Chapter-6
SUMMARY AND CONCLUSION

Few research and inventions have attempted to fabricate multiple-unit controlled-release tablet formulations by employing hydrophilic or swellable polymers as the release-controlling excipient for drug multiparticulates to achieve the desired objective of maintaining the same controlled-release characteristics as that prior to their compression into tablets. Limited work has been done on depositing a layer of cushioning excipients on the surface of membrane coated pellets to protect the release controlling membrane from getting damaged during the subsequent compaction. Little research has been done relating to use of small size of pellets and high density of pellets which when coated with an elastic membrane wherein the small size and low porosity of pellets coupled with high elasticity of polymer coating resist deformation of pellets and rupture of coating.

The present study was aimed at –
1. Employing swellable hydrophilic polymers in designing the controlled-release pellets of drug substances which when compacted along with the directly compressible cushioning dry powder as excipients, into multiple-unit tablets, the release kinetics of controlled-release drug pellets remain substantially unaltered.
2. Preparing small (size below 800 microns) and dense drug pellets with drug release controlled by application of elastic polymer coating such as acrylates and their compaction into multiple-unit tablets using easily deformable cushioning excipients.
3. Depositing a layer of cushioning excipient on the surface of membrane-coated pellets and their subsequent compaction into a multiple-unit tablet wherein the topmost layer of cushioning excipients fracture during compaction thereby preventing damage to the membrane.

4. Employing combination of techniques (2) and (3) enlisted above in preparing superior quality controlled-release pellets and thus a multiple-unit tablet.

The basic idea behind development of such formulations was to explore possibilities other than those already exploited to prepare multiple-unit tablets wherein the forces of compression do not have an adverse effect on the drug release properties.

Swellable Hydrophilic Polymers in the Development of Controlled-Release Multiple-Unit Tablets

The aims of this area of research investigation were –

- Employing swellable hydrophilic gum in designing the controlled-release pellets of drug substances (using Pseudoephedrine hydrochloride as the model drug) which when compacted, along with cushioning dry powder as excipients, into tablets, the release kinetics of the controlled-release drug pellets remain unaltered.

- Designing tablets of high tensile strength that have maintained the integrity of both the cores and release characteristics of the two components.

- Designing a cost-effective formulation that does not require use of – costly polymers and solvents, long processing times, and limitations
of employing high compaction forces for tabletting.

The formulation designed contained 120 mg Pseudoephedrine hydrochloride in controlled-release pellet form. Guar gum was used as the swellable hydrophilic polymer. Two pellet formulations A and B were prepared – the former containing a layer of drug on nonpareil seeds followed by a layer of swellable gum while the latter contained drug in matrix of swellable gum. Both the pellet formulations were subsequently coated with a protective layer of HPMC film-coating. The HPMC film-coat was applied to facilitate separation of pseudoephedrine pellets into discrete particles when the multiple-unit tablet is exposed to the dissolution environment. Both the pellet formulations were compressed into multiple-unit tablets by admixing with a mixture of spray-dried microcrystalline cellulose and spray-dried lactose in ratio 1:1 as the cushioning excipients. Sodium starch glycolate was used as the disintegrant and a mixture of talc and magnesium stearate was used as lubricant, glidants and antiadherent. The compressed tablets were given a final protective coating of HPMC.

The resulting multiple-unit tablet dosage forms were satisfactory. The compacts designed were of acceptable mechanical strength. The tablets disintegrated rapidly in vitro to release virtually intact pseudoephedrine hydrochloride pellets. Photomicrographs showed that pellets of both formulations had undergone deformation on compression. Significant deformation of pellets exposed to the tablet punches and die during compression had occurred.
In order to quantify in real terms the extent of damage to controlled-release pellets due to compaction, drug release profiles from un-compacted pellets and multiple-unit tablets were compared. The study showed that compaction further retarded the release of pseudoephedrine hydrochloride, which was owed to densification of pellets. This study thus demonstrated that hydrophilic gums that exhibit rapid swelling could be advantageously used to design controlled-release drug pellets, which retain their release characteristics even after compaction. Tablets of both pellet types — A and B showed comparable retarded drug release profile.

