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Study on the Feasibility of Using Shacryl™ 30D as An Aqueous Polymer For the Formulation of Delayed Release Spheroids of Diclofenac Sodium.

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ABSTRACT

Aqueous enteric coatings are preferred over the non aqueous coatings due to their advantages. An attempt was made to explore the feasibility of using shacryl™ 30D as an aqueous enteric polymer for coating of spheroids. An IR study was carried out to check the compatibility between the selected polymer and the drug and the results revealed that the selected Shacryl^{TM}30D polymer was compatible with the selected drug diclofenac sodium.Spheroids were prepared by spheronization extrusion method, and its physical characteristics such as particle size and size distribution, bulk density, angle of repose and porosity were studied. To evaluate the enteric properties of the new polymer, the spheroids were coated to two different weight gains such as 20% and 30% of dry polymer to sub coated spheroids. The efficacy of shacryl coated spheroids were compared with that of HPMCP coated spheroids at the similar coating weight gains of 20% and 30 %. The coated spheroids from both polymers were subjected to drug content uniformity test, disintegration test, and *in vitro* dissolution test. It has been concluded that, the batches of spheroids coated with 30% weight gain of dry polymers were found to be better, in terms of compliance with the USP dissolution test,and stability in acidic medium.

Keywords: Aqueous enteric coating, Shacryl 30D, Spheronization, diclofenac sodium.

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INTRODUCTION

Spheroids are agglomerates of fine powders or granules of bulk drugs and excipients. They consist of small, free-flowing, spherical or semi-spherical solid units, typically from about 0.5 mm to 1.5 mm, and are intended usually for oral administration [1]. When pellets containing the active ingredients are administered *in vivo* in the form of suspensions, capsules or disintegrating tablets, they offer significant therapeutic advantages over single unit dosage forms[2] because pellets disperse freely in the gastrointestinal tract, they invariably maximize drug absorption, reduce peak plasma fluctuations, and minimize potential side effects without appreciably lowering drug bioavailability. Pellets also reduce variations in gastric emptying rates and overall transit times. Thus, intra and inter subject variability of plasma profiles, which are common with single unit regimens are minimized [3] Controlled-release pellets are manufactured either to deliver the drug at a specific site within the gastrointestinal tract or to sustain the action of drugs over an extended period of time while these results have been traditionally achieved through the application of functional coating material [4]. Extrusion spheronization is a multiple step compaction process comprising dry mixing of the ingredients with excipients, wet granulation of the mass, extrusion of the wetted mass, charging of the extrudates in to the spheronizer to produce a spherical shape, drying the wet pellets in a dryer and, finally, screening to achieve the required size distribution [5,6] An enteric coating is a coating system that resists disintegration or dissolution in gastric medium but disintegrates or dissolves in intestinal fluids. Polyacids such as modified cellulosic polymers and synthetic acrylic polymers are commonly known as enteric coating polymers.Diclofenac sodium has also been implicated as causative agent in colonic ulceration, small bowel perforation and pseudo membranous colitis. So, enteric coated diclofenac sodium tablets are required in order to avoid high drug concentrations in the stomach. Diclofenac sodium enteric coated spheroids will be more effective in prolonging the gastric residence times spheroids are reported to prolong the gastric emptying time compared to enteric coated tablets [7,8] Though the existing polymers possess all basic requirements of ideal enteric polymers, the current advancements in controlled release technology requires some additional properties like ready dispersibility in aqueous or nonaqueous solvents and versatility, compatibility with the drug and plasticizers [9, 10]. Shacryl™ 30D is a methacrylic acid copolymer dispersion which was launched by the Shasun Chemicals and Drugs, India. Hence the present investigation has been focused on exploring the possibility of using shacryl 30D polymer for the development of enteric coated spheroids.

