Research Article

Study of Locust Bean Gum as Binder in Formulation of Immediate Release Atorvastatin Calcium Spheroids through Extrusion and Spheronization Technique

D.V. Gowda[1], Rohan D. Deshpande[1]*, Keerthy H.S[2], Siddaramaiaha[3]
[1]Department of Pharmaceutics, JSS College of Pharmacy, JSS University, S.S Nagar, Mysore, Karnataka, India.
[2]Department of Pharmaceutics, Mallige College of Pharmacy, Bangalore, Karnataka, India.
[3]Department of Polymer Science & Technology, Sri Jayachamarajendra College of Engineering, Mysore, Karnataka, India.
***Corresponding author's E-mail:** rohan11in@gmail.com

Accepted on: 10-06-2014; **Finalized on:** 30-06-2014.

ABSTRACT

An attempt was made to investigate the binding efficacy of locust bean gum in spheroid formulation in comparison with polyvinyl Pyrrolidone (PVP K-30) a standard binder. The Atorvastatin calcium spheroids were formulated using 1% w/w locust bean gum suspension, sodium starch glycolate/croscarmellose sodium (1-7%) and microcrystalline cellulose. Here the formulation variables were studied and the obtained spheroids were characterized for its properties. The formulation FR-14, were found to be ideal, based upon their physico-mechanical properties and *in-vitro* drug release profile. The results suggests that locust bean gum can be used as an alternative binder with 1% w/w concentration to produce spheroids better physico-mechanical properties and promising drug dissolution profile.

Keywords: Atorvastatin calcium, Locust bean gum, Polyvinyl Pyrrolidone, Spheroids.

INTRODUCTION

Extrusion/spheronization is an established technique in pharmaceutical industry which results in spherical pellets in a typical size range between 0.5 and 2 mm. These pellets possess high density, small particle size distribution, and regular shape. They are usually used for the production of multiple-unit dosage forms because of their advantages over single-unit dosage forms, for example, they maximize drug absorption, reduce peak plasma fluctuations and minimize potential side effects.[1,2]

Oral controlled release dose-forms have gained popularity in recent years. They broadly fall into two categories: single-unit and multiple-unit dose-forms. The single-unit dose-forms are either matrix tablets or coated tablets that do not disintegrate in the gastrointestinal tract. The multiple-unit dose-forms consist of pellets or microencapsulated drug contained in a capsule or a tablet. Various methods and approaches used in the formulation of multiple-unit dose-forms have been thoroughly discussed in many standard reference works e.g. Ghebre-Sellassie, 1994.[3] Thus, multi particulate dosage forms are pharmaceutical formulations in which the active substance is present as a number of small independent subunits. To deliver the recommended total dose, these subunits are filled into a sachet and encapsulated or compressed into a tablet.[4,5]

Gums of natural sources are biodegradable and non-toxic, and hydrate and swell on contact with aqueous media; and these have been used for the preparation of dosage forms.[6] Gums and mucilages are polysaccharide complexes formed from sugar and uronic acid units. They can absorb large a quantity of water and swell. They find a wide range of pharmaceutical applications that include their use as binders and disintegrants in tablets, emulsifiers, suspending agents, and gelling agents. They also are used as sustaining agents in tablets. Many gums and mucilage's have been reported to sustain the drug release from matrix tablets.[7-9]

Locust bean gum, also known as carob gum, is a galactomannan vegetable gum derived from the seeds of the leguminous plant *Ceratonia siliqua Linn* belonging to the family Fabaceae.[10,11] It consists chiefly of high molecular weight hydro colloidal polysaccharides composed of galactose and mannose units (1:4) combined through glycosidic linkages. This natural, non-starch polysaccharide forms water-insoluble films that degrade in colonic microflora, making it useful in a colon-targeting strategy.[11,12] On the other hand, locust bean gum has various properties that make it a good choice in drug delivery.[11,13-15]

MATERIALS AND METHODS

Materials

Locust bean gum and gum ghatti was purchased from Sigma Aldrich (Bangalore, India). Atorvastatin calcium was a kind gift from Micro Labs Ltd. (Bangalore, India). Sodium starch glycolate, croscarmellose sodium, microcrystalline cellulose (MCC), sodium lauryl sulfate, polyvinyl pyrrolidone K-30 (PVP K-30), magnesium stearate, polyethylene glycol and sodium bicarbonate was obtained from Loba Chemie (Mumbai, India). All other chemicals and reagents used in the present study were of analytical reagent grade.

