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EFFECT OF FORMULATION COMPONENTS ON DRUG RELEASE FROM MULTIPARTICULATES

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ABSTRACT

The effect of excipients on the release of drug from multiparticulates or pellets coated and uncoated prepared by the extrusion/spheronization and centrifugal processes is reviewed in this paper. A processing viewpoint has been taken because of the relationship between a rugged scaleable process and reliable excipients. Only aqueous coating dispersions have been reviewed because of their increasing usage due to environmental and cost reduction programs.

INTRODUCTION

This paper is a limited review of the effect of excipients on the drug release from multiparticulates. A processing viewpoint has been taken because it has been the author's experience that the art and science of formulation is a close union between process, reliable excipients and the medicament.

Though there are many methods available to the pharmaceutical scientist for the manufacture of multiparticulates or pellets, that range from the sugar coating pan to the wealth of fluid-bed processes available in todays' environment, this review has been limited to extrusion/spheronization and centrifugal processes. Additionally only aqueous dispersion coating systems will be discussed. Some of this is personal preference, but founded in the belief that these processes offer the best and most environmentally sound methods of producing multiparticulates.

Multiparticulates or pellets offer many advantages over other solid oral dosage forms used for immediate or modified release. They are suitable for drug combinations when incompatibility problems exist or when drugs are to be released at different rates from the same dosage form. They can be filled into capsules or compressed into tablets and retain their respective drug releasing characteristics.

The most critical feature of a dosage form whether it is designed for modified or immediate release is the proportion of drug that it contains. This can range from a small fraction, (less than 1%) to 95% or higher. This is especially important in capsule dosage form development where the maximum amount of mass that a number 0 capsule may contain is approximately 500 mg. This factor is not as important for a tablet where coated multiparticulates with a compression aid, i.e. microcrystalline cellulose may result in a tablet as large as 1 g.

Thus the processes reviewed in this paper combined with the appropriate excipients offer the formulator fast, efficient, and cost effective methods of producing multiparticulates or pellets that contain a high drug concentration for encapsulation or tabletting.

GENERAL

Extrusion/Spheronization Preparation of Multiparticulates

Extrusion and spheronizing as a process for the manufacture of multiparticulates has gained increased usage during the past decade because of the increased popularity of multiparticulate controlled release oral dosage forms. Although originally proposed as

a novel process, the mechanical mechanisms that produce a spherical multiparticulate using the extrusion/spheronization process are similar to those once used by the corner druggist in the traditional pill making process (1).

Spheronization ("Marumerization®" trade mark of the Fuji Denki Kogzo Co. in Osaka) was invented in 1964 by Nakahara (2). The process was not widely known until two review articles were published in 1970 by the Lilly organization (3,4). Equipment design change has been minimal since the original patent. The spheronizer consists basically of a grooved horizontal plate rotating at high speed within a stationary vertical cylinder fitted with a door to allow release of the pellets. Although extrusion is usually regarded as a continuous process, spheronization equipment design limits the extrusion/spheronization process to a batch process or a multiple batch process.

There are five unit operations involved in the extrusion/spheronization process. These are; blending, granulation, extrusion, spheronizing and drying (Fig.1). The moistened pre-compacted mass is extruded into strands, which are then rounded into pellets in a spheronizing machine, dried and subjected to further processing. The moisture content and composition of the mixture must be selected in order that the desired plastic deformability (extrudability) is obtained. The particle size distribution of the pellets obtained is primarily determined by the degree of extrudate density and water content (5).

Fundamentally, extrusion is an operation where a plastic deformable mass is forced through small openings under pressure. The pressure is created by a screw/conveyor which produces a steady material flow. Effective cooling of the extrusion head ensures a regulatable exit temperature of the extrudate. If the extruded material is too warm, the active or excipients may partially dissolve and the mixture will clog in the screw channel until the screen blocks. Additionally, the granulation fluid usually evaporates and the extrudate becomes too brittle for the spheronizing process. Normally this occurs during the development process but may carry over into scale-up activities, due to the limited amount of extrusion usually done during the early development phases because of the lack of a plentiful bulk drug supply.

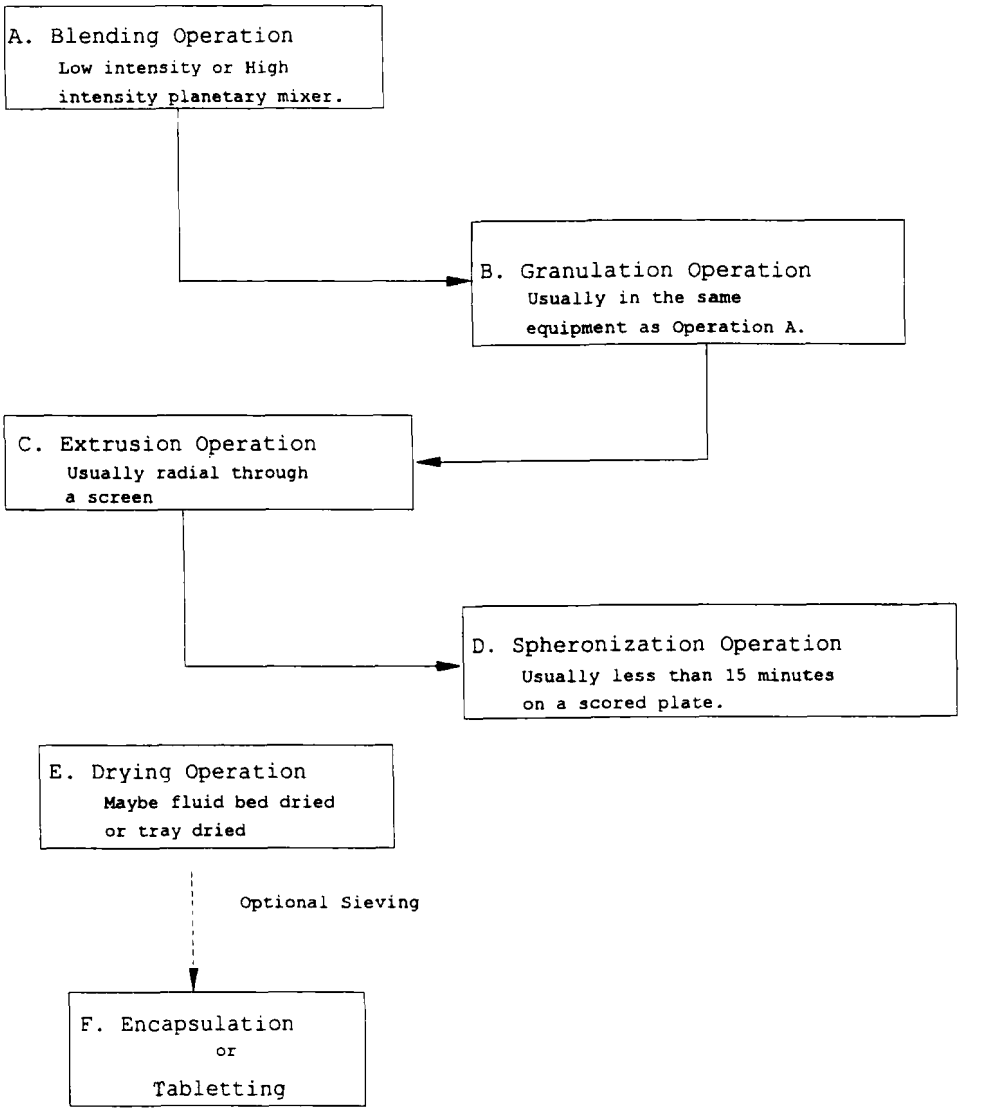

FIGURE 1

Flow chart for the spheronization process using the extruder/spheronizer.

