50°C to 55°C.
4. Filter the syrup through T-1500 ~lter pads (8p10) washed with puri~ed water. Collect the syrup in clean stainless steel tank. Avoid any loss of syrup quantity.
5. Disperse item 6 in 150 g of hot item 10 (70p80°C) in mixer while mixing.
6. Mix and homogenize at temperature 70°C to 80°C, mixer speed 18 rpm, homogenizer high speed, and vacuum 0.4 to 0.6 bar for 5 minutes.
7. Cool down to 25°C to 30°C with continuous mixing. Check the smoothness of dispersion.
8. Disperse item 5 in 250 g of item 10 (25p30°C) in stainless steel vessel, using stirrer. Keep on stirring for 30 minutes to make smooth dispersion. Check the smoothness of dispersion.
9. Transfer syrup mixer. Transfer Avicel mucilage to mixer.
10. Mix at high homogenizer speed and under vacuum for 5 minutes.
11. Dissolve item 7 in 10 g of item 10 and add to mixer while mixing. Add drug dispersion to mixer.
12. Rinse the drug container with 40 g of item 10 and add the rinsing to mixer.
13. Add item 9 to mixer while mixing.
14. Add item 10 up to ~nal volume 1 L.
15. Finally, mix and homogenize for 5 minutes at mixer speed 18 rpm, homogenizer at high speed, vacuum 0.4 to 0.6 bar.
16. Check the suspension for homogeneity. Transfer the suspension through 630-micron sieve to the stainless steel storage tank, previously sanitized.

Furosemide Syrup

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
5.00	1	Furosemide, 5% excess	1.05
9.00	2	Methyl paraben	1.80
1.00	3	Propyl paraben	0.20
1500.00	4	Sorbitol 70%	300.00
500.00	5	Glycerin	100.00
500.00	6	Propylene glycol	100.00
0.50	7	FD&C yellow No. 6	0.10
2.50	8	Orange avor	0.50
QS	9	Sodium hydroxide	0.44
QS	10	Water puri~ed	QS to 1 L

Manufacturing Directions

1. Charge 20% of item 10 to a suitable stainless steel jacketed vessel.
2. Add items 2 and 3 and heat to 90°C to 95°C to dissolve. Cool to 40°C after complete dissolution.
3. In a separate vessel, charge items 4, 5, and 6 and mix well.
4. Dissolve item 9 in a portion of item 10 in a separate vessel.
5. Add item 1 to step 4 and mix well.
6. In a separate vessel, dissolve item 7 in a portion of item 10.
7. Add to step 6.
8. Add step 2 to step 7.
9. Add item 8 and mix well.
10. Fill.

Ferrous Sulfate Oral Solution

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
75.00	1	Ferrous sulfate[a]	125.00
294.00	2X	Sucrose	490.00
147.00	3	Maltitol solution (Lycasin® 80/55)	245.00
0.30	4	Citric acid (monohydrate)	0.50
0.90	5	Citric acid (monohydrate)	1.50
0.06	6	FD&C yellow dye No. 6 (sunset yellow FCF)	1.00
3.12	7	Guarana avor 12144p33	5.20
0.33	8	Potassium sorbate	0.55
0.30	9	Saccharin sodium	0.50
q	10	Puri~ed water	QS to 1 L

[a]Equivalent to 15 mg iron (Fe).

Manufacturing Directions

1. Bubble nitrogen throughout the process.
2. Check and record pH of the puri~ed water (limit: 5.0p6.5).
3. Collect 166.67 g of puri~ed water in mixer.
4. Heat to 90°C to 95°C for 10 minutes.
5. Add item 8 and stir to dissolve to a clear solution.
6. Add item 2 and stir to dissolve to a clear solution.
7. Add item 3 and stir for 10 minutes and cool to 30°C to 35°C.
8. Dissolve item 4 in 10 g of puri~ed water (30p35°C) and add to ~rst step.
9. Dissolve item 9 in 10 g of puri~ed water (30p35°C) and add to ~rst step.
10. Dissolve item 5 in 273.33 g of puri~ed water (30p35°C).
11. Then add item 1 to the clear solution and dissolve slowly without aeration.
12. Add to mixer.
13. Dissolve item 6 in 10 g of puri~ed water (25p30°C) and add to ~rst step.
14. Add item 7 to ~rst step.
15. Mix at low speed for 10 minutes.
16. Bring volume up to 1 L with puri~ed water.
17. Check and record pH (target: 2.2, limit: 1.95p5.15).
18. Filter the drops with recirculation.
19. Transfer the ~ltered drops to a storage vessel under an N_2 blanket.
20. Use the nitrogen blanket in the tank throughout the storage and ~lling period.

