INFLUENCE OF FORM OF CUSHIONING AGENTS USED IN TABLETING OF PELLETS
5 INFLUENCE OF FORM OF CUSHIONING AGENTS USED IN TABLETING OF PELLETS

5.1. Introduction

A particular problem occurs if the polymer-coated pellets are compressed in tablet, as the tableting process can cause severe damage to the polymer film, altering the release characteristic of drug from the pellets. To protect the coated pellets from damage during tableting use of cushioning agents was effective, otherwise it get fragmented or deformed easily than the SR drug pellets. In the preparation of Multiple-Unit tablets the selection of form of cushioning agent can be the critical factor.

Cushioning agents can be used in different forms:

1. Powders
2. Granules
3. Soft pellets and
4. Layering of cushioning agents to the surface of the coated pellets

The selection of cushioning agent is important, as the release rate controlling polymer membrane of pellets may get spoiled during compaction. Cushioning agents are expected to prevent the incidence of film cracking in the coated pellets. Their compatibility in terms of particle size is also very critical since segregation is generally a drawback of adding fine powders as cushioning agents to larger size particles, like pellets in large-scale industrial production. Segregation occurs because of the particle size difference and difference in true density of cushioning agents and the coated pellets that results in many tableting problems such as weight variation, poor content uniformity, etc.

Adding cushioning agents that have nearly same size as that of coated pellets can solve such segregation problem. The use of soft-pellets, granules and layering of cushioning agent over coated pellets can minimize the segregation problem.

The term compressibility has been defined as the ability of a powder to decrease in volume under pressure, and the term compactability as the ability of the
material to be compressed into a tablet of specified strength \(^{112}\). While tableting, both compressibility and compactability occurs simultaneously and during compaction, a bed of particles is subjected to an uniaxial compression force by the punches whilst being confined in space by the die.

Powder compaction proceeds in three main stages 1) Particle rearrangement and closer packing, 2) elastic and plastic deformation, and 3) cold working with or without fragmentation \(^{113}\).

The compaction of granulated material is more complicated in the sense that there are both intergranular (between granules) and intragranular (inside granules) pores in the powder bed. Four steps in this volume reduction sequence are proposed 1) filling of inter-particle voids, \textit{i.e.} rearrangement of secondary particles, 2) fragmentation and plastic deformation of second particles, 3) filling of intraparticular voids, \textit{i.e.} rearrangement of primary particles rendering the agglomerates more dense, and 4) fragmentation and plastic deformation of the primary particles.

Pellets have been shown to react differently to compaction and consolidation than powders of the same material. On compaction pellets deform, deformation of the aggregates was found to depend on three deformation characteristics, namely, the capacity for, the mode of and the resistance to deformation, which mainly depends on the material used within it. The size of the pellets can also have a bearing on their compression behavior. Small pellets have been found to be less affected than larger ones by the compaction process while larger pellets were more readily deformed \(^{114,115}\).

To ensure that the coated drug pellet remained intact on compression, the soft-pellets or granules must be mechanically weaker than coated dug containing pellets. Additionally the soft pellets and granules should exhibit fragmentation then plastic deformation during their compression preferentially to the coated pellets, and should maintained their integrity of coated pellets with no significant change in their surface properties \(^{60}\). In fact, they should at least be strong enough to withstand the process up to the compaction stage and be easily broken apart when pressure is applied during compaction \(^{116}\). Ideally the soft-pellets or granules should fracture in to progeny primary powder particles thus facilitating maximum tablet bonding and should produce tablet of good strength (hardness).
Cushioning agent used in any form should also provide the tableting characters required for Multiple-Unit tablet drug delivery system. Cushioning agents should deform by fragmentation resulting in increased contact points that produces tablets with desired tensile strength and should disintegrate the tablet rapidly when came in contact with aqueous fluid to release large number of SR particles in the dispersing media. Such characters can be generated in the tablet by using blend of excipients.

Now a day’s use of antihistaminic preparations had increased and combination drugs are prescribed as decongestant, expectorant, mucolytic, anti-rhinitis and anti-hypersensitivity action. The drug combination of choice for such indication is Pseudoephedrine HCl along with Cetirizine HCl. Pseudoephedrine HCl and Cetirizine HCl is also often prescribe for upper respiratory symptoms such as running nose, nasal congestion associated with allergic or common cold.\(^\text{117}\)

Pseudoephedrine HCl a sympathomimetic drug is effective for treating nasal congestion, while Cetirizine HCl is potent, long acting, multifunctional antihistaminic that works beyond histamine antagonism, it is free from CNS side effect, and well-tolerated in the treatment for seasonal and allergic rhinitis, pruritis, and chronic Idiopathic urticaria.

Pseudoephedrine HCl has a half –life of 5 - 8 h, this lead to need of frequent administration of drug that results in several dose related side effects and also hampers patient compliance. So, the drug is required to be administered in a SR dosage form.

Owing to its advantages over monolithic sustain release dosage forms pellets were selected as SR drug deliver system for Pseudoephedrine HCl. Film coating of Eudragit\textsuperscript{®} RL100 and RS100 the polymethacrylates containing hydrophilic quaternary ammonium groups as functional units in the polymer chain were tried for sustaining the release of drug.
5.2. Aims of the Work

- Evaluating the influence of type of cushioning agents in dry powder, granules or in a soft pellets form, to protect the S.R. film coating of pellets, so that the release of the coated pellets remains unaltered.

- Designing a Multiple-Unit tablet of high tensile strength containing the S.R. pellets of Pseudoephedrine HCl and plain Cetirizine HCl as the model drugs in a dispersible tablet form, so as to facilitate easy swallowing of dosage form.
5.3. **Plan of Work**

The study included:

1) Designing the core pellets of Pseudoephedrine HCl by Extrusion Spheronization technique

2) Preparation of various forms of cushioning agent

3) Preparation of pellet formulation batches by spray coating technique using various concentrations of Eudragit® RS-100 and RL-100 elucidating SR as well as suitable mechanical characteristics

4) Evaluation of coated pellets for various properties
   - Mean pellet diameter
   - Density
   - Strength
   - Drug content
   - Assessment of release of drug from coated pellets
   - Surface characterization

5) Simultaneous estimation of Pseudoephedrine HCl and Cetirizine HCl

6) Designing and preparation of formulation batches for Multiple-Unit tablets of SR Pseudoephedrine HCl and immediate release Cetirizine HCl containing various forms of cushioning agent to retard the breakage of pellets during compression

7) Assessment of evaluation of compressed Multiple-Unit tablets containing SR coated pellets along with various forms of cushioning agents for various properties
   - Weight variation test
   - Tablet hardness
   - Friability
   - Disintegration time
   - Content uniformity
   - Dissolution test

8) Stability studies of selected pellet and tablet batches
5.4. Drug Profiles

5.4.1. Pseudoephedrine Hydrochloride

Structural formula:

\[
\begin{array}{c}
\text{H} \\
\text{118,119} \\
\text{NH} \\
\text{•CH.} \\
\text{CH}_3 \\
\text{HCl} \\
\text{OH} \\
\text{H}
\end{array}
\]

Chemical Name : (+)-(1S, 2S)-2-Methylamino-1-phenyl –propanol hydrochloride

Action : Pseudoephedrine is a direct- and indirect-acting sympathomimetic agent

Molecular formula : C\textsubscript{10}H\textsubscript{16}NO, HCl

Molecular weight : 201.7

Indications : Decongestant, expectorant and mucolytic.