Preparation of drug-loaded Atorvastatin calcium spheroids

For the preparation of spheroids, Extruder (R.R. Enterprises, Mumbai, India) and Spheronizer (R.R. Enterprises, Mumbai, India) were used. In the formulation of spheroids, MCC was used as spheronization enhancer. Here in the formulation MCC was used as spheronization enhancer, 1% w/w locust bean gum suspension in distilled water was used as binder, sodium starch glycolate and croscarmellose sodium was used as disintegrant, sodium lauryl sulfate as surfactant and sodium bicarbonate as pop-up excipient which aid the action of the super disintegrants to make the formulation fast dissolving. Here, different batches of spheroids like FR-1, FR-2, FR-3, FR-4, FR-5, FR-6 and FR-7 were prepared consisting of MCC-sodium lauryl sulphate-sodium starch glycolate-sodium bicarbonate-drug in different ratios such as 92:1:1:2:4% w/w, 91:1:2:2:4% w/w, 90:1:3:2:4% w/w, 89:1:4:2:4% w/w, 88:1:5:4% w/w, 87:1:6:4% w/w and 86:1:7:4% w/w. Further the disintegrant i.e., sodium starch glycolate was replaced with croscarmellose sodium and different batches of spheroids like FR-8, FR-9, FR-10, FR-11, FR-12, FR-13 and FR-14 were formulated comprising of MCC-sodium lauryl sulphate-croscarmellose sodium - sodium bicarbonate-drug in different ratios such as 92:1:1:2:4% w/w, 91:1:2:2:4% w/w, 90:1:3:2:4% w/w, 89:1:4:2:4% w/w, 88:1:5:4% w/w, 87:1:6:2:4% w/w and 86:1:7:2:4% w/w. Here, 1% w/w PVP K-30 suspension in distilled water was used as standard binder for comparison, and the formula consisted of MCC-sodium lauryl sulphate- croscarmellose sodium in ratio 86:1:7:2:4% w/w. The powder mixes were prepared as 100 g batches by geometric mixing in polyethylene bag for 10 min. Then the above mixture of dry blend was granulated by using 1% w/w locust bean gum suspension as granulation fluid. The wet mass was extruded using a cylinder roll type extruder with 1 mm opening diameter at 40 rpm. The obtained extrudates were spheronized in a spheronizer fitted with a cross-hatched rotor plate of 150 mm diameter and 2.5 mm thickness. The resulting spheroids were dried in hot air oven (Memmert 30, Germany) at 40 °C for 8 h. For the optimization of spheronization speed, extrudates from all the selected ratios were subjected to spheronization at different speeds such as 400, 800, 1400 and 1600 rpm. For optimization of spheronization time, the ideal batch of spheroids was subjected to spheronization at 1600 rpm for different duration of time such as 5, 10 and 15 min.

Characterization of spheroids

Micromeritic properties

Tap densities of the prepared spheroids were determined using tap density tester and percentage Carr's index was calculated.[5]

Angle of repose

Angle of repose was assessed by fixed funnel method to know the flow ability of spheroids. Drug loaded spheroids were carefully poured through the funnel until the apex of the conical pile just reaches the tip of the funnel. The radius (r) and height (h) of the pile were then determined[5]. The angle of repose (θ) for samples were calculated using the following Eq. (1):

$$\text{Angle of repose } (\theta) = \tan^{-1}(h / r) \quad \ldots\ldots\ldots\ldots\ldots (1)$$

Compressibility

Carr's index is a dimensionless quantity. This proved to be beneficial to the same degree as the angle of repose values for predicting the flow behavior. The compressibility of the spheroids was determined by Carr's compressibility index[5,16] using the Eq. (2) given below:

$$Carr's\ index = \frac{Tapped\ density - Bulk\ density}{Tapped\ density} \quad \ldots\ldots\ldots\ldots\ldots (2)$$

Scanning Electron Microscopic (SEM) studies

SEM photographs were taken with a scanning electron microscope Model Bruker Nano X flash detector 5010, Germany, at the required magnification at room temperature[5].