In the spheronizer the extrudate is initially broken down into short equal lengths, i.e. the cutting stage in pill-making. These are then transported by centrifugal forces to the edge of the spinning plate, where this spinning motion causes them to rise up the vertical wall and then fall as their momentum is lost. This movement along with the angular velocity causes the moving mass to form a toroidal rope-like shape. The overall process usually takes less than 15 minutes (1). A comparison of representative formulas for pill-making and spheronization is given in Table 1.

Screw Extrusion Equipment

Two different mechanisms are possible for screw extrusion, axial and radial, as well as two types of extruders, single screw and twin screw. The most commonly used type of extruder used for the extrusion/spheronization process in the pharmaceutical industry is the radial twin screw extruder (Fig 2). In radial extruders the material is extruded circumferentially through openings in a screen. The shape of the opening varies with the application. If a denser product is needed a thicker screen is used. The flow of the material through the holes (screen) is very complex and related not only to the characteristics of the material but also to screen configuration. The extruding material is usually somewhat curved because it bends under its own weight after leaving the screen. Gravity acting on the hanging mass breaks the mass at a weak cross section when the cohesive forces which hold the extruded mass together fail. Thus the extruded segments have irregular lengths that vary between two to three lengths of their diameters (6). Equipment specifications for the Xtruder® type twin screw extruder as an example of the type used in the pharmaceutical industry are in (Table 2). Additional suppliers are listed in (Table 3).

Spheronizing Equipment

Spheronization begins with damp extruded lengths that are broken into uniform segments and gradually transformed into spherical shapes. All three dimensions of the agglomerate are determined by the extrusion process. The most important part of the spheronizer is the friction plate which can have a variety of textures. The surface of this plate has small points in the form of truncated pyramids, from 1 to 2 mm in height and spaced from 2 to 4 mm by engraving groves in a grid pattern on the plate (Fig. 3).

TABLE 1

Comparison of Representative Placebo Formulations of Pills and Spheroids.

Pill		Spheroid	
Magnesium Oxide	84% w/w	Lactose	50% w/w
Glycyrrhiza	16% w/w	Microcrystalline Cellulose	50% w/w
Liquid glucose	q.s.	Water	q.s.

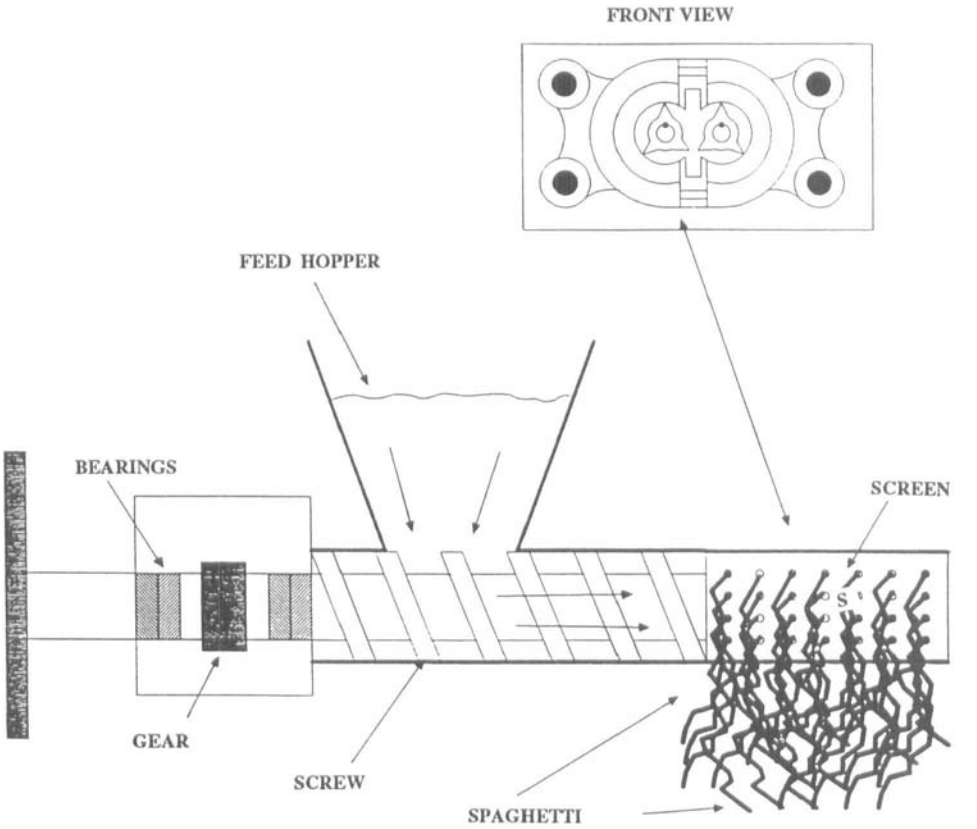

FIGURE 2

Schematic of a radial twin screw extruder.

TABLE 2[a]

Xtruder®-Type Twin-Screw Extruder.

Model Number					
Characteristic	EXD-60	EXD-100	EXD-130	EXD-180	EXD-230
Barrel diameter (mm)	60	100	130	180	230
Capacity (kg/hr)	30-50	100-300	200-900	800-3000	2000-4500
Drive motor (kw)	1.5	5.5	7.5	15-18.5	22-30
Weight (kg)	500	800	1100	1800	2500

[a] LUWA (Fuji Paudal) Corporation, Charlotte, NC 28297

The grid pattern should be chosen relative to the desired particle size. For example, extrudate through a 1.0 mm diameter screen should be processed on a friction plate with a 2.0 mm grove pattern. Usually the length to diameter ratio of fractured pellets is 1.0 to 1.2.

