Chapter-5
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

5.1 Introduction
Results of earlier to 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.

5.2 Aim and objective of present study
This study was thus carried out with a view to employ all the favorable 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-spheronization 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 subject to enteric
coating using Eudragit L 30 D 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 pellet 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 3 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 anti-adherent.

5. Multiple-unit tablets of stage 4 were finally film-coated with HPMC.

5.3 Experimental

5.3.1 Materials

5.3.1.1 Model drug - Omeprazole

Category: Antiulcerative (proton pump inhibitor).

Dose: For duodenal and gastric ulcers and for reflux oesophagitis, 20 to 40 mg daily; for Zollinger-Ellison syndrome, initially 60 mg; once daily; usual range, 20 to 120 mg daily.

Description: White or almost white powder.

Solubility: Freely soluble in dichloromethane and in chloroform; soluble in ethanol (95%) and in methanol; very slightly soluble in water. It dissolves in dilute solutions of alkali hydroxides.
**Storage**: Store in tightly-closed, light-resistant containers at a temperature between 2° and 8°.

**Melting Point**: Melts between 152° to 157°.

**Clarity of solution**: A 2.0% w/v solution in dichloromethane is clear.

**Loss on drying**: Not more than 0.2%, determined on 1 g by drying at 60° at a pressure not exceeding 0.7 kPa for 4 hours.

**Assay**: Carry out the method for high performance liquid chromatography, using the following solutions. Solutions (1) and (2) are 0.005% w/v solutions of the substance being examined and Omeprazole respectively in the mobile phase.

### 5.3.1.2 Excipients

Eudragit L30 D was obtained in 30% aqueous dispersion. The chemical name of Eudragit L 30 D is poly (Methacrylic acid, Ethylacrylate) 1:1. It is used as an enteric coating film former for solid dosage forms.⁵⁸

**Other excipients** -

Other excipients used in the study can be divided into two categories -

1. Those that were employed for making sustained release drug pellets, and
2. Those that were used to make multiple unit tablets.

Adjuvants used for making sustained release drug pellets of Omeprazole were Eudragit L 30 D, non-pariel seeds were prepared by using Extrusion spheronisation technique using MCC⁶⁴ as the spheronizing aid and containing 1% sodium bicarbonate as the alkaline buffer.

Additives employed to prepare the multiple unit tablet of Omeprazole includes - Non-Pariel seeds, Mannitol and MCC in the proportion of 1:1 was used as cushioning excipients, Sodium starch glycolate was used as super
disintegrant, purified talc and magnesium stearate used as lubricant, glidant and anti-adherent. The Tablet was given a final protective layering with HPMC.

5.3.2 Methods

5.3.2.1 Preparation of Non-Pariel seeds

The non-pariel seeds were prepared by using extrusion and spherization method as follows.

This complete technique is been divided in series of unit operations, each of which is associated with a number of individual processing variables. This technique begins with blending of drug with MCC to form a uniform, heterogeneous mixture. The mixing was done in the polyethylene bag. This mixed powder is then granulated using distilled water to form a wet mass. The wetted mass is passed in the extruder through a 1 mm bore extruder to obtain extrudates (rods). These wet rods are then processed in the spheronizer on a friction plate having 1 mm groove and at variable rpm to form the pellets which are dried in tray dryer. These dried pellets are sieved to obtain the fraction 14-20 mesh and 20-24 mesh.

In the present study MCC PH 101 is used as spheronizing aid and distilled water as an granulating and lubricating aid.

5.3.2.2 Preparation of Omeprazole pellets.

In the present study Omeprazole (20 mg.) was used as a model drug. The drug was spheronized using MCC as a spheronizing aid and containing 1% sodium bicarbonate as an alkaline buffer. Water was used as the granulating agent and the wet mass was extruded through 0.8 mm bore extruder to obtain extrudates. Extrudates were spheronized on a friction plate
having 1 mm groove at 900 rpm, and 1200 rpm respectively. The pellets so formed were dried and sieved to collect fraction of 14-20 mesh (formulation A & B) 20-24 mesh (formulation C). These pellets were subjected to enteric coating using Eudragit L 30 D aqueous dispersion with pH adjusted to 7. Approximately 10% weight increase was found due to coating with polymer, which gave less than 2% of drug release in an acidic medium.

The polymer coated drug pellets formulation A & C were powder layered with a mixture of MCC and mannitol. Weight increase of 100% was affected subsequent to powder layering with cushioning excipients. Pellet size after layering of cushioning excipient was 16-20 mesh.

