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ORIGINAL ARTICLE

Formulation and *In vitro* Evaluation of Polymers-Coated Spherules of Aspirin for Sustained Drug Delivery

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ABSTRACT
Maintaining poorly water-soluble and moisture-sensitive drugs, such as aspirin, in their solid form on an appropriate carrier matrix contributes significantly to enhancing their chemical stability. In this approach, the drug is mixed with suitable excipients and rapidly converted into a solid form using only a limited quantity of water necessary for granulation. The resulting granules are subsequently layered with diluents such as lactose and starch to produce spherules. This modified processing method minimizes water exposure during the entire formulation procedure, from granule preparation to the formation of coated spherules, thereby improving overall stability. Wet granulation method has been used for granulation followed by layering with lactose and starch as diluents to get spherules. The spherules, thus prepared, were coated woth rate controlling polymers to get coated spherules. The formulations were then evaluated for pre-coating and post-coating parameters. Spherules also ensure far better flow properties when compared with granules. This can be confirmed by angle of repose 36.86°-46.52° and 25.54°-32.24°, Carr's Index 6.94%-9.46% and 5.80%-10.00% and Hausner's Ratio 1.07-1.10 and 1.06-1.11 for granules and spherules respectively. In vitro drug release studies indicate that the release rate has been controlled by coating the spherules with the rate-controlling polymers. Drug release kinetics studies indicate that spherules coated with single coat of either of rate controlling polymer follow first order drug release kinetics like that of uncoated spherules whereas spherules coated with double coat of same polymers follow Higuchi's model of drug release kinetics.
Keywords: *Aspirin, Spherules, Granulation, Spheronization, Methyl cellulose, Hydroxypropyl methyl cellulose*

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INTRODUCTION

Cellulose derivatives like ethyl cellulose (EC) [1], hydroxyl propyl methyl cellulose (HPMC) [2], and carboxy methyl cellulose (CMC) [3] are widely explored for drug delivery applications alone or in combination [1-5]. It is desirable to assess and analyze the role of these macromolecules in the design of the drug reservoir and rate-controlling membrane for producing the required delivery profile of the drug [6]. Ethyl cellulose is a semi synthetic hydrophobic polymer [7] that is now being used as a sustained-release (SR) coating in various SR [8] and controlled release (CR) [9] formulations. Various EC-based value-added products are currently being developed [10-12]. The EC, a hydrophobic polymer, coating on solid dosage forms produces SR that helps in drug delivery for a long duration during the stay in the GIT [13]. EC coatings have better stability during storage, inertness, and good compressibility. On the other hand, the HPMC K4M is a hydrophilic polymer and has been used for controlled release and solubility improvement [14].

Aspirin is used in cardiovascular disorders for its inhibition of platelet activation and aggregation by irreversible inhibition of the platelet-dependent enzyme cyclooxygenase (COX), thereby preventing the synthesis of prostaglandins [15]. Two COX isoenzymes were identified by the subsequent researchers i.e. COX 1 and COX 2 [16, 17]. In platelets, the COX-1 enzyme produces thromboxane A2, a powerful promoter of platelet aggregation. Thus, aspirin, by irreversibly inactivating COX-1, thereby blocking the generation of thromboxane A2, derives a potential antiplatelet effect [18].

When aspirin (ASP) is administered in a sustained-release form over a larger surface area through particulate delivery systems such as spherules, the localized concentration of the drug can be significantly minimized. This approach enables the drug release to begin in the stomach and continue gradually throughout the entire gastrointestinal transit, thereby providing prolonged therapeutic action. Further, distributing the overall dose to a wide area has significance, as it enhances the mixing and release as well as the absorption from a wide area [19]. So, transforming the unit solid dosage form into a spherule-based capsule can be an effective approach.