Haloperidol Oral Liquid

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
2.00	1	Haloperidol	2.00
11.00	2	Lactic acid	11.00
0.20	3	Propyl paraben	0.20
1.90	4	Methyl paraben	1.90
QS	5	Sodium hydroxide for pH adjustment, approximate	0.24
QS	6	Water puri~ed, approximate	990.00 mL
QS	7	Nitrogen gas	QS
QS	8	Lactic acid	QS

Manufacturing Directions

1. Charge approximately 700 mL of water into a suitable mixing tank. Add and dissolve lactic acid with stirring; while mixing, add haloperidol. Mix until complete solution (approximately 15 minutes).
2. Charge 240 mL of water into a separate container and heat to boiling. Add and dissolve methyl and propyl parabens. Mix until complete solution. Add this solution to step 1 solution.
3. Check pH. If necessary, adjust to pH 2.75 (range: 2.5p3.0) with 2% sodium hydroxide. Continue mixing for 10 minutes after addition of sodium hydroxide. Record pH and amount of sodium hydroxide added. Lactic acid (No. 8) may also be used to adjust pH.
4. QS to 1 L with water and mix well.
5. Filter solution through 8-micron membrane ~lter (or similar) into a suitable container, under nitrogen protection.
6. Fill under nitrogen.

Heparin Nasal Spray

Charge 5 g of heparin into a pressure-addition vessel and suspend with stirring 50 g of ethanol in which 0.25 g of lecithin have previously been dissolved. After sealing and evacuation thereof, 1.5 kg of HFA 227 that has previously been aerated with carbon dioxide and adjusted to a pressure of 4.5 bar (20°C) in another pressure addition vessel is added with stirring and homogenized. The suspension obtained is dispensed into aluminum containers sealed with metering valves by means of the pressure-~lling technique.

Hydrocodone Bitartrate Elixir

Each 5 mL contains hydrocodone bitartrate 2.5 mg, acetaminophen 167 mg, and 7% alcohol. In addition, the liquid contains the following inactive ingredients: citric acid anhydrous, ethyl maltol, glycerin, methyl paraben, propylene glycol, propyl paraben, puri~ed water, saccharin sodium, sorbitol solution, sucrose, and D&C yellow No. 10 and FD&C yellow No. 6 as coloring and natural and arti~cial avoring.

Hydrocodone Polistirex Extended-Release Suspension

Each teaspoonful (5 mL) of Tussionex Pennkinetic extended-release suspension contains hydrocodone polistirex equivalent to 10 mg of hydrocodone bitartrate and chlorpheniramine polistirex equivalent to 8 mg of chlorpheniramine maleate Tussionex. Inactive ingredients: ascorbic acid, D&C yellow No. 10, ethylcellulose, FD&C yellow No. 6, avor, high fructose corn syrup, methyl paraben, polyethylene glycol 3350, polysorbate 80, pregelatinized starch, propylene glycol, propyl paraben, puri~ed water, sucrose, vegetable oil, and xanthan gum.

Hydromorphone Hydrochloride Oral Liquid

Hydromorphone hydrochloride, a hydrogenated ketone of morphine, is a narcotic analgesic. Each 5 mL (one teaspoon) contains 5 mg of hydromorphone hydrochloride. In addition, other ingredients include puri~ed water, methylparaben, propyl paraben, sucrose, and glycerin. It may contain traces of sodium bisul~te.

Hydroxyzine Pamoate Oral Suspension

Hydroxyzine pamoate 25 mg/5 mL; inert ingredients for the oral suspension formulation are carboxymethylcellulose sodium, lemon avor, propylene glycol, sorbic acid, sorbitol solution, and water.

