HANDBOOK OF
Pharmaceutical Manufacturing Formulations

Over-the-Counter Products

VOLUME 5

Sarfaraz K. Niazi

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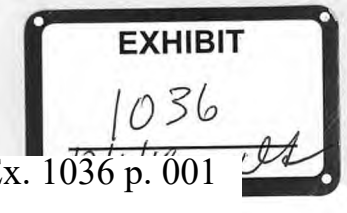

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Dedication

Dedicated to the memory of Dean Allen I. White

Preface to the Series

No industry in the world is more highly regulated than the pharmaceutical industry because of the potential threat to a patient's life from the use of pharmaceutical products. The cost of taking a new chemical entity to final 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 significant presence in this field.

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 first 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 five 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; of less importance is the bioavailability issue, which is an inherent problem of compressed dosage forms. These types of considerations have led to the classification of pharmaceutical products into these six categories. Each volume includes a description of regulatory filing techniques for the formulations described. Also included are regulatory guidelines on complying with Current Good Manufacturing Practices (cGMPs) specific 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 file by adopting formulae that have survived the test of time. Many of us who have worked in the pharmaceutical industry suffer from a fixed paradigm when it comes to selecting formulations: "Not invented here" 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 benefit 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 Volume

The *Handbook of Pharmaceutical Manufacturing Formulations: Over-the-Counter Products* is written for the pharmaceutical scientist and others involved in the regulatory filing and manufacturing of new OTC products. Because of the wide variety of products involved, from those bordering on cosmetics to proton pump inhibitors, the OTC products are manufactured by the most sophisticated global manufacturers as well as small one-room makeshift manufacturing houses.

The OTC products comprise a special category of healthcare products in that they can be dispensed without prescription, the rationale being that the use of these products does not expose patients to serious risks associated with side effects even if some misuse or overuse of these products occurs. The OTC category includes three types of products:

- Products that require full filing with the U.S. Food and Drug Administration (FDA) for marketing approval (the NDA/NADA or aNDA/aNADA process) including products or compositions not included in the monographs (see below) or administered in controlled release formulations
- Products that do not require filing with the U.S. FDA because they comply with the monographs issued by the U.S. FDA in its *Code of Federal Regulations* (CFR)
- Products that fall under the category of grandfather products which have been in use prior to the 1960s and have not been specifically excluded by the FDA; not all grandfather products fall under the OTC category — only those that are Generally Regarded As Safe (GRAS)

The U.S. FDA provides excellent support through its OTC website (http://www.fda.gov/cder/otc/index.htm) and formulators are highly encouraged to make use of the information available, particularly the updates in the monograph label requirements and withdrawal of approvals of formulations.

With the safety of consumers in mind, the U.S. FDA is in the process of establishing guidelines for all OTC products. Although the U.S. FDA began this work over three decades ago, much remains to be done. The U.S. FDA process begins with the issuance of Proposed Rules; this notification is like a warning (or advice) to the industry that this category of products is now under U.S. FDA watch. Often years go by before Proposed Rules are published in the *Code of Federal Regulations*. The Proposed Rules include not only identification of approved active ingredients but also inactive ingredients that are deemed compatible with the active ingredients and safe for consumers. The Proposed Rules are subject to criticism by the industry healthcare practitioners and consumers. After receiving these comments over what can be a period of several years, the U.S. FDA issues Final Rules on a specific category of products; these become official on the date of publication in the *Code of Federal Regulations*. In many cases, however, the U.S. FDA issues subsequent rules either to delay application of Final Rules or to modify the Final Rules if new information has become available.

The Final Rule requirements have primarily been applied to products on the market and a newcomer is well advised to study competitor products for market leaders as ample opportunities are available to innovate these products. Examples include the Tylenol® Hot Therapy products and loratidine tablets that dissolve in the mouth and do not require water. I foresee more such products entering into the ever-competitive OTC market.

It is imperative that any prospective entry into the OTC market should begin with a thorough consultation of the Final Rules; an examination of Proposed Rules and notifications to issue Proposed Rules is also helpful in determining what rules are about to become Final Rules. Reviewing the discussions about Proposed Rules that have affected their finalization can be very helpful in understanding the relevant issues of safety, efficacy and labeling. Because the marketing of OTC products requires a large investment in marketing efforts, it is prudent to develop a clear understanding of the legality of formulations and claims made in the initial phases of product development.