ASP is poorly water soluble [20] and water labile drug [2]. In those conditions, ideally, keeping the solid state of the drug intact on a solid matrix helps to improve the chemical stability of the drug [21]. Accordingly, ASP-like unstable drugs are incorporated with excipients and quickly processed into granules with the least possible water content, which are then successively coated with diluents for the preparation of spherules. This improvement of the process helps to ensure a minimum amount of water throughout the formulation; from granules to coated spherules (CS) [22].

Hydrophobic (EC) and/ or hydrophilic (HPMC K4M) polymers are being used for developing the SR drug release coatings [23-25]. For that, coating parameters need to be optimized [26].

The findings of the study demonstrated that this method can successfully produce spherules possessing excellent flow characteristics, high drug loading, and sustained-release behavior.

MATERIAL AND METHODS

Materials

Aspirin, lactose, starch, ethanol:water 1:1, methyl cellulose (MC), hydroxypropyl methyl cellulose (HPMC) and sodium lauryl sulphate (SLS) were used from SGT University laboratory. The SLS, Starch paste (5% w/v starch powder in water) was used as a wetting and wicking agent in the formulation. The machines used for evaluations are a bulk density apparatus, a dissolution test apparatus.

Methods

Preparation of ASP granules

ASP granules were formulated using the wet granulation technique. Specified amounts (**Table 1**) of ASP, lactose, starch, and SLS were precisely weighed and blended uniformly in a mortar following geometric mixing with the aid of a pestle. In the formulation, SLS served as both a wetting and wicking agent. A starch paste prepared as 5% w/v starch in water was gradually incorporated as a binder to obtain a cohesive wet mass. The resulting mass was passed through sieve no. 12 (aperture size 1.68 mm) and then dried at 50 °C [2].

Preparation of polymer-coated spherules

Wet granules were taken in a 250 ml beaker and were rotated at 20-25 rpm. To maintain the moisture of the granular bed, the ethanol: water (1:1 v/v) mixture was sprayed, and the 6-7 drops of 5% starch paste was added to improve the coating without aggregation of the particles. The granular bed was rotated nonstop until the spherical particles were detected. Spherules were then coated with the coating polymers i.e. ethyl cellulose (EC) and hydroxy-propyl methyl cellulose (HPMC) coating solution by spraying using conventional bottle sprayers into a 45° tilted glass beaker containing the spherule bed, and the spherules were then dried at 50-60 °C in a hot air oven for 20 minutes [27].

In this work, total five formulations i.e. F1, F2, F3, F4 and F5 were prepared out of which F1 was uncoated while rest four formulations i.e. F2-F4 were coated with various SR coatings where F2 and F3 were coated respectively with single and double coat of EC (2% solution in isopropyl alcohol (IPA) and acetone), and F4 and F5 were coated respectively with single and double coat of HPMC (2% solution in isopropyl alcohol and acetone) (**Table 2**). After coating the prepared spherules with sustained-release polymers, they are screened through sieve no. 22 (aperture size 0.71 mm) and 44 (aperture size 0.35 mm) to get desired particle size.

Table 1. Formula for the preparation of ASP granules

S. No.	Ingredients	Quantity
1	Aspirin	300 mg
2	Lactose	100 mg
3	Starch	24 mg
4	Sodium Lauryl Sulphate	1 mg
5	Starch Paste (5%)	q. s.

Table 2. Formulae for preparation of coating solution of EC and HPMC

S. No.	Ingredients	Coating solution for 10 g of spherules	
		Ethyl Cellulose (EC)	Hydroxy-Propyl Methyl Cellulose (HPMC)
1.	EC	0.400 g	-
2.	HPMC	-	0.400 g
3.	Talc	0.33 g	0.33 g
4.	PEG 400	0.20 g	0.20 g
5.	Acetone	20 ml	20 ml
6.	Dye	0.08 g	0.08 g

Microscopic evaluation of granules and spherules

A projection microscope was employed to assess shape and surface morphology of granules as well as spherules. The prepared samples were mounted on a glass slide and observed at 10× magnification, with emphasis on evaluating the particle shapes and edge appearance.