Iron Polystyrene and Vitamin C Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
125.00	1	Glycerin	125.00
1.40	2	Methyl paraben	1.40
0.16	3	Propyl paraben	0.16
79.61	4	Sorbitol; use sorbitol solution	364.33
3.30	5	Xanthan gum	3.30
10.00	6	Sucrose (granulated)	100.00
0.20	7	Saccharin (insoluble)	2.00
105.00	8	Elemental iron; use iron polystyrene sulfonate	530.31
50.00	9	Ascorbic acid, USP (35% excess)	61.95
0.10	10	Flavor	1.00 mL
0.10	11	Flavor (arti~cial guarana)	1.00 mL
QS	12	Sodium hydroxide	12. 1.0
QS	13	Dye	2.00
9.50	14	Distilled puri~ed water	~95.00 mL
10.00	15	Sorbitol solution	~10.00

Manufacturing Directions

1. Add glycerin (item 1) to the tank.
2. Commence heating with agitation.
3. Add and disperse parabens.
4. Continue heating to 70°C to 80°C and mix until solution is complete.
5. Force cool to 30°C, then add and disperse xanthan gum (item 5).
6. Add sorbitol solution (item 4) and 80 mL of puri~ed water (item 14) and heat with mixing to 60°C to 70°C until the xanthan gum is fully dissolved.
7. Add and disperse saccharin and sugar (items 6 and 7).
8. Mix at 60°C to 70°C until dispersion is complete.
9. Force cool to 25°C to 30°C with continuous mixing.
10. Commence N_2 gas protection and maintain for the remainder of the manufacturing process.
11. Add and disperse ascorbic acid.
12. Continue mixing for 30 minutes at 25°C to 30°C.
13. *Note*: Use suitable SS high-powered stirrer.
14. Mix the iron polystyrene sulfonate milled slurry in the original epoxy-lined drums under N_2 gas protection until uniform.
15. Add the slurry to the main batch and mix for 30 minutes at 25°C to 30°C.
16. *Note*: Avoid scraping the epoxy lining of the steel drum while mixing and use a plastic or rubber scraper to assist in complete transfer of the mixed slurry. Add and disperse the avors. Mix well.
17. Check and record pH. Adjust pH using a 20% sodium hydroxide solution (1 g in 5 mL water) to a value of 3 (range: 2.8p3.2).
18. Dissolve the dye in 5 to 7 mL of water at 40°C to 45°C by stirring for 10 minutes.
19. Add this solution to the main batch through a 420-μm screen with mixing.
20. Rinse container with 2 to 3 mL water at 40°C to 45°C and add to bulk through a 420-μm screen.
21. Continue to mix under vacuum until mixture is uniform.
22. Pass the suspension through the colloid mill at a gap setting of 100 to 150 μm.
23. Adjust the ow rate such that the temperature rise of the suspension does not exceed 10°C.
24. Collect the milled suspension in a stainless steel jacketed tank with vacuum.
25. Mix at 25°C to 30°C under vacuum until a uniform suspension is achieved.
26. Flush the bulk suspension with nitrogen and seal.
27. Hold at 25°C to 30°C.

Mebendazole Oral Suspension

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
102.00	1	Mebendazole[a]	20.40
10.00	2	Methyl paraben	2.00
1.00	3	Propyl paraben	0.20
750.00	4	Propylene glycol	150.00
8.25	5	Sodium citrate	1.65
7.50	6	Saccharin sodium	1.50
0.55	7	Citric acid (monohydrate)	0.11
52.50	8	Microcrystalline cellulose	10.50
25.00	9	Carboxymethylcellulose sodium	5.00
7.50	10	Polysorbate 80	1.50
12.50	11	All fruits avor	2.50
q	12	Water puri~ed	QS to 1 L

[a]2 mg/5 mL mebendazole added as an extra to compensate the loss on drying and assay of the material.

