SUMMARY AND CONCLUSIONS
Drugs are administered by the oral route in a variety of pharmaceutical dosage forms. The most popular dosage forms for oral administration are tablets, capsules, suspensions and solutions. Among the drugs that are administered orally, solid dosage forms represent the preferred class of products. They are versatile, flexible in dosage strength, relatively stable, present lesser problems in formulation and packaging and are convenient to manufacture, store, handle, transport and use. Solid dosage forms provide best protection to the drug against light, temperature, humidity, oxygen and stress during transportation. Amongst the solid oral dosage forms, tablets are the most widely preferred and used. However, coated drug multiparticulates are increasingly becoming popular for several reasons and they can be presented in either hard capsules or compressed as MUPS tablets.

Drug multiparticulates can be produced by various methods such as drug layering on nonpareil seeds, extrusion-spheronization, spray drying, spray congealing, drug layering, etc. Often drug crystals or granules are also used as core multiparticulates. Drug multiparticulates are often coated with certain polymeric and/or other suitable excipients to achieve various objectives. Some of the purposes for coating multiparticulates are –
1. Design controlled-release drug delivery system.
2. Prepare delayed- or enteric-release dosage form.
3. Reduce the incidence and severity of dose-related systemic and local adverse-effects.
4. Improve patient compliance through reduction of dosing frequency and incidence of side-effects and better control of disease condition.
5. Enhance oral bioavailability of poorly aqueous soluble drugs.
6. Enhance the physical characteristics of multiparticulates by enhancing flow and reducing friability.
7. Mask unpleasant colour, taste or odour and prevent leaching of core materials from the multiparticulates thereby improving patient acceptance of the product.
8. Enhance 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. Enhance the aesthetics of the dosage form.
10. Facilitate the identification of product and different dosage strengths of same product.
11. Extend patent protection, overcome competition and create brand loyalty.
Challenges abound when the objective is to design coated multiparticulates as compared to tablets, since coating of small particles that have inherently low bulk density and large surface area, requires proper optimization of equipment, process and formulation variables to arrive at the product possessing desired physicochemical and drug release characteristics.

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. More specifically, the study was aimed at preparing multiparticulate drug delivery systems of three model drugs for the preparation of coated pellets, each belonging to a different class –

i. Poorly aqueous soluble drug – Atorvastatin Calcium.

ii. Acid labile proton pump inhibitor (PPI) – Rabeprazole Sodium.

iii. Extended-release multiparticulate system – Tolterodine Tartrate.

The specific plan of work in the present investigation was as follows –

1. Design and evaluation of fast-dissolving Atorvastatin Calcium multiparticulates.

2. Design and evaluation of delayed-release Rabeprazole Sodium multiparticulates.

In the present study, an attempt was made to prepare and evaluate rapid-release solid dispersion pellets of Atrovastatin Calcium by utilizing hydrophilic polymeric excipients as the solubilizer(s). The various steps involved in the formulation of rapid-release pellets of Atorvastatin Calcium were as under –

4. Subjecting the blister packaged product to physicochemical characterization and accelerated stability testing at 40°C/75% RH for 3 months.

The prepared rapid-release solid dispersion pellets of Atorvastatin Calcium were evaluated for following characteristics –

1. Stereomicroscopy to assess uniformity of drug layering on nonpareil seeds.
2. *In vitro* dissolution testing to estimate rapid-release characteristics of pellets in relation to marketed formulation Storvas.
3. Stability studies at elevated storage condition to determine shelf-stability of product and conformance of product to desired quality attributes.
Rapid-release solid dispersion pellets of Atorvastatin Calcium with desired physicochemical attributes were successfully developed. Both hydrophilic polymers and hydrophilic surfactant and their combination were found to be effective solubilizers in producing fast-dissolving product. The four different solid dispersion compositions which were evaluated were –

a. Povidone K30 (formulation A)

b. Copovidone (formulation B)

c. Poloxamer 188 (formulation C)

d. Copovidone-poloxamer 188 in 1:1 ratio (formulation D).

In all the formulations, the drug-to-solubilizer ratio was kept constant at 1:1 to better evaluate the superiority of hydrophilic component in producing the rapid-release pellets. Processing of all products was also done under identical conditions to eliminate effect of process variables on drug release profile.