Flow property studies

The parameters such as Angle of repose, Carr's index, Hausner's ratio of spherules were studied [28-31].

Angle of repose

The angle of repose represents the maximum angle formed between the surface of a pile of spherules and the horizontal plane. Experimentally, the spherules were allowed to flow freely through a funnel onto a graph paper to form a conical heap. The height and radius of the resulting pile were measured, and the angle of repose was calculated using the equation-

$$\text{Angle of Repose} = \text{Tan}^{-1}\left[\frac{h}{r}\right]$$

where 'h' is the height and 'r' is the radius of pile.

Carr's Index

Carr's Index serves as a measure of the compressibility and flow behaviour of powders or granules. It also provides information regarding the extent of interparticle void spaces under compression, which indirectly reflects the shape and packing characteristics of the particles. For spherical particles, like spherules, the interstitial space remained low, thus, Carr's Index should be high, while for granular particles having an irregular shape, the interstitial space was high, so, the flow property and compressibility were low [2]. The Carr's Index can be calculated by applying the following equation-

$$\text{Carr's Index} = \frac{\text{Tapped Density} - \text{Bulk Density}}{\text{Tapped Density}} \times 100$$

Here, for measuring Bulk Density, the Bulk Volume (the maximum volume of the powder/ granules/ spherules obtained after keeping it in a measuring cylinder and rearranging the particles by simple tapping just to remove the excess space inside the powder bed) of 20 g spherules was measured in a measuring cylinder of appropriate capacity, and the bulk density was calculated using following equation-

$$\text{Bulk Density of Spherules} = \frac{\text{Weight of the Spherules}}{\text{Bulk Volume of the Spherules}}$$

Similarly, for measuring Tapped Density, the Tapped Volume (the minimum volume of the powder/ granules/ spherules obtained after tapping on Bulk Density Apparatus) of 20 g spherules was measured in a measuring cylinder of appropriate capacity, and the Tapped Density was calculated using following equation-

$$\text{Tapped Density of Spherules} = \frac{\text{Weight of the Spherules}}{\text{Tapped Volume of the Spherules}}$$

Hausner's Ratio

Hausner's ratio was calculated as the Tapped Density to Bulk Density ratio.

Drug content evaluation

ASP spherules, weighing 50 mg, were precisely weighed, powdered, and dissolved in phosphate buffer of pH 6.8. The resulting solution was filtered and spectrophotometrically estimated for drug content at (275 nm λmax) after suitable dilution using a UV–Visible spectrophotometer against phosphate buffer as blank.

***In vitro* drug release studies**

Drug release studies were performed using a USP type I basket dissolution apparatus to determine the percentage drug release over time. The dissolution medium consisted of 900 ml phosphate buffer pH 6.8, and 1.5 g of spherules were added to the medium. The test was conducted at 37 ± 0.5 °C with a basket rotation speed of 75 rpm. Agitation above 50 rpm in the USP type I apparatus is known to maintain steady-state sink conditions through continuous flow of dissolution medium. In addition, to accurately evaluate the release mechanism from polymer-coated spherules, turbulence-induced variability was minimized by selecting an optimized rotation speed of 75 rpm based on preliminary release studies of uncoated spherules. These conditions were adequate to maintain uniform diffusion-controlled drug release.

Aliquots of 1 ml were withdrawn at specified time intervals (0, 0.5, 1, 1.5, 2, 4, and 8 h) and replaced with fresh dissolution medium. The collected samples were suitably diluted and analysed at 275 nm using a UV–Visible spectrophotometer against phosphate buffer as blank. The coating composition was optimized to obtain nearly 10% modulation in drug release, while the stepwise coating strategy facilitated controlled and reproducible release behavior through adjustment of coating parameters.