A large number of products on the market today are not covered by the U.S. FDA monographs but does that make them legitimate? This is the often-asked question. The U.S. FDA has limited resources to tackle everything that is out there on the market. When emergencies arise, however, the U.S. FDA reacts immediately as it did in the case of phenylpropanolamine, pseudoephedrine and recently, kava kava. Here are some broad guidelines adopted by the U.S. FDA for the most commonly abused categories of products:

1. No treatments are approved for hair growth except for minoxidil.
2. No treatments are approved for enhancing sexual performance except for sildenafil citrate (and that only in MED).
3. The few treatments approved for weight loss include olristat phentermine and sibutramine (phenylpropanolamine is no longer a recommended compound).

It is noteworthy that the U.S. FDA does not differentiate between botanical products and chemical-based products. If a product bears an efficacy claim it must be governed by U.S. FDA rules; however a product that falls into a drug category that makes nutritional claims falls under a food category with its own set of detailed rules. Vitamins and minerals fall under food labeling guidelines; however a single-entity vitamin product with specific claims to treat or ameliorate a disease is a drug product. These definitions do not necessarily coincide with the rulings of regulatory authorities worldwide. In many countries nutritional products are controlled as drugs and require prescriptions; these same products would be considered non-prescription items in the United States. On the other hand a number of highly active drugs are available without prescription in many countries such as the Traditional Chinese Medicine (TCM) in China and Ayurvedic and Unani medicines in South Asia.

A reclassification of a drug to OTC status can be requested by drug manufacturers. Recent examples of such a prescription-to-OTC switch include ibuprofen (200 mg), ranitidine hydrochloride (75 mg), and loratidine (10 mg). Note that specific strengths, not necessarily the chemical entity itself, are made OTC. In other words it is not necessary to have an official monograph to secure OTC status for a drug. The decision to request reclassification of a drug as OTC is always a well-calculated business decision. Generally drugs with an OTC status will not qualify for medical reimbursement by insurance companies or federal assistance programs in the United States. This can substantially reduce sales of the product; on the other hand, ease of availability to a greater number of patients can easily compensate for this loss. The most lucrative opportunities arise when one strength is made OTC while other strengths remain available by prescription only.

It is noteworthy that the decision to allow a switch from prescription to OTC by the U.S. FDA is primarily driven by the side effects or toxicity of the drug. For example, in Australia a Roche request for a prescription-to-OTC switch for its weight-loss drug orlistat (Xenical®) was recently turned down because of extensive side effects associated with the use of Xenical. The drug itself is very safe as it does not enter the body and acts only locally to partially block absorption of fat. The unabsorbed fat produces many gastrointestinal symptoms which although temporary were sufficient to disallow the status switch. Obviously Roche would have been best advised to develop an OTC formulation with fewer side effects before requesting this switch. (In the case of orlistat, the solution was simple as described in U.S. Patent No. 6,251,421 by this author wherein combining orlistat with a natural fiber reduced the side effects by 70%.)

The OTC category of products represents a wide range of dosage forms. These formulations have much in common with their prescription counterparts but are presented in this volume of the *Handbook of Pharmaceutical Manufacturing Formulations* because of the development approach taken, labeling considerations, and support available from suppliers of ingredients in designing these products. Because the consumer is inevitably involved in the selection of these products, packaging considerations are much more important than in the prescription category of products. Additional considerations include ease of administration, palatability, and stability in storage as consumers are likely to keep leftovers around for a long time. Additionally, price constraints often make it difficult to enjoy some freedom of choice in formulations especially if the innovator company faces the competition of house brands. All of these considerations taken together make the OTC category one that should be presented in a single volume of this series of books.

Formulating OTC products is generally easier than formulating prescription products if the product is described in U.S. FDA monographs (either as Proposed Rules or Final Rules); such formulations become merely an exercise in mechanics. Whereas a manufacturer is not bound by these rules, complying with them reduces the costs and time involved securing approval from regulatory authorities. The multibillion-dollar market of OTC products has attracted major chemical suppliers to develop support ingredients that are much easier to use; they have also developed typical formulations for hundreds of these products.

