Development of controlled release spheroids using *Buchanania cochinchinesis* gum.

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ABSTRACT

Chirauli nut gum was isolated from the bark of *Buchanania cochinchinesis* (fam. Anacadiacea) and was used as a release modifier for the preparation of Diclofenac sodium spheroids using the extrusion spheronization technique. The process was studied for the effects on variables when making spheroids with satisfactory particle shape, size and size distribution. The prepared spheroids were characterized for surface morphology, qualitative surface porosity, friability, bulk density and flow properties. *In vitro* studies demonstrated that the release exhibited Fickian diffusion kinetics which was confirmed by the Higuchi and the Korsmeyer-Peppas models. The physico-chemical parameters of the gum could be correlated to the *in vitro* dissolution profile of the spheroids. The spheroids were not able to sustain the drug releases over 12 hours. A greater concentration of Chirauli nut gum and a process that can accommodate such greater concentrations may produce a formulation capable of significant sustained release.

KEY WORDS: Spheroids, Buchanania cochinchinesis, extrusion-spheronization, gum

INTRODUCTION

Spheroids are agglomerates of fine powder or granules of bulk drugs and/or excipients. They consist of small, free flowing, spherical or semispherical solid units, typically from 0.5 to 1.5 mm in diameter, and are intended usually for oral administration (1-3). Spheroids offer certain specific advantages over conventional solid dosage forms, including equipment invariant flow and ease of packing, resulting in greater reproducibility of fill weight of capsules (4). Spheroids are more amenable to film coating, due to their smooth, geometrically defined surface. Spheroids containing different drugs can be blended and formulated in a single dosage form including those that exhibit differential release rates for the same drug. Spheroids have the ability to disperse in the gastrointestinal tract as discrete subunits, which ensures a constant rate of drug absorption thus

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minimizing peak plasma fluctuations. Irritation produced by a high local concentration of a drug from a single unit dosage form can be avoided.

Many methods have been reported for the preparation of spheroids, such as compaction, drug layering, melt spheronization, globulation, ball milling, compression and extrusion-spheronization (4-8). Among these, extrusion-spheronization is the most widely reported (9, 10). The main objective of the spheronization processes is to manufacture spherical drug cores that are subsequently coated in order to modify the drug release. It is also possible to prepare spheroid cores that inherently possess specific release profiles. This is achieved by the incorporation of release modifiers into the cores that modify the drug release. Polymers such as shellac and waxes are often used to retard the release of the drug (11).

Gums and mucilages are composed of polysaccharides formed from sugars and uronic acid units. Because they are composed of multiple hydrophilic monomeric units, thus possessing a greater osmotic potential, they can absorb large quantities of water and swell to several times their unhydrated volume (12, 13). They are used in a wide range of pharmaceutical applications including as binders and disintegrants in tablets, as well as, as emulsifiers, suspending agents and gelling agents. Additionally they can be used as controlled release agents in tablets. Many gums and mucilage have been reported to sustain drug release from matrix tablets (12, 13). Thus, in the present study, the gum isolated from the Chirauli nut tree (*Buchanania cochinchinesis*) (CG) was used as a release modifying agent to formulate controlled release spheroids using diclofenac sodium as a model drug.

MATERIALS AND METHODS

Materials

The Chirauli nut tree gum was obtained from various locations throughout the state of Maharashtra (India) and was authenticated by the Botanical Survey of India, Pune (BSI/WC/Tech/2012/605) as *Buchanania cochinchinesis* (Lour.) Almeida (fam. Anacardiaceae). Microcrystalline Cellulose (Avicel® PH101), Sodium carboxymethyl cellulose (Blanose), Ethyl cellulose (Ethocel™) were obtained from Signet chemicals (Mumbai, India). Diclofenac Sodium was obtained from All fine chemicals (Chennai, India). All other chemicals and reagents used in the present study were of analytical reagent (AR) grade. When required, distilled water was used throughout the study.