Drug release kinetics

To investigate the kinetics and mechanism of drug release from the spherules, the dissolution data were analyzed using different mathematical models such as Zero-order, First-order, Higuchi, and Korsmeyer–Peppas models. The best-fitted model was confirmed using R2 and n values [31].

Zero-order release

It showed the drug release at a constant rate independent of concentration. To acquire the data a graph was plotted between cumulative percentage drug released against time (**Equation 1**). The linear curve indicates zero-order release kinetics

$$Q_t = Q_0 + K_0 t \quad \text{----------1}$$

where, Q_t = Drug released in time 't'; Q_0 = Initial drug content; K_0 = Rate constant of zero-order release.

First-order release

A drug release process is considered to follow first-order kinetics when the release rate depends on the first power of the remaining drug concentration. To evaluate this model, a graph was plotted between the logarithm of cumulative percentage drug remaining and time (**Equation 2**). The linear curve indicates first-order release kinetics.

$$\text{Log } Q_t = \text{Log } Q_0 + \frac{K_1}{2.303} t \quad \text{----------2}$$

where, Q_t = Per cent drug remaining at time 't'; Q_0 = Initial drug content; K_1 = Rate constant of first-order release.

Higuchi model

To acquire the data, a graph was plotted between cumulative percentage drug release against square root of time (**Equation 3**). A linear curve indicates Higuchi model of release kinetics.

$$Q_t = K_H (t)^{1/2} \quad \text{----------3}$$

Korsmeyer–Peppas model

After acquiring data, a graph was plotted between fraction of drug release v/s time raised to the power n (n<1) (**Equation 4**). A linear curve indicates Korsmeyer–Peppas release kinetics.

$$\frac{Q_t}{Q_0} = K_{KP} (t)^n \quad \text{----------4}$$

RESULTS AND DISCUSSION

In this work, five formulations with various SR coatings were prepared i.e. F1, F2, F3, F4 and F5 were prepared out of which F1 was uncoated while rest four formulations i.e. F2-F4 were coated with various SR coatings where F2 and F3 were coated with single and double coat respectively of EC (2% solution in isopropyl alcohol (IPA) and acetone), and F4 and F5 were coated with single and double coat respectively of HPMC (2% solution in isopropyl alcohol (IPA) and acetone) (Table 2). Post-coating they are sieved through sieve no. 22 (aperture size 0.71 mm) and 44 (0.35 mm) to get desired size spherules.

The parameters such as Angle of repose, Bulk Density, tapped Density, Carr's index and Hausner's ratio of spherules were calculated and presented in Table 3. The excellent flow properties ensure the uniform optimum coating of the granules to form the spherules. It also ensures the highly efficient coating (2).

Table 3. Spherules evaluation parameters

Batch	% Drug Content	Angle of Repose (°)	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Index (%)	Hausner's Ratio	Flow Property
F1	88.25	32.24	0.65	0.69	5.80	1.06	Excellent
F2	79.26	25.54	0.63	0.70	10.00	1.11	Excellent
F3	81.29	28.23	0.54	0.59	8.47	1.09	Excellent
F4	78.33	29.24	0.61	0.65	6.15	1.07	Excellent
F5	79.51	26.74	0.48	0.52	7.69	1.08	Excellent

Table 4. Comparison of flow properties granules and spherules

Batch	Angle of Repose (°)		Carr's Index (%)		Hausner's Ratio		Flow Property	
	Granules	Spherules	Granules	Spherules	Granules	Spherules	Granules	Spherules
F1	40.52	32.24	6.94	5.80	1.07	1.06	Very Good	Excellent
F2	38.63	25.54	9.33	10.00	1.10	1.11	Very Good	Excellent
F3	39.46	28.23	7.81	8.47	1.08	1.09	Very Good	Excellent
F4	37.33	29.24	9.46	6.15	1.10	1.07	Very Good	Excellent
F5	36.86	26.74	8.92	7.69	1.09	1.08	Very Good	Excellent

Further, on comparing the flow properties of granules and spherules from the same batch (Table 4) it has been observed that though both granules and spherules bore acceptable flow properties as per pharmaceutical perspective, spherules were found to have excellent flow properties while granules showed very good flow properties. The excellent flow properties ensure the uniform optimum coating of the granules to form the spherules.