All the four formulations were superior with regards to the *in vitro* dissolution characteristics as compared to the reference product Storvas. However, a direct influence of the physicochemical nature of the solubilizer on the drug release profile of the solid dispersion pellets was observed. Surfactant combination with copovidone (formulation D) resulted in the best product with regards to both *in vitro* dissolution profile and physical stability at accelerated storage conditions. Povidone K30 product (formulation A) was the poorest as compared to other formulations.

A summary of results obtained as a result of comparison of the four pellet formulations, *viz.* formulation A through D, is presented in table 5.1.
**TABLE 5.1**

Comparison of Evaluation Characteristics of
Atorvastatin Calcium Rapid-Release Pellets

<table>
<thead>
<tr>
<th>Evaluation Parameters</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pellet morphology (stereomicrography)</td>
<td>Smooth</td>
<td>Smooth</td>
<td>Smooth and</td>
<td>Smooth and</td>
<td>Pellets without poloxamer yields glossier pellets</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>glossy</td>
<td>glossy</td>
<td></td>
</tr>
<tr>
<td>In vitro dissolution in comparison to</td>
<td>Satisfactory</td>
<td>Good</td>
<td>Better</td>
<td>Best</td>
<td>Formulations with surfactant as solubilizer dissolve better</td>
</tr>
<tr>
<td>Storvas</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stability</td>
<td>Dissolution rate drops</td>
<td>Good</td>
<td>Pellets soften but dissolution unaffected</td>
<td>Good</td>
<td>Combination of high melting polymer and low melting surfactant yields optimum product</td>
</tr>
</tbody>
</table>

Formulating a stable rapid-release solid dispersion pellet composition of Atorvastatin Calcium thus requires proper selection of solubilizer type and/or their blend (polymer with thermal stability and optimum solubility enhancing characteristics) is required to achieve an optimum product.

An ideal rapid-release solid dispersion pellet product prepared by solvent deposition must possess following characteristics –

- About ≥ 85% drug release in ≤ 30 minutes.
- Good thermal/physical stability on prolonged storage.
- Consistent and unaltered *in vitro* drug release profile even when stored at elevated/accelerated storage conditions, for an extended period of time, in a suitable packaging.
Certain features desirable of a hydrophilic solubilizer used for the preparation of rapid-dissolving solid dispersion pellet product can thus be highlighted from the present study –

✓ Should not have too high a melting point or glass transition temperature.

✓ Should not soften at temperature less than 60°C.

✓ Should maintain the drug in amorphous state during shelf-storage.

✓ Should not promote drug crystallization once the solid dispersion is formed.

✓ Should facilitate drug dissolution by maintaining the drug in amorphous form as well as micellization.

In the present study, an attempt was made to prepare and evaluate delayed-release Rabeprazole Sodium pellets. The various steps involved in the formulation of pellets of acid-labile Rabeprazole Sodium were as under –

1. Preparation of core drug pellets by drug solution layering technique in a fluid-bed processor.

2. Application of seal-coating (comprising of hypromellose, base and pigment) on core drug pellets in fluid-bed processor to prevent direct contact of drug surface with the outermost enteric coating that has inherent acidic nature.
3. Application of delayed-release polymeric coating on seal-coated drug pellets to impart gastroresistance to the product. Four different types of enteric-coating compositions were applied on seal-coated pellets to evaluate their efficacy in protecting the drug core from acid, influencing their release in alkaline buffer milieu and the overall stability of pellets/capsules.


5. Subjecting the packed product to accelerated stability testing at 40°C/75% RH for 3 months.

Gastroresistant pellets of Rabeprazole Sodium with desired physicochemical and stability attributes were successfully developed. Gastroresistant acrylic and cellulosic pH-dependent polymers were used either alone, in combination or one over the other to impart delayed-release properties to the core drug pellets. Thus, four different enteric-coating compositions were evaluated –

   a. Enteric acrylic polymer alone (formulation A)

   b. Enteric + sustained-release acrylic polymers in combination (9:1 ratio) – formulation B

   c. Enteric cellulosic polymer (formulation C)

   d. Enteric acrylic polymer (inner layer) followed by enteric cellulosic polymer layer (outer layer) – formulation D.

All the four formulations were identical to each other with regards to composition of core drug pellets. They were also identical with respect to the total amount of enteric coating applied but differed from each other with regards to qualitative enteric-coating compositions.
A summary of results obtained as a result of comparison of all four pellet formulations, viz. formulation A through D, is presented in table 5.2.