MATERIALS AND METHODS

Materials

Shacryl™ 30D (15CPs) was a gift sample from Shasun Chemicals and Drugs Ltd., Chennai. Other ingredients suchas Hydroxypropyl methyl cellulose phthalate, Mcirocrystalline cellulose, Polyvinyl alcohol , Shellac, were of laboratory grade and purchased commercially. Diclofenac

sodium was a gift sample from Lupin Pharmaceuticals, Pune. Liquid reagents and solvents used were of analytical grade.

Infrared Spectroscopy

IR study was carried out to check the compatibility between the selected new polymer (Shacryl^{TM}30D) and the drug (diclofenac sodium). 10 mg of sample and 40 mg of KBr were taken in a mortar and pestle and triturated. A small amount of triturated sample was taken into a pellet maker and was compressed at 10 kg/cm^2 using a hydraulic press. The pellet was kept on the sample holder and scanned from 400 cm^{-1} to 400 cm^{-1} in Perkin Elmer FT-IR spectrophotometer. Samples were prepared for pure polymer, pure drug and for physical mixture of drug and polymer. The spectra obtained through those samples were compared and interpreted for shifting of major functional peaks and disappearance of functional peaks.

Formulation of diclofenac sodium spheroids by Extrusion spheronization

An Extruder model of RRE/EXT- 65/037 was used. The rate of Output was 10-25 Kg/hr with a speed of 30-30 rpm. Die roller perforation was 1mm. the salient feature of the machine is that the extruder is based on the external roller design and the machine has cutter arrangement. The Spheronizer of RRE/SPH – 150**/**010 model was used. It has a capacity of 100 – 125g per lot with a speed range of 100-3000 rpm. The extruder has a special feature where the friction plate rotates the wet cylindrical extrudates at high speed to cut these into uniform size and turn into spherical shape.

As it is shown in (Table1). required quantity of MCC, lactose, maize starch and drug (diclofenac sodium) were weighed. To this mixture, 0.2% w/v of methyl cellulose binder solution was added and made a suitable blend by using a mixture of water and iso propyl alcohol in 2:1 ratio. Sufficient quantity of solvent mixture was added to get a wet mass. The solid blend was passed through the extruder to form extrudates. The formed extrudates were introduced into the spheronizer to get spherical pellets (or) Spheroids.

Ingredients	Quantity (gm)
Diclofenac Sodium (Drug)	30
Lactose	38
Maize Starch	15.2
Micro crystalline Cellulose	16
Methyl Cellulose	0.8

TableNo.1 Composition of Diclofenac Sodium Spheroids

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Physical characterization of drug loaded Spheroids

Particle size analysis

The size distribution of spheroids is determined by different methods. The most common and widely used method is sieve analysis.[11] About 35g of spheroids were taken for analysis. The sieve numbers of 16, 22, and 25 were placed one over the other so that the coarse sieve was placed at the top and fine sieve placed at the bottom. The weighed spheroids were placed on the top sieve and the sieves were shaken for a particular period of 10 minutes in a mechanical sieve shaker and the quantity of spheroids retained on each sieve were collected separately and weighted[12] The mean particle size of the spheroids was calculated.

Bulk density

The density of spheroids can be affected by changes in the formulation or process, which subsequently affects other process or factors, such as capsule filling, coating and mixing. The bulk density of the spheroids was measured by an automated taper where a known quantity of spheroids were added to graduated measuring cylinder, the cylinder was fixed to the bulk density apparatus, it was set to get tapped until a constant volume was obtained.. The bulk density was calculated using the following formula[13]. Bulk density = Wt. of sample (g) / final volume (cc)

Angle of Repose

The flow characteristics of spheroids were measured by angle of repose. Improper flow is due to frictional forces between the particles. To determine the angle of repose, a dry clean funnel was kept on a burette stand at particular height (2-3cm). A graph paper was placed on the flat surface and a sufficient quantity of the spheroids was allowed to flow slowly through the funnel until the heap touched the tip of the funnel. The circumference of the heap was drawn and the mid point was located and its radius was measured. The experiment was repeated triplicate and the average radius was calculated.The angle of repose was calculated by following formula.

$$\text{Tan } \theta = h/r \text{ or } \theta = \tan^{-1} h/r.$$

Where h = height of pile, r = radius of the base of the pile and θ = angle of repose.