Work performed on the extrudate is also transformed into a temperature rise during processing. Because viscosity, plasticity, granulation fluid evaporation rate and sticking are temperature dependent, temperature control during the spheronization is recommended in order to obtain consistent results. Since this is essentially a batch process, a processing cycle consist of charging a predetermined amount of extruded material and waiting until the desired shape is obtained before discharging. Changing the processing time changes the mean number of particle collisions thus changing the particle shape and size (Table 4). Plate speed scale-up is obtained by maintaining the same tangential acceleration between pilot and production equipment (6). Equipment specifications for the Caleva® type spheronizers are given in (Table 5). Additional suppliers are listed in (Table 6).

TABLE 3

Extruder Manufacturers

Type	Manufacturer
Screw	Charles Ross & Son Company, Huappauge, NJ 11788 Werner & Pfleiderer Corporation, Ramsey, NJ 07446
Sieve and Basket	Key International Inc, (Frewitt), Englishtown, NJ 07726 LUWA (Fuji Paudal) Corporation, Charlotte, NC 28297 Niro Aeromatic, Columbia, MD 21045
Roll	Bepex Corporation, Minneapolis, NM 55413 California Pellet Mill Company, Crawsfordsville, IN 47933 LUWA (Fuji Paudal), Corporation, Charlotte, NC 28297 Sprout-Waldron (Sprout-Bauer), Muncy, PA 17756 Teledyne Readco (Amandas Kahl), York, PA 17405

Formulation

The formulas of multiparticulates obtained by extrusion/spheronization are similar to those used in classical tabletting wet granulation methods. In general, the formulations contain: a diluent; lactose, sucrose, dicalcium phosphate, a bonding agent; gums, gelatins, povidone, cellulose derivatives, i.e. microcrystalline cellulose, microcrystalline cellulose/sodium carboxymethylecellulose, a disintegrant; starches,

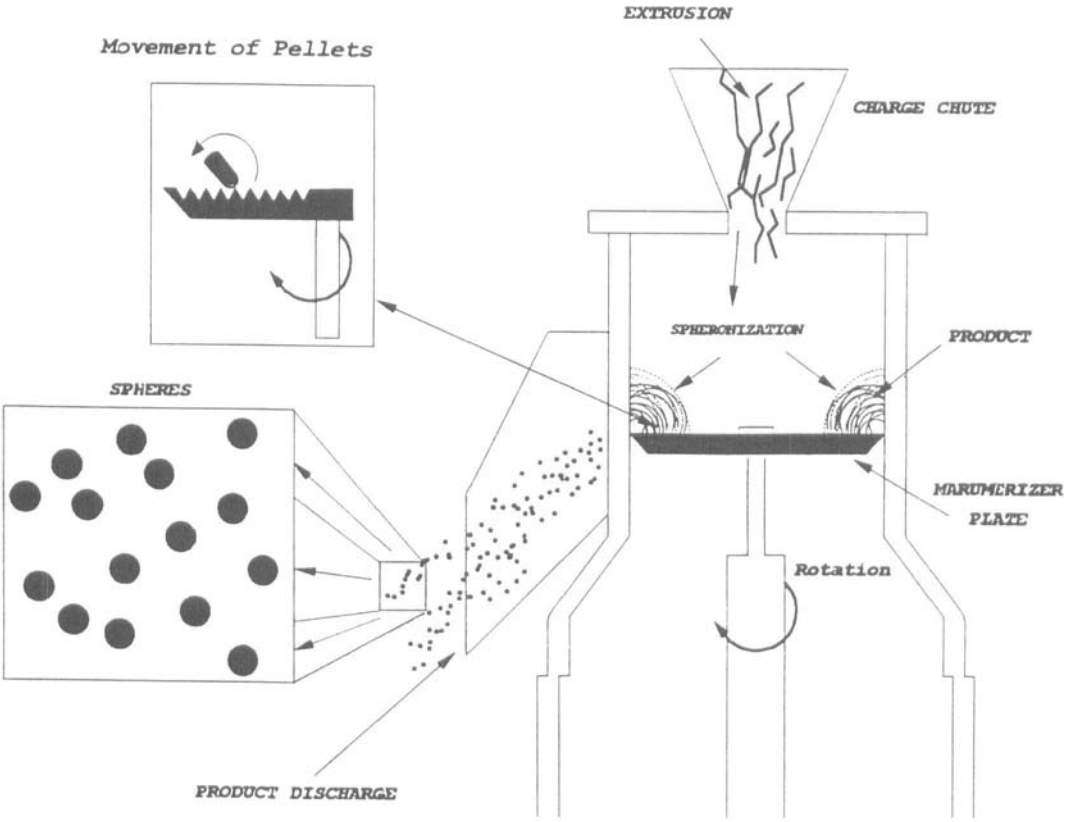

FIGURE 3

Schematic of a spheronizer.

TABLE 4[a]

Change in shape of extrudate with increasing spheronizer residence time.

Residence Time (min)	Shape
< 0.5	Cylinder
1 - 2	Cylinder with rounded ends
3 - 4	Dumbbells/Ellipoids
5 -6	Spheroids

[a] Adapted from Ref. 1.

TABLE 5[a]

Celeva[b] Type Spheronizers

Characteristic	Model			
	9	15	27	36
Diameter of Plate (mm)	229	381	686	915
Speed Range (rpm)	200-2000	200-1200	81-500	80-380
Circumferential Speed (m/sec)	2-24	4-24	3-18	4-18
Approximate Load Range (kg)	0.2-1.0	0.5-5.0	10-25	30-60
Motor Power (kw)	0.75	1.5	5.5	7.5
Approximate Weight (kg)	300	300	1000	1600

[a] Adapted from Ref. 1.

[b] Machines Collette (Caleva) Inc., Wheeling, IL 60090

colloidal silica, hydroxypropyl methylcellulose, and croscarmellose sodium. The granulation or wetting liquids usually are water, alcohol, or water/alcohol mixtures. If necessary a lubricant; oils (mineral oil, vegetable oil), silicones, stearic acid or magnesium/calcium stearate may be incorporated into the formulation.

The object of the formulation is to obtain for the extrusion process a mass that is homogeneous, nonabrasive and self lubricating so as not to stick to the extruder screws or to itself. For spheronization the goal is to obtain cylinders with enough brittleness to break at the desired length and not too large so as not to break completely. In addition the cylinders (spaghetti) should not stick either to themselves or the spheronizer and must have sufficient plasticity to form spheres.