Spheroid size

Spheroidal size was determined using an image analysis system. Photomicrographs were taken with a digital camera (Sony, Cyber-shot, DSC-H300, Japan). The obtained images were processed by image analysis software (AnalySIS®; Soft Imaging System, Münster, Germany) to characterize each individual spheroid by mean Feret diameter[5,17].

Differential Scanning Calorimetry (DSC)

DSC studies were carried out on Shimadzu thermal analyzer (TA-60WS). A few milligrams of sample, were hermetically sealed into aluminium pans and heated under nitrogen atmosphere with the heating rate of 10 °C/min[5,18].

Evaluation of spheroids

Friability

Friability was determined by using the Roche friabilator tester (Electrolab, India). 10 g of spheroids were subjected to impact testing at 25 rpm for 4 min[5,19].

Percentage yield

The yield of spheroids was determined by the whole weight of spheroids formed against the combined weights of drug, polymer and other excipients. The formula for calculation of % yield is as follows Eq. (3).[5]

$$\%\ Yield = \left[\frac{Wt.\ of\ pellets}{Wt.\ of\ drug\ +\ wt.\ of\ Polymer}\right] X\ 100 \quad \ldots\ldots\ldots\ldots\ldots (3)$$

Drug loading and entrapment efficiency

To determine the entrapment efficiency, specific amount of Atorvastatin calcium spheroids were crushed and suspended in 100 ml of freshly prepared phosphate buffer of pH 6.8 with constant agitation at room temperature for 24 h. Finally, the solution was filtered through whatman filter paper, and drug content was determined by UV absorption spectrophotometer (Shimadzu 1801, USA), at the wavelength of 244 nm. The entrapment efficiency was calculated by using the Eq. (4)[5].

$$\% \ Drug \ Entrapment = \left[\frac{Calculated \ drug \ content}{Theortical \ drug \ content} \right] X \ 100 \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (4)$$

Percent drug loading was calculated by using the following Eq. (5):

$$\% \ Drug \ Loading = \left[\frac{Amt. \ of \ drug \ in \ the \ sampled \ spheroids}{Weight \ of \ spheroids} \right] X \ 100 \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (5)$$

Spheroid disintegration test

Formulations were evaluated for their disintegration in a standard tablet disintegration apparatus (Electrolabs ED-2, India). Special transparent tubes of 10 mm diameter and 15 mm length were used. Sieves of 710 mm mesh size were at the bottom and the top of this tube. After filling 10 mg Atorvastatin calcium equivalent dose spheroids in each tube, they were inserted in the standard tablet disintegration tester. The disintegration time of six dried samples at 37°C was determined at a speed of 30 dips per minute in purified water.

In Vitro Dissolution

To study the in vitro dissolution profile, Atorvastatin calcium spheroids equivalent to 10 mg of were filled in hard gelatin capsule. Dissolution studies were carried out using dissolution apparatus USP-XXIII attached with paddle (Electrolab, Mumbai, India). Freshly prepared phosphate buffer of pH 6.8 (900 ml) was used as dissolution medium at 37±1 °C. The paddle was rotated at 75 rpm. The 5 ml of samples were withdrawn at definite time intervals and immediately replaced with an equal quantity of fresh buffer. The amount of drug released was quantified using the high-performance liquid chromatography (HPLC) method. The HPLC (SHIMADZU LC-2010 AHT) system consisted of UV-Visible detector with LC10 software. The analytical column used was Phenomenex C 18 (25 cm, 4.6 mm i.d., particle size 5 µm) at a temperature of 30 °C. The mobile phase consisted of acetonitrile and triple distilled water containing 1% v/v triethylamine (pH was adjusted to 5.6 with orthophosporic acid) at a ratio of 55:45 v/v which was pumped at a flow rate of 1.0 ml/min. The detection wavelength was 230 nm.[20]