Isolation of water-soluble fraction of Chirauli nut tree gum

100 gr of the ground raw Chirauli nut tree gum was dissolved in 300 ml water. The solution was filtered through several folds of muslin cloth to remove insoluble extraneous matter, and the filtrate was collected. The filtrate was then centrifuged at 3000 RPM for 10 minutes (R4C, Remi Laboratory Instru-ments, Mumbai, India). The supernatant fluid was collected, evaporated to dryness and the solid mass was ground and then passed through sieve No 80 and stored in an airtight container at 25°C.

Characterization of gum

The isolated and purified gum was characterized for organoleptic properties and surface characteristics using a scanning electron microscope (SEM), pH, swelling index, loss on drying, hygroscopicity, ash value (total ash, acid insoluble ash, water soluble ash), microbial count, and surface tension (14). The surface tension of 1% w/v gum solution was determined by the drop count method (15), using a stalagmometer (Stalagmometer straight form, Advanced Technocracy, Ambala, India).

Extrusion-Spheronization: Process optimization

For the preparation of the spheroids, Extruder (EXT-65/037, R. R. Enterprises, Thane, India) and spheronizer (SPH-150/010, R. R. Enterprises, Thane, India) were used (Figure 1).

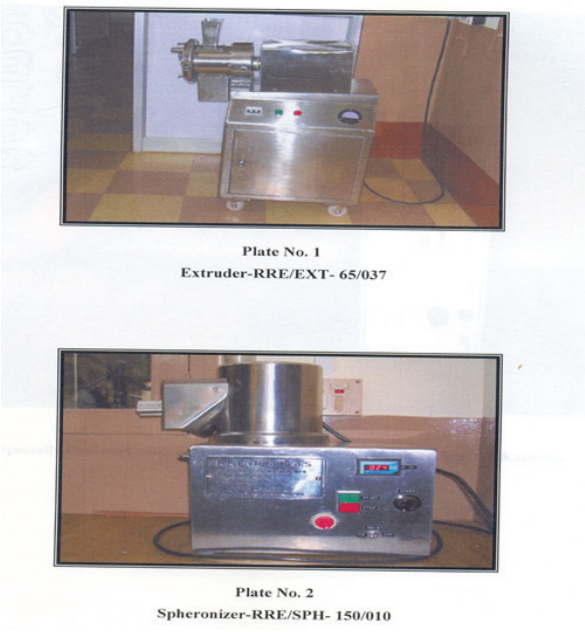

Figure 1 Photograph of Extruder-RRE/EXT-65/037 and Spheronizer-RRE/SPH-150/010

Microcrystalline Cellulose (MCC) was used as a spheronization enhancer and the Chirauli nut tree gum as the release modifier. For the optimization of the spheroid formulation, different ratios of Drug-CG-MCC (M1 through M4 in Table 2), were selected and subjected to extrusion–spheronization. For the optimization of spheronization speed, extrudates from all the selected ratios of Drug-CG-MCC were subjected to spheronization at different speeds ranging from 1000 to 3000 RPM. Optimized batches were selected based on acceptable physical characterization. For the optimization of spheronization time, the optimized batch of spheroids was subjected to spheronization at 2500 RPM for different durations ranging from 10 to 60 minutes. The optimized batch was compared with a comparator formulation containing MCC-Sodium CMC-Drug-Ethyl cellulose (batch E) (63:2:20:15) and the model drug formulation. For the comparator formulation, ethyl cellulose was used as a synthetic release modifier. The comparator formulation was formulated using the extrusion spheronization process parameters described later in this text.

Physical characterization of spheronization

The prepared spheroids were characterized for different physical properties. The particle size and size distribution were determined by sieve analysis (EMS-8 Plus, Electrolab, Mumbai, India) (16). The surface morphology and qualitative surface porosity of the spheroids were analyzed using a SEM. Additionally a surface analysis was performed using a SEM (Jeol, JED-2300, Japan). The spheroids were evaporated with carbon and then sputtered with gold to make the sample electrically conductive. Carbon and gold were layered to thicknesses of approximately 10 nm and 25 nm respectively (17, 18). The bulk density, true density, angle of repose, Carr's index, porosity and friability of the spheroids were determined using standard methods (19).