Dose : 60 mg three to four times by mouth or 120 –150 mg twice daily as SR form.

Description : It is a fine white or off-white crystals or crystalline powder; odorless.

Solubility : Freely soluble in water and in alcohol; sparingly soluble in chloroform

Adverse effects:

Dry mouth, anorexia, insomnia, anxiety, tension, restlessness, tachycardia, and palpitations are the some common adverse effects of drug.

Pharmacokinetics:

It is absorbed from the gastrointestinal tract. It is resistant to metabolism by monoamine oxidase and is largely excreted unchanged in the urine together with small amount of hepatic metabolite. It achieves peak plasma concentrations between 1 to 3 h after oral dosing. It has a half - life of 5.4 - 8 h, following oral dosing. Although CNS effects are observed, there is no specific information concerning its penetration in to the CNS. Pseudoephedrine is likely to cross the placenta barrier.
Pharmacology:

Pseudoephedrine is a stereoisomer of ephedrine with similar but less potent pharmacological activity. It is sympathomimetic agent with direct and indirect effects on adrenergic receptors. It has direct agonist activity, particularly on cardiac β-adrenoreceptors and peripheral α₁ receptors. It provides symptomatic relief of nasal congestion. It is also used for the relief of cough and cold symptoms.

Uses and administration:

It is widely used as a constituent in proprietary nasal and bronchial decongestant preparations.

It is given by mouth in the form of solid and liquid dosage form, for the symptomatic relief of nasal congestion. They are also commonly combined with other ingredients in preparations intended for the relief of cough and cold symptoms.

5.4.2. Cetirizine Hydrochloride

Structural formula:

\[
\text{Chemical Name: } 2[4(4-	ext{Chlorobenzhydryl}) 	ext{pipazin}-\text{yl}] 	ext{ethoxyacetic acid hydrochloride}
\]

\[
\text{Action: } \text{Potent H₁ antagonist, antihistaminic with some mast cell stabilizing activity.}
\]

\[
\text{Molecular formula: } \text{C}_{21}\text{H}_{25}\text{ClN}_{2}\text{O}_{3}.\text{HCl}
\]

\[
\text{Molecular weight: } 461.8
\]

\[
\text{Indications: } \text{Used in hypersensitivity reactions, rhinitis and chronic urticaria}
\]

\[
\text{Dose: } 10 \text{ mg once a day}
\]

\[
\text{Description: } \text{It occurs as white or almost white powder}
\]

\[
\text{Solubility: } \text{Freely soluble in water, practically insoluble in acetone and dichloromethane}
\]
Adverse effects:

Hepatitis, sedation, drowsiness, nausea, vomiting, dry mouth, and hyperpyrexia are some common adverse effects of the drug.

Pharmacokinetics:

Cetirizine HCl is rapidly absorbed from the gastrointestinal tract after oral administration, peak plasma concentration being attained within about one h. Food delays the time to peak plasma concentrations but does not decrease the amount of drug absorbed. It is highly bound to plasma proteins and has an elimination half-life of about 10 h. Cetirizine has been detected in breast milk but does not appear to cross the blood brain barrier to a significant extent. It is excreted primarily in urine mainly as unchanged drug.

Pharmacology:

It is a potent, multifunctional antihistaminic that works beyond histamine antagonism. It has marked affinity for peripheral histamine H₁ receptors and is also free from CNS side effects. It has some mast cell stabilizing activity. It inhibits eosinophil chemotaxis as well as infiltration of neutrophils and platelet infiltration.

Uses and administration:

Cetirizine HCl is described as a long acting, non-sedative antihistamine. It appears to have a low potential for drowsiness in usual doses. It is used for the symptomatic relief of allergic conditions including rhinitis and chronic urticaria, pruritus, conjunctivitis, seasonal rhinitis. In adults and children of 6 yrs and over, Cetirizine HCl is given by mouth is in a dose of 10 mg once daily or 5 mg twice daily.
5.5. Profile of Formulation Excipients

5.5.1. Eudragit® RL 100

Chemical name: Poly (ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1:2:0.2

Functional category: It acts as a SR coating material that is independent of pH

Description: It is a solid substance colorless, transparent to slightly opaque granules, with weakly aromatic odor. It contains at least 97% of dry lacquer substance.

Properties: The true density is 0.816-0.836

Solvents: Preferably acetone, methyl alcohol and methylene chloride, as well as solvent mixtures of approximately equal parts of acetone/isopropyl alcohol and isopropyl alcohol/methylene chloride. It is insoluble in petroleum ether, carbon tetrachloride, tetrachloroethylene and white spirit.

Characteristics of the film: Films are colorless, transparent and somewhat brittle. Although insoluble, they swell in water, in natural and artificial digestive juices.

Eudragit RL is a polymer synthesized from acrylic and methacrylic acid esters with a low content of quaternary ammonium groups. It is having 10% of functional quaternary ammonium groups. The ammonium groups are present as salts and give rise to the permeability of the lacquer films. They afford water-insoluble, but permeable, film coatings.

It is recommended that plasticizers (polyethylene glycols, dibutyl phthalate, triacetin, castor oil) be added to enhance the elasticity of the films. The addition of 10% of plasticizer, calculated on the dry lacquer substance content, is generally adequate.
### 5.5.2. Eudragit® RS 100

<table>
<thead>
<tr>
<th><strong>Chemical name</strong></th>
<th>Poly (ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1:2:0.1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Functional category</strong></td>
<td>It acts as a SR coating material that is pH independent</td>
</tr>
<tr>
<td><strong>Description</strong></td>
<td>It is solid, Colorless-clear to white-opaque granules with weakly amine-like odor. It contains at least 97% of dry substance.</td>
</tr>
<tr>
<td><strong>Properties</strong></td>
<td>True density is 0.816 – 0.836 mg/cm³</td>
</tr>
<tr>
<td><strong>Solvents</strong></td>
<td>Preferably acetone, methyl alcohol and methylene chloride, as well as solvent mixtures of approximately equal parts of acetone/isopropyl alcohol and isopropyl alcohol/methylene chloride. It is insoluble in petroleum ether, carbon tetrachloride and white spirit</td>
</tr>
<tr>
<td><strong>Characteristics of the film</strong></td>
<td>Eudragit RS 100 lacquer films are colorless, transparent and somewhat brittle. Although insoluble, they swell in water. In natural and artificial digestive juices and in suitable buffer solution and is permeable to these liquids.</td>
</tr>
</tbody>
</table>

Eudragit RS 100 is a copolymer of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups. It is having 5% of functional quaternary ammonium groups, so the RS 100 films swell less easily and so are slightly permeable to drug as compared to RL films. They form a pH independent water-insoluble, but permeable, film coatings.