Table 1: Optimization of IR Atorvastatin calcium pellets spheronization speed

Formulation	Spheronization speed (RPM)	Spheroid Description
FR-1	400	Dumbbell shape
	800	Dumbbell shape
	1400	Spheroids with wide size range
	1600	Spheroids with narrow size range
FR-2	400	Dumbbell shape
	800	Dumbbell shape
	1400	Spheroids with wide size range
	1600	Spheroids with narrow size range
FR-3	400	Dumbbell shape
	800	Dumbbell shape
	1400	Dumbbell shape
	1600	Spheroids with narrow size range
FR-4	400	Dumbbell shape
	800	Dumbbell shape
	1400	Dumbbell shape
	1600	Spheroids with narrow size range
FR-5	400	Dumbbell shape
	800	Dumbbell shape
	1400	Dumbbell shape
	1600	Spheroids with narrow size range
FR-6	400	Dumbbell shape
	800	Dumbbell shape
	1400	Dumbbell shape
	1600	Spheroids with narrow size range
FR-7	400	Dumbbell shape
	800	Dumbbell shape
	1400	Dumbbell shape
	1600	Spheroids with narrow size range
FR-8	400	Dumbbell shape
	800	Dumbbell shape
	1400	Dumbbell shape
	1600	Spheroids with narrow size range
FR-9	400	Dumbbell shape
	800	Dumbbell shape
	1400	Spheroids with wide size range
	1600	Spheroids with narrow size range
FR-10	400	Dumbbell shape
	800	Dumbbell shape
	1400	Dumbbell shape
	1600	Spheroids with narrow size range
FR-11	400	Dumbbell shape
	800	Dumbbell shape
	1400	Dumbbell shape
	1600	Spheroids with narrow size range
FR-12	400	Dumbbell shape
	800	Dumbbell shape
	1400	Dumbbell shape
	1600	Spheroids with narrow size range
FR-13	400	Dumbbell shape
	800	Dumbbell shape
	1400	Dumbbell shape
	1600	Spheroids with narrow size range
FR-14	400	Dumbbell shape
	800	Dumbbell shape
	1400	Dumbbell shape
	1600	Spheroids with narrow size range
FR-15	400	Dumbbell shape
	800	Dumbbell shape
	1400	Dumbbell shape
	1600	Spheroids with wide size range
	1800	Spheroids with narrow size range

Table 2: Optimization of IR Atorvastatin calcium pellets spheronization time

Formulation	Spheronization speed (RPM)	Spheronization time (min)	Spheroid Description
FR-1	1600	5	Spheroids not formed
		10	Spheroids not formed
		15	Spheroids formed
FR-2	1600	5	Spheroids not formed
		10	Spheroids not formed
		15	Spheroids formed
FR-3	1600	5	Spheroids not formed
		10	Spheroids not formed
		15	Spheroids formed
FR-4	1600	5	Spheroids not formed
		10	Spheroids not formed
		15	Spheroids formed
FR-5	1600	5	Spheroids not formed
		10	Spheroids not formed
		15	Spheroids formed
FR-6	1600	5	Spheroids not formed
		10	Spheroids not formed
		15	Spheroids formed
FR-7	1600	5	Spheroids not formed
		10	Spheroids not formed
		15	Spheroids formed
FR-8	1600	5	Spheroids not formed
		10	Spheroids not formed
		15	Spheroids formed
FR-9	1600	5	Spheroids not formed
		10	Spheroids not formed
		15	Spheroids formed
FR-10	1600	5	Spheroids not formed
		10	Spheroids not formed
		15	Spheroids formed
FR-11	1600	5	Spheroids not formed
		10	Spheroids not formed
		15	Spheroids formed
FR-12	1600	5	Spheroids not formed
		10	Spheroids not formed
		15	Spheroids formed
FR-13	1600	5	Spheroids not formed
		10	Spheroids not formed
		15	Spheroids formed
FR-14	1600	5	Spheroids not formed
		10	Spheroids not formed
		15	Spheroids formed
FR-15	1600	5	Spheroids not formed
		10	Spheroids not formed
		15	Spheroids not formed
		20	Spheroids formed

RESULTS AND DISCUSSION

Here the ability of locust bean gum to form IR spheroids was demonstrated in mixture with MCC.

