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Formulation And Evaluation Of Polymers-Coated Spherules From Granules

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Abstract:

This study investigates the impact of polymer coatings on the formulation and stability of aspirin spherules using a novel method termed Bed Coating during Spheronization (BCDS). The method was used to produce uniformly sized spherules which were then coated with Methyl cellulose (MC) and hydroxypropyl methylcellulose (HPMC K15) to evaluate their effects on drug release kinetics and flow properties. The spherules were analyzed for their angle of repose, bulk and tapped densities, Carr's index, and Hausner's ratio, indicating excellent flow properties with both polymer coatings. Drug content analysis revealed significant drug loss during the granulation and coating process, with the highest drug content retained in MC-coated spherules. The drug release profile followed a first-order kinetics model with a maximum release of 99% within 10 hours. This study demonstrates that BCDS can effectively produce spherules with improved flow properties and controlled drug release, though further optimization is needed to reduce drug loss during processing.

Keywords: Aspirin spherules, Bed Coating during Spheronization (BCDS), Methyl cellulose, Hydroxypropyl methylcellulose, Drug release kinetics, Flow properties, MC-coated, Polymer coating.

INTRODUCTION

Spheronization is a widely used method for creating spherules, or particles with a spherical form.[1] Spherules offer greater flow properties than pellets, which enhances their overall loading characteristics and loading capacity.[2] Granules and pellets have a spherical form, albeit their nature doesn't always dictate this.[3] Spherule's surface properties can be altered and enhanced by covering them with a polymer layer.[4] During the processing phase, spherules are coated on the outside to enhance the look, integrity, and drug release of

the particles. Spherules require less coating solution than granules because of their smaller surface area to volume ratio.[5] Fluidized bed drying is the most widely used technique for spheronization in the bed (FBD).[6] The fast drying process produces unevenly shaped spherules in both large and small operations, necessitating the deployment of alternative technologies for consistent spherule manufacture.[5] Sieving and scaling can be used to achieve granulation.[7]

The BCDS spheronization method turns granules into spherules by producing evenly sized particles from coated starch particles. The surfaces of spherules can be altered by covering them with polymer films.[8] Methyl cellulose (MC), a polymer derived from cellulose, is commonly utilized in formulations for prolonged release due to its unique physical properties.[9] Hydration causes HPMC K15 to erode, which allows the drug to be released into the environment as it gels and absorbs stomach acid. HPMC K15 is utilized to enhance the drug release properties from particles.[10] By applying a wet coating with the appropriate colors and excipients, spheres can have their stability and appearance altered. This process is accessible for both small- and large-scale manufacturing, and it may affect the stability of therapeutic compounds. Granules, spherules, and coated spherules are effectively prepared in this study by examining the effects of polymer coating, BCDS, and wet granulation on aspirin stability.

MATERIALS AND METHODS

Materials

The following materials were acquired from Sudarshan Scientific Laboratories in Nandgaon, Maharashtra: aspirin, lactose, acetone, starch, ethanol, Methyl cellulose (MC), and hydroxy propyl mMethyl cellulose (HPMC) K15. Every chemical and reagent that was utilized was of laboratory quality. Every reagent and buffer was made in accordance with normal procedure. UV/Visible spectrum analysis (SHIMADZU V-730 UV Visible spectrophotometer) and drug release experiments were conducted using this equipment.