It is recommended that plasticizers (polyethylene glycols, dibutyl phthalate, citric acid esters, triacetin, castor oil) be added to enhance the elasticity of the Eudragit RS 100 films. The addition of 10% of plasticizer, calculated on the dry polymer substance content is generally adequate.
5.6. Experimental

5.6.1. Materials

Following materials were used for the experimental work:

<table>
<thead>
<tr>
<th>Chemicals</th>
<th>Suppliers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudoephedrine HCl</td>
<td>Dr. Reddy’s Laboratories Ltd., Hyderabad</td>
</tr>
<tr>
<td>Cetirizine HCl</td>
<td>Dr. Reddy’s Laboratories Ltd., Hyderabad</td>
</tr>
<tr>
<td>Microcrystalline Cellulose PH 101</td>
<td>Chemfields Ltd., Nagpur</td>
</tr>
<tr>
<td>Lactose monohydrate</td>
<td>Research-Lab Fine Chem Industries, Mumbai</td>
</tr>
<tr>
<td>Polyvinyl Pyrrolidon K30</td>
<td>ISP Technologies, New Jersey</td>
</tr>
<tr>
<td>Aerosil®</td>
<td>Degussa India Ltd, Mumbai</td>
</tr>
<tr>
<td>Eudragit® RS and RL 100</td>
<td>Degussa India Ltd, Mumbai</td>
</tr>
<tr>
<td>Sodium starch Glycolate</td>
<td>J. Rettenmaier &amp; Sohne, Germany</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>Dipa Chemical Industries, Aurangabad</td>
</tr>
<tr>
<td>Pineapple flavor</td>
<td>Zim laboratories, Nagpur</td>
</tr>
<tr>
<td>Potassium dihydrogen phosphate</td>
<td>Research labs fine chemicals, Mumbai</td>
</tr>
<tr>
<td>Concentrated HCl</td>
<td>Dipa Chemical Industries, Aurangabad</td>
</tr>
</tbody>
</table>

Equipments / Instruments used were as mentioned in chapter 4.

5.6.2. Preparation of Core Pellets

Pseudoephedrine HCl pellets were prepared by using Extrusion Spheronization technique. 4% PVP K30 aqueous solution was used as agglomeration liquid for the preparation of pellets.

Procedure

a. Microcrystalline cellulose and Pseudoephedrine HCL were passed through sieve No. 80. A mixture of 50:50 containing MCC and Pseudoephedrine HCl were blended in plastic bag.

b. Aqueous 4% PVP-K30 agglomeration liquid was added to powder blend gradually, and after each addition it was kneaded thoroughly in mortar by hand in order to achieve a wet mass that would readily form pellets.
c. Resultant wet mass was immediately extruded through roller type extruder using die-roller of 1 mm pore diameter at a constant speed of 15 rpm.

d. Extrudates so obtained were spheronized in spheronizer attached with 1 mm crosshatch pattern friction plate. The spheronization was carried out for 03 min at 1100 rpm.

e. Resulting pellets were dried at 45°C for 08 h.

f. Sieve fraction of 18-22 was used for coating.

5.6.3. Preparation of Cushioning Agents

From the previous results it was revealed that no single ingredient could provide cushioning to the coated pellets as well as required tablet characteristics. The blend of ingredients containing materials that deform plastically and by fragmentation, on compression can produce the required characters for a successful Multiple-Unit SR tablet. The 1:1 ratio of MCC 101 and Lactose had resulted in the required cushioning as well as tableting characters. So, in the present study the same ingredients were used but in different form for the preparation of Multiple-Unit SR tablet.

5.6.3.1. Cushioning Agent in Powder Form:

The dry powder form of cushioning agent was prepared by blending pre-sieved MCC 101 and lactose at 1:1 ratio in a plastic bag.

5.6.3.2. Cushioning Agent in Granule Form:

Preweighed, sieved and blended MCC 101 and Lactose monohydrate (1:1) were mixed in the mortar by using 5% warm starch paste so as to form damp mass. The damp mass was then passed through sieve No 14 and dried in oven at 50°C the dried granules of sieve fraction 14-20 mesh were used as cushioning agent in further studies.
5.6.3.3. Cushioning Agent in Soft Pellet Form:

a. A blend of MCC 101 and Lactose monohydrate (1:1) was passed through sieve No. 80 and were blended in plastic bag.

b. With proper kneading, distilled water was added to powder blend as agglomeration liquid to achieve a wet mass that would readily form pellets.

c. Resultant wet mass was immediately extruded through roller type extruder using die-roller of 1.8 mm pore diameter at a constant speed of 15 rpm.

d. Extrudates so obtained were spheronized in an spheronizer attached with 1 mm crosshatch pattern friction plate. The spheronization was carried out for 2.5 min at 800rpm.

e. Resulting pellets were dried at 45°C for overnight.

f. Sieve fraction of 14 - 18 was used as cushioning agent.

5.6.4. Sustained Release Coating of Drug Pellets

The drug containing pellets were coated by using pneumatic spray system with ammoniomethacrylate copolymers Eudragit RL 100 and RS 100 in six batches to confer upon them slow release properties. The process conditions required for coating the drug pellets in the coating pan are given in Table 5.1.