In the formulation in formulation of IR Atorvastatin calcium spheroids 1% w/w locust bean gum suspension was used as binder. Table 1 and Table 2 reveal the process of optimization of extrusion and spheronization of IR Atorvastatin calcium spheroids. Here the binder concentration was pegged based upon the quality of the spheroids in terms of sphericity data and the uniformity of size. This 1% w/w level of binder liquid produced the spheroids in the most frequently occurring sieve fraction (800–1500 µm) with the highest value for roundness assessment.[21] In above Atorvastatin calcium spheroids formulations sodium starch glycolate and croscarmellose sodium were used separately, as super disintegrant in the concentration range of 1-7% w/w. The formulations with optimum amount of binder fluid demonstrated a narrower size distribution. However, some formulations prepared using lower amount of binder liquid produced the spheroids with a smaller size (or fines) with a broader size distribution. This is probably due to the insufficient binding ability of the powder blends by binder suspension or to form the homogenous wet mass.[22]

From the SEM studies Figure 2, it was observed that the IR Atorvastatin calcium spheroids formulated with sodium starch glycolate, and 1% w/w locust bean gum suspension as binder produced smoother surface spheroids with increasing, amounts of wet massing liquid. While pellets prepared using 1% w/w locust bean gum suspension as binder and croscarmellose sodium showed chapped surface.

The micromeritic properties of different batches of IR Atorvastatin calcium spheroids as shown in Table 3, like average size (µm), angle of repose, tapped density, carr's index, friability and percentage yield revealed no significant difference among all batches. Angle of repose of all batches of IR Atorvastatin calcium spheroid formulations ranged between 24.19±1.33 – 27.46±1.37°, indicating good flow properties of spheroids, which can be attributed to their spherical shape as evident in (Fig. 1) SEM photomicrographs. The bulk density results of different batches of IR Atorvastatin calcium spheroids indicated close packing settlement because of narrow particle size distribution.

The entrapment efficiency and drug loading of IR Atorvastatin calcium spheroids are given in Table 4. The entrapment efficiency and drug loading of Atorvastatin calcium in its formulations were in the range of 87.00 ± 0.96 – 95.19 ± 1.76% and 3.06 ± 0.18 – 3.80 ± 0.31%.

The thermal analysis of pure Atorvastatin calcium API (Figure 2) shows a sharp endothermic peak at its melting point i.e., at 156.87°C demonstrating its crystalline nature. On the other hand identical but broad peaks were found on DSC analysis of formulation FR-7 FR-14 and FR-15, indicating no interaction of Atorvastatin calcium with its polymers and excipients.

The characterized locust bean gum polysaccharide in the concentration of 1% w/w aqueous suspension was evaluated for its binding efficacy associated with IR Atorvastatin calcium spheroids. The reason behind selecting a natural source polysaccharide as a binder was

due to its distinguishing benefits such as low cost, abundant availability, ease of isolation, stickiness and viscosity.[23] The IR Atorvastatin calcium spheroids were filled in a single hard gelatin capsule and evaluated for *in-vitro* drug release study. The fourteen different batches of IR Atorvastatin calcium spheroids were prepared (FR-1 – FR-14), each containing 1% w/w concentration of the locust bean gum suspension as a binder. From the *in-vitro* release data Figure 3 and Figure 4, it was found that formulations FR-1, FR-2, FR-3, FR-4, FR-5, FR-6 and FR-7 each containing sodium starch glycolate in the concentration range of 1% w/w, 2% w/w, 3% w/w, 4% w/w, 5% w/w, 6% w/w and 7% w/w released 65.46 ± 2.41, 68.71 ± 2.05, 76.82 ± 1.97, 81.14 ± 2.53, 83.94 ± 2.20, 91.61 ± 1.71 and 97.29 ± 2.33% drug at the end of the 45 min dissolution study. Similarly from the *in-vitro* release studies of batches FR-8, FR-9, FR-10, FR-11, FR-12, FR-13 and FR-14 each containing croscarmellose sodium in the concentration range of 1% w/w, 2% w/w, 3% w/w, 4% w/w, 5% w/w, 6% w/w and 7% w/w released 76.31 ± 2.24, 81.86 ± 2.46, 84.78 ± 1.94, 87.03 ± 2.07, 90.51 ± 1.40, 96.21 ± 1.83 and 98.70 ± 1.83% of the drug at the end of 45 min study.