5.3.2.3 Compaction of pellets into Tablets

Tablets were prepared in an instrumented single punch machine. The pellets coated with cushioning agent were subjected to compaction into multiple unit tablets using sodium starch glycolate (superdisintegrant) and a mixture of talc and magnesium stearate (lubricant, glidant and anti-adherent) in a single punch machine equipped with round flat faced punches and die, 14 mm in diameter. The upper punch force was kept constant in order to get the tablet hardness of 4 kg/cm². The compressed tablets were given a final protective coating of HPMC.

5.3.2.4 Film coating of multiple unit Tablet

Film coating composition includes HPMC - 50 cps. as the film former, Dibutyl phthalate as elastifier and titanium dioxide as the opacifier, Isopropyl alcohol and methylene chloride were used as solvent system.
5.3.2.5 Evaluation of film coating pellets

i) Friability

Friability of pellets were measured by friabillator. Friability was measured with Roche friabillator. In this case weighted amount of pellets were taken on the suitable sieve and sieved for 5 minutes on automatic sieve shaker. The upper portion was added in the Roche friabillator where the pellets are subjected to the combined effects of abrasion and shock in a plastic chamber that revolves at 25 rpm, dropping the pellets from a distance of 6 inches with each revolution. After 100 revolution, the tablets were dedusted carefully and weighted again. The friability was determined as the percentage loss in weight of the pellets.

ii) Size distribution

The particle size distribution of the pellets was determined through dry sieving with a set of standard sieves of number 14, 16, 18, 20, 22, 30 and they were arranged in ascending order and are arranged on the sieve shaker. This automatic sieve shaker. (Indian Equipment Corporation, Mumbai. Model No. IEC-238) was set ON for 10 mins. Sample of 100 g. of pellets were placed on top most sieve and weight fraction retained on each sieve was noted.

The particle size distribution curve was calculated by a standard method.

iii) Dissolution studies

Dissolution of pellets for Pseudoephidrine HCl, Chlorpheneramine maleate and omeprazole was performed for 10 hours. Samples were withdrawn after every 30 mins. Amount of drug dissolved was determined by employing different methods for different drugs using a centrifuge portion of
the solution under test in comparison with standard solution having a known concentration of respective drug.

5.3.2.6 Evaluation of multiple unit Tablets

i) Hardness

Hardness of the tablet was measured with Monsanto tablet hardness tester. It measures the pressure required to fracture the diametrically placed tablet by applying the force with two plungers and a coiled spring. For each batch of tablets, the hardness of at least 10 tablets was determined. From the obtained data, average hardness, standard deviation were then calculated.

ii) Friability

Friability was measured with Roche Friabilator. In each case, 20 tablets were weighted and placed in the Roche friabilator where the tablets were subjected to the combined effects of abrasion and shock in a plastic chamber that revolves at 25 rpm, dropping the tablets at a distance of 6 inches with each revolution. After 100 revolutions, the tablets were dedusted carefully and weighed again. The friability was determined for each drug as the percentage loss weight of the tablet.

iii) Weight variation

The uniformity of weight was taken by 20 tablets which were weighed individually and the average weight was calculated. From the data of weight of 20 tablets of each drug, standard deviation was calculated. Finally percent weight variation and standard deviation was calculated.

iv) Disintegration time

The disintegration test apparatus according to I.P. specification was
used for the determination of disintegration time of the tablets. The procedure followed was according to Indian Pharmacopoeia.

v) **Dissolution studies**

Dissolution of tablets of Omeprazole was performed for 7 hours. Samples were withdrawn after every 1 hour. Amount of drug dissolved was determined by employing different methods for different drugs using a centrifuge portion of the solution under test in comparison with standard solution having a known concentration of respective drug.

5.4 **Result and Discussion**

5.4.1 **Finding of film coated pellets**

5.4.1.1 **Friability**

All the formulations shown a negligible friability due to highly compact nature of polymers. The coatings are so thick and compact that the friability of all the formulations were very negligible. The friability of all the batches was below 1%. The results were as shown in table - 12. The friability of non-pariel seed was found to be 0.53%.

**Table No.- 43 : Friability of Omeprazole pellets**

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Formulation</th>
<th>% Friability</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Omeprazole pellet - A</td>
<td>1.18</td>
</tr>
<tr>
<td>2</td>
<td>Omeprazole pellet - B</td>
<td>1.08</td>
</tr>
<tr>
<td>3</td>
<td>Omeprazole pellet - C</td>
<td>1.24</td>
</tr>
</tbody>
</table>

5.4.1.2 **Average particle size**

Generally, the pellets were almost spherical as shown in the figure 16 (Stereomicrographic view of non-pariel seed plain). The average particle size
of Non-Pariel seed was found to be 973.68 μm.

5.4.1.3 Dissolution studies

Figure-35: Release profile of Omeprazole pellets.

