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

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## ABSTRACT

The process of creating these combinations into multi-unit tablets requires careful consideration of excipients, guaranteeing compatibility, stability, and controlled release. Optimal drug dispersion and consistency in the dosage form can be achieved by utilizing advanced pharmaceutical technologies, such as hot melt extrusion or spray drying. The development process also considers the pharmacokinetic properties of specific medications, guaranteeing coordinated release and absorption. By doing so, not only are the therapeutic benefits optimized, but also the adverse effects and the potential for medication interactions are minimized. The selection of excipients and manufacturing methods plays a vital role in obtaining the required release profiles, such as immediate, sustained, or delayed, based on the therapeutic requirements of the chosen drug combinations.

The potential consequences of using multi-unit tablets for specific combinations of drugs have a wide-ranging effect. The pills offer a notable benefit by improving patient adherence, as they streamline intricate treatment regimens, hence decreasing the chances of missing doses. Furthermore, the combination of medication delivery methods might lead to enhanced therapeutic results, accelerated healing, and, in certain instances, decreased dosage needs, thus minimizing potential adverse effects.

From a pharmaceutical market standpoint, the implementation of multi-unit tablets for specific therapeutic combinations presents new opportunities for drug advancement and commercialization. It tackles medical demands that have not been satisfied and creates a competitive advantage by delivering treatment solutions that are more effective and convenient.

**KEYWORDS:** Cushioning Agents, Tableting Of Pellets, multi-unit tablets, pharmaceutical technologies

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## INTRODUCTION

The tableting process can severely degrade the polymer film, changing the drug release characteristic from the pellets, which is a particular difficulty if the pellets are coated with polymer then squeezed into tablets. Use of cushioning agents effectively protected the coated pellets from harm during tableting; without them, they would have been more easily broken or distorted than the SR drug pellets. The choice of cushioning agent form can be a deciding element in the manufacturing of Multiple Unit tablets.

**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

Because pellets' release rate controlling polymer membranes might degrade during compaction, choosing the right cushioning agent is crucial. Coated pellets are less likely to experience film cracking thanks to cushioning chemicals. Because segregation is a common problem when using tiny powders as cushioning agents to bigger particles, like pellets, in industrial production on a large scale, it is extremely important that they have compatible particle sizes. Many tableting issues, including weight variation, poor content homogeneity, etc., arise from segregation, which is caused by the difference in particle size and the difference in real density of the cushioning agents and the coated pellets.

## DRUG PROFILES

### Adverse effects:

Some of the most common side effects of drugs are dry mouth, anorexia, sleeplessness, anxiety, tension, restlessness, rapid heartbeat, and palpitations.

### Pharmacokinetics:

It travels through the digestive system and is absorbed there. It mainly passes intact into the urine with a trace quantity of hepatic metabolite since monoamine oxidase cannot metabolize it. It takes 1–3 hours after an oral dose to reach its peak plasma concentrations. After an oral dose, its half-life is between three and eight hours. No particular information is available regarding its penetration into the central nervous system, however effects on the CNS have been noted. The placenta

barrier is likely to be crossed by pseudoephedrine.

**Pharmacology:**

The stereoisomer of ephedrine, pseudoephedrine has comparable but less pharmacological effects. It has both direct and indirect effects on adrenergic receptors, making it a sympathomimetic agent. It acts as a direct agonist, especially on peripheral ai receptors and cardiac padrenoreceptors. It alleviates the discomfort associated with stuffy noses. Cough and cold symptoms might also be alleviated with its use.

**Uses and administration:**

It is a common ingredient in specialized decongestants for the nose and bronchi. For the temporary alleviation of nasal congestion symptoms, it is taken orally in the form of either solid or liquid dose forms. To alleviate the symptoms of a cold or cough, they are often used with other components in remedies.