Friability

The essential requirement of spheroids is to have an acceptable friability, to with stand further processing. It may be more realistic indication of friability if the technique used to simulate the environment that spheroids may be exposed to. In this view, the formulated spheroids may be eventually exposed to pan coating process. Thus the friability was done using coating pan,[14] where about 10g of the spheroids were taken in a coating pan which was fixed

to Kalveka multi purpose machine and its horizontal aixis which acts as the rotating shaft. The rotating pan was allowed to rotate for 15 min at a fixed rpm (25 rpm). The percentage of weight loss before and after rotations was studied as friability.

Development of an aqueous coating formula using Shacryl™30Dand formulation of coated spheroids

The seal coating formula is shown (Table 2). The seal caoating solution was prepared using the shellac and ethanol as it is in the formula.The aqueous coating solution was prepared according to the formula given in (Table 3). To prepare 100ml of coating solution , Shacryl and Diethyl-phthalate were dissolved in water. Titanium dioxide was added and mixed thoroughly to the polymer solution, after the addition of colouring agent.(Erythrosine)Finaly the solution was filtered using a muslin cloth and the resultant solution was filled into the gun sprayer.

Table No.2 Physical characterizations of diclofenac sodium spheroids

Bulk density	Friability	Angle of repose (θ)	Average Particle Size (mm)
0.82	0.3%	21.03	2.6
N= 3 the value represents the average of 3 determinations			

Aqueous Coating of Diclofenac sodium Spheroids by Pan Coating

The coating was done using a specialy designed minipan to accommodate small quantity of core substance specially designed mini coating pan fitted into a rotating shaft device of Kalweka multi purpose unit. 100g of uncoated spheroids were taken in the pan. The speed of the pan was kept at 50rpm and coating solution was applied through spray gun system using low volume of spray was 0.5 ml per 2 seconds. The drying of coating solution was accomplished by a hair dryer which exerted a heat of 60-70°C. During the coating process, first spheroids were coated with the seal coating solution i.e shellac, which increased the spheroids weight by 2%. After seal coating, The coating was done using Shacryl™30D and two different coated batches like S1 and S2 were produced by the application of sufficient quantity of coating solution to produce a dry polymer weight of 20% and 30% to sub coated spheroids respectively. The weight gains were calculated based upon the quantity (percentage) of dry Shacryl present in the whole volume of coating solution.

Development of non aqueous coating formula and coating of drug loaded spheroids using hydroxy propyl methyl cellulose pthalate (HPMCP)

The non aqueous coating solution using HPMCP was prepared by the use of ingredients shown (Table 4)The coating of spheroids by non aqueous polymer was accomplished by the same method where the equipments,and process variables, were similer to that of method adopted earlier in aqueous coating process. But the coating composition varied. Using the nonaqueous coating formula two different batches of coated spheroids containg 20% and 30% of dry polymer to seal coat were made and named as H1 and H2 repectively.

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Evaluation of drug content uniformity of coated products

Spheroids coated with both aqueous and non aqueous coatingcompositions were tested for their drug content uniformity as per USP procedure. Where 1 g of coated spheroids from each polymer was weighted and powdered. From the powder mass 200mg was weighted and dispersed in 100ml of phosphate buffer pH 6.8. it was mixed using a sonicator for 30 minutes and then filtered . Uv absorbence was measured after suitable dilution at 276.2nm against reagent blank.The same procedure was repeated thrice. Drug content was calculated from the absorbance.

***In Vitro* Disintegration Study of coated spheroids**

The disintegration of individual coated spheroids in 900 ml of non-agitated 0.1 N HCl and pH 6.8 phosphate buffer at 37 $\pm$ 0.5°C was determined.(15) Each spheroid was placed into 0.1 N HCl and pH 6.8 phosphate was recorded. At least 30 spheroids in each batch of two different coatings from both Shacryl™30D and HPMCP were tested and the mean time was calculated.