**TABLE 5.2**

**Comparison of Evaluation Characteristics of Rabeprazole Sodium Delayed-Release Pellets**

<table>
<thead>
<tr>
<th>Evaluation Parameters</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pellet morphology</td>
<td>Smooth and glossy</td>
<td>Smooth and glossy</td>
<td>Smooth but less glossy</td>
<td>Smooth but less glossy</td>
<td>Pellets with outermost acrylic coating are glossier than those with cellulosic coating.</td>
</tr>
<tr>
<td>Acid release (in 2 hours)</td>
<td>&lt; 5 %</td>
<td>&lt; 5 %</td>
<td>&lt; 5 %</td>
<td>&lt; 5 %</td>
<td>All the products had good acid resistance. However, formulation A with lone coating of Eudragit L30D55 was poorest of all.</td>
</tr>
<tr>
<td>Buffer release (in 45 minutes)</td>
<td>&gt; 75%</td>
<td>&gt; 75%</td>
<td>&gt; 75%</td>
<td>&gt; 75%</td>
<td>Release was satisfactory for all pellets. However, the ones having a top coat of enteric cellulosic polymer were the best.</td>
</tr>
</tbody>
</table>

Formulating a stable, delayed-release pellet composition thus requires proper selection of polymer type (right type and blend of pH-dependent polymers) and polymer membrane thickness and plasticity in order to achieve an optimum product. An ideal delayed-release pellet product must possess following characteristics –

- Good pellet surface morphology (spherical shape and smooth surface).
- Rapid and complete drug release in simulated buffer milieu (to demonstrate enteric properties).
- Storage stability – unaltered drug release (at both acid and buffer stages) characteristics even when stored at adverse storage conditions.
Designing a delayed-release pellet product which possesses all the above characteristics is difficult. However, in the current study and with the approaches adopted, it can be concluded that, as far as Rabeprazole Sodium is the drug under consideration, dual coating with two different enteric polymers – an inner acrylic coating followed by an outer cellulosic coating yields the best product that provides all the desired characteristics.

In the present study, an attempt was made to prepare and evaluate extended-release Tolterodine Tartrate pellets/capsules by a technology different from that adopted by the innovator Pfizer, in their product Detrol LA®. Following were the differences in the prototypes designed vis-à-vis composition of Detrol LA® –

1. Absence of seal coating on nonpareil seeds used as substrate for drug layering.

2. Absence of polymer for use as binder to deposit the drug layer. Instead, sucrose was used as the binder.

3. Use of customized organic polymer coating system to design the extended-release formulation, as against the aqueous dispersion of ethylcellulose in Detrol LA®.


The various steps involved in the formulation of extended-release pellets/capsules of Tolterodine Tartrate were as under –
1. Preparation of core drug pellets by drug solution layering technique in a fluid-bed processor.

2. Application of extended-release polymeric coating on core drug pellets to impart release-control properties to the product. Four different types of extended-release coating compositions were applied on core drug pellets to evaluate their efficacy in imparting the desired release profile in comparison to reference product – Detrol LA®.


4. Subjecting the packed product to accelerated stability testing at 40°C/75% RH for 3 months.

Extended-release pellets and capsules of Tolterodine Tartrate with desired physicochemical, stability and drug release attributes were successfully developed. The pH-independent, cellulosic polymers were used as the primary release-controlling polymer while pH-dependent cellulosic polymer was used optionally to impart partial delayed-release properties to extended-release coating with the objective of controlling drug release in the acid stage. In all the prototypes, hypromellose (low viscosity) was used as the release-modifier and dibutyl sebacate as the plasticizer. Thus, four different extended-release coating compositions were evaluated –

1. Ethylcellulose 10 cps as the lone pH-independent extended-release polymer (formulation A).

2. Ethylcellulose 10 cps and 45 cps (in ratio 60:40) as the two pH-independent extended-release polymers (formulation B).

3. Ethylcellulose 10 cps as the primary extended-release coating with an outermost coating of hypromellose phthalate HP55 as the secondary
coating to impart partial delayed-release properties to the product (formulation C).

4. Ethylcellulose 10 cps as the extended-release polymer and hypromellose phthalate HP55 as the auxiliary pH-dependent delayed-release polymer used together in a single coating composition (formulation D).

All the four formulations were identical with regards to composition of core drug pellets. They, however, differed from each other with regards to qualitative extended-release coating compositions.

A summary of results obtained as a result of comparison of all four pellet formulations, viz. formulation A through D, is presented in table 5.3.

