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Formulation and Evaluation of Matrix Tablet of Cefpodoxime proxetil by Sintering Technique

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ABSTRACT

The idea of formulation of controlled release drug delivery has become beneficial in the treatment of diseases. At this time, the increased understanding in the community and the significance of safe use of drugs encouraged to develop novel drug delivery system. In the present study, an attempt was made to expand the release of Cefpodoxime proxetil from matrix tablets by sintering technique. This has been an evolving one in the study of effect of heating on mechanical properties of pharmaceutical powders that is used in the formulation of sustained release matrix tablet. The tablets were formulated by direct compression method. The punched tablets were subjected to sintering process and exposed to three different durations of sintering (1.5, 3.0 and 4.5 hours). This type of system provides a important and suitable method for achieving controlled release in oral dosage forms. The release of the drug form un-sintered matrix tablets containing 100 mg polymer was 100% within 90 minutes. For a particular sintering time, the release rate decreased with increasing polymer concentration. For 1.5, 3.0, and 4.5 hours sintering durations the least retardation is offered by least polymer concentration. The highest retardation was offered by matrices with highest polymer concentration.

Keywords: Cefpodoxime proxetil, Sintering technique, Matrix tablets, Direct compression

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INTRODUCTION

Matrix tablets reduce the frequency of dose administration, and are found to have increased patient compliance. A relatively recent technique called sintering technique is involved in the formulation which aims to extend the release of Cefpodoxime proxetil from the matrix tablets. After formulation the tablets where subjected to preformulation studies, micromeritics studies, stability studies and other tablet evaluation methods. Matrix tablets are considered the commercially feasible sustained action dosage forms that involve the least processing variables, utilize the conventional facilities and accommodate large doses of drug.

Cefpodoxime proxetil is third generation cephalosporin antibiotic, it is a prodrug. It is active against most Gram positive and Gram negative organisms. It is commonly used to treat acute otitis media, pharyngitis, and sinusitis. It also finds use as oral continuation therapy when intravenous Cephalosporins (such as ceftriaxone) are no longer necessary for continued treatment. It is incompletely absorbed from the gastrointestinal tract and has an oral bioavailability of only 50% and biological half life 2 hours.Matrix tablet is able to prolong the release of drug and thereby possibly improve oral bioavailability of cefpodoxime proxetil. The half life of cefpodoxime proxetil is 2.2 hours. Cefpodoxime proxetil is a β lactum antibiotic. Its mechanism of action is by binding to specific penicillin binding proteins (PBPs) located inside the bacterial cell wall; it inhibits the bacterial cell wall synthesis. It is highly stable in the presence of beta- lactamase enzymes

Sintering:

Sintering is defined as the bonding of adjacent particle surfaces in a mass of powder, or in a compact, by the application of heat. Conventional sintering involves the heating of a compact at a temperature below the melting point of the solid constituents in a controlled environment under atmospheric pressure. The changes in the hardness and disintegration time of tablets stored at elevated temperatures were described as a result of sintering. The sintering process has been used for the fabrication of sustained release matrix tablets for the stabilization and retardation of the drug release.

MATERIALS AND METHODS:

Cefpodoxime proxetil is the drug used, Eudragit RS 100 is the polymer used. Sodium starch glycolate and aerosols were the other excipients used in its formulation. Fused Calcium Chloride, acetone, Potassium dihydrogen o-phosphate and Sodium hydroxide were the reagents used. Instruments like Hardness tester, Friabilator, Single punch tablet compression machine,

Dissolution apparatus, UV Visible spectrophotometer, FTIR and Vacuum desiccators were used.

Formulation of tablets:

To study the influence of different polymers, polymer concentrations and time period of sintering on the physicochemical and *in-vitro* release behaviour of matrix tablets the following steps were conducted.

- Formulation of drug polymer mixture for direct compression.
- Compression of formulated powder mixture into tablets
- Sintering of compressed tablets
- Comparison of formulated Eudragit matrix tablets with marketed sustained release tablet
- Ageing studies

Table 1: Composition of Cefpodoxime Proxetil - Eudragit RS100 matrix tablets

Ingredients	D-RS 1 (mg)	D-RS 2 (mg)	D-RS 3 (mg)	D-RS 4 (mg)
Cefpodoxime Proxetil	250	250	250	250
Eudragit RS100	50	75	100	125
Sodium Starch Glycolate	12.5	12.5	12.5	12.5
Aerosil	0.75	0.75	0.75	0.75

Procedure:

The punched tablets were subjected to sintering process. The lower chamber of the dessicator was filled with acetone, closed and kept aside for saturation. After saturation the compressed tablets were taken in Petri dishes and placed over a wire-mesh which is kept above the lower chamber of the dessicator containing acetone. The dessicator is made airtight by closing the lid with the help of wax.