Methodology

When aspirin granules are wet granulated, this is a crucial stage in the aspirin manufacturing process. Aspirin (14 grams), lactose (8 milligrams), and starch powder (76 milligrams) were combined and ground into a fine powder in a mortar and pestle. Then, starch paste (5% w/v) was added and well mixed to form a cohesive mass. The cohesive mass was run through a series of sieves to get wet granules.[12,11]

Preparation of Polymer Coated Spherules

A 250 ml beaker was filled with 10 grams of wet granules, which were carefully weighed. The beaker was then rotated 45 degrees in a clockwise direction. A 50:50 v/v ethanol and water mixture was sprayed over the granule bed while it was rotating to keep it wet. A tiny amount of starch powder was added while the granule bed was rotating in order to improve the flow characteristics. To further enhance the binding of the tiny starch powder particles to produce spherules, 7-8 drops of starch solution which was prepared by combining 4 drops

of 5% starch paste with 7 milliliters of distilled water were sprayed or applied to the granule bed. The produced spherules were sieved using sieve numbers 25 and 45 to produce spherules of a uniform size. 500 mg of polymer, 100 mg of dye, and 400 mg of talc were dissolved in 25 milliliters of acetone to make a coating solution. The coating solution was sprayed over the spherule bed while it was rotating continuously. The coated spherules were spread out on a petri dish and baked to 60°C in a hot air oven for 20 minutes to create dried polymer-coated spherules.

Flow property determination

Features such as Hausner's ratio of spherules (retained in sieve numbers 25 and 45), Carr's index, and the angle of repose were measured.[1]

Microscopical evaluation of spherules and granules

The morphology and surface properties of granules and spherules were examined using a projection microscope. The produced granules and spherules were each placed separately on a glass slide and examined using a projection microscope (10x) to look at their edges and shape. The shape of fifteen randomly selected particles was investigated. A projection microscope was used to collect and analyze the particles. During analysis, the number of edges in each of the three particles 450, 900, and 1200 was tallied.

Angle of Repose

The angle of repose is the largest angle that forms between the cone of the solid material pile and the horizontal plane, representing the free flow of materials. Spherules were allowed to freely flow down a funnel and onto graph paper in order to form a pile. The angle of repose may be calculated using the formula below.[13]

$$\text{Angle of Repose } (\tan \theta) = h/r$$

where "r" is the pile's radius and "h" is its height.

Particle packing parameters

Determining spherule homogeneity is the main use of bulk density. This helps ensure uniformity in the selection of production tools and equipment, as well as in the size, closures, and capsules of the containers. Twenty grams of spherules were put in a ten milliliter measuring cylinder in order to calculate the bulk density and tapped density. The volume filled by the spherules was measured after two manual taps on the flat surface in order to determine the bulk density. The measuring cylinder holding spherules was connected to a tapped density device, and the volume occupied by spherules on a level table top after 100 tappings was recorded to determine the tapped volume. Bulk and tapped density were obtained from bulk and tapped volume using the following formula.

Bulk density = Spherule weight/ Bulk volume

Tapped density = Spherule weight/ tapped volume

Carr's Index

The Compressibility Index, or Carr's Index, measures the tendency of spherules to clump together by accounting for interparticulate interactions. The following formula is used to compute it.[13,14,15]

Carr′s index = [Tapped density - Bulk density/Tapped density] 100

Drug content evaluation

50 milligrams of aspirin spherules were precisely weighed, dissolved in 50 millilitres of appropriate phosphate buffer (6.4 or 7.4), selected based on the polymer used for coating, swirled for half an hour, and then filtered. Phosphate buffer was used as a blank in the UV spectrophotometer used to measure absorbance at 265 nm.[15]

In vitro dissolution study

The USP type 2 basket device was used to measure the amount of medication released from spherules in relation to time. A suitable pH 6.8 or 7.4 phosphate buffer was introduced to a dissolving basket containing 1500 mg of spherules. To maintain sink conditions, the apparatus was kept at 37 ± 0.5°C with the basket rotating at 75 revolutions per minute. Five millilitre samples were taken out at different intervals (1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 hours), and each interval was followed by a replacement of the same volume of buffer. Absorbance using a UV spectrophotometer measured at 265 nm.[15]

Kinetic Modelling

By fitting the in vitro drug release data into the Zero order, First order, Higuchi and Korsmeyer - Peppas model, the kinetics and mechanism of drug release from spherules were ascertained. Using R^2 and n value, the best-fitted model conformed.[16]