<table>
<thead>
<tr>
<th>Process parameters</th>
<th>Setting for coating pan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equipment speed</td>
<td>~ 36RPM</td>
</tr>
<tr>
<td>Tilt angle pan</td>
<td>~ 45°</td>
</tr>
<tr>
<td>Spray gun location</td>
<td>Top spray perpendicular to pellets</td>
</tr>
<tr>
<td>Air pressure</td>
<td>2bar</td>
</tr>
<tr>
<td>Bed to gun distance</td>
<td>~ 8 cm</td>
</tr>
<tr>
<td>Spray rate</td>
<td>2-4 ml/min</td>
</tr>
<tr>
<td>Hot air system</td>
<td>Occasional</td>
</tr>
<tr>
<td>Talc application</td>
<td>As required</td>
</tr>
</tbody>
</table>

Table 5.1: Process Conditions for Coating of Drug Loaded Pellets.
The SR coating to the pellets was carried out in a coating pan with hot air supply. The cores were warmed to a bed temperature of 37°C. The polymer solutions were then sprayed with the help of pilot type pneumatic spray gun at a pressure of about 2 bars. To prevent the agglomeration, talc was applied whenever necessary. After application of required amount of solution, determined on coat weight gain basis, the pellets were allowed to roll with warm air at 40-45°C for 10 min and dried in hot air oven at 40°C overnight. Coated pellets of Sieve fraction 16-18 was used for further processing.

Drug loaded pellets were coated with 10% solution of Eudragit® RL 100 in acetone and IPA (1:1) mixture. Dibutyl phthalate was used as plasticizer at 10% concentration by weight of polymer. Three coated pellet formulations with 12.5% (P-1), 15% (P-2) and 17.5% (P-3) coat weight gain were collected and preceded for further studies.

Same process was carried out for coating of pellets with Eudragit® RS 100. But, as it is a low permeable polymer the different amount of weight gain were tried. Three coated pellet formulations containing 7.5% (P-4), 10% (P-5) and 12.5% (P-6) coat weight gain were collected and preceded for further studies.

5.6.5. Preparation of SR Multiple-Unit Tablets.  

Multiple-Unit tablet formulations PT-A, PT-B and PT-C were prepared in an instrumented single punch tablet press equipped with round, flat-faced punches and die, of 13 mm diameter. Different forms of cushioning agents as in the form of dry powder, dry granules and soft pellets were used for the preparation of Multiple-Unit tablet.

SSG, talc, Aerosil® and Cetirizine HCl were sieved through sieve No.80 weighed accurately and were bended with SR pellets of Pseudoephedrine along with respective cushioning agent by hand in plastic bag. In all the tablet formulations the ratio of drug pellets to cushioning agents was kept constant as 40:60.
Influence of form of cushioning agents used in tableting of pellets

<table>
<thead>
<tr>
<th>Ingredients (mg)</th>
<th>PT-A</th>
<th>PT-B</th>
<th>PT-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pellets(^{\text{a}})</td>
<td>292</td>
<td>292</td>
<td>292</td>
</tr>
<tr>
<td>Cetirizine HCl</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Cushioning agent (^{*})</td>
<td>438</td>
<td>438</td>
<td>438</td>
</tr>
<tr>
<td>SSG</td>
<td>29</td>
<td>29</td>
<td>29</td>
</tr>
<tr>
<td>Aspartame</td>
<td>14.6</td>
<td>14.6</td>
<td>14.6</td>
</tr>
<tr>
<td>Aerosil</td>
<td>3.6</td>
<td>3.6</td>
<td>3.6</td>
</tr>
<tr>
<td>Talc</td>
<td>3.6</td>
<td>3.6</td>
<td>3.6</td>
</tr>
<tr>
<td>Flavour</td>
<td>14.6</td>
<td>14.6</td>
<td>14.6</td>
</tr>
<tr>
<td>Total Weight</td>
<td>800.4</td>
<td>800.4</td>
<td>800.4</td>
</tr>
</tbody>
</table>

\(^{\text{a}}\) = Pellets equivalent to 120 mg. Pseudoephedrine HCl  
\(^{*}\) = PT-A contains cushioning agent in the powdered form  
PT-B contains cushioning agent in the granules form  
PT-C contains cushioning agent in the Pellets form

Table 5.2: Formulations of Disintegrating Tablets Containing Cetirizine hydrochloride and SR Pellets of Pseudoephedrine hydrochloride

5.6.6. Characterization of Coated Pellets

Physical testing of polymer coated pellets includes:

1. Mean pellet diameter
2. Density
3. Strength
4. Drug content
5. Dissolution studies
6. Surface characterization

Mean pellet diameter, density and strength were calculated as mentioned previously in chapter 4.

\* Drug content:

Pellets (2 g) were crushed to powder. Accurately weighed crushed powder equivalent to 120 mg of Pseudoephedrine HCl was transferred to 100 ml volumetric flask and diluted to 100 ml with pH1.2 buffer and stirred magnetically for 1 h for complete dissolution of drug. The resultant solution was filtered with Whatmann filter paper 44. One ml of this solution was taken and it was diluted appropriately with buffer solution
and absorbance was noted at 225.5 nm from second order derivative spectra and drug content was determined using calibration curve.

**Dissolution test:**

The coated pellets were evaluated for *in vitro* release profile using type-II dissolution test apparatus by using 900 ml of dissolution medium. For the first h pH 1.2 buffer was used thereafter pH 6.8 was used up to the end of study. The speed of pedal was maintained at 100 revaluations per minute. The medium was maintained at 37±0.5°C for the complete run of dissolution study. 5ml aliquots were withdrawn after every h and replaced by fresh dissolution medium. The filtrate was analyzed at 225.5 nm from second order derivative spectra and the amount of drug present in sample solution was calculated from the following formula

\[ C_x = \frac{A_u}{A_s} \times C_s \]

Where,
- \( C_x \) is the concentration of unknown drug,
- \( A_u \) is the absorbance of unknown drug,
- \( A_s \) is the absorbance of standard drug and
- \( C_s \) is the concentration of standard.

**Optimization of Pellets:**

From the pellet batches, batch that gave the superior SR of drug and strength required for minimizing the damage during tableting was optimized. This optimized formulation was subjected to the further studies of surface characterization and stability studies as per the previously mentioned processes.

**5.6.7. Simultaneous Estimation of Pseudoephedrine HCl and Cetirizine HCl**

Second order derivative spectrophotometry revealed that two wavelengths of which one drug have zero absorbance and the other have positive significant absorbance at the same wavelength, and vice versa for another drug can be used for simultaneous estimation of two drugs. Pseudoephedrine HCl and Cetirizine HCl showed zero absorbance at 225.5 and 244nm respectively from second derivative spectra. Hence these two wavelengths were effectively employed for undertaking the estimation of Pseudoephedrine HCl and Cetirizine HCl, without any interference from the other drug.
Influence of form of cushioning agents used in tableting of pellets

in the combined formulation. The amount of drug present in sample solution was calculated from calibration curve.

- **Preparation of calibration curve for Pseudoephedrine HCl:**

  Pseudoephedrine HCl (100 mg) was placed in a volumetric flask and the volume was made up to 100ml with the 0.1 N HCl. The drug solution was further diluted to obtain serial dilutions of 20 - 160 µg/ml by using 0.1 N HCl. The absorbance of these dilutions was measured at 225.5 nm using solution blank.