Excipients

Early workers in the extrusion/spheronization field always included microcrystalline cellulose in their example formulas for use with this technique (3,4). Miyake et al

TABLE 6

Spheronizing Equipment Manufacturers

Type	Manufacturer
Standard	LUWA (Fuji Paudal) Corporation, Charlotte, NC 28297
	Lejus Medical AB, Molndal, Sweden
	Niro Aeromatic, Columbia, MD 21045
	Wips and Probst Engineering, Altdorf, Switzerland
Air-Assited	Glatt Air Techniques, Inc., Ramsey, NJ 07446
	LUWA (Fuji Paudal) Corporation, Charlotte, NC 28297
	Niro Aeronatic, Columbia, MD 21045
	Patterson Kelley (Nara) East Stroudsburg, PA 18301

reported in 1973 that microcrystalline cellulose exhibited the elasticity required for extrusion/spheronization whereas corn starch and lactose could not be extruded and spheronized when mixed with various quantities of water. Additional work done by Harrison and coworkers (8) demonstrated that microcrystalline cellulose has the ability to take up water into its intraparticulate voidage and become readily deformable. It was also shown that this excipient is insensitive to moisture concentration changes when compared to a water soluble crystalline material such as lactose.

Schwartz et al evaluated the spheronization process using commonly employed soluble and insoluble tabletting excipients such as; lactose monohydrate, diabasic calcium phosphate, microcrystalline cellulose, various types of starch and two grades of

microcrystalline cellulose with sodium carboxymethylcellulose as single component systems. These workers found that only the systems that contained microcrystalline cellulose were amenable to the extrusion/spheronization process (9).

Effect of Excipients on Drug Release

A series of experiments were conducted employing an EXDS®-60 type extruder and a Q250® marumerizer with a formulation consisting of 80% w/w acetaminophen and 20% w/w microcrystalline cellulose - sodium carboxymethylcellulose. It was demonstrated that the differences in the water content of the beginning granulation/extrudate resulted in significant differences in the hardness and dissolution rates of the resultant tablets (10).

The effect of drug solubility and the drug diluent ratio was studied using microcrystalline cellulose and two grades of microcrystalline cellulose - sodium carboxymethylcellulose by O'Connor and Schwartz. Anhydrous theophylline USP and quinidine sulfate USP were evaluated at drug/diluent ratios from 10:90 to 80:20. Chlorpheniramine maleate USP and hydrochlorothiazide USP were incorporated into one system to study the influence of the more extreme values of water solubility on drug release. Theophylline release from these drug/diluent mixtures varied with drug, and the diluent ratio (Table 7). Additionally it was found that drug release from a 10:90 drug/diluent microcrystalline cellulose matrix was directly related to the solubility of the drug (Table 8) (11).

In the processing of pellets by extrusion/spheronization, formulations may obtain pH adjusters as well as release modifiers. Bianchini et al recently evaluated both of these methods (12). Standard pellets composed of d-indobufen a carboxylic acid, microcrystalline cellulose and lactose, ratio 55:30:15 by weight were prepared by conventional extrusion/spheronization techniques. Sodium citrate, tartaric acid and fumaric acid were included in the standard formulation as pH adjusters instead of the lactose. Acrylic resins, Eudragit® RS/RL 30D (1:1) and ethylcellulose, Aquacoat® ECD 30 were included in fumaric acid formulations as liquid granulation. The amount of resin in the final pellets was 9% w/w. Drug release in USP apparatus 2, pH 7.5, 37°C and 200 rpm demonstrates that the presence of the pH adjusters affect

TABLE 7[a]

Dissolution Summary for Pellets Containing Theophylline.

Drug Diluent Ratio	Avicel® Type	Percent Dissolved	
		30 min	60 min
10:90	PH-101	46.9	65.8
	RC-581	9.4	16.2
	CL-611	6.3	12.6
50:50	PH-101	69.5	88.1
	RC-581	38.3	49.7
	CL-611	14.8	25.5
80:20	PH-101	53.9	77.0
	RC-581	27.1	48.6
	CL-611	29.7	60.3

[a] Adapted from Ref. 11.

TABLE 8[a]

Dissolution Summary for Pellets Containing 10% Drug in Avicel® PH-101

Drug	Solubility	Percent Released (120 min)
Hydrochlorothiazide	very slightly soluble	38
Theophylline	slightly soluble	83
Quinidine Sulfate	sparingly soluble	83
Chlorpheniramine Maleate	freely soluble	100

[a] Adapted from Ref. 11.

TABLE 9[a]

D-Indobufen Release (Percent).

Time (hours)	Sodium Citrate	Lactose	Fumaric Acid	Fumaric Acid Eudragit® RSRL	Fumaric Acid Aquacoat®
0.16	40	28	16	--	--
0.50	88	52	33	27	26
1.0	94	72	52	38	39
2.0	100	93	78	62	62
3.0		100	90	80	78
4.0			97	90	88

[a] Adapted from Ref. 12.

the release rate of d-indobufen from the pellets (Table 9). In addition, Table 9 displays the delayed release effect caused by the incorporation of insoluble polymers into the pellet matrix.

GENERAL

Centrifugal Preparation of Multiparticulates

The traditional or oldest method of building up spherical particles is agglomeration granulation in the coating pan or otherwise known as nonpareil manufacture. It is a slow process which takes several days or weeks and requires highly skilled operators (13).

A high speed adaptation of this process was developed in the late 70's and called roto or centrifugal granulation. This fluidized-bed, unique at the time, consists of a

rotating disk in a right circular cylinder. Some machines are equipped with a non-perforated disc which can be moved up and down to create a larger or smaller opening between the exterior perimeter of the disk and the wall of the cylinder. This enables control of the air speed independent of the air volume. The disk has a variable rotation speed, draws in air through the slit around the disk, thus fluidizing the material on the circumference of the product cylinder's wall. The material forced toward the outside of the spinning disk by centrifugal force is lifted by the current of fluidizing air into an expansion zone similar to the one seen in the spheronizer. The material descends to the center of the disk and repeats the cycle.

Originally these machines were developed to improve upon the type of granule produced by the fluid-bed granulation process. A study of granules manufactured in the rotor system showed that when compared with the same formulation processed in a top spray fluid-bed system, the rotor system produced granules with an apparent density increase of 10%, a 33% improvement in powder flow, and a friability reduction of five fold (14).

But by far the most interesting application of this type of equipment has been the coating of powders onto nonpareils or drug seed crystals and further coating with various types of film coating materials inorder to create pelletized drug delivery systems. Actives can be layered onto seed crystals or nonpareils with large build-ups (200-500%)very quickly (15).

Equipment

Two different centrifugal or rotary granulator systems have been made available to the pharmaceutical industry and were initially produced by Glatt GmbH, Binzen, Germany and Freund Industrial Co., Ltd., Tokyo, Japan (Figs. 4 and 5). Initially the Glatt was designed for installation in a fluid-bed granulator while the Freund machine was more or less a stand alone piece of equipment (16). Additional improvements have been made by Glatt and Freund (Tables 10 and 11) and additional manufacturers have entered the field (Table 12).