The acetone vapors in the saturated dessicator enter the pores of tablets, solubilize the surface of the polymer particles which results in the fusion of particles, thus bringing about sintering. 90 tablets of each formulation were divided into three batches and exposed to three different durations of sintering (1.5, 3.0 and 4.5 hours).

Table. 2: Cefpodoxime proxetil -Eudragit RS100 matrix tablets sintered for different durations of time

Formulation	1.5 hour	3.0 hour	4.5 hour
D-RS 1	D-RS 1 (1.5)	D-RS 1 (3.0)	D-RS 1 (4.5)
D-RS 2	D-RS 2 (1.5)	D-RS 2 (3.0)	D-RS 2 (4.5)
D-RS 3	D-RS 3 (1.5)	D-RS 3 (3.0)	D-RS 3 (4.5)
D-RS 4	D-RS 4 (1.5)	D-RS 4 (3.0)	D-RS 4 (4.5)

EXPERIMENTAL METHODS:

Preformulation study [13, 14, 15, 16]:

Preformulation study is performed to choose the correct form of the drug substance, evaluate its

physical properties and generate a thorough understanding of the material's stability under the conditions that will lead to development of an optimal drug delivery system. It is the investigation of physical and chemical properties of a drug substance and excipients. The physical and chemical properties help in planning for the correct formulation development strategy and process. The overall objective of preformulation testing is to generate information useful to the formulator in developing stable dosage forms or drug delivery system that can be mass-produced. The classical preformulation studies include the physicochemical characterization of the solid and solution properties of compounds that would be useful in formulating the drug into a suitable delivery system. The drug sample was subjected to preformulation studies such as appearance, micromeritics and drug-excipient compatibility.

Standardization of Cefpodoxime Proxetil:

i. Organoleptic properties: This includes recording of colour, odour and taste of the drug using descriptive terminology. Recording of colour for initial batches is very useful in establishing appropriate specifications which would be useful later on for production batches. Most of the drugs generally have a characteristic odour and taste.

ii. Density: Density is the ratio of the mass of an object to its volume and for solids this term describes the arrangement of molecules. Density may influence compressibility, tablet porosity, dissolution and other properties.

A) Bulk density (ρ_b):

It is a measure used to describe packing of particles or granules. The equation for determining bulk density is

$$\rho_b = m/ vb$$

Where, m= Weight of sample taken, vb= Bulk volume

B) Tapped density (ρ_t):

It is the maximum packing density of a powder (or blend of powders) achieved under the influence of well defined, externally applied forces. The tapped density is a limiting density attained after "tapping down," usually in a device that lifts and drops a volumetric measuring cylinder containing the powder at a fixed distance. It can be used to predict its flow properties. It is carried out by the method in which powder is filled in measuring cylinder. After that, it is mechanically tapped on device. After 50 taps the volume is measured and again tapped for further 50 taps or till constant volume is attained or till the difference between succeeding measurements is less than 2 %. The tapped density is calculated by using the equation

$$\rho_t = m/ vt$$

Where, m = Weight of sample taken, vt = Tapped volume

C) Compressibility Index (CI):

Compressibility is indirectly related to the relative flow rate, cohesiveness and particle size distribution of the powder. Powders with compressibility values less than about 20 % have been found to exhibit good flow properties. Tapped (ρt) and apparent bulk density (ρb) measurements can be used to estimate the compressibility of a material. It is often referred to as Carr's Index.

$$\text{Compressibility index (\%) (Carr's index)} = [(\rho t - \rho b) / \rho t] \times 100$$

Table 3: Scale of Flowability according to Compressibility index (USP chapter <1174>)

Compressibility Index (%)	Flow Character
≤10	Excellent
11–15	Good
16–20	Fair
21–25	Passable
26–31	Poor
32–37	Very poor
>38	Very, very poor

D) Hausner's Ratio:

Hausner's ratio is an indication of the flowability of a powder. It measures the friction condition in a moving powder mass. It is the ratio of bulk volume to tapped volume or tapped density to bulk density. Hausner's ratio less than 1.5 indicates good flowability.

$$\text{Hausner's Ratio} = vb / vt \quad \text{or } \rho t / \rho b$$

Table 4: Scale of Flowability according to Hausner's Ratio (USP chapter<1174>)

Hausner's Ratio	Flow Character
1.00–1.11	Excellent
1.12–1.18	Good
1.19–1.25	Fair
1.26–1.34	Passable
1.35–1.45	Poor
1.46–1.59	Very poor
>1.60	Very, very poor

iii.Flow properties:

The flow properties of powder are critical for an efficient tableting operation. The flow properties from a material result from many forces that can act between solid particles like frictional forces, surface tension forces, mechanical forces caused by interlocking of particles of irregular shapes, electrostatic forces and cohesive or Van der Waal's forces etc. These forces can affect granule properties such as particle size, particle size distribution, particle shape, surface texture or roughness, residual surface energy and surface area. The two methods for determining

the flow properties are angle of repose and hopper flow rate measurements.

Angle of repose (θ):

It is the very simple and most commonly used method for the determination of flowability. The typical method is to pour the powder in a conical heap on a level, flat surface and measure the included angle with the horizontal. Angle of repose is the tan inverse of angle between height (h) of pile of powder and the radius (r) of the base of conical pile. The angle of repose values range from 25 to 50 degree, with lower values indicating better flow characteristics.

$$\theta = \tan^{-1}(h/r)$$

Values for angle of repose less than or equal to 30 degrees suggest a free flowing material and angles greater than or equal to 40 degrees suggest a poorly flowing material.

Table 5: Category for Angle of Repose (USP chapter <1174>)

Angle of repose (degrees)	Flow property
25-30	Excellent
31-35	Good
36-40	Fair—aid not needed
41-45	Passable—may hang up
46-55	Poor—must agitate, vibrate
56-65	Very poor
>66	Very, very poor

iv. Loss on Drying (LOD):

LOD of compound measures % content of water present in the compound. This was performed by using Mettler Toledo halogen moisture analyzer at 105 °C.

v. Particle morphology:

Various physicochemical properties of drug substances are affected by their particle size distribution and shapes which may affect their biopharmaceutical behaviour. Particle size plays an important role in dissolution of poorly water soluble drugs. Particle size distribution of narrow range and shape affects flow rate and homogeneous mixing of drug with other excipients affecting homogeneity of final product. Various techniques suitable for specific size ranges are summarized in the table. 6.

Table 6: Techniques for Particle Size Determination

Analysis Method	Size Range (in µm)
Microscopy	1-100
Sieving	>50
Sedimentation	>1
Elutriation	1-50
Centrifugation	<50
Permeability	>1
Light Scattering	0.5-50

Particle size determination of Cefpodoxime proxetil was carried out by using sieve analysis and microscopic technique.

a) Particle size analysis by Sieving:

Sieving is one of the simplest and most commonly used methods for determination of particle size distribution. The technique basically involves retention of particles based on their sizes on different sieves. It is to be carried out by using Electro lab sieve shaker.

In this technique, particles of a powder mass are placed on a nest of sieves made up of uniform aperture arranged in descending order of their mesh number. By the application of motion to the nest of sieves, the particles larger than the apertures of the appropriate sieve are retained, which are then determined for percentage retained on each sieve.

Procedure: 20 grams of API sample was placed in the top of the nest of standard sieves arranged in the descending order (Sieves from mesh no. # 20 to # 100). Set of sieves was placed on sieve shaker and fitted it properly with the help of screws. Switched on the apparatus and run it for 10 minutes at 15 % amplitude level. After completion of 10 minutes the weight of each fraction retained was determined and the percentage retained and cumulative percentage retained on each sieve was calculated.

b) Particle size analysis by microscopic technique:

Procedure: A small quantity of sample to be analyzed was mixed with 1-2 drop of liquid paraffin and dispersed uniformly. A drop of this was taken on glass slide and was observed by "LABOVISION Binocular Microscope with Digital Camera and Image Analyzer" at magnification of 10X. About 100 particles in five different fields were counted and their shape and size was noted.