<table>
<thead>
<tr>
<th>Concentration (mcg/ml)</th>
<th>Absorbance at 225.5 nm</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>20</td>
<td>0.002</td>
</tr>
<tr>
<td>40</td>
<td>0.004</td>
</tr>
<tr>
<td>60</td>
<td>0.006</td>
</tr>
<tr>
<td>80</td>
<td>0.008</td>
</tr>
<tr>
<td>100</td>
<td>0.01</td>
</tr>
<tr>
<td>120</td>
<td>0.012</td>
</tr>
<tr>
<td>140</td>
<td>0.014</td>
</tr>
<tr>
<td>160</td>
<td>0.016</td>
</tr>
</tbody>
</table>

Table 5.3: Absorbance of Serial Dilutions of Pseudoephedrine hydrochloride.

![Calibration Curve of Pseudoephedrine HCl](image)

- **Preparation of calibration curve for Cetirizine HCl:**

  Cetirizine HCl (100 mg) was placed in a volumetric flask and the volume was made up to 100ml with the 0.1 N HCl. The drug solution was further diluted to
obtain serial dilutions of 10 - 60 μg/ml by using 0.1 N HCl. The absorbance of these dilutions was measured at 244 nm using solution blank.

<table>
<thead>
<tr>
<th>Concentration (mcg/ml)</th>
<th>Absorbance at 244 nm</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>0.006</td>
</tr>
<tr>
<td>20</td>
<td>0.013</td>
</tr>
<tr>
<td>30</td>
<td>0.021</td>
</tr>
<tr>
<td>40</td>
<td>0.027</td>
</tr>
<tr>
<td>50</td>
<td>0.033</td>
</tr>
<tr>
<td>60</td>
<td>0.041</td>
</tr>
</tbody>
</table>

Table 5.4: Absorbance of Serial Dilutions of Cetirizine hydrochloride.

Calibration Curve of Cetirizine HCl

\[ y = 0.0007x - 0.0003 \]

\[ R^2 = 0.9985 \]

Figure 5.2: Calibration Curve of Cetirizine hydrochloride.
5.6.8. Characterization of Multiple-Unit Tablets

All the tablet formulations were evaluated for following tests:

1. **Weight variation test**
2. **Tablet hardness**
3. **Friability**
4. **Disintegration time**
5. **Content uniformity**
6. **Dissolution studies**

Weight variation test, tablet hardness, friability, disintegration time and stability studies of tablet formulations were carried out as mentioned previously in chapter 4.

- **Content uniformity:**

Two tablets were randomly selected and individually grinded into fine powder. The powder was placed in the 100 ml volumetric flask and dissolved by adding 0.1 N HCl up to the mark. The solution was filtered through Whatmann filter paper 44. 1ml of this filtered solution was diluted to 100 ml with 0.1 N HCl and the absorbance of the sample solutions were recorded at 225.5 and 244 nm from second derivative spectra and amount of drug present in sample solution was calculated from calibration curve.

- **Dissolution test:**

The disintegrating Multiple-Unit tablet was evaluated for *in vitro* release profile using type-II dissolution test apparatus by using 900 ml of dissolution medium. For the first h pH 1.2 buffer was used thereafter pH 6.8 was used up to the end of study. The speed of pedal was maintained at 100 revaluations per minute. The medium was maintained at 37 ± 0.5°C for the complete run of dissolution study. Initially 5ml aliquots were withdrawn after every 10 min for an h followed by withdrawal of dissolution media at hourly intervals and replaced by fresh dissolution medium. The filtrate was analyzed for absorbance of sample solution at 225.5 and 244 nm from second order derivative spectra and the amount of drug present in sample solution was calculated from the formula as given in dissolution test of pellets.
Stability Study of Tablet:

The optimized formulation of tablets were kept in aluminum foil and placed in oven at 45°C for 30 days. After 30 days the tablets were analyzed for the content uniformity by the method as described earlier.

5.7. Results and Discussion

5.7.1. Pellet Properties

Owing to its advantages over monolithic sustain release dosage forms pellets were selected as drug deliver system for Pseudoephedrine HCl. Film coating of Eudragit® RL100 and RS100 the polymethacrylates containing hydrophilic quaternary ammonium groups as functional units in the polymer chain were evaluated for sustaining the release of drug.

1. Mean pellet diameter:

Coated pellets of Sieve fraction 16-18 were studied, as they were used for the preparation of tablets so as to minimize the effect of size of pellets during compression. From the Table 5.5 it clearly revealed that the mean diameter of pellets increases with the increase in coating weight gain.

2. Density:

It was observed from Table 5.5 that tapped density of all the pellet formulations was within 0.61 to 0.69 that indicates sufficient pores present in between the pellets. The intraparticullar pores are essential while compression of pellets, so that the pores will be filled by the cushioning agent and distributes the forces in nearby cushioning particles. As the Hausner ratio value of pellets was less than 1.25, it indicates that the pellets were free flowing in nature.

3. Strength:

From the Table 5.5 it was observed that as the coating weight gain on the pellets increases the strength was also found to increase. This indicates that increased amount of coating increases the strength of pellets. From the results it can be concluded that, MCC along with drug provide effective binding and formation of strong pellet.
results are clearly indicative of achieving desired strength of pellets by using PVP 4% solution as agglomeration liquid and by coating the pellets.

4. Drug content:

Drug containing coated pellets were used to determine drug content, and it was found that all the pellets contain drug that were within 40.51 to 42.02 % of pellets.

<table>
<thead>
<tr>
<th>Pellet formulation No.</th>
<th>Mean Diameter (μ)</th>
<th>Poured density (g/ml)</th>
<th>Tapped density (g/ml)</th>
<th>Hausner ratio</th>
<th>Strength (kg/cm²)</th>
<th>Drug content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-1</td>
<td>907 ± 13.46</td>
<td>0.67</td>
<td>0.65</td>
<td>0.97</td>
<td>3.0 ± 0.08</td>
<td>42.02</td>
</tr>
<tr>
<td>P-2</td>
<td>918 ± 13.59</td>
<td>0.68</td>
<td>0.66</td>
<td>0.97</td>
<td>3.1 ± 0.1</td>
<td>41.01</td>
</tr>
<tr>
<td>P-3</td>
<td>947 ± 14.67</td>
<td>0.7</td>
<td>0.69</td>
<td>0.98</td>
<td>3.4 ± 0.12</td>
<td>41.1</td>
</tr>
<tr>
<td>P-4</td>
<td>861 ± 12.41</td>
<td>0.63</td>
<td>0.61</td>
<td>0.97</td>
<td>2.9 ± 0.12</td>
<td>40.85</td>
</tr>
<tr>
<td>P-5</td>
<td>884 ± 12.38</td>
<td>0.65</td>
<td>0.63</td>
<td>0.97</td>
<td>3.0 ± 0.1</td>
<td>40.51</td>
</tr>
<tr>
<td>P-6</td>
<td>897 ± 14.17</td>
<td>0.66</td>
<td>0.64</td>
<td>0.97</td>
<td>3.1 ± 0.1</td>
<td>41.21</td>
</tr>
</tbody>
</table>

Table 5.5: Physicochemical Characteristics of Coated Pellets.