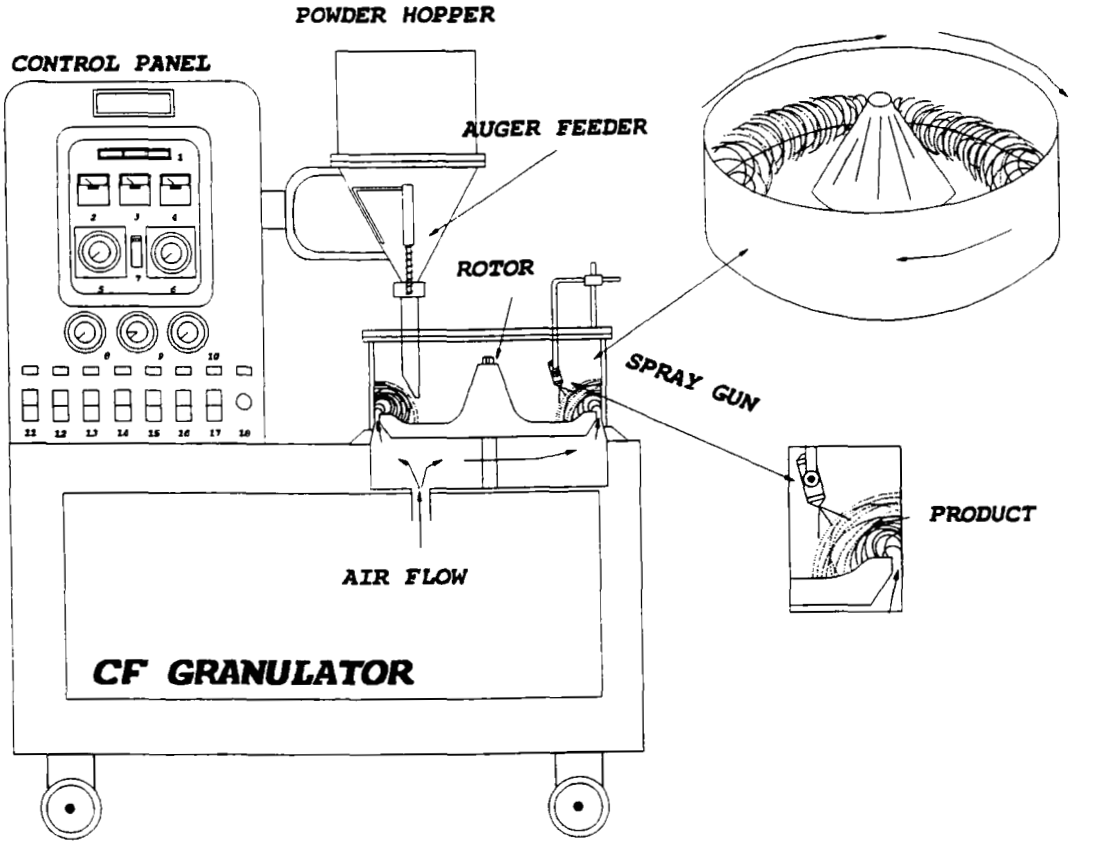

FIGURE 4

Schematic of a fluid bed type centrifugal granulator.

The Glatt type of rotogranulator can carry out fluid-bed granulation as previously noted by spraying the binder solution onto a rotating bed through tangentially oriented spray guns immersed in the moving powder bed. The rotogranulator in addition offers many significant advantages over the pan and Wurster processes for drug layering onto nonpareil seeds or drug crystals when a dry powder layering process is used. The principle advantage is the direct feeding of powder at a constant rate directly through a feeder tube buried in the rotating power bed. Therefore very little powder is lost through over fluidization to the filter bags or to the sides of the product chamber. Additionally there is an intimate mixing of powder, nonpareil and binder

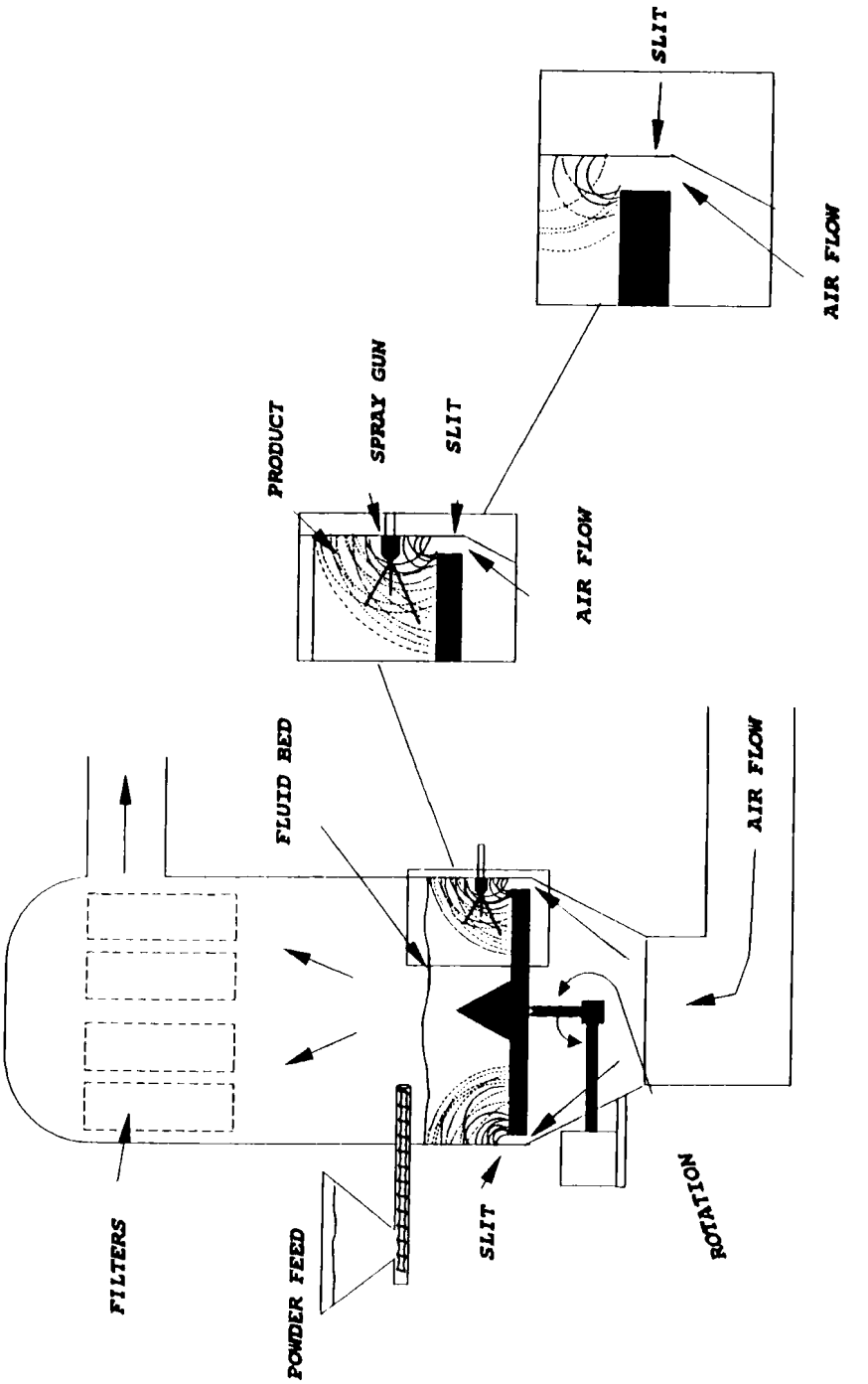

FIGURE 5

Schematic of the CF-Granulator.