The most notable industry leaders include:

- Amerchol
- American Colloid
- Aqualon
- BASF
- BF Goodrich
- Calgon
- Colorcon
- Croda
- Dow Corning
- FMC
- Gattefose
- General Electric
- Henkel
- Hormel

- Huls America
- ICI Americas
- Inolex
- International Sourcing
- International Specialty
- Laboratoires Serobioligique
- Lonza
- NIPA
- PPG Industries
- R.I.T.A.
- Reheis
- Rheox
- Rhone-Poulenc
- Rohm and Haas
- Southern Clay
- Sutton
- Vanderbilt

The formulations recommended by these and other companies have acquired almost a universal appeal; throughout this book you will find formulations recommended by these laboratories, as acknowledged by the listing of a brand name in the formula. The best way to connect to these companies is to search the Internet for contact information; it is no longer necessary to reproduce such information here. Whereas many companies prefer to use generic components in the dosage form, it has been found that the use of proprietary components can indeed reduce costs in the long run.

The choice of color is a highly sensitive issue in the formulation of OTC products; only FD&C colors are allowed. Whereas there is a great need to make the products attractive and appealing, the choices of safe colors are dwindling quickly, such as for red colors. The formulator is encouraged to review the status of approved colors around the world before committing to a specific color.

Many OTC solid dosage forms are available in coated form. Sugar coatings have yielded to film coatings, and this book contains a large number of sugar-coating, seal-coating, subcoating, film-coating, and polish-coating formulations that can be easily adapted to various dosage form sizes. The use of organic solvent-based coatings has become prohibitive because of environment considerations, but in those cases where formulations are extremely sensitive to moisture, organic coatings may still offer a valid choice. A few companies offer ready-made coating formulations, and these are worth considering. The Appendix to this book includes a large number of formulations of coatings of solid dosage forms. A keen formulator will have no difficulty based on these formulations in adopting a coating system that will provide the necessary protection and offer esthetic appeal as well. Solid dosage forms are coated for many reasons, including masking the taste, making them easier to swallow, and providing protection against the environment.

Stability considerations remain paramount, and the data in the final packaging must be evaluated carefully before adjusting formulae for excesses; in this book, most formulations are provided without this consideration. A strip or blister dosage form is more popular around the world, but the plastic bottle is the most popular final form in the United States.

The development of OTC products is similar to the development of prescription dosage forms; as a result, cGMP and Good Laboratory Practice (GLP) considerations apply equally. The first chapter describes in greater detail the cGMP considerations. An Appendix to Chapter 1 provides a comprehensive checklist of items to review to ensure that a manufacturing facility is in compliance with cGMP standards. Appropriate identification is made in this checklist of those items that comply with EC guidelines. The U.S. FDA guidelines are available from the U.S. FDA website: http://www.fda.gov. The World Health Organization (WHO) provides GMP guidelines that are less stringent than those of the U.S. FDA and EC, and formulators should be aware of the fact that all of these are simply *guidelines*. One should be fully cognizant of the fact that no agencies are bound by these guidelines, particularly the U.S. FDA. Manufacturers cannot take refuge in the defense that they have complied with these guidelines. It is further worthwhile remembering that all of these guidelines are continuously revised, and the "c" in the cGMP does refer to *current*.

The second chapter deals with the most popular category of dosage forms encountered in OTC offerings — solids. Issues specific to manufacturing of these dosage forms are described from a practical viewpoint, indicating the problem areas frequently encountered in manufacturing practice.

The third chapter deals with liquids and suspensions and includes, like the chapter above, practical advice on how to bring manufacturing practices into compliance with regulatory requirements.

The fourth chapter offers highlights of cleaning validation, a topic often ignored by OTC manufacturers as not being significant because of the safety of ingredients used. It is true that the same stringent standards may not apply, but compliance with cleaning standards and validation of processes go a long way toward ensuring overall compliance.

The first four chapters were drawn from advice the U.S. FDA gives to its inspectors before they inspect a manufacturer. The CFR includes complete details of what is considered acceptable by the U.S. FDA; this advice is of a practical nature, and I find it to be extremely helpful in enhancing awareness of the guidelines of regulatory authorities. It is noteworthy that EC guidelines, particularly in light of the harmonization of specifications, are somewhat identical to the U.S. FDA guidelines; in chapter 1, specific references are made to EC guidelines. The

Appendix includes formulations of coating solutions; these should prove useful for the pharmaceutical formulation teams.