**Preparation of Cushioning Agents**

It was previously shown that no one component could give the coated pellets the necessary cushioning and tablet properties. To make a Multiple-Unit SR pill, you need a combination of substances that can flex plastically and fracture upon compression. With a 1:1 ratio of MCC 101 to lactose, the desired cushioning and tableting properties were achieved. This means that the ingredients for the Multiple Unit SR tablet were the same as those in the previous trial, but they were prepared differently for this investigation.

**Cushioning Agent in Granule Form:**

In order to create a wet mass, the mortar was mixed with 5% heated starch paste and a 1:1 ratio of preweighed, sieved, and blended MCC 101 and lactose monohydrate. After that, the wet material was dried in an oven set at 50°C after passing through filter No. 14. In further investigations, the cushioning agent utilized dried granules from sieve fraction 14–20 mesh.

**Cushioning Agent in Soft Pellet Form:**

a. In a plastic bag, a mixture of 1 part MCC 101 and 1 part lactose monohydrate was mixed after passing it through sieve No. 80.

b. To make a wet mass that could be easily worked into pellets, distilled water was added to the powder mixture while kneading properly to act as an agglomeration liquid.

c. Under continuous speed of 15 rpm, the die-roller with a pore diameter of 1.8 mm was used to extrude the resultant wet mass right away through a roller type extruder.

d. A spheronizer was used to spheronize the extrudates, which were mounted to a friction plate with a 1 mm Crosshatch pattern. We spheronized the sample for 2.5 minutes at SOOrpm.

e. Overnight at 45°C, the pellets that were produced were dried. f. A cushioning agent was made from the fraction of the sieve that was 14–18.

**Sustained Release Coating of Drug Pellets**

Pellets carrying the medicine were coated in six separate batches with the ammoniomethacrylate copolymers Eudragit RL 100 and RS 100 using a pneumatic spray technique. This gave them the ability to release their contents slowly. Coating the pellets with SR required a coating pan and a source of hot air. The bed temperature of the cores was raised to 37 C. Next, a pilot-type pneumatic spray gun was used to apply the polymer solutions at a pressure of approximately 2 bars. Applying talc as needed prevented the agglomeration. The pellets were dried in a hot air oven at 40° C overnight after being rolled in heated air at 40-45*^ C for 10 minutes after the necessary amount of solution had been applied, which was determined based on the coat weight growth. Proceeding with the processing, pellets coated with Sieve fraction 16–18 were utilized. Pellets containing drugs were covered with a 10% solution of Eudragit® RL 100 in a 1:1 combination of acetone and IPA. At a concentration of 10% by weight of polymer, dibutyl phthalate was employed as a plasticizer. Prior to doing more research, three coated pellet formulations were gathered: P-1, which had a coat weight gain of 12.5%, P-2, which was 15%, and P-3, which was 17.5%. Applying the Eudragit RS 100 coating to the pellets followed the same procedure. It is a low-permeability polymer, hence experiments with varying degrees of weight increase were unsuccessful. We gathered three coated pellet formulations—P-4, which had a coat weight gain of 7.5%, P-5, which had a 10% gain, and P-6, which had a 12.5% gain—in preparation for our experiments.

**Preparation of SR Multiple-Unit Tablets**

A 13 mm diameter die and round, flat-faced punches were used to create the PT-A, PT-B, and PT-C multiple-unit tablet formulations in an instrumented single punch tablet press. The Multiple-Unit tablet was made using a variety of cushioning agents, including dry powder, dry granules, and soft pellets. After passing through sieve No. 80, the following ingredients were carefully measured: talc, Aerosil, Cetirizine HCl, SSG, and SR pellets of

Pseudoephedrine. Each ingredient was then hand-bent with its corresponding cushioning agent and placed in a plastic bag. A consistent 40:60 ratio of medication pellets to cushioning ingredients was maintained in all tablet formulations.

**Drug content:**

Pulverized from 2 grams of pellets. The medication was completely dissolved after accurately weighing 120 mg of crushed Pseudoephedrine HCl, which was transferred to a 100 ml volumetric flask, diluted to 100 ml with pHl.2 buffer, and swirled magnetically for 1 hour. Whatmann filter paper 44 was used to filter the resulting solution. The drug concentration was estimated by taking one milliliter of the solution, diluting it with the required amount of buffer solution, and then measuring the absorbance at 223.5 nm using second order derivative spectra.