TABLE 10

Centrifugal equipment manufacturers.

Type	Manufacturer
CF SF	Manufactured by Freund and supplied by Vector Corporation, Marion, Iowa 52302
GRG	Glatt Air Techniques, Inc., Ramsey, New Jersey 07802
Roto-Processor	Niro Aeromatic, Columbia, MD 21045

TABLE 11

Partial Specifications for Glatt GRG Rotor Granulator.

	Type	Disc Diameter (mm)	Container Volume (liters)	Rotor Speed (rpm)	Circumferential Speed m/sec
Rotor Inserts	GRG 3/5	306	4.5	200-1000	3-16
	GRG 5/9	480	30	200-1000	4-23
	GRG 15/30	620	60	150-735	5-25
	GRG 30/60	780	105	120-615	5-25
Rotor Units	GRG 60/100	1000	180	100-500	5-25
	GRG 120/200	1400	430	70-340	5-25

TABLE 12

Partial Specifications for the Freund CF - Granulator.

Type	Disc Diameter (mm)	Capacity (Kg)	Rotor Speed (rpm)	Circumferential Speed (m/sec)
CF-360	360	3-5	150-360	3-7
CF-750	750	10-30	80-160	3-6
CF-1000	1000	30-60	60-120	3-6
CF-1300	1300	40-80	45-90	3-6

solution because the addition of substances to the product bed is by direct injection deep into the moving bed.

A major difference between the C F Granulator® and the Glatt type of equipment is that the powder bed is not enclosed in a fluid-bed granulator type of system. On one side of the disc, in the C F Granulator®, there is a powder feeder with a feed tube that is above the moving powder bed. Diametrically opposed to the powder feeder is a spray gun that adds binder to the top of the bed. Because of this physical arrangement the rates of addition of solid and liquid are sensitive to material restraints and thus drug build up on the starting materials is not as fast as in the Glatt type equipment or equipment where binder and powder are injected into the powder bed and not layered on top of it (Table 13).

Formulation and Excipients

Wet agglomeration to obtain particle growth is a technique common to the following pharmaceutical operations: tabletting, extrusion/spheronization, balling agglomeration in coating pans (nonpareil manufacture), fluidized-bed granulation and the centrifugal agglomeration process. Thus pellet formulations usually contain drug, starter drug

TABLE 13[a]

Fluid-bed Rotary Granulator Configuration Compared to CF Granulator®

	Fluid-bed Rotary Granulator in Combination with Fluid-bed granulator unit	CF Granulator®
System	Closed	Open
Rotor	Can be lowered	Stationary
Width of Air Slit	Adjustable	Non-adjustable
Air Supply	Suction through slit	blown
Binding feeding device	Immersion nozzle in fluid-bed	Nozzle above fluid-bed

[a] Adapted from Ref. 16.

crystals/nonpareil seeds, diluent, binder and a disintegrant. A typical pellet formulation may contain lactose, microcrystalline cellulose, and sucrose as diluents; starches, and croscarmellose sodium as disintegrants and various, usually water soluble polymers, such as hydroxypropyl cellulose, povidone, hydroxypropy methylcellulose and methylcellulose as binders. Depending upon the pH solubility characteristics of the drug, a pH modifier may be added to the formulation in the form of a commonly used pH buffering agent.

The steps involved in processing a formulation for powder layering centrifugal equipment consist of blending drug, diluent, and disintegrant/pH modifiers, if needed, in a suitable blender. Preparing a binder solution and loading these ingredients into the appropriate receptacles on the centrifugal equipment and processing by adding these ingredients simultaneously to a bed of starter material in the processor (Fig. 6).

