Chapter 6.

Summary and Conclusions
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6.1. Introduction

Better patient compliance, reduced adverse-effects and more efficient delivery of active ingredients are primary goals of product researchers and formulators, who have at their disposal an array of new drug delivery technologies to assist them with their work. The range of considerations in formulating and administering the drugs is as diverse as the populations they target.

The oral route is the most dominant route for drug delivery. Amongst the various formulations for controlled drug delivery used orally, the multiple-unit systems are gaining popularity and their market presence has increased several folds in the last several years.

Coating of small particles requires sophisticated technologies, special polymers for precise functions and refined processing conditions to achieve the desired product. Often formulation of polymer composition requires greater skill and understanding with regards to designing superior coated multiparticulate drug product that elicits more consistent in vivo behaviour and thus better control of disease conditions.

Multiparticulates may be coated for following reasons –

1. Designing controlled-release drug delivery system.
2. Preparing delayed- or enteric-release dosage form.
3. Reducing the incidence and severity of dose-related systemic and local adverse effects.
4. Improving patient compliance by reduction of dosing frequency and incidence of side-effects and better control of disease condition.

5. Enhancing oral bioavailability of poorly aqueous soluble drugs.

6. Enhancing the physical characteristics of multiparticulates by enhancing flow and reducing friability.

7. Masking unpleasant colour, taste or odour and preventing leaching of core materials from the multiparticulates thereby improving patient acceptance of the product.

8. Enhancing the stability of acid-labile, photo-labile, oxidation-labile, moisture-sensitive or hydrolysis-labile drugs - coats may serve as barriers that protect incompatible or unstable core materials from one another and from environmental elements such as light, oxygen, water and carbon dioxide.

9. Enhancing the aesthetics of the dosage form.

10. Facilitating the identification of product and different dosage strengths of same product.

11. Extension of patent protection, overcome competition and create brand loyalty.

The most common shape of individual cores for the development of coated multiparticulate systems is a sphere since –

- A spherical shape has minimum surface-to-volume ratio thereby requiring minimum coating on weight percent basis for obtaining a desired drug release profile.

- Spherical shape enables easy processing, especially coating of particles at a rapid rate with a more uniform deposition of applied coating.
• Spherical shape offers a consistent and definite surface for uniform drug release.

An ideal spherical pellet is the one that has –

• Smooth surface to facilitate uniform deposition of film coat.

• Narrow size distribution which will ensure minimum variation in coating thickness throughout the batch of pellets and therefore result in a uniform performance of pellets within the batch, and minimise segregation during blending and capsule filling/compression into tablets.

• As much as possible of the active ingredient to keep the size of the final dosage form within reasonable limits.

Coats formed from various polymeric coating materials are broadly classified as –

1. Polymeric solutions
2. Aqueous polymer dispersions
3. Molten polymers, and
4. Dry powders.

6.2. Objectives of the Study

Drug pellet/particle/ granule coating is a big challenge and is not as easy as conventional coating of tablets because of their small size, low density and large surface area. The case with which pellets can be coated depend upon –

1. Coating composition employed viz. organic solutions, aqueous dispersions or hot melt system.
2. **Coating technology** employed to coat the drug pellets viz. coating pan, centrifugal granulator (tangential-spray coater), fluid-bed devices, etc.

The aim of the present study was to evaluate the various coating formulation strategies and coating technology for preparation of coated drug pellets (having the desired characteristics) in the production of multiparticulate formulations, using certain model drugs.

The plan of work was as follows –

1. Comparison of pellet coating efficiency of Wurster coater, tangential spray coater and modified coating pan using aspirin as the model drug.

2. Comparison of organic and aqueous coating compositions for pellet coating in the preparation of delayed-release rabeprazole sodium pellets.

3. Comparison of taste-masking efficiency of Eudragit polymers in the preparation of ciprofloxacin hydrochloride Pellets.

4. Evaluation of cellulosic and acrylic polymers in the design of controlled-release propranolol hydrochloride pellets.

6.3. **Comparison of Pellet Coating Efficiency of Wurster Coater, Tangential Spray Coater and Modified Coating Pan using Aspirin as the Model Drug**

Uniform deposition of coating on a small spherical substrate called pellets is often a challenge. The type of coating equipment used to apply coatings on
such substrate can have a remarkable influence on the performance of coating.

In the present study, an attempt was made to evaluate and compare bottom-spray fluid-bed coater (Wurster coater), tangential-spray centrifugal coater and modified coating pan (coating pan equipped with three baffles) for enteric-coating aspirin pellets with regards to –

1. Effect of coating device on the microstructure of film-coating as evaluated by the uniformity of coating, integrity of coating, which in turn can have an influence on drug release.