**Dissolution test:**

Using 900 cc of dissolution medium, the coated pellets were tested for their in vitro release profile using a type-II dissolution test device. The pH of the buffer was 1.2 for the first hour, and then 6.8 for the remainder of the experiment. One hundred revaluations per minute was the constant pedal pace. The dissolution investigation was carried out with the medium kept at 37+0.5 C. At the end of each hour, 5 ml portions were removed and replaced with new dissolving medium. The amount of drug present in the sample solution was determined using the following formula, which involved analyzing the filtrate at 223.5 nm using second order derivative spectra.

**Optimization of Pellets:**

We refined the pellet batches based on the strength required to minimize damage during tableting and the batch that provided the superior SR of medication. Following the aforementioned procedures, this refined formulation underwent additional surface characterisation and stability testing.

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

Using two wavelengths where one medication has no absorbance and the other has a positive substantial absorbance at the same wavelength (or vice versa for another drug), second-order derivative spectrophotometry allowed for the simultaneous estimate of two medicines. From the second derivative spectra, we can see that Pseudoephedrine HCl and Cetirizine HCl both have zero absorbance at 223.5 and 244 nm, respectively. Without any interference from the second drug in the

combined formulation, these two wavelengths were successfully used to undertake the esfimafion of Pseudoephedrine HCl and Cetirizine HCl. Using the calibration curve, we were able to determine the concentration of the medication in the sample solution.

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

A volumetric flask was used to fill it up to 100 ml with the 0.1 N HCl after 100 mg of pseudoephedrine HCl was added. The drug solution was further diluted with 0.1 N HCl to achieve dilutions ranging from 20 to 160 ng/ml. Using a solution blank, we measured the absorbance of each of these dilutions at 223.5 nm.

**Multiple-Unit Tablet Properties**

To reduce the amount of damage to the coated particles during compression, it is vital to add excipients with good compressibility to Multiple-Unit tablets. The present study found that a mixture of maltodextrin (MCC) and lactose (1.1) was a good choice for the Multiple-Unit tablet formulation's filler material due to its high dilution capacity, ability to form hard tablets that dissolve rapidly to release the intact pellets in dispersing media, and excellent compressibility. Thiree pill formulations were produced and tested to determine the effect of different sorts of cushioning agents. The medication pellet to cushioning agent ratio was maintained constant in all formulations at 40:60 to avoid any potential harm that could be caused by this ratio. Both the PT-A and PT-B tablet formulations meet all the necessary tablet characteristics; however, PT-B's friability was almost at the limit, possibly because the tableting ingredients were less bound. Although formulation PT-C passes both the disintegration test and the weight uniformity test, it takes longer than the others (79 seconds). The polymer coating on the pellets may have broken during tableting, releasing water-soluble polymer that swells to slow the tablet's disintegration time (DT). Strength and friability were severely lacking in the PT-C formulation. All of the tablet forms meet the requirements for Pseudoephedrine HCl and Cetirizine HCl content homogeneity.

**Effect of Powder as Cushioning Agent**

The medication release profile was found to be identical in both the PT-A formulation and the pellet formulation P-3, suggesting that the powdered cushioning ingredient was effective in both absorbing the pressure during compaction and producing tablets with the desired features. Pellets are stressed from multiple directions at once when held in a confined space, like a