The formulations in this book generally fall into three categories. Some formulations are presented in greater detail, including indications of where quality assurance (QA)/quality control (QC) sampling is to be done and describing the tooling and in-process and finished product specifications. The other extreme is a mere listing of components with a bare minimum of manufacturing methods. This was necessary for two reasons: first, to contain the size of this book, and, second, to keep from presenting superfluous information, as formulators would eventually adopt such a formula to their own delivery forms. Also, at times the various strengths are merely achieved through adjustment of dosage size, so it was considered unnecessary to reproduce manufacturing steps where they are obvious.

The primary source of these formulations is publicly available knowledge about formulae that have proven to provide stable products. No representation is made that these formulations meet U.S. FDA monographs or any other regulatory guidelines for safety of inert ingredients. The formulator is advised to determine guideline compliance before adopting any of the formulations given in this book. Those interested in obtaining detailed information about these formulations are encouraged to contact the author at http://www.pharmsci.com. Because of the wide variety of sources from which the information has been gathered in the book, the format of formulations also varies. For example, in some instances scale is provided, whereas in others a percentage by weight is described. In still other instances, quantities for a specific batch size are provided. Obviously, it would be desirable to convert these formulations into a uniform format, but the task would be daunting and inevitably would lead to inclusion of errors. Professional formulators should not encounter any difficulty in adapting these formulations to their own system.

As mentioned before, not all formulations contain the required overages for stability considerations and losses during manufacturing; formulators are expected to develop these based on the final packaging chosen for the product. The author would appreciate being notified of any special problems encountered in adopting these formulations or of any errors (niazi@pharmsci.com). Whereas much care has gone into ensuring the accuracy of quantities and proper identification of ingredients, such errors shall remain in a work as large as that presented here.

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About the Author

Dr. Sarfaraz K. Niazi has been teaching and conducting research in the pharmaceutical industry for over 30 years. He has authored hundreds of scientific papers, textbooks, and presentations on the topics of pharmaceutical formulation, biopharmaceutics, and pharmacokinetics of drugs. He is also an inventor with scores of patents and is licensed to practice law before the U.S. Patent and Trademark Office. Having formulated hundreds of products from consumer products to complex biotechnology-derived products, he has accumulated a wealth of knowledge in the science of formulations and regulatory filings of Investigational New Drugs (INDs) and New Drug Applications (NDAs). Dr. Niazi advises the pharmaceutical industry internationally on issues related to formulations, pharmacokinetics and bioequivalence evaluation, and intellectual property issues (http://www.pharmsci.com).

Acknowledgments

Many have assisted me in the development of this work that has taken years to compile, and I am thankful to scores of my graduate students and colleagues for their help.

The diligent and ardent editorial support offered by CRC Press was exemplary; nevertheless, any remaining errors are altogether mine. I am grateful to CRC Press for taking this lead in publishing what is possibly the largest such work in the field of OTC products. It has been a distinct privilege to have known Stephen Zollo, a Senior Editor at CRC Press, for many years. The editorial assistance provided by CRC Press staff was indeed exemplary, particularly the help given by Erika Dery, Susan Fox, and others.

I have dedicated this book to Dean Allen I. White, whom I met in 1970 when I began my graduate work at the Washington State University (WSU) in Pullman. Until his death last December, we stayed in touch, and I continued to benefit from his advice and kindness. He served as Dean of the WSU College of Pharmacy for 19 years. With a distinct lean disposition and straightforward approach to the profession he loved and the life he cherished, he taught us many things. I am so fortunate to have had this opportunity to know such a great educator, scientist, and leader.

Calamine Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
80.00	1	Polawax GP200	80.00
10.00	2	Polysorbate 60	10.00
50.00	3	Caprylic/capric triglyceride	50.00
QS	4	Deionized water	QS to 1 kg
100.00	5	Witch hazel distillate	100.00
50.00	6	Glycerin	50.00
20.00	7	Zinc oxide	20.00
20.00	8	Calamine	20.00
QS	9	Preservative, color	QS

MANUFACTURING DIRECTIONS

Heat oil and water phases separately to 65 to 70°C. Add water phase to oil phase while stirring. Add zinc oxide and calamine under high shear. Stir to cool.