Zero order release:

The medicine is released in zero order at a steady pace. The data on drug release acquired is shown as the cumulative proportion of drugs released over a certain period of time.[16,17]

$$Qt = Q_0 + K_0t$$

Where,

Qt = Drug released in time ‘t’

Q_0 = Initial drug content

K_0 = Rate constant of zero order release

First order release:

According to first order release, the release depends upon the concentration. The release data plotted as log cumulative percentage drug remaining against time.[16,17]

$$\textbf{Log } Q_t = \log Q_0 - K_1 t / 2.303$$

Where,

Q_t = Drug release at time 't'

Q_0 = Initial drug content

K_1 = Rate constant of first order release

Higuchi model:

The cumulative proportion of drug release versus the square root of time is how the drug release data is displayed. 16, 17

$$Qt = KH\ t^{½}$$

Where,

Q_t = amount of drug release at time 't'

K_H = Higuchi release rate constant

Korsmeyer-Peppas model:

Plotting drug release data as a log cumulative percentage vs time.[18]

$$Qt/ Q_0 = K_k p\ t^n$$

Where,

Qt/Q_0 = fraction of drug release at time 't'

K_K p = Korsmeyer- Peppas release rate constant

Based on the release exponent (diffusion constant "n") from the Korsmeyer-Peppas model, the release mechanism was identified.

Table no. 1 Angle of repose, Bulk density, Tapped density, Carr's Index and Hausner's Ratio of Spherules

Spherules	Spherules reatained in sieve No.	Angle of Repose (^{0})	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's Index (%)	Hausner's Ratio
Methyl cellulose	25	22.67	0.475	0.509	6.6797	1.07
Methyl cellulose	45	21.84	0.608	0.615	1.1382	1.01
HPMC K15	25	25.91	0.495	0.528	6.25	1.06
HPMC K15	45	26.57	0.547	0.579	5.52	1.05

Table no. 2 Drug content evaluation of Spherules

Spherules	Percentage Drug content (%)
Methyl cellulose	44.15
Methyl cellulose	45.35
HPMC K15	41.95
HPMC K15	39.94

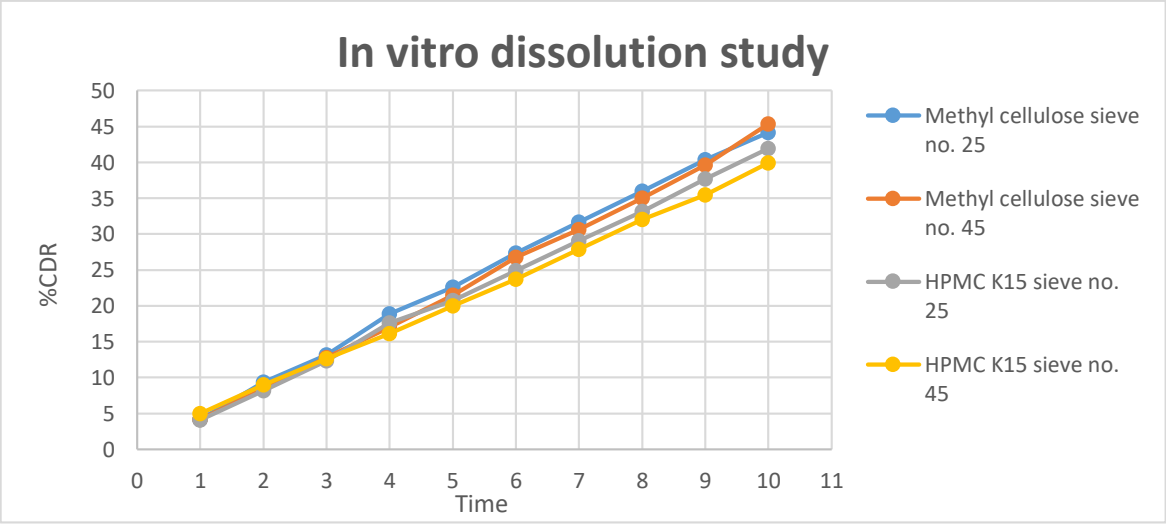

Figure no. 1 Different polymer coated Spherules and its Drug release profile.