***In-vitro* Dissolution Studies [6]:**

The *in-vitro* dissolution studies of the tablets were carried out by using USP-dissolution apparatus type-II, using 900 ml of phosphate buffer pH 6.8 as medium maintained at 37 ± 1° C at 100 rpm for 8 hour. Samples of 5 ml volume were withdrawn at predetermined time intervals, which were later filtered diluted and assayed spectrophotometrically at 233 nm. An equal volume of fresh medium was immediately replaced to maintain the dissolution volume constant. The amount of cefpodoxime proxetil release at each time interval was calculated from the absorbance of the samples. Dissolution studies were performed in three-sets and mean values were reported. The percentage drug release was then graphed against time and the release profiles were studied.

RESULTS AND DISCUSSION:

Preformulation studies:

Standardization of Cefpodoxime Proxetil:

i. Physical properties of drug:

Cefpodoxime Proxetil was evaluated for physical properties. Results are shown in table 7

Table 7: Standardization of Cefpodoxime Proxetil

Tests	Results of Analysis	Inference
Description	White powder.	Complies
Taste	Extremely Bitter	-
Odour	Characteristic odour	-
Bulk density	0.59 g/mL	-
Tapped density	0.75 g/mL	-
Compressibility index	21.33 %	Passable flow
Hausner's ratio	1.27	Passable flow ability
Angle of repose (°)	27.02°	Excellent flow
LOD at 105°C for 5 minutes (%)	3.86 %	Complies

The Cefpodoxime Proxetil has excellent flow property and passable flow ability with compressibility index and hausner's ratio.

i. Particle Size Determination:

For the given formulation, particle size determination of Cefpodoxime Proxetil was carried out by using sieve analysis and microscopic technique.

a) Particle size analysis by sieving:

Particle size distribution was carried out by sieve analysis using sieve shaker and the data obtained was summarized in the table. 8

Table 8: PSD by sieve analysis

Mesh (microns)		% Retained	% Cumulative Retained
On 20 #	(> 850 µ)	0.00	0.00
On 40 #	(> 425 µ)	0.00	0.00
On 60 #	(> 250 µ)	0.50	0.50
On 80 #	(> 180 µ)	0.36	0.86
On 100 #	(> 150 µ)	0.06	0.92
On 200 #	(< 75 µ)	92.88	93.81
Below 200# sieve (<75 µ)		6.20	100
Total		100	-

Cefpodoxime Proxetil is very fine and more than 99 % of the particles were below sieve # 100 and almost 93% particles were retained on sieve # 200.

b) Particle size analysis by microscopic technique:

Microscopic images of Cefpodoxime Proxetil are shown in figure 1 whereas PSD results are summarized in table 9 (Magnification: 10X, Number of particles counted: 100)

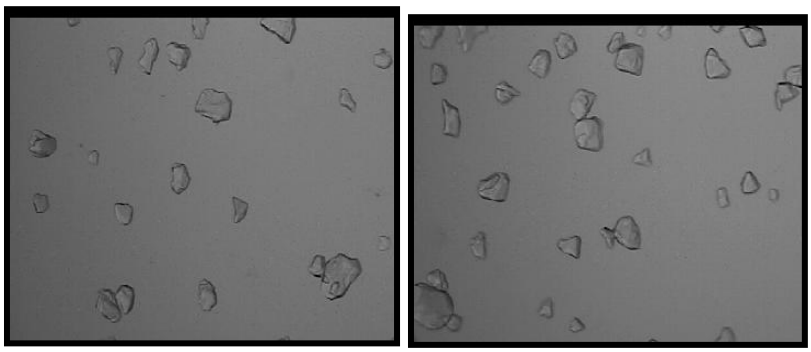

Figure 1: Microscopic images of Cefpodoxime Proxetil

Table 9: PSD by Optical microscopy

Particle size range (microns)	% of Particle size distribution
0-20	5.34
21-40	48.86
41-60	35.88
61-80	8.40
81-100	0.76
101-120	0.76

About 80 % particles were in the range of 21-60 microns. Drug particles are having very fine particle size which would help in faster dissolution and in turn faster absorption.