A given mass of the sample was transferred to a measuring cylinder and was tapped mechanically, using a bulk density apparatus (EDT-1020, Electrolab, Mumbai, India) until a constant volume was obtained, which was to be referred to as bulk volume (Vb). This was used to calculate the bulk density. The true density of the sample was determined using the liquid displacement method, using xylene as the displacement liquid. The angle of repose of the prepared pellets was measured by using a funnel. A dry clean funnel was kept on a burette stand at a constant height from the surface (2-3 cm). 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, the mid point was located and its radius was measured. The angle of repose was calculated using Equation 1.

$$\theta = \tan^{-1} h/r. \qquad \text{Eq.1}$$

Where,

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

The Carr's index and the percentage porosity of the granules were calculated using standard volume and density attributes. About 5 grams of the prepared spheroids were allowed to rotate for 15 minutes at 25 RPM in a friabilator (EF-2W, Electrolab, Mumbai, India). The percentage weight loss was expressed as friability.

In- vitro dissolution

To study the *in-vitro* dissolution profile, 150 mg of spheroids, equivalent of 100 mg of diclofenac sodium were manually filled into hard gelatin capsules (ACG Associated capsules, Mumbai). Content uniformity of the capsules was performed by weighing 10 capsules individually. The contents of each capsule was removed and the weight of the content was determined. Individual capsule content was assayed according to the USP monograph.

Dissolution studies were carried out using the USP-XXIII dissolution apparatus (Lab India DS 8000, Mumbai, India) with a paddle attached. Freshly prepared phosphate buffer of pH 6.8 (900 ml) was placed in the dissolution flask and allowed to attain a temperature of 37°C ± 0.5. The capsules were placed at the bottom of the dissolution flask. The paddle was rotated at 50 RPM. Samples of 5 ml were withdrawn at predetermined intervals and replaced with an equal quantity of fresh buffer. The sample was diluted with buffer and analyzed spectrophotometrically at 275.6 nm using an ultra violet spectrophotometer (Cyberlab UV-100, Cyberlab,USA).

RESULTS AND DISCUSSION

The gum from the *Buchanania cochinchinesis* tree was collected from various locations throughout the state of Maharashtra, India. The gum was purified using water as the solvent. The yield was 82 % w/w. The water-soluble portion was separated from the purified gum. The identification of the isolated and purified gum was confirmed by the appearance of a pink color upon reaction with ruthenium red and corallin soda. A gelatinous mass of gum was obtained by heating and cooling the solution in water. The gum precipitated by alcohol tested positive (development of a purple color) for the Molish test. The purity of the gum was determined by phyto-chemical tests, which indicated the absence of alkaloids, flavonoides, oils and fats, saponins, amino acids, steroids, tannins and phenols. Only carbohydrates and glycosides were found to be present. These results are shown in Table 1. The water soluble gum was characterized for surface characters by SEM, pH, viscosity and surface tension to assess the gum as an excipient for use in formulating drugs. The scanning electron microscopy microphotograph showed that the gum was smooth and crystalline in nature exhibiting a fairly regular, elongated appearance as shown in Figure 2.

Table 1 Physicochemical properties of *Buchanania cochinchinesis* gum

PARAMETERS	RESULTS
Phyto-chemical Evaluation	
Alkaloids, Falvonoids, steroids, amino acids, saponins, oils and fats, tannins, phenols	Negative
Glycosides, carbohydrates	Positive
Physicochemical Characters	
Color and clarity	Brownish and turbid
pH	7.8±0.00
Hygroscopicity (%)	2.67±0.00
Loss on drying (%)	1.63± 0.12
Total ash (% w/w)	1.80 ± 0.00
Acid Insoluble ash (% w/w)	0.17±0.01
Water soluble ash (% w/w)	0.74± 0.01
Bulk density (g/ml)	0.93 ±0.01
Tapped density(g/ml)	0.98 ±0.01
Compressibility (%)	7.30±0.00
Housner ratio	1.08±0.01
Angle of repose	$25^0 57''$
Porosity (%)	68.30± 0.83
Surface tension(dyne/cm)	32.6 ± 0.00
Viscosity (NS/m^2)	5.27 ±0.05
Microbial load	
Bacteria	< 30± 0.00 cfu/g
Fungi, E.coli, Salmonella, Pseudomonas, Staphylococcus	Not detected