5. Dissolution studies:

From the dissolution studies it was observed that pellet formulations P-3 and P-6 were able to show the SR of drug up to 10 h and resulted in almost linear drug release curve. Whereas the strength of P-3 formulation was quite high (3.4) that was desirable for compaction of pellets, as compared to formulation P-6 (3.1). If although pellet formulation P-2 and P-5 showed better drug release character the strength of these formulations limit their use in compaction studies. In contrast pellet formulations P-1 and P-4 showed nearly 90 % drug release at 6th h. The drug release profile of coated pellets is given in Figure 5.3.
Influence of form of cushioning agents used in tableting of pellets

Figure 5.3: Drug Release Profile for Pellets Formulations P-1 to P-6

Table 5.6: Cumulative % Release of Pseudoephedrine hydrochloride From Formulation of Coated Pellets P-1 to P-6.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>P-1</th>
<th>P-2</th>
<th>P-3</th>
<th>P-4</th>
<th>P-5</th>
<th>P-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17.24</td>
<td>12.59</td>
<td>8.14</td>
<td>17.43</td>
<td>12.33</td>
<td>7.27</td>
</tr>
<tr>
<td>2</td>
<td>41</td>
<td>26.23</td>
<td>17.38</td>
<td>34.7</td>
<td>25.51</td>
<td>18.15</td>
</tr>
<tr>
<td>3</td>
<td>58.4</td>
<td>37.6</td>
<td>29.15</td>
<td>50.92</td>
<td>37.49</td>
<td>28.43</td>
</tr>
<tr>
<td>4</td>
<td>71.7</td>
<td>52</td>
<td>39.31</td>
<td>66.52</td>
<td>49.1</td>
<td>39.3</td>
</tr>
<tr>
<td>5</td>
<td>83.2</td>
<td>62.13</td>
<td>53.69</td>
<td>79.26</td>
<td>60.7</td>
<td>50.91</td>
</tr>
<tr>
<td>6</td>
<td>90.2</td>
<td>75.31</td>
<td>64.55</td>
<td>88.9</td>
<td>72.34</td>
<td>63</td>
</tr>
<tr>
<td>7</td>
<td>94.27</td>
<td>83.25</td>
<td>73.12</td>
<td>93.68</td>
<td>82.97</td>
<td>75.12</td>
</tr>
<tr>
<td>8</td>
<td>-</td>
<td>92.42</td>
<td>82.4</td>
<td>94.75</td>
<td>90.11</td>
<td>83.67</td>
</tr>
<tr>
<td>9</td>
<td>-</td>
<td>94.28</td>
<td>89.56</td>
<td>-</td>
<td>94.67</td>
<td>90.42</td>
</tr>
<tr>
<td>10</td>
<td>-</td>
<td>95.21</td>
<td>-</td>
<td>-</td>
<td>95.41</td>
<td>-</td>
</tr>
</tbody>
</table>

Polymers used Eudragit® RL100 and RS100 were the polymethacrylates, containing hydrophilic quaternary ammonium groups as functional units in the polymer chain that have high softening temperature and forms hard film under room temperature. They were used without the additional incorporation of release controlling excipients. The permeability of polymer was directly proportional to the content of methylammonioethyl methacrylate chloride (hydrophilic units). RL 100 contains 10 % w/w of this unit resulting in permeable membrane whereas RS 100 contains 05% of this unit and so exhibited very low permeability. RL 100 at 17.5 % increase in film coat weight, containing dibutyl phthalate as hydrophobic plasticizer at 10% concentration by
weight of polymer and talc as antistick agents drop down the release rate, to give SR of Pseudoephedrine HCl up to 10 h. Diametrical strain of the formulation P-3 was highest i.e. 3.4 kg/cm² due to the increase in coating.

- **Optimization of Pellets:**
  
  From the prepared batches of the pellets; formulation P-3 and P-6 showed the better release of drug. Pellets for tableting should have essential strength to resist the compression forces and so the other deciding factor for optimization of pellet batch P-3 was the strength of pellet that was high as compared to P-6 formulation. This optimized formulation of pellets P-3 was subjected to the further studies of surface characterization, and stability studies.

- **Surface Characterization**
  
  From the Surface topography studies of the pellets investigated from images obtained by Scanning Electron Microscopy (SEM), it can be concluded that Pellets coated with Eudragit® RL100 grade was found to have smooth surface. The SEM photomicrographs of an optimize pellet formulation P-3 is shown in Figure 5.4.

![Figure 5.4](image)

**Figure 5.4:** SEM Photographs of Pellet Formulation [A] P-3 at 60 x and [B] 1,000 x Magnifications.

From the SEM photographs at 60 and 1000 x magnification it can be concluded that the pellets were coated uniformly and the higher magnification showed the continuous coating of pellets, which resulted in SR of drug through the pellets. The shape of the pellet was nearly spherical, which indicates the success of Extrusion Spheronization process by using MCC 101 as spheronizing aid and aqueous 4% PVP solution as agglomeration liquid.
The drug is mainly transported through the membrane of Eudragit® RL100 via passive diffusion. Pore free membrane showed more effective retardation and a more reproducible release pattern. Use of high layer thickness showed positive results to achieve pore free membrane.

**Stability Studies**

No considerable changes in drug content and crushing strength were observed after storage of optimized pellet formulation batch P-3 at 45°C for one month. The drug content of pellets before and after stability studies was 41.1 and 41.38% respectively while the strength remains as such.

The release profile of drug after end of 30 days at 45°C ± 1°C is shown in Figure 5.5. The result showed no significant change on the drug release characteristics from the pellet formulation P-3. This indicates that drug pellets coated with Eudragit® RL100 at 17.5% coat weight gain resulted in stable formulation.