Manufacturing Directions

1. Load 300 g of item 12 (25p30°C) in mixer. In it dissolve items 5, 6, and 7 while stirring at a speed of 18 rpm.
2. Dissolve items 2 and 3 in 30 g of item 4 (45°C) in a stainless steel container while stirring by stirrer.
3. Cool to 25°C to 30°C.
4. Add the paraben solution into step 1 while mixing.
5. Disperse item 8 in 200 g of item 12 (25p30°C) in a stainless steel container while stirring by stirrer. Keep aside for 1 hour for complete hydration.
6. Disperse item 9 in 100 g of item 12 (70°C) in a stainless steel container while stirring by stirrer.
7. Cool to 25°C to 30°C. Keep aside for 1 hour for complete gelation. Cooling is necessary for gelation.
8. Dissolve item 10 in 20 g of item 12 (50°C) in a stainless steel container while stirring by stirrer.
9. Cool to 30°C. Add 120 g of item 4 while mixing.
10. Disperse item 1 while mixing. Keep aside for complete levigation.
11. Add the Avicel dispersion and sodium CMC dispersion from step 3 and step 4 into mixer in step 1. Mix and homogenize at mixer speed 18 rpm, homogenizer low speed, and vacuum 0.4 to 0.6 bar for 10 minutes.
12. Add the mebendazole dispersion from step 5 into mixer in step 1. Mix and homogenize at mixer speed 18 rpm, homogenizer low speed, and vacuum 0.4 to 0.6 bar for 10 minutes.
13. Add item 11 into step 6. Make up the volume up to 1 L with item 12. Mix at a speed of 18 rpm for 5 minutes.
14. Check the suspension for homogeneity. Transfer the suspension through 630-micron sieve to stainless steel storage tank, previously sanitized by 70% ethanol.

Mebendazole Suspension

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
20.00	1	Mebendazole	20.00
30.00	2	Lutrol F 127	30.00
1.80	3	Methyl paraben	1.80
0.20	4	Propyl paraben	0.20
QS	5	Water puri~ed	QS

Manufacturing Directions

1. Charge 80% of item 5 in a stainless steel jacketed vessel. Heat to 90°C to 95°C.
2. Add items 3 and 4 and stir to dissolve.
3. Cool to 40°C and add item 2. Stir to dissolve completely.
4. Add item 1 and mix well. Homogenize if necessary.

10. Cool to room temperature.
11. Add dimethyl polysiloxane emulsion and mix well.
12. Add avor and mix well.
13. Dissolve citric acid in twice the quantity of puri~ed water and adjust pH if necessary.
14. Check and record pH (range: 7.5p8.0). Add puri~ed water to volume and mix well for a minimum of 30 minutes.
15. Filter through a 180-μm aperture nylon cloth and store in a suitable tank.

Magaldrate with Simethicone Suspension

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
QS	1	Water puri~ed	QS to 1 L
9.00	2	Methyl paraben	1.80
1.00	3	Propyl paraben	0.20
5.00	4	Acid benzoic	1.00
3.75	5	Saccharin sodium powder dihydrate	0.75
2.00 g	6	Magaldrate wet cake (18 to 20%)	400.00
1.00 g	7	Sorbitol solution	260.00
12.50	8	Silicon dioxide colloidal (international)	2.50
QS	9	Acid citric powder hydrous	QS
200.00	10	Dimethyl polysiloxane emulsion (30%)	40.00
0.005 mL	11	Flavor	1.000 mL
1.26 g	12	Glycerin	252.00
25.00 g	13	Potassium citrate monohydrate	5.00
13.30	14	Xanthan gum	2.66

Manufacturing Directions

This product is highly prone to microbial contamination. All equipment coming into contact with the product should be treated with a freshly prepared sodium hypochlorite solution (100 ppm) made with freshly boiled and cooled town water on the day of use. Bottles and caps should also be so treated. Freshly boiled and cooled puri~ed water should be used for rinsing.

1. Charge 285 mL puri~ed water into a suitable jacketed tank and heat to 90°C to 95°C.
2. Add and dissolve parabens, acid benzoic, saccharin sodium, and potassium citrate.
3. While maintaining temperature at 85°C to 90°C, add, in small quantities, half the quantity of magaldrate cake or powder, if used, and disperse well. (Adjust the speed of agitator and of the homogenizer to ensure effective mixing and to maintain free mobility of the suspension.)
4. Add sorbitol solution and mix well. Raise the temperature, if necessary, maintaining temperature at 85°C to 90°C.
5. Add, in small quantities, the remaining half of magaldrate cake or powder and disperse well. Mix for 1 hour and then remove heat. (Adjust the speed of the agitator and of the homogenizer to maintain the mobility of suspension.)
6. Separately blend silicon dioxide colloidal with xanthan gum and disperse the blend in glycerin with constant mixing.
7. While maintaining temperature at 85°C to 95°C, add and disperse the suspension from previous step to the main tank and mix well. Avoid lump formation at any stage. Cool to room temperature.
8. Add dimethyl polysiloxane emulsion and mix well.
9. Add avor and mix well. Dissolve acid citric in twice the quantity of puri~ed water and adjust pH if necessary. Check and record pH (range: 7.5p8.0).
10. Add puri~ed water to volume and mix well for a minimum of 30 minutes.
11. Filter through a 180-micron aperture nylon cloth and store in a suitable tank.