2. Efficiency of coating device in depositing the film-forming polymer as assessed by rapidity of processing, degree of agglomeration during coating and percent yield.


Aspirin pellets prepared by extrusion-spheronization were enteric-coated using organic coating composition in the above three mentioned devices. Pellet and its coating composition were kept constant in order to evaluate the performance of the coating devices in effectively depositing the enteric polymer on the drug pellets with regards to their expected performance. Parameters such as –

- Uniformity of coating
- Integrity of coating
- Rapidity of processing
- Degree of agglomeration
• Percent yield
• *In vitro* drug dissolution, and
• Storage stability

were used to assess the performance of the coating devices. Highly sophisticated piece of coating equipment such as Wurster coater was found to be most efficient of the three facilities evaluated. The superiority of this device apparently could be owed to its ability to—

✓ Efficiently fluidize the pellet bed into discrete particles during application of polymer solution
✓ Rapidly evaporate the solvent and its exchange with the drying air
✓ Completely deposit the coating polymer uniformly on the fluidized pellet-bed without affecting spray drying and/or impingement of the droplets on the coating or expansion chamber.

Pellets processed in Wurster coater were superior compared to pellets created in tangential coater and coating pan with regards to—

1. Better performing pellets as assessed by the *in vitro* dissolution to evaluate the enteric properties of the product.
2. Better resistance to moisture and humidity during hostile storage conditions as evaluated by moisture uptake, formation of salicylic acid and drug content.
3. Better morphological characteristics of pellets as assessed by the uniformity of coat deposition by stereomicrography.

The equipment also was also found to be most efficient when evaluated on scales that demonstrated—
1. Greater product yield
2. Better weight gain
3. Lowest degree of agglomeration
4. Rapidity of processing.

Thus, although the installation and energy input costs of Wurster coater are highest, in totality, processing in such a device is more economical considering quality of product produced.

6.4. **Comparison of Organic and Aqueous Coating Compositions for Pellet Coating**

Many factors may affect film formation and the interaction between the film and the substrate as well as the stability of the film upon aging. These factors are substrate-related, film-related, and process-related. Substrate-related factors include formulation components, physicochemical properties, thermal expansion, compatibility characteristics, wettability of the surface, and surface porosity. Factors related to the polymeric film and process include coating composition (solvent, polymers, plasticizers, pigments, channelizing agents), viscosity and surface tension of the coating liquid, thermal expansion of film coat and thermal stresses due to different thermal properties of the film coat and the core, the processing equipment, spraying conditions, drying process and moisture effect, solvent evaporation rate, film-formation, film integrity, uniformity of thickness, type of film, and bonding between the film and the substrate.

The aim of the present study was to prepare enteric-coated pellets of the model acid-labile drug rabeprazole sodium by employing Eudragit L-100 55 as the delayed-release polymer in the form of organic solution and as aqueous polymeric dispersion, in a Wurster coater. Furthermore, the
objectives of the study included evaluating the enteric-coated products so produced with regard to –

1. Effect of coating-composition on the microstructure of film formed as evaluated by the uniformity of coating, integrity of coating and adhesion of coating to substrate surface, which in turn can have an influence on drug release and stability.

2. Efficiency of coating-composition in depositing the film-forming polymer as assessed by rapidity of processing, degree of agglomeration during coating and percent yield.

3. Effect of coating-composition and coating-level on the performance of film i.e. enteric property as evaluated by in vitro drug dissolution and storage stability of the product.

Rabeprazole sodium pellets were prepared by solution layering the drug onto nonparel seeds in a Wurster coater. The drug pellets were first coated with a seal-coat to prevent direct contact of acid-labile rabeprazole sodium with the subsequent outer layer of enteric-coating polymers having acidic nature. The seal-coated drug pellets were divided into two lots and further coated with acrylic enteric polymer – one lot with aqueous dispersion Eudragit L30D 55 and the other with organic solution of Eudragit L100 55. Coating parameters and weight gain were kept constant in order to evaluate the performance of the coating compositions in effectively depositing the enteric polymer on the drug pellets with regards to their expected performance.