![Figure 5.5: Effect of Temperature (45°C ± 1°C) on in-vitro Drug Release of Batch P-3](image)

**5.7.2. Multiple-Unit Tablet Properties**

It is essential to incorporate excipients of good compressibility into Multiple-Unit tablets in order to limit the extent of damage to the coated particles during compression. In the present study, based on previous results, blend of MCC and lactose (1:1) was selected as an appropriate choice as the filler material for Multiple-Unit tablet formulation, mainly because of its excellent compressibility, high dilution capacity and ability to form hard tablets that disintegrates quickly to release the intact pellets in
Influence of form of cushioning agents used in tableting of pellets

dispersing media. To evaluate the effect of forms of cushioning agent three tablet formulations were prepared and evaluated. In all the formulations the ratio of drug pellets to cushioning agent was kept constant as 40:60 to prevent the damage that may occur due to the ratio of pellets to cushioning agents.

Tablet formulations were evaluated for weight variation, hardness, friability, disintegration and dissolution studies. The results of physicochemical characters of tablets are depicted in Table 5.7.

| Parameters | Formulations | Disintegration time (Sec) (n=6) | Weight variation | Hardness (kg/cm²) (n=3) | Friability (%) (n=10) | Content uniformity (%)
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PT-A</td>
<td>41 ± 2.04</td>
<td>Pass</td>
<td>4.5 ± 0.12</td>
<td>0.2</td>
<td>93.64</td>
</tr>
<tr>
<td></td>
<td>PT-B</td>
<td>39 ± 2.16</td>
<td>Pass</td>
<td>3.8 ± 0.15</td>
<td>0.91</td>
<td>95.91</td>
</tr>
<tr>
<td></td>
<td>PT-C</td>
<td>79 ± 2.99</td>
<td>Pass</td>
<td>2.3 ± 0.21</td>
<td>#</td>
<td>96.48</td>
</tr>
</tbody>
</table>

# = Tablet looses its integrity during the friability testing

Table 5.7: Comparative Physical Characteristics of Disintegrating Tablet Formulations PT-A, PT-B and PT-C.

Tablet formulation PT-A and PT-B passes all the required characters of tablet while the friability of tablet PT-B was near to the limit which might be due to the less binding of tableting additives. Formulation PT-C passes the disintegration test and weight uniformity but the disintegration time was 79 sec, which is more than others. This might be due to breakage of polymer coated pellets during tableting and the free polymer on contact with water swells, to retard the DT of tablet. Formulation PT-C showed very less strength and friability. All the tablet formulations pass as the content uniformity limits of Pseudoephedrine HCl and Cetirizine HCl. The dissolution profile of tablet formulations PT-A to PT-C is given in Figure 5.6.
Influence of form of cushioning agents used in tableting of pellets

Figure 5.6: Drug Release Profile of Tablet Formulations PT-A to PT-C.

Table 5.8: Release Profile of Tablet Formulations PT-A to PT-C.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Cumulative % Drug Released</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pellet formulation P-3</td>
</tr>
<tr>
<td>1</td>
<td>8.14</td>
</tr>
<tr>
<td>2</td>
<td>17.38</td>
</tr>
<tr>
<td>3</td>
<td>29.15</td>
</tr>
<tr>
<td>4</td>
<td>39.31</td>
</tr>
<tr>
<td>5</td>
<td>53.69</td>
</tr>
<tr>
<td>6</td>
<td>64.55</td>
</tr>
<tr>
<td>7</td>
<td>73.12</td>
</tr>
<tr>
<td>8</td>
<td>82.4</td>
</tr>
<tr>
<td>9</td>
<td>89.56</td>
</tr>
<tr>
<td>10</td>
<td>95.21</td>
</tr>
</tbody>
</table>

The study represents an attempt to broaden our understanding of the mechanisms involved in the compression of bioactive pellets along with cushioning agents in powder, granular and soft pellet forms, and to investigate how these cushioning agents affect the tablet structure, strength and release characteristics.

5.7.2.1. Effect of Powder as Cushioning Agent

The results showed that formulation PT-A and pellet formulation P-3 has same drug release profile and so it can be concluded that cushioning agent in powdered form was successful to absorb the pressure during compaction as well as producing tablets with desired characteristics. When, a pellet is held in a confined space as in
Influence of form of cushioning agents used in tableting of pellets

powdered matrix and subjected to compression force, the pellets are stressed from several directions simultaneously, making fracturing of the pellets relatively difficult and the individual pellet respond preferentially to the applied force by deformation rather than fragmentation. The schematic view of the pellets in such situation is shown in Figure 5.7 (A). At the deformation pressure, the compaction forces transmitted from pellets are spread out over larger contact areas via the powdered cushioning agents as depicted in Figure 5.7 (B), hence the stress at these contact areas will level out. Thus no further damage of the coated pellets occurred which results in no significant change in release of drug from the coated pellets, even after compaction. Such concept will never be possible for cushioning agent in granulated and pelletized form.

Figure 5.7 [A]
Compressional forces on the pellets are well distributed in the matrix of nearby powdered cushioning agent particles, thereby prevents damage to the coated pellets.

Figure 5.7 [B]

**Figure 5.7**: Schematic View of (A) Pellet During Compression in a Die of Tableting Machine, and (B) Transmission of Compressive Forces Via Cushioning Agents in Powdered Form.

Less deflection of release as that of uncompacted pellets, thus indicated a low degree of destruction of the integrity of the coated pellets, which reflects favorably the effectiveness of MCC along with lactose as a cushioning or protective and spacer agent (as it keeps two pellets away from each other) for the coated pellets during the compression process. MCC and lactose exhibit marked stress relaxation, which account for its ability to deform and fragment respectively under the influence of compression force. This property facilitates the rapid dissipation of the applied stress; thereby reducing corresponding damage to the tabletted pellets and produces the tablet with desired characters.

As predicted Silicon dioxide (Aerosil), being glidant, improved the flow and packaging arrangement of the material particles during the compression process by reducing interparticulate friction and cohesion. The slippage of the spherical Aerosil particles over each other further helped in relieving the applied stress on the compressed pellets, thus augmenting the protective function of MCC and lactose.

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Surprisingly the content uniformity of the tablet was also within limit and the segregation problem was not observed. It was proposed that Segregation is generally a drawback of adding fine powders as cushioning agents to larger size particles, like Pellets because of the particle size difference and difference in density of powdered cushioning agents and the coated pellets. However the answer of achieving content uniformity in limits lies in the percolation theory. According to the percolation theory “if the level of the powder excipient is high enough (60 – 70 %), acceptable content uniformity can occur” In the present study more than 60 % powder excipient were used resulting in tablets with desired content uniformity. The photomicrographic evidence of broken surface of tablet formulation PT-A in Figure 5.8 showed segregated pellets within the cushioning matrix that slightly deform plastically but no fissures were observed.