Each value is the mean ±SD (n= 3)

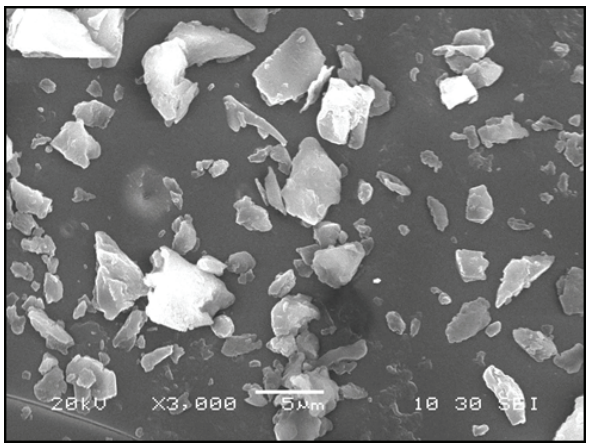

Figure 2 Microphotograph showing SEMs of the Chirauli nut tree gum at X3000 magnification

The pH of the gum solution (1% w/v) was 7.8. Knowledge of the pH of an excipient can be an important parameter in determining an approach to formulating a specific drug. The viscosity of a 1% dispersion in water and the surface tension of a 1% dispersion in water of the gum was 5.2 Ns/m^2 and 32.5 dyne/cm respectively.

The moisture content of the Chirauli nut tree gum was low, suggesting that it may be suitable for use in formulations containing moisture sensitive drugs. At favorable temperatures, moisture increases the rate of degradation of most drugs and the proliferation of microorganisms, thereby affecting the shelf life of most solid dosage formulations. It is important to investigate the moisture content of the material because the economic importance of an excipient is not only based on the cost and availability of the raw material, but also on the optimization of production processes such as drying, packaging and storage. The total ash, acid insoluble ash and water soluble ash value of the Chirauli nut tree gum was found to be 1.80, 0.17 and 0.74% w/w respectively. For organic materials, the ash value may be reflective of the level of adulteration upon isolation and handling. Adulteration by sand or earth is detected as the total ash is normally composed of inorganic mixtures of carbonates, phosphates, silicates and silica. Therefore, the low values of total ash, acid insoluble ash and water soluble ash obtained in this study are indicative of low levels of contamination during gathering and handling of the raw Chirauli nut tree gum. The bulk and tapped densities provides an insight of packing arrangement of the particles, as well as, the compaction profile of a material. The bulk density, tapped density, compressibility, Housner ratio, angle of repose and porosity of the Chirauli nut tree gum powder values are shown in Table 1. The values indicate that the Chirauli nut tree gum possesses good flow properties and moderate compressibility properties. Although an excipient may be, by weight, a minor part of the formulation, knowledge of these properties are important for subsequent scale-up processes.

Table 2 shows the results of the optimization of the extrusion spheronization processes. As the concentration of gum was increased, the granulating mass increased in elasticity and extrudes were not formed. At very low concentrations of gum, spheroids were formed but a major fraction of the particles was irregular in shape with a wider size distribution. Hence the MCC-Drug-CG ratio of batch M4 (65:20:15) was selected as an optimal batch. This batch was compared with the comparator batch E (63:2:20:15) and with the model drug formulation.

Table 2 Optimization of the pelletization technique using Chirauli nut tree gum, MCC pH101

Drug: Gum: MCC pH101	Water content (ml)	Spheronization speed (RPM)	Residence time (Min)	Pellet description
M1(20:2.5:77.5)	15	2000	30	Spheroids with more fines
M2 (20:5:75)	15	2500	15	Spheroids with more fines
M3 (20:10:70)	15	2500	50	Spheroids with narrow range
M4 (20:15:65)	11	2500	60	Spheroids with narrow range

At lower spheronization speeds, a greater number of rod and dumbbell-shaped particles were formed. At speeds at the higher end of the range studied, spheronization did not occur properly, probably due to the overwhelming preponderance of the centrifugal force, again

leading to the formation of rod and dumbbell shaped particles.