Higher level of aqueous enteric polymer was required to obtain the same release characteristics in comparison to that possible with coating from organic solution indicating that the latter composition produced a more coherent, dense and effective enteric layer as compared to aqueous
dispersion. However, the organic composition has its own cognizable disadvantages whereas the aqueous dispersion has known merits over the organic composition. Despite these differences, it is still a matter of concern regarding the degree of polymer applied on the pellets since there is also a limit to polymer intake orally. In the light of above, it appears that the product coated with organic solution is more suited than that coated with aqueous dispersion as it offers following advantages –

1. Use of lesser polymer to achieve the desired enteric release making it suitable for compliance according to US FDA regulations on intake of Eudragit polymer orally on per day basis.

2. Lesser processing time and thus more cost effective process in terms of equipment held-up, labour cost, cost of energy input, etc.

3. Lower cost of polymer owing to decreased level of coating.

4. Ability to produce final pellets smaller in size in comparison to that produced with aqueous dispersion.

5. Greater stability of product on long term storage.

6. Yields product with good surface morphology.

6.5. **Comparison of Taste-Masking Efficiency of Eudragit Polymers in the Preparation of Ciprofloxacin HCl Pellets**

Taste, smell, texture and after-taste are important factors in the development of dosage forms. These are important factors in product preference. Good flavour and texture are found to significantly affect sale of the product. Undesirable taste is one of the important formulation problems encountered
with most of the drugs. The methods most commonly involved for achieving taste-masking include various chemical and physical methods that prevent the drug substance from interaction with taste buds. The simplest method involves use of flavour enhancers. Where these methods fail more complex methodologies are adopted.

The aim of this study was to prepare micropellets of intensely bitter drug ciprofloxacin hydrochloride (size below 30 mesh) and coat them with pH-dependent polymers viz. Eudragit E-100 and Eudragit L-100 with or without combination with waxes, to mask the bitter taste.

In detail, the objectives of the present study were –

1. Prepare the drug micropellets by extrusion-spheronization since such pellets, owing to their compact/dense nature, would dissolve slowly as compared to pellets prepared by drug layering on nonpareils.

2. Coat the drug pellets with pH-dependent polymers, Eudragit E-100 and Eudragit L-100, without or in combination with hydrophobic wax, cetyl alcohol, at various core-to-coat ratios, to mask the bitter taste of drug.

3. Evaluate the ability of the coating composition and thickness of coat in effectively masking the taste of bitter drug.

4. Evaluate the *in vitro* drug dissolution and storage stability of the product.

Taste-masked ciprofloxacin hydrochloride pellets were successfully prepared by employing both the polymers especially in combination with hydrophobic wax. From this study it was found that formulating a stable taste-masked pellet composition requires proper selection of polymer type
and its combination with suitable excipients in order to achieve an optimum product at the lowest coating level. An ideal taste-masked pellet product must possess following characteristics –

- Good pellet surface morphology.
- Resistant to drug release in salivary milieu in order to have effective taste-masking properties.
- Rapid and complete drug release in both simulated gastric fluid and intestinal fluid, especially in the former medium.
- Storage stability — unaltered drug release and taste-masked characteristics even when stored at adverse storage conditions.

Designing a product which possesses all the above characteristics is difficult. However, in the current study and approaches adopted, it can be concluded that, as far as ciprofloxacin HCl is the drug under consideration in which case the more common method such as complexation with ion-exchange resin is not successful, particle or pellet coating with pH-dependent polymer appears to be the most suited method.

Pellet coating was considered more suitable since –

- Pellets have near spherical shape as compared to granules or drug particles and thus have least surface area per unit volume or weight and would be effectively coated with lesser amount of polymer.

Smaller pellet size was considered necessary since –

- The final product could be formulated as melt-in-mouth dispersible tablet or dispersed into a suitable base for formulation
as dry or ready-to-use suspension without the loss of taste-
masking characteristics.

Certain desirable formulation features can thus be highlighted from
the present study –

✓ Eudragit L-type polymer (soluble in alkaline pH) is better in
comparison to E-type polymer (soluble in acidic pH) since Eudragit
L-100 film –
- Has lesser permeability
- Dissolves slowly in salivary milieu
- Coated pellet although may dissolve slowly in gastric milieu,
after emptying (which will occur rapidly owing to small pellet
size) into the intestine will show complete polymer dissolution
and availability of drug particles for dissolution and absorption
in the large pool of intestinal fluid and large intestinal area.

✓ Inclusion of a hydrophobic material such as a wax like cetyl alcohol
in the coating composition that imparts to the pellets following
characteristics –
- Decreases membrane permeability and thus makes the polymer
effective for taste-masking at lower coating levels.
- Increases shelf-stability of the product since permeability
characteristics of film remains unaltered owing to its poor
wettability and greater hydrophobicity while imparting
desirable surface morphology to the pellet product.
- Lesser coating thickness required for taste-masking which in
turn offers the advantage of formulating the product with lesser
acrylic polymer whose daily intake limits are set by US FDA to not more than 120mg/day.