***Invitro* dissolution study of coated spheroids**

In order to find out the release profile of drug, from different coated products, dissolution test was carried out on all 4 different products such as S-1, S-2, H-1 and H-2. From each product, an amount of spheroids equivalent to 50 mg of drug was filled into hard gelatin capsule. From each batch such 6 capsules were selected at random and tested for their dissolution pattern in 0.1 N HCl for 2 hrs and pH 6.8 phosphate buffer for 45 min as per USP specification. *In Vitro* dissolution test was conducted in 900 ml of 0.1N HCl and pH 6.8 phosphate buffer at 37 $\pm$ 0.5°C using USP (XXIII) dissolution apparatus–II (paddle method) at a speed of 50 rpm.

In the first stage of the dissolution 0.1N HCl was used as medium and testing was carried out for 2 hrs. Sample intervals were set at 15, 30, 45, 60, 75, 90 and 120 min.The product was transferred to Phosphate buffer medium pH 6.8 and the dissolution was carried out for 45 min. The sample intervals were set at 5, 10, 15, 20, 30 and 45min. The absorbance of each sample was observed in UV visible spectrophotometer at 276.2 nm against reagent blank. A minimum of 3 samples were subjected to dissolution study from each batch of spheroids.

The dissolution acceptance criteria(16,17) for delayed release dosage forms by USP *invitro* test was checked for spheroids.

RESULTS AND DISCUSSION

IR study was carried out to check the compatibility between the selected new polymer (Shacryl^{TM}30D) and the drug . The results obtained from the IR study through the interpretation of spectrums, it was confirmed that there are no major shifting of functional peaks, apperance or disapperence of new peaks of drug , polymer and physical mixture of drug and polymer. Hence it was concluded that the selected new polymer (Shacryl™ 30D) is found to be

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compatible in entrapping the selected drug. The spheroids were prepared by extrusion spheronization.The composition of spheroids (table 1) and its morphological view are shown (Figure 1). The physical characterization of spheroids was done and variables like of particle size, size distribution, bulk density, angle of repose and porosity were studied. The average particle size of the spheroids was found to be 2.6 mm. The bulk density of spheroids was found to be 0.82 which indicated that the spheroids were 'heavy' in nature, due to the closest packing arrangement. The flow behavior of the ideal batches of the spheroids was determined (Table 2) by angle of repose and it was found to be 21.03, which indicated that they exhibited good flow property. The enteric coating of spheroid by pan coating using aqueous and nonaqueous coating compositions (Table 3) to different weight gains through dry polymer to subcoating were coded as S-1, S-2 and H-1, H-2 respectively for shacryl and HPMCP. It resulted in spheroids with uniform coating thickness and free flowing nature (Figure2,3).

Fig.1: Scanning electron micrograph of diclofenac sodium spheroids.

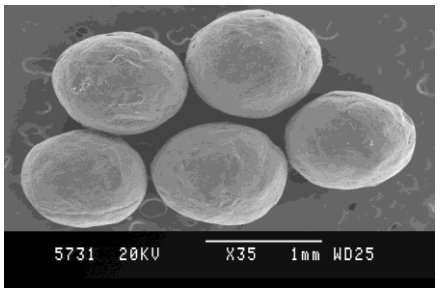

Table No .3 various enteric coating formulas for spheroid coating

Various enteric coating compositions		
Formula	**Ingredients**	**Quantity for 100gm(w/w)**
Seal coating	Shellac	2g
	Ethanol	to produce 100g
Aqueous coating using shacryl 30D	Shacryl™30D	40g
	Diethyl phthalate	4g
	Titanium Dioxide	3g
	Coloring agent	0.05g
	Purified Water	q.s (100g)
Non-aqueous Coating formula using HPMCP	HPMCP	20g
	Span 80	3g
	Propylene glycol	4g
	Ethanol	40g
	Colouring agent (Brilliant Blue)	0.05g
	Acetone	q.s (100g)