At lower spheronization times, i.e., <15 minutes, a major portion of the granulating mass was not converted into spheroids, while at a longer residence time, size reduction was observed, probably due to increased drying. Under optimal conditions, i.e., the MCC-Drug-CG ratio of 65:20:15 (M4), a spheronization time of 30 minutes at 2500 RPM speed, a maximum yield of spherical particles of the desired size distribution and morphology was obtained. Spheroids were formed at 2000 RPM at the spheronization time of 30 minutes for the comparator batch E, MCC-Sodium CMC-Drug-Ethyl cellulose ratio (63:2:20:15) (Table 3).

Table 3 Optimization of the pelletization technique using sodium CMC (2%), Ethyl Cellulose, MCC pH 101

Drug: sodium CMC (2%): Ethyl Cellulose: MCC pH101	Water content (ml)	Spheronization speed (RPM)	Residence time (min)	Pellet description
E (20:2:15:63)	15	2000	30	Spheroids formed

Batches of the optimized spheroids had a narrow range of size distribution with 85.8% spheroids within the range of 0.69–0.71 mm and size distribution was found to be normal. 95% of particles were less than 0.66 mm in diameter. The SEMs of spheroids from batches M4 and batch E (Figure 3) clearly shows that the spherical shape of the spheroids very smooth and non porous in nature.

The bulk density and true density of the spheroids were found to be 0.50 and 0.53 g/cm^3 respectively. The friability value of the optimized batch was found to be 1.60%. The low friability may be due to the spherical shape and smooth surface of the spheroids, as indicated by the SEMs. The angle of repose and the Carr's index value for the optimized batch of spheroids indicated acceptable flow properties which could also be attributed to the spherical shape and smooth surface of the spheroids. The results for various batches are shown in Table 4.

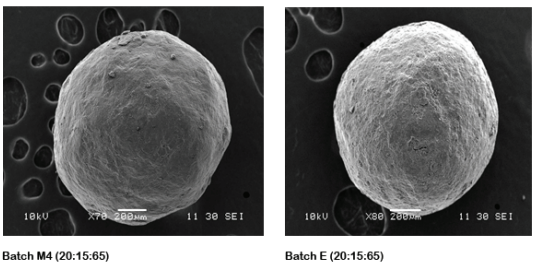

Figure 3 Microphotograph showing SEMs of batch M4 (20:15:65), E (20:2:15:63)

Table 4 Physio-chemical properties of pellets formulated with (Drug: Gum: MCC pH101) and (Drug: sodium CMC (2%): Ethyl Cellulose: MCC pH101)

BATCH	M1	M2	M3	M4	E
Average Particle size (mm)	0.69±0.00	0.69±0.03	0.70±0.00	0.69±0.03	0.71±0.01
Bulk density (g/cc)	0.50±0.01	0.50±0.01	0.49±0.00	0.50±0.01	0.45±0.00
Tap density (g/cc)	0.53±0.01	0.53±0.01	0.53±0.00	0.53±0.00	0.52±0.03
Carr's Index	4.78±0.01	4.78±0.01	4.78±0.00	4.69±0.01	2.30±0.05
Angle of repose (degrees)	26°31''	24°38''	23°33''	28°91''	28°56''
Porosity	0.06±0.01	0.05±0.01	0.05±0.00	0.05±0.03	0.12±0.01
Friability (%)	1.60±0.01	1.40±0.00	1.80±0.00	1.60±0.03	3.70±0.00
Drug content (%)	98.5±0.02	97.3±0.00	98.1±0.01	98.8±0.02	99.0±0.00

Each value is the mean ± SD (n=3)

The *in vitro* release studies were carried out for the spheroids using phosphate buffer of pH 6.8 Different batches were subjected to *in vitro* dissolution studies using USP (XXIII) dissolution apparatus-II (paddle method). The capsules disintegrated in the dissolution vessels in 8-10 minutes. The cumulative % drug release for batches M4, E and the model drug formulation was found to be 77.16%, 86.99% and 96.51% respectively for a period of 12 hours (Figure 4 and Table 5).