![Digital Photomicrograph of Fractured Surface of Tablet Formulation Pt-A at 60 x Magnification.](image)

5.7.2.2. Effect of Granules as Cushioning Agent

To match the particle size of the excipients with the pellets a wet granulation process was carried out using MCC and lactose that prevented segregation resulting in more uniform content uniformity. The poured and tapped density of granules was found to be 0.40 and 0.49 g/ml. Granules on compression formed small agglomerates that apparently resulted in increased excipient-excipient interaction and thereby produced an environment in which the compression forces impacted less directly upon the pellets. From the dissolution studies it was observed that granules as cushioning agents didn’t succeed completely in preventing the damage to pellets. On compression the enhanced release of drug from the tabletted coated pellets compared with
uncompressed pellets, thus suggested a loss of physical integrity of the coated pellets, and that a major portion of coated pellets in the tablet was tainted during compression. This might be due to the increased size of cushioning agent particles that were unable to transmit the compaction forces efficiently in the nearby cushioning particles. The schematic representation is given in Figure 5.9.

![Schematic View of Transmission of Compressive Forces Via Cushioning Agents in Granule or Soft Pelletized Form](image)

**Figure 5.9:** Schematic View of Transmission of Compressive Forces Via Cushioning Agents in Granule or Soft Pelletized Form.

Furthermore, the supporting evidence is obtained from the photomicrograph of tablet formulation in Figure 5.10. Most of the pellets were found to be fractured in the tablet cross-section resulting in increased drug release from the compressed pellets (PT-B).
Tablets prepared by using granules as cushioning agent PT-B offered desirable DT but the hardness was less as compared to formulation PT-A. The friability value of 0.91% was also near to failure limit. The less hardness and high friability values indicates poor mechanical interlocking and bonding between the excipient particles that might be ensuing due to increased size of excipient particles.

From the studies of using granules as cushioning agent, it was observed that the deformation and probably breaking of coating increased with increasing cushioning agent particle size. Hence to minimize the change in release rate, excipient particles of small size and high porosity should be incorporated in the tablet formulation.

5.7.2.3. Effect of Soft-Pellets as Cushioning Agent

It is postulated that anticipated problems associated with blending and segregation of drug containing pellets and excipients might be prevented or at least minimized by admixing active and soft-pellets. To ensure that the coated drug pellet remained intact on compression, the soft-pellets should be mechanically weaker than coated drug containing pellet. The soft-pellets were intentionally prepared weaker that were having 1.7 kg strength. Additionally, the soft-pellets should exhibit elastic deformation and brittle fragmentation rather then plastic deformation during their compression and was achieved by preparing the high porosity product.
The degree of deformability and fragmentation of individual pellets during compression was higher for larger pellets. Larger pellets were more readily deformed and that was explained by reduced number of force transmission points with increasing size of the pellets and therefore an increased contact force on each pellet, that resulted in higher deformation. So, in this study bigger, soft-pellets were used as cushioning material for coated pellets containing drug.

From the photomicrograph of tablet formulation PT-C in Figure 5.11 it was observed that on compression the soft-pellets fractures but were unable to produce progeny primary powder particles. These large sized particles failed to provide effective cushioning to the coated pellets and the results of dissolution studies supports the hypothesis that compressive forces were not effectively transmitted from the coated pellets to the cushioning particles that resulted in formation of cracks in the coating and fragmentation of pellets to a certain extent, which resulted in faster release of drug from their compacts. The less contact points due to large sized particles and elastic deformation nature of soft-pellets resulted in very poor strength (hardness) and friability to the tablet formulation PT-C. So, the admixing of drug containing pellets and soft-pellets was not a viable proposition for formulating a successful SR Multiple-Unit tablet.

Figure 5.11: Digital Photomicrograph of Fractured Surface of Tablet Formulation PT-C at 60 x Magnification, Deformation of Pellets Without Formation of Intact Tablet.

It was thought that Segregation is generally a drawback of adding fine powders as cushioning agents to larger size particles, like Pellets because of difference in the particle size and true density of cushioning agents and the coated drug pellets. It was
observed from the results of present study that, by using larger particles as granules and soft-pellets effective cushioning was not possible resulting in increased drug release, however tablet strength could decrease.

**Stability Studies**

From the content uniformity study of tablet formulation PT-A it was observed that no substantial changes were occurred during storage at 45\(^\circ\) + 1\(^\circ\) C for 30 days. The content uniformity of tablet formulation PT-A for Pseudoephedrine HCl before and after study was 93.64 and 94.02\% respectively. Whereas, for Cetirizine HCl it was 94.54 and 95.2 \% respectively.

This indicates that tablet containing Cetirizine HCl and Eudragit\textsuperscript{®} RL 100 (17.5\% coat weight gain) coated pellets of Pseudoephedrine HCl along with other tableting materials resulted in stable formulation.

The Multiple-Unit tablet formulation was meant for quick release of Cetirizine HCl and SR of Pseudoephedrine HCl for effective relief from allergic disorders. From the dissolution study data of Cetirizine HCl (Figure 5.12) it was observed that more than 90\% of drug was released within 30 min that might be due to fast disintegration of directly compressed tablet.

![Figure 5.12: Release of Cetirizine hydrochloride from Tablet Formulation-PT-A.](Image)
Influence of form of cushioning agents used in tableting of pellets

<table>
<thead>
<tr>
<th>Time (Min)</th>
<th>Cumulative % Cetirizine HCl release</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>42.54</td>
</tr>
<tr>
<td>20</td>
<td>75.7</td>
</tr>
<tr>
<td>30</td>
<td>91.4</td>
</tr>
<tr>
<td>40</td>
<td>93.5</td>
</tr>
<tr>
<td>50</td>
<td>94.28</td>
</tr>
</tbody>
</table>

Table 5.9: Release of Cetirizine hydrochloride From Tablet Formulation PT-A.

5.8. Conclusion

When compacting coated drug-loaded pellets, the use of small cushioning agents, i.e. the blend of MCC and lactose powder, resulted in intact pellets without creating segregation problems. While the use of cushioning agents in the form of granules and soft pellets can result in the change in release of drug from the coated pellets.

When large particle size additives were used, the drug release behavior of the tablet was drastically changed upon compressions. Less change was observed when cushioning agents of smaller particle sizes were used. However, they did not indent the coated drug pellets, thereby resulting in pellets that were protected during compaction. Smaller cushioning agent particle size was superior in protecting the membrane from damage as well as provides all the prerequisite characters of tablet.

It was thus concluded from this study that drug-pellets prepared by Extrusion Spheronization method coated with S.R. Ammoniomethacrylate co-polymer and cushioned with dry powdered cushioning agent form containing MCC PH 101 and Lactose monohydrate (1:1) are best suited to produce the Multiple-Unit tablets with nearly unaltered release of drug as that of uncompacted pellets.