Magaldrate Suspension

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
100.00	1	Magaldrate USP	100.00
80.00	2	Kollidon® CL-M	80.00
20.00	3	Kollidon® 90F	20.00
10.00	4	Orange avor	10.00
0.50	5	Coconut avor	0.50
0.80	6	Banana avor	0.80
0.20	7	Saccharine sodium	0.20
QS	8	Preservatives	QS
QS	9	Water	QS to 1 L

Manufacturing Directions

1. Dissolve or suspend all the solids in water under aseptic conditions; pH should be approximately 9.

Magaldrate with Simethicone Suspension

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
QS	1	Distilled puri~ed water	285.00 mL
9.00	2	Methyl paraben	1.80
1.00	3	Propyl paraben	0.20
5.00	4	Benzoic acid	1.00
3.75	5	Saccharin sodium (dihydrate powder)	0.75
400.00	6	Magaldrate (wet cake; 18p20%)	400.00
1.00 g	7	Sorbitol solution (70%)	260.00
12.50	8	Silicon dioxide (colloidal) (International)	2.50
QS	9	Citric acid (hydrous powder)	QS
200.00	10	Dimethyl polysiloxane emulsion (30%)	40.00
0.005 mL	11	Flavor	1.00 mL
1.26 g	12	Glycerin	252.00
25.00 g	13	Potassium citrate monohydrate	5.00
13.30	14	Xanthan gum	2.66

Manufacturing Directions

This product is highly prone to microbial contamination. All equipment coming into contact with the product should be treated with a freshly prepared sodium hypochlorite solution (100 ppm), made with freshly boiled and cooled down water on the day of use. Bottles and caps should also be so treated. Freshly boiled and cooled deionized water should be used for rinsing.

1. Charge 285 mL puri~ed water into a suitable jacketed tank and heat to 90°C to 95°C.
2. Add and dissolve parabens, benzoic acid, saccharin sodium, and potassium citrate.
3. While maintaining temperature at 85°C to 90°C, add, in small quantities, half the quantity of magaldrate cake or powder, if used, and disperse well.
4. Adjust speed of the agitator and homogenizer to ensure effective mixing and to maintain free mobility of the suspension. Add sorbitol solution and mix well.
5. Raise the temperature, if necessary, maintaining temperature at 85°C to 90°C.
6. Add in small quantities the remaining half of the magaldrate cake or powder and disperse well.
7. Mix for 1 hour and then remove heat. (Adjust speed of the agitator and homogenizer to maintain the mobility of suspension.) Separately blend colloidal silicon dioxide with xanthan gum and disperse the blend in glycerin, with constant mixing.
8. While maintaining temperature at 85°C to 95°C, add and disperse the suspension from the previous step to the main tank and mix well.
9. Avoid lump formation at any stage.

Nystatin Oral Suspension

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
21.05	1	Nystatin micro~ne (particles size not less than 90% below 45 (im, 100% below 80 (im; based on potency of 5500 U/g anhydrous; adjust accordingly; 10% overage)	21.050
600.00	2	Sucrose	600.000
1.80	3	Methyl paraben	1.8000
0.20	4	Propyl paraben	0.2000
150.00	5	Sorbitol (70% solution)	150.000
5.00	6	Microcrystalline cellulose	5.000
10.00	7	Glycerin	10.000
2.00	8	Carboxymethylcellulose sodium	2.000
2.00	9	Polysorbate 80	2.000
50.00	10	Glycerin	50.000
2.50	11	Saccharin sodium	2.500
2.00	12	Flavor	2.000
30.00	13	Alcohol (ethanol 95%)	30.000
QS	14	Sodium hydroxide	0.174
QS	15	Hydrochloric acid (37%)	0.296
q	16	Water puri~ed	QS to 1 L