In the *in vitro* release study, the spheroids from the optimized batch M4 exhibited first order Fickian diffusion kinetics as shown in Table 6, The moderate non linearity associated with the Higuchi plot may be indicative of a minor non-diffusive component contributing to release, which in turn could arise from the swelling of the gum in the spheroidal matrix.

The dissolution data were also plotted according to the Koresmeyer-Peppas model,

where the log cumulative percentage of drug released was plotted against log time (21).

Table 5 Comparative *in vitro* dissolution profile of capsules containing pellets

TIME INTERVAL (HOURS)	M4	E	MARKETED FORMULATION
0.25	16.61±0.267	26.39±0.467	13.10±0.318
0.5	19.90±0.778	38.75±0.497	27.91±0.697
0.75	24.46±0.705	48.26±0.810	44.97±0.716
1	26.26±0.656	50.66±0.387	55.13±0.871
1.5	47.92±0.753	53.75±0.930	64.08±0.465
2	53.82±0.711	59.73±0.862	72.62±0.744
4	70.55±0.972	63.71±0.967	79.47±0.777
6	71.30±0.821	69.06±0.290	85.01±0.853
8	72.94±0.414	78.05±0.838	88.54±0.747
10	74.92±0.763	83.79±0.877	93.98±0.549
12	77.16±0.804	86.99±0.911	96.51±0.706

Each value is the mean ± SD (n=6)

The log-log plot for the Chirauli nut tree gum spheroids was also a straight line (r^2= 0.91), with a slope of 0.43 indicating that the release of the drug followed Fickian diffusion kinetics (Table 6).

Table 6 Parameters derived from first order plot, Koresmeyer-Peppas and Higuchi's plot

BATCH	FIRST ORDER PLOT		KORESMEYER-PEPPAS PLOT		HIGUCHI'S PLOT
	r^2	K	r^2	Slope	r^2
M4	0.95±0.01	-0.11±0.02	0.91±0.01	0.43±0.00	0.89±0.01
E	0.96±0.02	-0.05±0.01	0.93±0.01	0.26±0.00	0.92±0.03
Marketed Formulation	0.93±0.00	-0.23±0.04	0.82±0.03	0.42±0.01	0.85±0.04

Each value is the mean ± SD (n= 3)

CONCLUSION

The isolated gum from the tree of *Buchanania cochinchinesis* was studied for its potential as a sustained release agent in extrusion-spheronization formulations. The spheroids developed using the Chirauli nut gum as a release modifier, microcrystalline cellulose (Avicel® pH 101) as spheronization enhancer and Diclofenac sodium as model drug were found not to exhibit similar release kinetics as the formulation containing ethyl cellulose as a synthetic release modifier (similarity factor f_2=43.8)

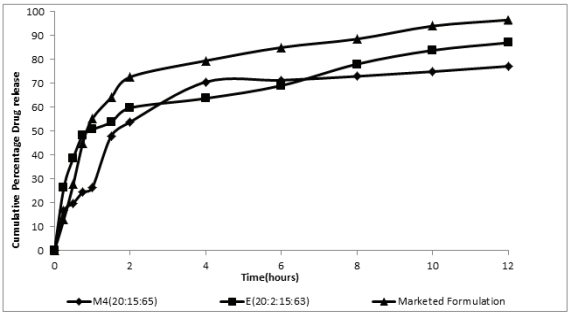

Figure 4 Comparative in-vitro study of spheroids

The results from the *in vitro* dissolution study did not conclusively demonstrate that the Chirauli nut tree gum, at the concentration used in this study, would be an effective release modifier for controlled release spheroids. The study, however, did demonstrate that the release profile exhibited by the formulation containing the Chirauli nut gum was not similar to that containing a synthetic controlled release agent, ethyl cellulose (f_2 = 43.8). A process of extrusion-spheronization, that can accommodate a greater concentration of Chirauli nut gum may produce a formulation capable of significant sustained release.