Calamine Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
20.00	1	Cellulose (microcrystalline) (Avicel™ RC-591)	20.00
100.00	2	Glycerin	100.00
1.80	3	Methylparaben	1.80
0.20	4	Propylparaben	0.20
100.00	5	Glyceryl stearate and PEG-100 stearate	100.00
25.00	6	Cetyl alcohol	25.00
50.00	7	Zinc oxide	50.00
50.00	8	Calamine	50.00
653.00	9	Distilled water	653.00

MANUFACTURING DIRECTIONS

Mix item 2 with item 9, and heat to 75°C. Add items 3 and 4; mix until dissolved using a shearing mixer. Maintain temperature at 75°C, and gradually add item 1, continue mixing at 75°C for 15 minutes, or until item 1 is homogeneously dispersed. Mix well. When temperature drops to 60 to 65°C, gradually add items 7 and 8; mix well until powders are homogeneously dispersed. Pass through homogenizer, if necessary; adjust theoretical weight with warm distilled water, and continue mixing until the cream congeals.

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

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/L (g)
0.001 mL	1	Ipecac fluid 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 flavor	0.80
100.00	16	Propylene glycol	100.00
QS	17	HyFlo filter aid	0.50
QS	18	Water purified	~450.00 mL

MANUFACTURING DIRECTIONS

Charge Balsam of Tolu and 25 mL of water in a steam bath. Raise the temperature, stirring continuously in order to mix water with the balsam. Boil for half an hour, and allow to decant while cooling. Discard extracted Balsam of Tolu. Filter the supernatant liquid through filter paper, and store apart. Charge 150 mL water in a jacketed mixing tank, and heat to boiling. Add and dissolve parabens with mixing. Add and dissolve sugar with constant mixing. Heat to 70 to 75°C. Once sugar is dissolved, add glucose, sorbitol, and saccharin sodium. Mix well until dissolved. Dissolve ammonium chloride in 28 mL water. Add to mixing tank. Add extract Balsam of Tolu from first step with mixing. Mix well and cool to 25 to 30°C. Add and dissolve ephedrine and carbinoxamine in 20 mL water, and add to mixing tank. Mix well. Add and dissolve chlophedianol in 50 g of propylene glycol, and add to mixing tank. Add balance of propylene glycol to mixng tank. Add and dissolve Ipecac fluid extract and raspberry flavor in alcohol. Add to mixing tank. Dissolve dye in 5 mL water, and add to tank with continuous mixing. Rinse container with 5 mL of water, and add rinsing. Adjust to volume with purified water. Add HyFlo filter aid to syrup, and mix well. Recirculate through filter press or equivalent until sparkling clear.

Chlorhexidine Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
20.00	1	Chlorhexidin diacetate	20.00
300.00	2	1,2-Propylene glycol (Pharma)	300.00
220.00	3	Lutrol F 127	220.00
460.00	4	Water	460.00

MANUFACTURING DIRECTIONS

Dissolve chlorhexidin diacetate in propylene glycol at >70°C. Stir well, and slowly add Lutrol F 127 and water. Maintain the temperature until the air bubbles escape. A clear, colorless gel is obtained.

Iron Polystyrene and Vitamin C Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/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 (artificial guarana)	1.00 mL
QS	12	Sodium hydroxide	12. 1.0
QS	13	Dye	2.00
9.50	14	Distilled purified water	~95.00 mL
10.00	15	Sorbitol solution	~10.00

MANUFACTURING DIRECTIONS

Add glycerin (item 1) to the tank. Commence heating with agitation. Add and disperse parabens. Continue heating to 70 to 80°C and mix until solution is complete. Force cool to 30°C, then add and disperse xanthan gum (item 5). Add sorbitol solution (item 4) and 80 mL of purified water (item 14), and heat with mixing to 60 to 70°C until the xanthan gum is fully dissolved. Add and disperse saccharin and sugar (items 7 and 6). Mix at 60 to 70°C until dispersion is complete. Force cool to 25 to 30°C with continuous mixing. Commence N_2 gas protection and maintain for the remainder of the manufacturing process. Add and disperse ascorbic acid. Continue mixing for 30 mins at 25 to 30°C. (*Note:* Use suitable SS high-powered stirrer). Mix the iron polystyrene sulfonate milled slurry in the original epoxy-lined drums under N_2 gas protection until uniform. Add the slurry to the main batch and mix for 30 minutes at 25 to 30°C. (*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 flavors. Mix well. Check and record pH. Adjust pH using a 20% sodium hydroxide solution (1 g in 5 mL water) to a value of 3 (range, 2.8 to 3.2). Dissolve the dye in 5 to 7 mL of water at 40 to 45°C by stirring for 10 minutes. Add this solution to the main batch through a 420-µm screen with mixing. Rinse container with 2 to 3 mL water at 40 to 45°C and add to bulk through a 420-µm screen. Continue to mix under vacuum until mixture is uniform. Pass the suspension through the colloid mill at a gap setting of 100 to 150 µm. Adjust the flow rate such that the temperature rise of the suspension does not exceed 10°C. Collect the milled suspension in a stainless-steel-jacketed tank with vacuum. Mix at 25 to 30°C under vacuum until a uniform suspension is achieved. Flush the bulk suspension with nitrogen and seal. Hold at 25 to 30°C.