Manufacturing Directions

1. Add 200 g of item 16 (90p95°C) into mixer and heat to 90°C to 95°C. Dissolve items 3 and 4 while mixing. Add and dissolve item 2 while mixing at a speed of 18 rpm.
2. Cool down to approximately 50°C to 55°C.
3. Filter the syrup. Collect the syrup in a clean stainless steel tank. Avoid any loss of syrup. Clean the mixer.
4. Transfer the sugar syrup from the stainless steel tank into the mixer.
5. Add 100 g of item 5 into mixer while mixing.
6. Disperse item 6 in the mixture of 50 g of item 16 (25p30°C) and 50 g of item 5 in a stainless steel drum while mixing with stirrer.
7. Disperse item 8 in item 7 in a stainless steel drum while mixing with stirrer. Add 30 g of item 16 (90°C) to the solution. Stir until it becomes clear. Cool to 30°C.
8. Transfer the dispersion from step 3 and 4 into mixer.
9. Mix and homogenize under vacuum 0.4 to 0.6 bar for 10 minutes.
10. Stop homogenizer and keep continuous mixing.
11. Dissolve item 9 in 50 g of item 16 (50°C) in a stainless steel container while mixing by stirrer.
12. Add item 10 into it. Disperse item 1 while stirring by stirrer. Cool to 30°C.
13. Add the drug dispersion into mixer while mixing.
14. Dissolve item 11 in 15 g of item 16 (25p30C) in a stainless steel container while stirring by stirrer. Add to mixer while mixing.
15. Add items 12 and 13 into mixer while mixing.
16. Homogenize high speed and vacuum 0.4 to 0.6 bar. Mix and homogenize for 10 minutes.
17. Dissolve item 14 in 7 g of item 16 in a stainless steel container. Add slowly into the mixer while mixing.
18. Dissolve item 15 carefully in 7 g of item 16 in a stainless steel container. Slowly add the required quantity into mixer to adjust the pH between 6.8 and 7.1.
19. Make up the volume with item 16, up to 1 L. Mix for 5 minutes.

Peptide Topical Liquid

Formulation

Peptide such as thymic fraction 5, glycerin 44.5, propylene glycol 44.9, methyl nicotinate 0.1, water 50, polysorbate 80, 0.5% by weight.

Pheniramine Maleate Syrup

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
15.00	1	Pheniramine maleate	3.00
2980.00	2	Sugar	596.00
5.40	3	Methyl paraben	1.08
0.60	4	Propyl paraben	0.11
0.60	5	Citric acid monohydrate	0.11
1.50	6	Sodium citrate	0.30
3.50	7	Flavor	0.70
QS	8	Water puri~ed	QS to 1 L

Manufacturing Directions

1. Charge 700 mL item 8 in a suitable mixing vessel and heat to 90°C to 95°C.
2. Add and mix item 2.
3. Add items 3 and 4 and mix to dissolve.
4. In separate vessels in approximately 100 mL item 8, add and dissolve items 5 to 7 and item 1 separately.
5. Add the two mixtures in step 3 to step 2 at room temperature.
6. Make up the volume.

Phenobarbital, Hyoscyamine Sulfate, Atropine Sulfate, and Scopolamine Hydrobromide Elixir

Each 5 mL (teaspoonful) of elixir (23% alcohol) contains phenobarbital 16.2 mg, hyoscyamine sulfate 0.1037 mg, atropine sulfate 0.0194 mg, and scopolamine hydrobromide 0.0065 mg; D&C yellow No. 10, FD&C blue No. 1, FD&C yellow No. 6, avors, glucose, saccharin sodium, water.

Phenylephrine Tannate and Chlorpheniramine Tannate Pediatric Suspension

Rynatan® pediatric suspension is an antihistamine/nasal decongestant combination available for oral administration as a suspension. Each 5 mL (one teaspoonful) of the slate purple-colored, natural strawberry, arti~cial currant- avored suspension contains phenylephrine tannate 5 mg, chlorpheniramine tannate 4.5 mg, benzoic acid, FD&C blue No. 1, FD&C red No. 3, FD&C red No. 40, FD&C yellow No. 5, avors (natural and arti~cial), glycerin, kaolin, magnesium aluminum silicate, methylparaben, pectin, puri~ed water, saccharin sodium, and sucrose.