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REFERENCES

1 Gajdos B., Rotary granulators-evaluation of process technology for pellet production using factorial design. Drugs Made Ger, 27: 30-36, 1984.

2 Kristensen H.G., Schaefer T., Granulation: A review of pharmaceutical wet granulation. Drug Dev Ind Pharm, 13: 803-872, 1987.

3 Ghebre-sellassie, I., Pharmaceutical Pelletization Technology. Marcel Dekker, New York, NY, pp. 1-13, 1989.

4 Vuppala M.K., Parikh D.M., Bhagat H.R., Application of powder layering technology and film coating for manufacture of sustained release pellets using rotary fluid bed processor. Drug Dev Ind Pharm, 23: 687-694, 1997.

5 Kader A., Jalil R., *In vitro* release of theophylline from poly(lactic acid) sustained release pellets prepared by direct compression. Drug Dev Ind Pharm, 24: 527-534, 1998.

6 Zimm K.R., Schwartz J.B., Connor R.E,. Drug release from multiparticulate pellet system. Pharma Dev Technol, 1: 37-42, 1996.

7 Nantharat P., Roland B., Dry powder coating pellets with micronized Eudragit RS for extended drug release. Pharm Res, 20: 1970-1976, 2003.

8 Conine J.W., Hadley, H.R., Small solid pharmaceutical spheres. Drug Cosmet Ind, 90: 38-41, 1970.

9 Ghali E.S., Contractor A.M., Mankad A.D., O'Connor R.E., Schwartz. A high-speed mixer for continuous wet granulation. Pharm Tech, 60-66, 1990.

10 Reynolds A.D., A new technique for the production of spherical particles. Manuf Chem*,* 41: 40-43, 1970.

11 Harns M.R., Ghebre-sellassie, I., Formulation variables. In Pharmaceutical Pelletization Technology. 1st ed., Marcel Dekker, INC, New York, NY, pp 217-240, 1989.

12 Kulkarni G.T., Gowthamarajan K., Brahmajirao G., Suresh B., Evaluation of binding properties of selected natural mucilages. J Sci Ind Res, 61: 529-532, 2002.

13 Bavega S.K., Rangarao K.V., Arora J., Examination of natural gums and mucilages as sustaining materials in tablet dosage forms. Ind J Pharm Sci*,* 50: 89-92, 1998.

14 Gowthamarajan K., Phanikumar G.K., Gaikwad N.B., Suresh B., Preliminary study of *Anacardium occidentale* gum as binder in formulation of paracetamol tablets. Carbohyd Poly*,* 83 (2): 506-511, 2011.

15 Parrot EL., Experimental Pharmaceutics, 4th ed., Surjeet Publications, New Delhi, pp 216-227, 1985.

16 Martin, A., Bustamante, P., Chun, A.H.C.., Physical Pharmacy. B. I. Waverly, New Delhi. pp 426-446, 1994.

17 Bajaj A.N., Savarkar S.P., Pelletization by Extrusion-spheronization technique process optimization. Ind Drugs, 36: 44-49, 1999.

18 Mehta, A.M., Evaluation and characterization of pellets. In Pharmaceutical Pelletization Technology. 1st ed., Marcel Dekker, INC, New York, NY, pp 241-265, 1989.

19 Banker, G.S., Neil, R.A., In: Lachman L, Lieberman HA, Kanig JL, editors. The Theory and Practice of Industrial Pharmacy. 3rd ed., Varghese Publishing House, Bombay, pp 297-321, 1987.

20 Higuchi T., Mechanism of sustained action medication. Theoretical release of solid drugs dispersed in solid matrices, J Pharm Sci, 52 : 1145-1149, 1963.

21 Peppas N.A., Analysis of Fickian and non-Fickian drug release from polymers. Pharm Acta Helv, 60: 110-111, 1985.