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Fig.2: Shacryl coated Spheroids (S-2)

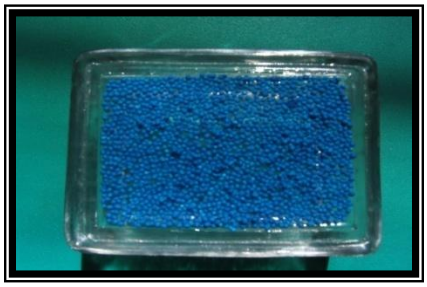

Fig.3: HPMCP Coated spheroids (H-2)

All the four batches of spheroids suchas as S-1, S-2 and H-1 ,H-2 were subjected to drug content uniformity test as per USP requirements. The quantity of spheroids equivalent to 50mg of diclofenac sodium was subjected to content uniformity test. All the four batches were found to be within the limits (Table 4) of drug content uniformity test as per USP specification(limit is ±10% of the lebel claim). From the disintegration test of enteric coated spheroids, it has been observed that the batches S-2 and H-2 with 30% (Quantity of dry polymer to sub coated spheroids) weight gain were found to be comparatively better than batches S-1 and H-1 in terms of better stability in acidic medium and optimum rate of disintegration in pH 6.8 phosphate buffer.(Table 4). From the dissolution profile of all four different products, it can be readily understood that the batches S-2 and H-2 with 30% (Quantity of dry polymer to sub coated spheroids) weight gain were found to be in compliance with USP dissolution test and acceptance limits (Table 5) for enteric coated products.These batches were found to produce a comparatively higher drug release in intestinal pH such as 88.4 % and91.2 % respectively for batches S-2 and H-2. Similarly the release of drug from batches of S-2 and H-2 in acidic media was found to be 9.15% and 8.81% , It is found to be in compliance with USP dissolution limits for enteric coated products.The comparative release profile these batches in acidic buffer and phosphate buffer are shown (Figure 4,5). From the data, it was also evident that the batches S-1 and H-1 were not found to be in compliance with acceptance limits of USP dissolution test for enteric coated spheroids, since they showed higher amount of drug release in acidic medium (more than 10%) and lesser than the specified amount in intestinal buffer.

Table No .4 Drug content uniformity and Disintegration test of spheroids

Batch Codes	Drug content (Average mg ± SD)	Observation in 0.1N HCl medium for 2 hrs	Observation in 6.8 pH buffer medium for 45 minutes (± mean minutes)
S-1 (Quantity of dry Shacryl to sub coated spheroids- 20%)	48.61 ± 0.25	Slight rupture of coat occurred at 1 hr and 30 minutes	5 min ± 2
S-2(Quantity of dry Shacryl to sub coated spheroids- 30%)	49.52 ± 0.25	No signs of rupture or softening of coat after 2 hrs	12 min ± 2
H-1 (Quantity of dry HPMCP to sub coated spheroids- 20%)	52.13 ± 0.18	Slight rupture of coat occurred in 1 hr and 45 minutes.	7 min ± 2
H-2 (Quantity of dry HPMCP to sub coated spheroids- 30%)	51.2 ± 0.18	No signs of rupture or softening of coat after 2 hrs.	14 min ± 2
(N=30)30 spheroids from each batch were selected at random and checked for disintegration			

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TableNo.5 *In vitro* Dissolution Profile of various coated spheroids in acidic and buffer stage