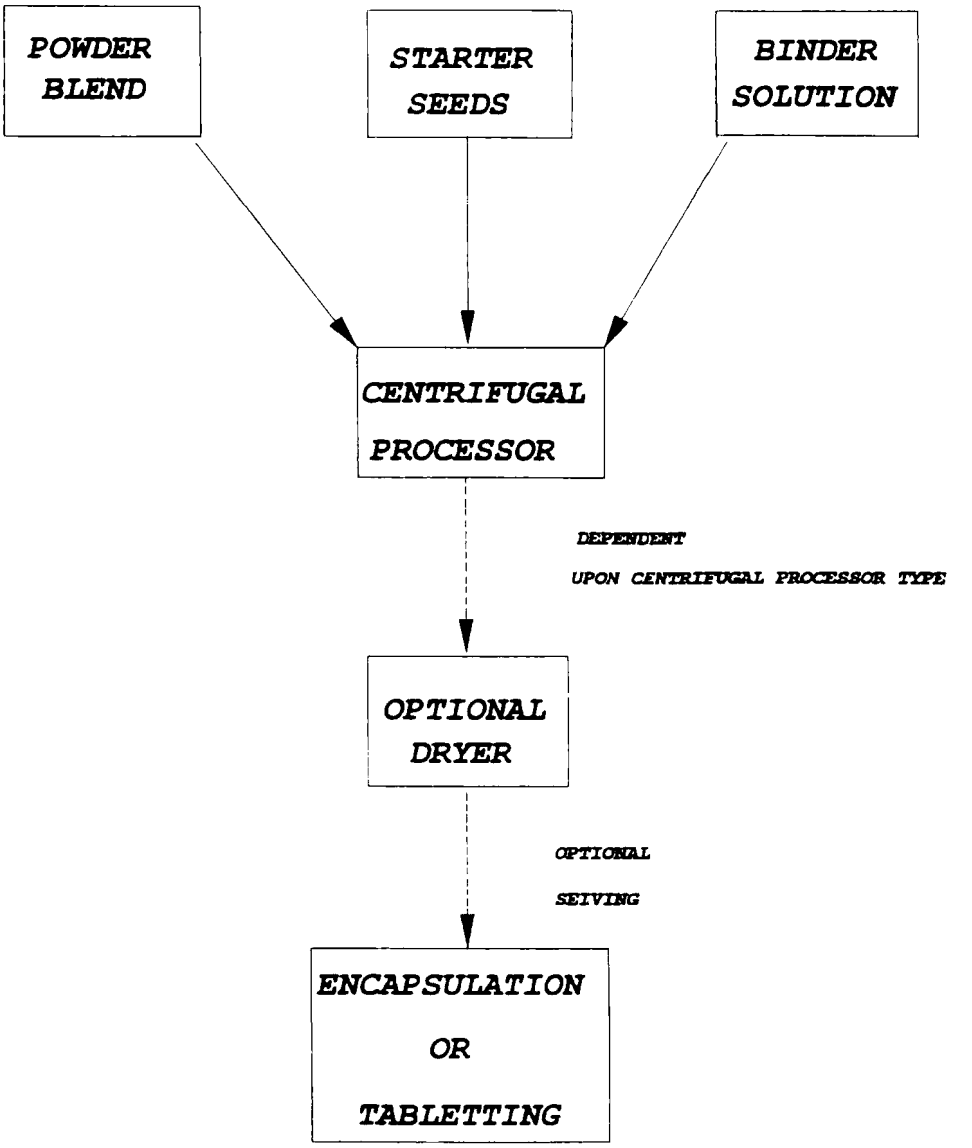

FIGURE 6

Flow chart for powder layer in centrifugal processing equipment.

The powder blend should have a flow comparable to that needed for high speed encapsulation and the binder solution should meet the requirements needed for ordinary fluid-bed granulation.

Ghebre-Sellassie et al found that this type of process is amenable to all hydrophilic drugs irrespective of their physico-chemical properties. These workers also found that different processing conditions were required for drugs of limited water solubility such as theophylline. Additionally the two most critical parameters, powder feed-rate and binder solution flow-rate must be adjusted to match the hydrophobic or hydrophilic characteristics of the drug powder blend. With friability as a measure of binder acceptability and using a 8% w/w binder solution, gelatin appeared to be the best binder followed by sodium carboxymethylcellulose, hydroxypropyl cellulose, kaolin/ Eudragit® E30D mixture and povidone. The size of the finale pellets was found to be proportional to the corresponding starter seeds, with the drug content of the pellets varying accordingly (Table 14) (17).

Effects of Excipients on Drug Release

Since the majority of pellets or multiparticulates are usually prepared for subsequent coating with a drug release rate controlling membrane and either encapsulated or tabletted, the effect of excipients on drug release will be discussed first from the view point of the coated substrate (pellet/multiparticulate) and then from the viewpoint of the membrane as a substrate for additives.

The release profiles of coated (ethylcellulose aqueous polymeric dispersion); centrifugally prepared diphenhydramine hydrochloride, a very highly soluble drug, and theophylline, a slightly soluble drug; pellets (Table 15) demonstrate the importance of drug solubility in the design of drug delivery systems. Because of its very high level of water solubility, diphenhydramine hydrochloride migrates into the film coat making it discontinuous and permeable during dissolution. In contrast theophylline does not dissolve nor migrate as far as diphenhydramine during the coating operation (Table 15) (18). Yang and Ghebre-Sellassie (19) extended this work and sealcoated diphenhydramine hydrochloride pellets prepared by centrifugal processing with hydroxypropyl cellulose before applying a controlling pseudolatex ethylcellulose membrane. The release of drug from these pellets was found to be

TABLE 14[a]

The drug content of 18 Mesh Diphenhydramine Hydrochloride Pellets Prepared from 40-60 and 20-25 Mesh Non-pareil Seeds in a CF Granulator®.

Mesh Size of Non-Pareil Seeds	Percent w/w Drug Content
20-25	67.3
40-60	82.5

[a] Adapted from Ref. 17.

TABLE 15[a]

Effect of Substrate Solubility on the Drug Release of Pellets Coated with the same Coating Formulation

Time (h)	Percent Released Diphenhydramine HCl	Percent Released Theophylline
0	0	
0.5	60	2.0
1.0	78	5.0
2.0	85	9.0
4.0	90	17.0
6.0	95	20.0
8.0	96	25.0
10.0	97	32.0
12.0	98	38.0

[a]Adapted from Ref. 18.

slower than pellets prepared the same way but with no seal coat. This indicated that the sealcoat prevented drug migration during the coating process and that the drug did not interfere with the formation of the ethylcellulose barrier membrane from the pseudolatex application system.

Polymers used as membrane formers in pharmaceutical applications may be classified accordingly to their water solubility and permeability (Table 16). Presumably the most widely used water insoluble polymer in film coating is ethylcellulose. Although it is sometimes applied alone, but plasticized in many coating formulations, the polymer is usually combined with a water soluble polymer to give to the membrane some sort of water permeability by forming holes in the membrane during dissolution. Workers have shown that centrifugally prepared pellets coated with pseudolatex ethylcellulose formulations containing 2%, 5% or 10% hydroxypropyl cellulose, based on the coating solids, yielded faster rates of release than those coated with the pseudolatex alone (18) (Table 17). Another very important group of water insoluble but water permeable polymers are the methacrylester-copolymer and methacrylic ester copolymers. Their permeability is a function of the number of hydrophilic groups that are attached to the polymer backbone. It is also possible to blend these polymers to obtain membranes of various permeabilities. U.S. Patent 4,912,146 teaches that the release of diphenhydramine hydrochloride from centrifugally prepared pellets, coated at the same level with a suspension of kaolin in water, combined with an aqueous dispersion of methacrylester-copolymer can be modified, as the amount of kaolin in the membrane is varied from 4% to 2% based on the solids content of the aqueous dispersion of the copolymer (Table 18) (20).

All the polymers in the alkaline soluble group contain carboxyl groups and are thus soluble at higher pH's and insoluble at low pH's. These characteristics were used to their best advantage in U.S. Patent 5,167,964 in the formulation of a semi-enteric drug releasing system (21). Wherein the drug doxycycline hydate is irritating to the stomach but effective plasma levels must be maintained for antibacterial effectiveness. Therefore an enteric coating was designed with a leak rate that would maintain adequate plasma levels and provide gastro-protection. The system comprises an inert core, a first coating layer over the core consisting of drug and a second coating layer

TABLE 16

Polymers of different water solubility suitable for Membrane formulation (Aqueous Coatings)

Freely Soluble in Water	Water Insoluble & Impermeable
Methylcellulose	Ethylcellulose
Hydroxypropyl methylcellulose	- pseudolatex, Aquocoat®
Hydroxypropyl cellulose	- pseudolatex, Surelease®
Povidone	
Polyethylene glycol (PEG)	
Water Insoluble but Permeable	**Soluble in Alkaline Media (anionic polymers)**
Methacrylester - copolymer	Cellulose acetate phthalate
- latex, Eudragit® NE30D	- water redispersible Aquateric®
Methacrylic ester copolymers	Polyvinyl acetate phthalate
- pseudolatex, Eudragit® RS/RL30D	- water redispersible, Coateric®
Cellulose acetate	Methacrylic acid copolymers
- pseudolatex, FMC	- latex, Eudragit® L30D

TABLE 17[a]

Effect on the Rate of Drug Release of Various Levels of Hydroxypropylmethylcellose (HPMC) in the Sustaining Ethylcellulose[b] Coat of Highly Water Soluble Drug Pellets.