It has been observed (Table 5 and Figure 1) that the uncoated spherules (F1) give a burst release of 80.30%±1.8% within one and a half hour, whereas formulation F2 (single-coated spherules with EC), F3 (double-coated spherules with EC), F4 (single-coated spherules with HPMC) and F5 (double-coated spherules with HPMC) show a decrease in the release rate i.e. 59.50%±"?2.8%, 43.23%±3.2%, 56.56%±3.3% and 35.37%±3.5% respectively in one and a half hour. This indicates that the release rate has been controlled by coating the spherules with the rate-controlling polymers.

Table 5. Cumulative per cent drug release versus time

Time (Hours)	Cumulative % Drug Release*				
	F1	F2	F3	F4	F5
0	0	0	0	0	0
0.5	55.18±2.2	28.22±3.3	15.33±4.2	29.24±3.9	10.31±4.2
1	70.40±2.1	45.27±3.2	32.23±3.6	45.52±4.1	22.33±3.5
1.5	80.30±1.8	59.50±2.8	43.23±3.2	56.56±3.3	35.37±3.5
2	85.60±2.7	69.22±3.1	55.46±2.6	64.88±3.9	46.43±3.1
3	93.20±3.2	76.11±2.6	62.34±2.5	72.28±2.9	55.22±2.9
4	97.90±3.2	82.23±2.8	66.15±2.6	77.21±3.1	61.13±3.5
6	98.10±2.6	86.43±1.9	68.15±1.9	79.05±2.4	64.77±3.2
8	98.00±1.9	89.56±2.7	70.15±2.3	80.53±2.6	66.44±3.1