Tablet Evaluation Parameters:

Table 10: Physical parameters of tablets

Parameters	Batch no.			
	D-RS 1	D-RS 2	D-RS 3	D- RS 4
Appearance	White colored round shaped			
Thickness (mm)	3.37-3.41	3.26-3.29	3.32-3.39	3.21-3.27
Hardness (N)	75-80	73-78	66-72	80-86
Weight Variation (mg)	313-316	335-339	361-364	387-390

Hardness [6]

The hardness of the tablets was determined by Monsanto hardness tester. There is a significant difference between the hardness of the un-sintered and sintered matrix tablets which may be attributed to the bridge formation between the polymer particles during sintering which strengthens the tablet. The hardness of the tablets was found to increase with an increase in both the polymer concentration and sintering time. This may be due to more number of bridges and formation of thicker bridges respectively. The formulation D-RS 4 was found to have maximum hardness (8.5) at 4.5hrs

Weight variation [6]:

The weight variation of the tablets was determined and reported. The individual weight variation of twenty tablets was calculated. All the batches of tablets complied with the weight variation

limits as per Indian Pharmacopoeia i.e., The percentage weight variation of the individual tablets remained within 5% and not more than 2 tablets in a batch of 20 deviated from ±5% weight variation. All the formulations passed the test for weight variation.

Friability [6]:

The friability test of all batches of tablets was done. The exceptionally low friability of the matrix tablets may be attributed to inter-particulate bridges formed during sintering which holds the drug and excipients particles between them very strongly. Some batches that are having higher polymer concentration and subject to longer sintering duration showed no friability which may be because of thicker bridges formed during sintering time as the depth to which the polymer particle is solubilized is more, and more such bridges formed due to higher polymer proportion in the matrix.

***In-vitro* dissolution studies [6]:**

Dissolution test was performed on three tablets from each formulation. The cumulative drug release of all the formulations at the end of 12 hours was calculated. In case of Eudragit RS 100 matrices, the least retardation was achieved by D-RS20% 1.5 with 92.62 % in 8 hours, while the highest retardation was achieved by D-RS50% 4.5 with only 52.63 % drug release in 8 hours for a particular sintering time, the release rate decreased with increasing polymer concentration. For 1.5, 3.0, and 4.5 hours sintering durations the least retardation is offered by least polymer concentration of 100 mg for Eudragit RS 100 matrices. The highest retardation was offered by matrices with highest polymer concentration. The cumulative drug release of all formulations at the end of 12 hours is given in the following table. The samples were compared with that of the marketed product Oxipod (200 mg)

Table 11: *In-vitro* dissolution data

Formulation	% drug release
D- POLYMER 20 % 1.5 hr	92.62 ± 0.89
D- POLYMER 20 % 3 hr	79.23 ± 0.52
D-POLYMER 20 % 4.5 hr	73.63 ± 0.68
D- POLYMER 30 % 1.5 hr	82.62 ± 1.47
D- POLYMER 30 % 3 hr	75.43 ± 1.89
D- POLYMER 30 % 4.5 hr	63.24 ± 0.97
D- POLYMER 40 % 1.5 hr	83.01 ± 1.89
D- POLYMER 40 % 3 hr	62.03 ± 1.45
D- POLYMER 40 % 4.5 hr	57.61 ± 0.62
D- POLYMER 50 % 1.5 hr	80.01 ± 0.38
D- POLYMER 50 % 3 hr	62.63 ± 0.79
D- POLYMER 50 % 4.5 hr	52.63 ± 1.89
Marketed sample (Oxipod 200)	**66.57 ± 8.57**

CONCLUSION

This work deals with the objective of developing oral controlled release formulations through matrix tablets of cefpodoxime proxetil using plastic polymers such as EudragitRS100 by sintering technique in varying concentration and sintering time and comparative evaluation of their controlled release potential were also investigated. In conclusion, among the different strategies employed for the design of a controlled release dosage forms, sintering technique for the preparation of polymer matrices for controlled release of cefpodoxime proxetil appears to be an alternative technique. This new method for controlling the release rate of cefpodoxime proxetil has been developed using Eudragit and was tested. At room temperature when exposed to acetone vapours, Eudragit RS 100 powder particles fused or welded to each other due to coming in contact with other particles were the particles get contacted. The extend of fusion was depends on concentration of polymer and sintering time. This type of system provides a significant and convenient method for achieving controlled release in oral dosage forms. The release of the drug form un-sintered matrix tablets containing 100mg polymer was 100% within 90minutes. This clearly shows that Eudragit RS100 polymer does not have drug release retardant properties when employed as matrix materials by direct compression.

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