Formulating a stable, extended-release pellet composition of Tolterodine Tartrate thus requires proper selection of polymer type (right type and blend of pH-independent polymers and/or pH-dependent polymer) and polymer membrane thickness and plasticity in order to achieve an optimum product. An ideal extended-release pellet product which is expected to demonstrate identical in vivo plasma profile as that of an innovator drug product must possess following characteristics –

- Comparative dissolution in all the biorelevant media viz. pH 1.2, pH 4.5, pH 6.8 and dissolution by change-over method.

- Good pellet surface morphology (spherical shape and smooth surface).

- Storage stability – unaltered drug release (in all biorelevant media) characteristics even when stored at adverse storage conditions.
TABLE 5.3
Comparison of Evaluation Characteristics of Tolterodine Tartrate Extended-Release Capsule Prototypes with Detrol LA® Capsules

<table>
<thead>
<tr>
<th>Evaluation Parameters</th>
<th>A</th>
<th>B</th>
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<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pellet morphology</td>
<td>Smooth and glossy</td>
<td>Smooth and glossy</td>
<td>Smooth and glossy</td>
<td>Smooth and glossy</td>
<td>Indicative of uniform deposition of polymer layer</td>
</tr>
<tr>
<td>Release in pH 1.2</td>
<td>Faster than Detrol</td>
<td>Faster than Detrol</td>
<td>Comprable to Detrol</td>
<td>Comprable to Detrol</td>
<td>Inclusion of enteric polymer imparts better release control in acid stage</td>
</tr>
<tr>
<td>Release in pH 6.8</td>
<td>Slower than Detrol</td>
<td>Slower than Detrol</td>
<td>Comprable to Detrol</td>
<td>Comprable to Detrol</td>
<td>Indicates independence of effect of pH on drug release</td>
</tr>
<tr>
<td>Release by changeover method</td>
<td>Comprable to Detrol</td>
<td>Comprable to Detrol</td>
<td>Comprable to Detrol</td>
<td>Comprable to Detrol</td>
<td>Indicates that all prototypes will perform fairly well under in vivo physiological conditions</td>
</tr>
<tr>
<td>Release in pH 4.5</td>
<td>Comprable to Detrol</td>
<td>Comprable to Detrol</td>
<td>Slower than Detrol</td>
<td>Slower than Detrol</td>
<td>Coating composition dictates the release profile, especially enteric polymer which prevents release in pH 4.5</td>
</tr>
</tbody>
</table>

Designing a delayed-release pellet product which possesses all the above characteristics is a challenge. However, in the current study and with the approaches adopted, it can be concluded that, designing an extended-release dosage form of Tolterodine Tartrate which has comparative in vitro dissolution profile as that of the innovator drug product Detrol LA® in biorelevant media, by adopting altogether different core and coating composition is possible by proper choice of pH-independent release-controlling and release-modifying polymers as well as pH-dependent enteric polymer. Often, a coating composition can be tailored to contain all the desired polymers in suitable proportion that modulate the drug release in various dissolution media pHs to
provide a product such as prototype D, that compares well in all biorelevant media with the innovator product Detrol LA®.

In conclusion, the present study was a modest attempt at exploring the various means and ways of preparing coated multiparticulates of 3 different categories of drugs – poorly aqueous soluble drug Atorvastatin Calcium, acid-labile drug Rabeprazole Sodium and drug with short elimination half-life Tolterodine Tartrate. Very different strategies for preparing coated drug multiparticulates for each of the said drugs were adopted compared to those already developed or patented. Solid dispersion multiparticulates of poorly soluble Atorvastatin Calcium, delayed-release coated multiparticulates of acid-labile Rabeprazole Sodium and extended-release coated pellets of Tolterodine Tartrate were prepared successfully. The investigation demonstrated -

- Making the best possible use of hydrophilic polymers and surfactants to prepare solid dispersion pellets of poorly water soluble drug, by solution layering on nonpareil seeds, that yield stable and fast dissolving multiparticulate product.

- Use of two different polymer layers applied separately from aqueous dispersions (acrylic) and organic solvent system (cellulosic) to produce a stable gastroresistant formulation of an acid labile drug.

- Employment of combination of pH-independent polymer(s) and pH-dependent polymer (delayed-release) in a combined, single extended-release coating to produce controlled-release multiparticulate dosage form of a drug having short elimination half-life.