One can thus enlist the advantages of the current technique for the design of multiple-unit tablet formulations—

1. Ease of processing — the controlled-release drug pellets could be prepared in equipment as simple as a coating pan. Use of expensive equipments such as fluid-bed coater for the application of membrane was not required.

2. Rapidity of processing — the controlled-release pellets could be prepared in a single go as in the case of formulation B. Moreover, there was no need to prepare the drug pellets first and then apply the membrane coating later on in another equipment. This saved time and the number of equipments used for processing.

3. Economy of processing — since the controlled-release drug pellets contained only swellable hydrophilic gums as the release-retarding material, that too a gum as economic as the guar gum, these systems are far more cheaper than those that employ polymeric membrane for sustaining the drug release where polymers such as ethyl cellulose
itself is costly and so also the solvents (if organic solvent system is used) employed for depositing such polymers. Moreover, the lesser number of steps required for preparing the drug pellets and the simplicity of equipment used for processing also add to the economy of the swellable multiple-unit tablet formulations.

4. Ease of process validation – it is difficult to validate membrane-coated controlled-release pellet manufacturing process since projecting the influence of compaction on membrane damage is difficult. On the contrary present technique of preparing controlled-release drug pellets can be easily validated since the impact of compaction on drug release characteristics is minimal.

5. Unaltered/consistent zero-order release profile – since there was no membrane to control the drug release, virtually no damage to the release pattern of controlled-release pellets was observed. This could be attributed to the fact that swelling of gum was responsible for controlling the drug release. The densification of pellets that occurs as a result of compaction in fact retards further the amount of drug released.

Such formulations are also advantageous as compared to conventional capsules containing controlled-release pellets in that the –

- Size of dosage form is relatively small.
- Cost of formulation is low since there is no capsule shell.

The formulation designed here is also superior in comparison to controlled-release matrix tablets in that –
One can combine two or more drugs having different release characteristics in a single-unit conveniently, and zero-order release of the controlled-release component can still be retained.

Influence of Pellet Size, Density and Elasticity of Polymer Coating in the Development of Controlled-Release Multiple-Unit Tablet Formulation

The energy required to reduce the size of particles is inversely proportional to the size raised to some power. In other words, the energy requirement for size reduction is directly proportional to the increase in surface or inversely proportional to size of the particle. It can thus be implied from this statement that a smaller pellet is difficult to deform or fracture in comparison to larger one. Moreover, a denser pellet can resist fracture and deformation better in comparison to the one that is porous and less dense. In one of the studies, by Aulton et al, it was concluded that extrusion-spheronization yields pellets that are more dense and less porous than those produced by powder layering. Further, pellets containing microcrystalline cellulose as the spheronizing aid are stronger than those containing lactose. Yet another concluded fact from previous research is that acrylic polymers are more resilient and elastic than cellulosic polymers like ethyl cellulose. Taking advantage of these findings, the present study was aimed at employing the three properties namely –

- Pellet size
- Pellet density
- Polymer elasticity

in developing a robust sustained release pellet product that can withstand the destructive forces of compaction and yield a multiple-unit tablet having
the same release pattern as that of controlled-release pellets before compaction.

In the present study, Chlorpheniramine Maleate (8 mg/tablet) was used as the model drug. The drug was spheronized using microcrystalline cellulose (Avicel PH101) as the spheronizing aid (192 mg). Drug and MCC mixture was granulated with water and the wet mass was extruded through a 1 mm bore extruder to obtain extrudates, which were spheronized on a friction plate having 1 mm groove and 1000 rpm. The pellets so formed were tray dried and sieved to obtain two fractions – 14-20 mesh (formulation A) and 20-24 mesh (formulation B) fractions. Both the fractions were evaluated for crushing strength, bulk density and porosity. These pellets A and B were then coated with an organic solution of Eudragit RS 100 using dibutyl phthalate as the plasticizer using pneumatic spray system, in a coating pan. About 6% polymer coat was applied on both pellet formulations which gave drug release for 8 hours (suitable for bid dosing). Multiple-unit tablets of both pellet types were prepared using MCC-lactose mixture (1:1) as the cushioning excipient and the pellet to excipient mixture ratio being 1:1. Sodium starch glycolate was used as the disintegrant and a mixture of talc and magnesium stearate was used as lubricant, glidants and antiadherent. The tablets (hardness 4 Kg) prepared from both pellet types A and B were finally coated with HPMC. Both the formulations were then subjected to in vitro drug release studies. As anticipated, results indicated that drug release from tablets of pellet A were little affected as compared to that produced with pellets B. Stereomicrography revealed that pellets on the surface of tablets were damaged as compared that in the tablet core.