Percent HPMC in Coat	Time 50% Drug Released (h)
0	>6
2	4.5
5	3.5
10	1.8

[a] From Ref. 18. [b] Prepared from a pseudolatex

TABLE 18[a]

Effect on the Rate of Drug Release of Various Levels of Kaolin in the Sustaining Methacrylester-Copolymer[b] Coat of Diphenhydramine Hydrochloride Pellets Coated at the Same Level.

Percent Kaolin in Coat	Time 50% Drug Released (h)
4	1.1
9	5.0
20	>12.0

[a] From Ref. 20. [b] Prepared from a latex.

over the first coating layer made up of a mixture of methacrylic acid copolymer and povidone (Table 19). The semi-enteric nature of this system is displayed in (Table 20).

Mechanism of Release from Coated Multiparticulates

Formulating techniques such as excipient addition to the rate controlling membrane and the coating process itself contribute to the permeability of membranes formed from aqueous dispersions.

TABLE 19[a]

Semi-Enteric Drug Delivery System

Centrifugal Preparation.

Ingredient	Percent w/w Total Drug Delivery System	Function
Doxycyline Hydate	59	Drug
Nonpariels	30	Starter Seeds
8% Hydroxypropyl Cellulose Solution	2	Binder
Colloid Silicon Dioxide	0.1	Glidant

Barrier Coat.

Ingredient	Percent w/w Total Coating Layer	Function
Eudragit® L30D	28	Enteric Coating
Povidone	1.36	Pore Former
Triethyl citrate	0.90	Plastizer
Kaolin	1.65	Antiadherent
Water	q.s. 100	Solvent

[a] From Ref. 21.

TABLE 20[a]

Amount of Doxycycline Hydate Released from a Semi-enteric Drug Delivery System.

Time (min)	Percent Released	
	0.06 NHC1	pH 5.5
0	0	0
15	5	4
30	12	8
45	20	19
60	30	30
90	46	48
120	58	60

[a] Adapted from Ref. 21.

This increased permeability is usually the result of membrane pore formation. During dissolution, the rate controlling mechanism is expected to be drug diffusion through water filled pores and not through a water insoluble membrane (22). However, drug solubility will effect all phases of the release curve. The more soluble the drug the lower the fraction of drug that can be released at a constant rate. In addition to simple diffusion, osmotic and convective forces are expected to play a role in drug release depending upon drug solubility (23).

SUMMARY

Formulation components play an important role in the release of drug from a dosage form composed of pellets or multiparticulates. Microcrystalline cellulose has been

found to be of primary importance in the processing of multiparticulates by the extrusion/spheronization process. This excipient and in combination with sodium carboxymethylcellulose influences the release of drug from multiparticulate dosage forms depending on the solubility of the drug in the dosage form. The centrifugal multiparticulate process is a general process which is amenable to hydrophilic and hydrophobic drugs and excipients.

The use of latex or pseudolatex film coating systems for controlled release has increased and evolved from empirical use to one based on sound physical chemical properties. The importance of substrate intractions with the film during the coating process and the addition of soluble polymers to the coating mixture have been acknowledged. Thus within the last few years, with the recognition of excipient functionality it is now more apparent than ever that the art and science of formulation is a coupling process which includes the excipient, the medicament and the process.

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REFERENCES

1. Rowe, R.C., Pharm. Int., 6, 119 (1985).
2. Nakahara, N., U.S. Patent 3 277 520, 1964.
3. Conine, J.W. and Hadley, H.R., Drug Cosmet. Ind., Apr, 38 (1970).
4. Reynolds, A.D., Manuf. Chem. Aerosol News, 41, 40 (1970).
5. Dietrich, R., Manuf. Chem. 60, 29 (1989).
6. Hicks, D.C., Notes, Extrusion and Spheronizing Equipment, Center for Professional Advancement, East Brunswick, N.J., Course: "Briquetting, Pelletizing and Extrusion: The Technology of Particle Size Enlargement," Course Director, Engelleitner, W.H., Apr 24-26, 1989, Princeton, N.J.

7. Miyake, Y., Shinoda, A., Furukawa, M., Uesugi, K., and Nasu, T., Yakazaigaku 33, 161 (1973).
8. Harrison, P.J., Newton, J.M., and Rowe, R.C., J. Pharm. Pharmocol. 37, 686 (1985).
9. O'Conner, R.E., Holinej, J., and Schwartz, J.B., Am. J. of Pharm., 156, 80 (1984).
10. Malinowski, H.J., and Smith, W.E., J. Pharm. Sci., 63, 285 (1974).
11. O'Conner, R.E. and Schwartz, J.B., Drug Dev. Ind. Pharm., 11, 1837 (1985).
12. Bianchini, R., Bruni, G., Gazzaniga, A., and Vecchio, C., Drug Dev. Ind. Pharm., 18, 1485 (1992).
13. Gamlen, M.J., Manuf. Chem., 56, 55 (1985).
14. Jäger, K.F., and Bauer, K.H., Drug Made in Ger., 25, 61 (1982).
15. Olsen, K., Plant/Operations, 4, 135 (1985), Glatt Air Techniques, Inc., Ramsey, NJ 07446
16. Gajdos, B., Drugs Made Ger., 27, 30 (1984).
17. Ghebre-Sellassie, I., Gordon, R.H., Fawzi, M.B., and Nesbitt, R.U., Drug Dev. Ind. Pharm., 11, 1523 (1985).
18. Ghebre-Sellassie, I., Iyer, U., Kubert, D., Fawzi, M.B., Pharm. Techn. 12, 96 (1988).
19. Yang, S.T., Ghebre-Sellassie, I., Int. J. Pharm. 60, 109 (1990).
20. Ghebre-Sellassie, I., and Nesbitt, R. U., U.S. Patent 4 912 146, 1990.
21. Muhammad, N., Harris, M., Weiss, J., Nesbitt, R.U., U.S. Patent 5 167 964, 1992.
22. Ghebre-Sellassie, I., Gordon, R.H., Nesbitt, R.U., and Fawzi, M.B., Int. J. Pharm., 37, 211 (1987).
23. Ragnarsson, G., Sandberg, A., Johansson, M.O., Lindstedt, B., and Sögren, J., Int. J. Pharm., 79, 223 (1992).