*Mean±SD of 6 replicate observations

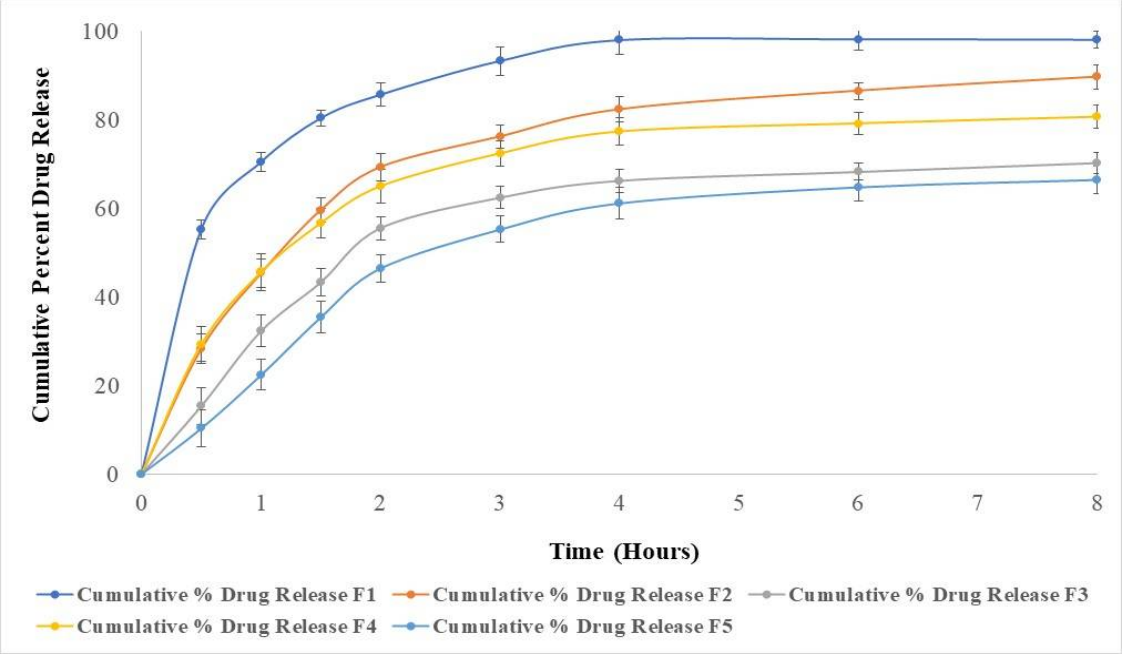

Figure 1. Cumulative per cent drug release versus time curve

The decrease in drug release observed with single-coated formulations containing EC (F2) and HPMC (F4), showing release values of 59.50% ± 2.8% and 56.56% ± 3.3%, respectively, was not as significant as anticipated. This could be due to uncontrolled spray rates and variations in the rolling characteristics of the spherules during coating. Nevertheless, formulations F3 (43.23% ± 3.2%) and F5 (35.37% ± 3.5%), which received double coatings of the same EC and HPMC solutions, demonstrated better regulation of drug release.

Table 6. Drug release kinetics of the prepared formulation batches F1-F5

Release Kinetics	Equation	Parameter	Formulation				
			F1	F2	F3	F4	F5
Zero Order	$Q_t = Q_0 + K_0\, t$	Regression Coefficient	0.7975	0.8512	0.8163	0.8255	0.8585
		Release Rate Constant	4.7444	6.9922	6.1458	5.7673	6.8171
First Order	$\text{Log}\, Q_t = \text{Log}\, Q_0 + \frac{K_1}{2.303}\, t$	Regression Coefficient	0.9095	0.9549	0.8742	0.9859	0.9081
		Release Rate Constant	0.4479	0.2467	0.1276	0.1902	0.1283
Higuchi	$Q_t = K_H\, (t)^{1/2}$	Regression Coefficient	0.8885	0.9274	0.9017	0.9093	0.9326
		Release Rate Constant	19.036	27.429	24.446	22.876	26.666
Korsmeyer Peppas	$\frac{Q_t}{Q_0} = K_{KP}\, (t)^n$ n = 0.5	Regression Coefficient	0.8886	0.9274	0.9017	0.9093	0.9326
		Release Rate Constant	0.1904	0.2743	0.2445	0.2288	0.2667

F1: Uncoated Spherules; F2: Single Coated Spherules Coated with EC; F2: Double Coated Spherules Coated with EC; F3: Single Coated Spherules Coated with HPMC; F2: Double Coated Spherules Coated with HPMC

As far as the drug release kinetics is concerned (**Table 6**), where spherules coated with single coat of either of rate controlling polymer i.e. EC (F2) and HPMC (F4) follow first order drug release kinetics like that of uncoated spherules (F1), spherules coated with double coat of same polymers i.e. F3 and F5 follow Higuchi's model of drug release kinetics. This indicates dissolution dependent drug release kinetics which was due to less water solubility of the drug.

CONCLUSION

In the present work, a rate-controlling film was coated over the drug reservoir system with the aim of optimizing the coating process. The coating conditions were experimentally adjusted to get an intact membrane capable of controlling the release rate, with at least a 10% reduction in drug release as the target criterion. Depending on the coating characteristics, the subsequent coating layer could either enhance release through increased osmotic pressure and diffusion or retard release by forming a less

water-permeable intact membrane. The sequential application of these coatings was collectively termed CPC over the drug reservoir.

This concept was investigated using formulations F1 to F5. F1 consisted of uncoated spherules serving as the drug reservoir, while F2 represented single EC-coated spherules having partially coated surfaces with larger diffusible pores. F3 was prepared with a double EC coating to obtain a more intact rate-controlling membrane. In contrast, F4 and F5 were coated with HPMC using single and double coating, respectively, to develop intact release-controlling membranes over the drug reservoir.

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