It was concluded from the present study that small, dense and less
porous pellets with an elastic polymer coating to control drug release are better suited to produce successful multiple-unit tablets with little aggravation of drug release after compression.

Influence of Layered Cushioning Excipient Over Coated Pellets in the Development of Controlled-Release Multiple-Unit Tablet Formulation

One of the approaches to prevent damage to sustained-release polymer coating on pellets during compaction is use of either –

- Cushioning excipients such as a blend of spray-dried MCC and spray-dried lactose, or
- Cushioning placebo pellets which are porous and fracture and deform easily thus preventing the drug pellets from getting damaged.

An alternative to this approach is application of such cushioning excipients as a layer over the coated drug pellets such that during subsequent compression, the topmost layer bears the pressure of compaction and fragment easily into primary particles preventing damage to the coated pellet underneath. This approach was used for the first time by Altaf et al, but the technique was too complicated and suffers from several drawbacks as it involved –

- Application of alternate layers of drug and polymer coating followed by a final layer of cushioning excipient.
- Layering the cushioning excipient by spray coating.

Such a methodology is not feasible on large scale and cannot be exploited commercially.
The present study was aimed at application of a layer of cushioning excipient over the coated drug pellets by powder layering technique and that this layer is porous, mechanically weak and can fracture easily thereby obviating the need to add any cushioning excipient or cushioning bead during subsequent compaction stage.

Omeprazole (20 mg per tablet), an acid labile anti-ulcer agent was used as the model drug for the present study. The coating normally applied over such a medicament is a delayed release (enteric-release) coating to prevent its release into the stomach. Omeprazole pellets were prepared by powder layering the drug-mannitol mixture over the nonpareil seeds followed by its enteric coating using Eudragit L 30D aqueous dispersion (with pH adjusted to 7.0 with a buffer) in a coating pan. About 10% coating polymer was applied over the drug pellets and it was assessed by in vitro dissolution that not more than 2% drug is released in the acidic milieu in 2 hours. The coated drug pellets were divided into two portions – one was subsequently layered with cushioning excipient mixture comprising of mannitol and MCC (1:1) by powder layering technique in a coating pan (formulation A). About 100% weight increase in the pellet was affected by the cushioning excipient. These layered pellets were then subjected to compaction into a multiple-unit tablet (hardness 4 Kg) such that each tablet contained 20 mg omeprazole. The second portion of pellets (formulation B) were compacted into multiple-unit tablets by simple admixture with the same amount of MCC and mannitol as cushioning excipient as that used for layering the coated drug pellets. Sodium starch glycolate was used as the disintegrant and a mixture of talc and magnesium stearate was used as lubricant, glidants and antiadherent
for both the tablet formulations. The tablets were given a final protective coating with HPMC.

Evaluation of omeprazole multiple-unit tablets with regards to in vitro dissolution revealed that the drug release from formulation A during acid stage increased to 15% as a result of compaction. Photomicrography confirmed that this was attributed to the damage to pellets especially on the surface of tablets while pellets within the tablet bed were substantially unaffected. In contrast, formulation B showed tremendous damage to pellets both on the surface as well as within tablet core indicating that cushioning excipient were not completely successful in preventing deformation of pellets and development of cracks in the coating. Omeprazole release was more than 90% for both formulations in alkaline buffer in 30 minutes.

In conclusion, the present study confirmed that a layer of cushioning excipient over the coated drug pellets functions better in preventing damage to the polymer coating beneath as well as pellet deformation in comparison to simple use of cushioning excipients as powder filler.