powdered matrix, and compressed. This makes fracturing the pellets relatively difficult, and each pellet reacts to the force more by deforming than breaking apart. The coated pellets showed less deflection of release compared to uncompacted pellets, which means that they were not severely damaged during compression. This is a positive outcome of using MCC and lactose as a protective and spacer agent, as it keeps the coated pellets from touching each other. Their capacity to deform and fracture under compression force is due to the considerable stress relaxation of MCC and lactose, respectively. Because of this quality, the applied tension dissipates quickly, which in turn reduces damage to the tabletted pellets and yields the necessary tablet characteristics. Anticipated, the glidant properties of silicon dioxide (Aerosil) enhanced the compression process by facilitating better particle flow and package arrangement through less interparticulate friction and cohesion. The protective role of MCC and lactose was enhanced as the spherical Aerosil particles slipped over each other, further alleviating the applied stress on the compressed pellets. Interestingly, there was no segregation problem and the tablet's content consistency was likewise within the limit. Because of the size and density difference between the powdered cushioning agents and the coated pellets, segregation is a common problem when using tiny powders as cushioning agents with bigger particles, such as pellets.

**Effect of Granules as Cushioning Agent**

A wet granulation procedure was employed with MCC and lactose to ensure that the excipients and pellets had similar particle sizes. This process prevented segregation and produced more consistent content. The granules' poured and tapped densities were determined to be 0.40 and 0.49 g/ml, respectively. The compression of granules created tiny clumps, which likely led to more interaction between the excipients and created a setting where the pellets were less directly affected by the compression forces. Dissolution experiments revealed that granules, when used as a buffer, weren't entirely effective in protecting pellets from damage. Compression caused an increase in drug release from coated pellets in tablets compared to uncompressed pellets, which meant the coated pellets had lost some of their physical integrity and that most of the coated pellets in the tablet had been contaminated. The surrounding cushioning particles may not have been able to effectively transmit the compaction forces because the agent particles were too large.

**Effect of Soft-Pellets as Cushioning Agent**

One possible solution to the expected issues with mixing and separating drug containing pellets and excipients is to combine active and soft-pellets. The coated medication pellet had to be mechanically weaker than the soft pellets to keep it intact when compressed. The purposeful preparation of the soft-pellets was to make them weaker, with a strength of 1.7 kg. The preparation of the high porosity product also allowed the soft-pellets to display elastic deformation and brittle fragmentation instead of plastic deformation during compression. Pellets of greater size were more easily deformed and fragmented upon compression. A decrease in the number of force transmission points as pellet size increases and, consequently, an increase in contact force on each particle, leading to higher deformation, explains why larger pellets were more easily deformed. Therefore, larger, softer pellets were utilized as a cushioning material for drug-containing coated pellets in this research. Dissolution studies confirm that the coated pellets' ineffective cushioning was due to cracks in the coating and fragmentation of the pellets to some degree, which led to faster drug release from their compacts, and the results show that the cushioning particles were too large to adequately transmit compressive forces from the coated pellets. The tablet formulation PT-C had extremely low strength (hardness) and friability since there were fewer contact points caused by the largesized particles and the elastic deformation nature of the soft-pellets. Therefore, creating an effective SR Muhiple-Unit tablet by blending drug-containing pellets and softpellets was not a feasible concept.

**CONCLUSION**

The creation of multi-unit tablets that are specifically designed for use with certain medication combinations is the objective of this study, which aims to enhance the field of pharmaceutical science. When it comes to modern medicine, it is often necessary to administer many medications at the same time in order to successfully treat complicated health issues or to create synergistic therapeutic effects. Conventional dosage forms, on the other hand, may not be able to fully handle the obstacles that are associated with such combinations. These concerns include varying absorption rates, negative interactions between drugs, and problems with patient compliance. Therefore, the purpose of this study is to find a way to circumvent these limits by developing and perfecting multi-unit tablets that are

capable of accommodating many different pharmacological combinations inside a single dose form. By using cutting-edge formulation strategies and excipients, the objectives is to obtain precise control over the kinetics of drug release, increase bioavailability, reduce the risk of adverse interactions, and make the patient's experience more convenient. The purpose of this study is to show the effectiveness, safety, and therapeutic benefits of the multi-unit tablets that have been produced via the use of detailed characterisation studies and pharmacokinetic assessments. Ultimately, the outputs of this research effort have the potential to considerably increase the efficiency and effectiveness of drug delivery systems, ultimately contributing to developments in pharmaceutical research and enhancing patient outcomes in clinical practice.

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