Table no. 3 R^2 and n values based on Drug release profile

Kinetic Models	MC Coated Spherules retained in Sieve No. 25		MC Coated Spherules retained in Sieve No. 45		HPMC K15 Coated Spherules retained in Sieve No. 25		HPMC K15 Coated Spherules retained in Sieve No. 45	
	R^2	n	R^2	n	R^2	n	R^2	n
Zero Order	0.998	0.9989	0.999	4.5234	0.9993	4.1801	0.9994	3.8565
First Order	0.997	-0.026	0.989	-0.0265	0.9941	-0.0239	0.9931	-0.0218
Higuchi Model	0.9842	18.868	0.972	19.068	0.9787	17.678	0.9738	16.267
Korsmeyer-Peppas Model	0.998	1.0172	0.9997	0.9681	0.999	1.0108	0.9984	0.9074
Hixon-Crowell model	0.9989	-0.0838	0.9938	-0.0852	0.997	-0.0776	0.9961	-0.0711

RESULT AND DISCUSSION

The granulation followed by bed coating during sliding (BCDS) with starch leads to the formulation of spherules which is further coated with functional polymers. The spherules are then sieved to obtain 2 different population of uniformly sized spherules (sieve no 25 and 45). In this study the effect of spherionization on flow properties, net aspirin content and kinetics of drug release from the spherules (sieve no 25 and 45) are analysed.

The spherical shape of the granules, spherules and coated spherules retained in sieve no 25 and 45 are compared based on the number of sharp edges present. For this, the surface angle at the corner or edge regions of randomly selected particles are observed under a projection microscope. An acute (45°) or right angle (90°) is regarded as indicator of sharp edges while obtuse angle (120°) as indicator of smooth spherical shape. The percentage number of edges making an acute or right angle is highest in granules (>85%) and decrease in case of spherules (<15%) and polymer coated spherules (<30%) while the percentage number of edges making an obtuse angle is highest in spherules (appr. 85%). This indicates BCDS process reduce the sharp edges of the granules and bring a smooth spherical morphology in spherules.

The flow properties in terms of angle of repose and packing parameters in terms of bulk and tapped density, Carr s index as well as Hausner's ratio of 2 differently sized spherules (sieve no 25 and 45) prepared by coating with different polymers (MC, HPMC K15) are given in Table no: 1. The different sized spherules coated with all the 2 polymers exhibited angle of repose (22.67-26.57), Carr's index (1.1-6.6), Hausner's ratio (1.01-1.07) indicating excellent flow properties.

Figure 1 shows cumulative percentage drug release from different polymer coated spherules during dissolution in phosphate buffer and the release kinetics as in table 3. The drug release profile of all the 2

polymer coated spherules found to follow a 1" order release kinetics with maximum release of 99% within 6 hour duration.

The table 2 shows the drug content comparison between different spherules retained in sieve no 25 and 45. In all the spherules, the drug content has significantly reduced to less than 24% showing more than 66% of the drug is lost during the granulation to coating process. Among this the percentage drug content is least with MC coated smaller sized spherules (sieve no 45) while maximum drug content of spherules.

CONCLUSION

The research highlights the effectiveness of the BCDS method in producing spherules with improved flow properties and controlled drug release. However, the significant drug loss observed during processing indicates a need for further optimization. The study's findings suggest that MC-coated spherules exhibit superior stability and drug release properties, making them suitable for sustained-release formulations. Future research should focus on enhancing the drug retention rate during the spheronization and coating processes.

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