Phenylephrine Tannate and Pyrilamine Tannate Suspension

RYNA-12 S suspension is an antihistamine/nasal decongestant combination available for oral administration as a suspension. Each 5 mL (one teaspoonful) of the pink-colored, natural strawberry, arti~cial currant- avored suspension contains phenylephrine tannate 5 mg, pyrilamine tannate 30 mg, benzoic acid, FD&C red No. 3, avors (natural and arti~-cial), glycerin, kaolin, magnesium aluminum silicate, methyl paraben, pectin, puri~ed water, saccharin sodium, and sucrose.

Adjust, if necessary, with a solution of 10% sodium hydroxide or 10% hydrochloric acid depending on the test results.

21. Adjust the volume of the product with the remaining 30 g of the sorbitol solution or, if necessary, puri~ed water to 1 L.
22. Mix for 1 hour. Allow to stand overnight to eliminate entrapped CO_2 gas. Readjust volume to 1 L with puri~ed water. Mix for 1 hour. Filter by adding HyFlo ~lter aid and mixing it, followed by passing through ~lter press. Do not allow temperature to exceed 30°C. Bubble CO_2 gas into clear ~ltrate for 5 minutes. Then seal tank and hold product under CO_2 protection.

Vitamin B Complex and Iron Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
910.00	1	Sorbitol solution	910.00
0.019	2	Propyl paraben	0.019
0.17	3	Methyl paraben	0.17
1.50	4	Niacinamide (white powder)	1.50
0.30	5	Ribo avin	0.30
103.60	6	Propylene glycol	103.60
126.40	7	Glycerin	126.40
26.13	8	Iron sulfate (granular)	26.132
0.037	9	Dye	37.50 mg
0.25	10	Pyridoxine hydrochloride	0.25
1.20	11	Saccharin sodium (dihydrate powder)	1.20
22.00	12	Sodium cyclamate (powder)	22.00
30.00	13	Ascorbic acid (white powder)	30.00
0.80	14	Sodium bicarbonate (powder)	0.80
0.36	15	Thiamine hydrochloride (powder, regular)	0.36
0.625	16	D-Pantothenyl alcohol (dexpanthenol)	0.62
0.002	17	Vitamin B_{12} (cyanocobalamin)	2.00 mg
0.007	18	Flavor	0.70 mL
QS	19	Deionized puri~ed water	QS to 1 L
QS	20	HyFlo ~lter aid	QS
QS	21	Hydrochloric acid	QS
QS	22	Sodium hydroxide	QS

Manufacturing Directions

1. Manufacture under complete carbon dioxide (CO_2) protection.
2. Load 780 g (portion of item 2) of sorbitol solution into a jacketed stainless steel tank; the remaining sorbitol will be used later.
3. Add parabens (unless added previously), niacinamide, and ribo avin to the sorbitol or glucose solution.
4. Heat solution to 85°C to 90°C and mix until the ingredients are dissolved.
5. Remove heat.
6. While mixing, cool the main solution to 50°C to 60°C.
7. Hold at this temperature while bubbling CO_2 into it.
8. CO_2 protection must be continued for the remainder of the manufacturing procedure.
9. Heat 50 mL of puri~ed water to boiling and bubble CO_2 into it while cooling to 55°C.
10. Add and dissolve, with mixing, iron sulfate with 30 mL of puri~ed water at 55°C.
11. Use CO_2 protection.
12. Warm the solution to 50°C to 55°C while mixing to dissolve, then slowly add the solution, with good mixing, to the solution above.
13. The above addition should be made as soon as possible to prevent oxidation.
14. Add the pyridoxine, saccharin sodium, and sodium cyclamate and mix until dissolved.
15. Cool the solution to 30°C.
16. Add the ascorbic acid, with good stirring, to 78 g of reserved sorbitol. Make a slurry.
17. Use a container that has plenty of headspace.
18. Then add the sodium bicarbonate slowly in small portions to the ascorbic acid slurry, with stirring, until all of the powder has been added and most of the foaming has stopped.
19. Add this slurry slowly to the solution from the step above with vigorous mixing until a uniform solution results.