- ▲ = A = Large size having low density layered with cushioning agent.
- ■ = B = Large size pellets with low density without cushioning agent.
- ● = C = Small size pellets with high density layered with cushioning agent.

5.4.1.4 Stereomicrographs

Figure-36: Stereomicrographic view of Omeprazole pellet formulations
5.4.1.5 Scanning Electron Microscopy

SEM of Omeprazole Pellet-A

SEM of Omeprazole Pellet-B

SEM of Omeprazole Pellet-C

Figure -37 : SEM view of Omeprazole pellet formulations

5.4.2 Findings of film coated multiple unit Tablets.

5.4.2.1 Hardness

The Hardness of tablet was highly dependent on the material used for compaction and force applied. Tablet requires certain degree of hardness to resist the shock and abrasion during transportation and storage.

The average hardness of Omeprazole tablet formulations were found as below-
Table No.- 44: Hardness of Omeprazole tablet formulations

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Formulation</th>
<th>Hardness kg/cm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Omeprazole tablet - A</td>
<td>4.5 ± 0.10</td>
</tr>
<tr>
<td>2</td>
<td>Omeprazole tablet - B</td>
<td>4.3 ± 0.12</td>
</tr>
<tr>
<td>3</td>
<td>Omeprazole tablet - C</td>
<td>4.3 ± 0.10</td>
</tr>
</tbody>
</table>

5.4.2.2 Friability

All the formulation show a negligible friability due to coating with HPMC which forms a very compact layer over the tablets. The friability of all the batches was below 1%. Therefore, all the batches passes the friability test.

The % friability of film coated Omeprazole tablet formulations were found as below-

Table No.- 45: Friability of Omeprazole tablet formulations

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Formulation</th>
<th>% Friability</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Omeprazole tablet - A</td>
<td>0.46</td>
</tr>
<tr>
<td>2</td>
<td>Omeprazole tablet - B</td>
<td>0.23</td>
</tr>
<tr>
<td>3</td>
<td>Omeprazole tablet - C</td>
<td>0.27</td>
</tr>
</tbody>
</table>

5.4.2.3 Weight variation

The weight variation tolerance for the tablet weighing more than 324 mg. is 5%. All the tablets passes the weight variation test as the weight variation was below 5%.

The percent weight variation of the film coated Omeprazole tablet formulations were found as below.
Table No. -46: Percent weight variation of Omeprazole tablet formulations

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Formulation</th>
<th>% weight variation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Omeprazole tablet - A</td>
<td>3.26 ± 0.01</td>
</tr>
<tr>
<td>2</td>
<td>Omeprazole tablet - B</td>
<td>3.20 ± 0.01</td>
</tr>
<tr>
<td>3</td>
<td>Omeprazole tablet - C</td>
<td>3.22 ± 0.07</td>
</tr>
</tbody>
</table>

5.4.2.4 Disintegration time

Disintegration time of tablet depends on type and amount of disintegrant and pressure applied. In the present study, applied pressure was kept constant and except Omeprazole tablet formulation - A, the type of disintegrant used was the combination of lactose, Microcrystalline cellulose and sodium starch glycolate. Due to which, a very narrow disintegration time was observed.

The Disintegration time of Omeprazole tablet formulations were found as below-

Table No.-47: Disintegration time of Omeprazole tablet formulations

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Formulation</th>
<th>Disintegration time(minute)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Omeprazole tablet - A</td>
<td>6.72</td>
</tr>
<tr>
<td>2</td>
<td>Omeprazole tablet - B</td>
<td>5.20</td>
</tr>
<tr>
<td>3</td>
<td>Omeprazole tablet - C</td>
<td>2.46</td>
</tr>
</tbody>
</table>
5.4.2.5 Dissolution studies

Figure -38 : Release profile for Omeprazole Tablet formulation.

- ▲ = A = Large size having low density layered with cushioning agent.
- ■ = B = Large size pellets with low density without cushioning agent.
- ● = C = Small size pellets with high density layered with cushioning agent.

5.4.2.6 Stereomicrographs

Magnified photographs of film coated tablet and fractured tablet of Chlorpheniramine maleate were taken using digital microscope Intelscan Qx3 attached to a personal computer. The photographs were taken at magnification 60X and is shown below -

A

B
Figure -39 : Fractured Stereomicrographic view of Omeprazole Tablet formulations.
Fractured stereomicrographic view of Omeprazole Multiple Unit Tablet Formulation- A
Fractured stereomicrographic view of Omeprazole Multiple Unit Tablet Formulation- B
Fractured stereomicrographic view of Omeprazole Multiple Unit Tablet Formulation- C

5.5 Conclusions

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 in 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.