Combined Influence of Pellet Size, Density and Elasticity of Polymer Coating and the Layered Cushioning Excipient in the Development of Controlled-Release Multiple-Unit Tablet Formulation

Results of earlier two studies suggest that a better alternative to prepare functional multiple-unit tablets would be to have a drug pellet system having following properties –

- Small pellet size.
- High pellet density.
High elasticity of polymer coating.

- High porosity of cushioning excipient layer.

- Easy fracturability and deformability of topmost cushioning excipient layer.

This study was thus carried out with a view to employ all the favourable factors enlisted above in designing a successful multiple-unit tablet. Omeprazole was used as the model drug. Preparation of multiple-unit tablet system of this drug involved –

1. Preparation of drug pellet by extrusion-spherization using MCC as the spheronizing aid and containing 1% sodium bicarbonate as the alkaline buffer. Water was used as the granulating agent and extrudates had a diameter of 0.8 mm. Extrudates were spheronized on a friction plate having 1 mm groove and 1200 rpm.

2. Dried pellets of 20-24 mesh were collected and subjected to enteric coating using Eudragit L 30D aqueous dispersion with pH adjusted to 7.0. A 10% weight increase was affected subsequent to polymer coating. In vitro release of omeprazole in acid medium was less than 2% after polymer coating.

3. The dried polymer-coated drug pellets of size fraction 20-24 mesh were powder layered with a mixture of MCC and mannitol. A weight increase of 100% was affected subsequent to powder layering with cushioning excipients. Pellet size after layering of cushioning excipient was 16-20 mesh.

4. The pellets of stage three were then subjected to compaction into multiple-unit tablets (hardness 4 Kg) using sodium starch glycolate as the disintegrant and a mixture of talc and magnesium stearate as the
lubricant, glidant and anidiadherent.

5. Multiple-unit tablets of stage four were finally film-coated with HPMC.

The film-coated multiple-unit tablets of Omeprazole were evaluated with regards to in vitro dissolution (for enteric-release characteristics) and photomicrography of tablet surface and its fractured surface. Results revealed that the tablets showed drug release of not more than 8% in acid medium in 2 hours and about 89% drug dissolved in buffer in 30 minutes. Photomicrography of the uncoated tablet surface as well fractured surface of tablet indicated that the pellets were almost intact although little deformation was apparent. The prepared formulation was thus better in comparison to an earlier formulation of Omeprazole where pellets of comparable size but lower density and high porosity were used to prepare multiple-unit tablets. One can thus conclude from the present study that while designing a successful controlled-release multiple-unit tablet formulation where drug release is primarily controlled by polymer coating, following features are essential –

- Drug loaded pellets should be small in size (preferably smaller than 800 microns). Larger sized pellets fracture easily at a given compression pressure as compared to small sized pellets.

- Drug loaded pellets should be of high bulk density (preferably prepared by extrusion-spheronization rather than by powder layering) so that the pellets do not deform easily during subsequent compaction.

- The release-controlling membrane should be of high elasticity. Acrylic polymers (e.g. Eudragits) should be preferred over cellulosic polymers.
The cushioning excipient must be layered over the drug pellets rather than their use as filler powder or filler beads to better absorb the forces of compression. Moreover, at least 100% pellet weight increase with such a cushioning layer should be affected for better performance during compaction. In addition, such a cushioning layer must be porous and easily deformable so that during compaction, the pressure of compression is absorbed by the deformation and fracture of this top layer and force is not transmitted to the coated drug pellet core underneath thereby preventing its integrity.

The present study was a modest approach at exploring the alternate possibilities in successful preparation of controlled-release multiple-unit tablets that have maintained the integrity of drug release characteristics present in the pellets before compaction.

The most feasible and easy approach in the preparation of controlled-release pellets for subsequent use in the preparation of multiple-unit tablets is use of swellable hydrophilic polymer applied as a layer over the drug pellets or the use of this gum with drug in its matrix. In formulations where drug release cannot be controlled by the use of swellable polymer, and use of polymer coating is inevitable (for e.g. in the design of delayed-release formulations) the alternate and better approach is designing high density pellets of small size and coating it with a layer of highly elastic polymer after which the cushioning excipient is applied as a porous, less dense layer that deforms or fractures easily during the compression cycle.