Vitamin B Complex and Iron Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
910.00	1	Sorbitol solution	910.00
0.019	2	Propyl paraben	0.019
0.170	3	Methyl paraben	0.170
1.500	4	Niacinamide powder white	1.500
0.300	5	Ribo avin	0.300
103.600	6	Propylene glycol	103.60
126.400	7	Glycerin	126.40
26.132	8	Iron sulfate granular	26.13
0.0375	9	Dye	0.037
0.250	10	Pyridoxine hydrochloride	0.25
1.200	11	Saccharin sodium powder dihydrate	1.20
22.000	12	Sodium cyclamate powder	22.00
30.000	13	Acid ascorbic white powder	30.00
0.800 g	14	Sodium bicarbonate	0.80
0.360	15	Thiamine hydrochloride powder regular	0.36
0.625	16	D-Pantothenyl alcohol (dexpanthenol FCC)	0.62
0.0020	17	Vitamin B_{12} μg (cyanocobalamin)	2.00 mg
0.007	18	Flavor	0.700 mL
QS	19	Water puri~ed	QS to 1 L
QS	20	Filter aid HyFlo	QS
QS	21	Acid hydrochloric	QS
QS	22	Sodium hydroxide	QS

Manufacturing Directions

1. Manufacture under complete CO_2 protection.
2. Load 780 g (portion of item 2) of sorbitol solution into a stainless steel jacketed tank. Remaining sorbitol to be used later.
3. Add parabens (unless added previously), niacinamide, and ribo avin to the sorbitol or glucose solution.
4. Heat solution to 85°C to 90°C and mix until the ingredients are dissolved.
5. Remove heat. While mixing, cool the main solution to 50°C to 60°C.
6. Hold at this temperature while bubbling CO_2 into it. CO_2 protection is continued for the remainder of the manufacturing procedure.
7. Heat 50 mL puri~ed water to boiling and bubble CO_2 into it while cooling to 55°C.
8. Add and dissolve, with mixing, iron sulfate with 30 mL puri~ed water at 55°C. Use CO_2 protection.
9. Warm the solution to 50°C to 55°C while mixing to dissolve. Then add the solution slowly, with good mixing, to the solution.
10. The above addition should be made as soon as possible to prevent oxidation. Add the pyridoxine, saccharin sodium, and sodium cyclamate and mix until dissolved.
11. Cool the solution to 30°C. Add the ascorbic acid with good stirring to 78 g of reserved sorbitol; make a slurry. Use a container that has plenty of headspace.
12. Add the sodium bicarbonate slowly in small portions to the ascorbic acid slurry with stirring until all of the powder has been added and most of the foaming has stopped.
13. Add this slurry slowly to the solution from the step above with vigorous mixing until a uniform solution results.
14. Rinse the mixing container with 22 g of the reserved sorbitol and add to the product with stirring.
15. Add and dissolve thiamine hydrochloride with mixing. If necessary, warm the D-pantothenyl alcohol until lique~ed and add it to the 0.5 mL CO_2-saturated puri~ed water.
16. Use an additional 0.5 mL CO_2-saturated puri~ed water to thoroughly rinse the container of D-pantothenyl alcohol and add this to the D-pantothenyl alcohol solution.
17. Mix the D-pantothenyl alcohol solution thoroughly until homogeneously dispersed.
18. Add the D-pantothenyl alcohol solution to the main solution with mixing. Use an additional 0.5 mL CO_2-saturated puri~ed water to rinse out the container in which the D-pantothenyl alcohol solution is made and add to the product with mixing.
19. Dissolve vitamin B_{12} in 0.5 mL puri~ed water to make a clear solution and add this solution to the product with good mixing.
20. Dissolve the avor in 10 g of propylene glycol, reserved from step above, with good stirring. Add this solution to the product with good mixing. Check pH (range: 3.0p3.3).

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Pharmaceutical Science

about the book...

While liquid drugs do not share the compression problems of solid dosage forms, the filling problems of powder dosage forms, or the consistency problems of semisolid dosage forms, they do have their own set of considerations in the formulation and manufacturing stages.

Highlights from ***Liquid Products, Volume Three*** include:

- practical details involved in complying with the current good manufacturing practice requirements in liquid manufacturing
- access to what an FDA auditor would be looking for during a liquid manufacturing audit
- issues that may arise during a US FDA inspection
- the protocols used for stability testing for new drugs and new dosage forms, drawn from the most current ICH guidelines

about the author...

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