Magaldrate with Simethicone Suspension

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Quantity/L (g)
QS	1	Distilled purified 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; 18 to 20%)	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. Charge 285 mL purified water into a suitable jacketed tank and heat to 90 to 95°C. Add and dissolve parabens, benzoic acid, saccharin sodium, and potassium citrate. While maintaining temperature at 85 to 90°C, add, in small quantities, half the quantity of magaldrate cake or powder, if used, and disperse well. (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. Raise the temperature, if necessary, maintaining temperature at 85 to 90°C. Add in small quantities the remaining half of the magaldrate cake or powder, and disperse well. 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. While maintaining temperature at 85 to 95°C, add and disperse the suspension from the previous step to the main tank, and mix well. Avoid lump formation at any stage. Cool to room temperature. Add dimethyl polysiloxane emulsion and mix well. Add flavor and mix well. Dissolve citric acid in twice the quantity of purified water, and adjust pH if necessary. Check and record pH (range, 7.5 to 8). Add purified water to volume and mix well for a minimum of 30 minutes. Filter through a 180-µm aperture nylon cloth, and store in a suitable tank.

Vitamin B-Complex and Iron Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/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	Riboflavin	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 B12 (cyanocobalamine)	2.00 mg
0.007	18	Flavor	0.70 mL
QS	19	Deionized purified water	QS to 1 L
QS	20	HyFlo filter aid	QS
QS	21	Hydrochloric acid	QS
QS	22	Sodium hydroxide	QS

MANUFACTURING DIRECTIONS

Manufacture under complete carbon dioxide (CO_2) protection. Load 780 g (portion of item 2) of sorbitol solution into a jacketed, stainless steel tank; the remaining sorbitol will be used later. Add parabens (unless added previously), niacinamide, and riboflavin to the sorbitol or glucose solution. Heat solution to 85 to 90°C, and mix until the ingredients are dissolved. Remove heat. While mixing, cool the main solution to 50 to 60°C. Hold at this temperature while bubbling CO_2 into it. CO_2 protection must be continued for the remainder of the manufacturing procedure. Heat 50 mL of purified water to boiling, and bubble CO_2 into it while cooling to 55°C. Add and dissolve, with mixing, iron sulfate with 30 mL of purified water at 55°C. Use CO_2 protection. Warm the solution to 50 to 55°C while mixing to dissolve, then slowly add the solution, with good mixing, to the solution above. 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. 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. 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. Add this slurry slowly to the solution from the step above with vigorous mixing until a uniform solution results. Rinse the mixing container with 22 g of the reserved sorbitol, and add to the product with stirring. Add and dissolve thiamine hydrochloride with mixing. If necessary, warm the D-pantothenyl alcohol until liquified, and add it to the 0.5-mL CO_2-saturated purified water. Use an additional 0.5 mL of CO_2-saturated purified water to thoroughly rinse the container of D-pantothenyl alcohol, and add this to the D-pantothenyl alcohol solution. Mix the D-pantothenyl alcohol solution thoroughly until it is homogeneously dispersed. Add the D-pantothenyl alcohol solution to the main solution with mixing. Use an additional 0.5 mL of CO_2-saturated purified water to rinse out the container in which the D-pantothenyl alcohol solution was made, and add to the product with mixing. Dissolve the vitamin B12 in 0.5 mL of purified water to make a clear solution, and add this to the product with good mixing. Dissolve the guarana flavor in the 10 g of propylene glycol, reserved from earlier step, with good stirring. Add this solution to the product with good mixing. Check pH (range: 3.00 to 3.30). Adjust, if necessary, with a solution of 10% sodium hydroxide or 10% hydrochloric acid depending on the test results. Adjust the volume of the