	Batch S-1		Batch S-2		Batch H-1		Batch H-2	
Time (Minutes)	Cumulative % Release		Cumulative % Release		Cumulative% Release		Cumulative % Release	
	Acidic medium (0.1N HCl)	Phosphate buffer medium (pH 6.8)	Acidic medium (0.1N HCl)	Phosphate buffer medium (pH 6.8)	Acidic medium (0.1N HCl)	Phosphate buffer medium (pH 6.8)	Acidic medium (0.1N HCl)	Phosphate buffer medium (pH 6.8)
15	8.50	70.49	1.05	72.22	8.93	70.71	0.61	71.80
30	9.37	72.26	2.36	74.87	9.59	71.36	1.92	74.43
45	10.25	72.90	3.24	77.50	10.47	72.68	2.58	77.43
60	11.13	74.65	5.65	79.03	10.91	75.09	5.21	78.59
75	12.0	77.50	7.40	82.10	12.22	77.72	6.96	82.32
90	13.3	81.44	8.06	87.57	13.53	83.22	7.84	89.71
120	14.6	81.42	9.15	88.44	14.85	83.24	8.81	91.24
N = 6 'N' is the Number of capsules (filled with coated spheroids) subjected to dissolution test								

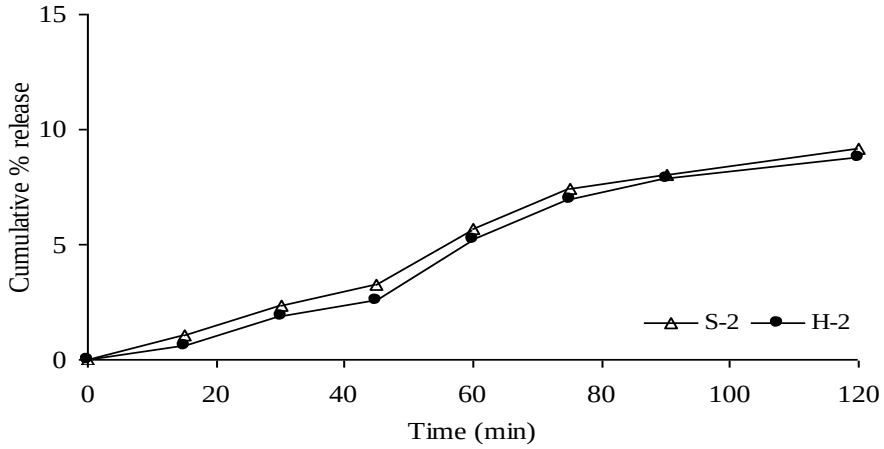

Fig.4 comparative *Invitro* release of best batches of spheroids in acidic medium

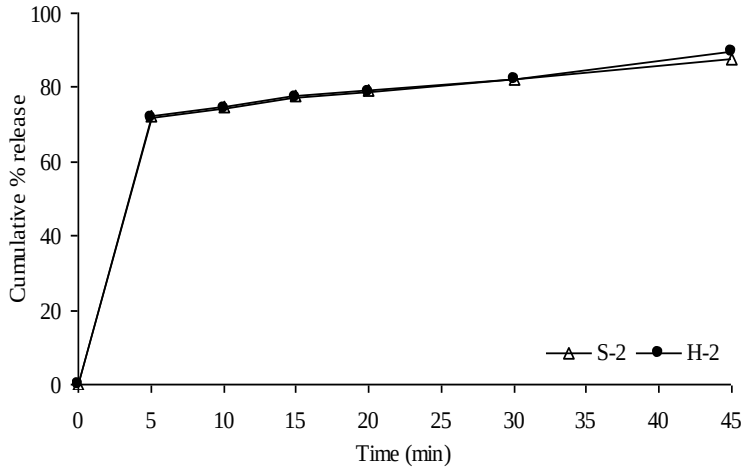

Fig.5 comparative *Invitro* release of best batches of spheroids in Phosphate buffer

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CONCLUSION

From these invstigations it is evident that the selection of coating thickness has a significant role in coating of spheroids, and the selected new polymer is found to be suitable for the enteric coating of spheroids. It also indicates that the formulated aqueous based enteric coated spheroids of diclofenac sodium could be a better alternative for non-aqueous enteric coated tablets and spheroids, in terms of better physico chemical and *in vitro* release characteristics.

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