- The fatty wax will have little or no tendency to prevent drug dissolution once the product reaches intestine since the coating will be readily disrupted by the bile salts which emulsify the fats/fatty alcohol thus ensuring drug release. If a hydrophobic pH-independent polymer such as ethyl cellulose is used instead, the product may fail to deliver or release the drug.

6.6. Evaluation of Cellulosic and Acrylic Polymers in the Design of Controlled-Release Propranolol HCl Pellets

Polymeric film-coatings are frequently used to control drug release from solid pharmaceutical dosage forms. Several natural and synthetic macromolecules have proven to be suitable coating materials, providing different types of drug-release behaviour, e.g. zero-order kinetics, pulsatile and sigmoidal patterns. However, each polymer has specific physicochemical properties, and it is often difficult to obtain a particular, desired release profile which is adapted to the pharmacokinetic/pharmacodynamic characteristics of the drug. Little knowledge is presently available on the use of polymer blends to control the drug release. The major objective of coating of pellet in order to obtain the desired controlled release profile, is modulating the properties of coating polymers keeping in view their physicochemical properties and, often a blend of two different polymers, a blend of polymers with waxes or a blend of polymers with the right plasticizer (water-soluble or insoluble) and a proper ratio of the two or three polymers mixed together is required.
The aim of this study was to prepare propranolol hydrochloride pellets by powder layering technique in a coating pan and coat them with suitable pH-independent acrylic polymer Eudragit RS100 and cellulosic polymer ethyl cellulose, in combination with other excipients that modify film structure, in imparting the controlled-release characteristic/profile that complies with USP drug release monograph.

In detail, the objectives of the present study were

1. Prepare the drug pellets by drug layering on nonpareils in a coating pan.
2. Coat the drug pellets with various pH-independent cellulosic and acrylic polymer or their blends with other polymers and/or waxes and added plasticizer.
3. Evaluate the ability of the applied polymer coating composition in effectively controlling the release of medicament.
4. Evaluate the storage stability of the product.

Controlled-release drug pellets were successfully prepared by employing both the polymer types especially in combination with hydrophobic wax. The products prepared complied with the USP drug release studies.

A highly flexible coating with a strong sustained-release effect is an essential requirement for almost all sustained-release solid dosage forms. Formulating a stable controlled-release pellet composition requires proper selection of polymer type, proper ratio of different polymers having differing solubility characteristics and proper combination with suitable excipients – water soluble or insoluble, especially plasticizer, in order to
achieve an optimum product at the lowest coating level. An ideal controlled-release pellet product must possess following characteristics –

- Good pellet surface morphology.
- Good release-retarding characteristics in aqueous milieu of different pH.
- Storage stability – unaltered drug-release and controlled-release characteristics even when stored at adverse storage conditions.

Designing a pellet product which possesses all the above characteristics is a challenge. The task becomes tougher when the drug under development is a highly water-soluble drug such as propranolol hydrochloride since controlling the release of such a drug requires significant amount of coating.

Certain desirable formulation features can thus be highlighted from the present study –

- Ethyl cellulose is a better polymer compared to Eudragit RS 100 since its film has lesser permeability.
- Inclusion of a hydrophobic material such as a wax like cetyl alcohol in the coating composition imparts to the pellet following characteristics –
  - Decreases membrane permeability and thus makes the polymer effective for retarding drug release at lower coating levels.
  - Increases shelf-stability of the product since permeability characteristics of film remains unaltered owing to its poor wettability and greater hydrophobicity while imparting desirable surface morphology to the pellet product.
Lesser coating thickness required for release-retarding which in turn offers the advantage of formulating the product with lesser cellulosic/acrylic polymer.

Care should be exercised for inclusion of water soluble additives since they modulate the membrane permeability as well influence storage stability of product. A proper ratio is very essential.

Water soluble plasticizers are not desirable for addition in coating compositions.

To conclude, the present investigation was a modest attempt to explore the various possibilities for coating drug multiparticulates with regards to –

Employing various coating technologies, from the most conventional system such as the coating pan to the most sophisticated one Wurster coater.

Exploring and comparing the influence of organic solution coating composition with aqueous polymeric dispersion on film properties to achieve a desired objective (enteric-release).

Evaluating polymers of particular category, pH-dependent acrylic ones to be specific, to effectively mask the bitter taste of drug.

Comparing the most commonly used pH-independent cellulosic and acrylic polymers for designing controlled-release drug pellets.