Table 3: Characteristics of IR Atorvastatin calcium spheroids

Formulation code	Average size (µm)	Angle of repose θ°	Granule density (g/cm^3)	Tapped density (g/cm^3)	Carr's index (%)	Friability (%)	Yield (%)	Disintegration Time (sec)
FR-1	1127±41	25.14±1.52	1.09±0.04	0.79±0.05	8.11±0.42	0.52±0.02	74.8±1.21	84±3.20
FR-2	1177±30	26.42±1.24	1.04±0.02	0.81 ±0.04	8.19±0.49	0.54±0.04	79.1±1.57	72±2.47
FR-3	1255±43	25.25±1.46	1.07±0.08	0.80±0.05	9.21±0.44	0.47±0.02	81.4±1.83	57±2.88
FR-4	1274±45	24.19±1.33	1.03±0.06	0.75±0.05	8.01±0.18	0.51±0.05	80.5±1.17	48±2.12
FR-5	1371±50	27.21±1.69	1.05±0.04	0.76±0.04	8.24±0.80	0.44±0.03	76.8±1.34	42±3.04
FR-6	1204±57	26.18±1.27	1.05±0.06	0.83±0.03	9.09±0.41	0.49±0.04	78.4±1.92	35±3.51
FR-7	1140±27	25.06±1.29	1.08±0.03	0.80±0.05	8.21±0.61	0.54±0.05	75.9±1.51	27±2.86
FR-8	1208±32	26.65±1.47	1.06±0.05	0.84±0.02	8.54±0.54	0.44±0.02	80.2±1.66	54±2.71
FR-9	1219±44	26.55±1.24	1.02±0.04	0.81±0.04	8.05±0.87	0.49±0.02	79.7±1.77	48±2.44
FR-10	1244±37	26.04±1.35	1.07±0.06	0.85±0.05	8.46±1.03	0.48±0.04	78.3±1.54	34±1.98
FR-11	1247±42	24.54±1.42	1.01±0.05	0.79±0.02	8.21±1.13	0.54±0.03	79.1±1.80	27±4.31
FR-12	1265±47	27.46±1.37	1.05±0.04	0.81±0.05	8.48±0.14	0.54±0.02	80.8±1.68	25±3.17
FR-13	1341±34	26.35±1.41	1.08±0.03	0.80±0.05	9.04±0.22	0.48±0.05	82.4±1.49	17±3.04
FR-14	1280±29	26.41±1.35	1.07±0.04	0.82±0.03	8.47±0.27	0.51±0.02	78.6±1.57	13±2.53
FR-15	1318±36	27.11±1.32	1.04±0.05	0.81±0.06	8.21±0.60	0.45±0.04	77.1±1.61	18±2.83

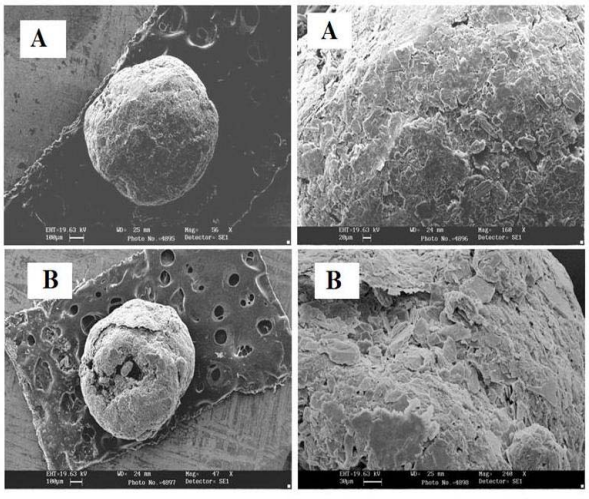

Figure 1: SEM of IR Atorvastatin calcium spheroids: A) Formulation FR-7 and B) Formulation FR-14 at different magnifications.

A high disintegration time for spheroids containing sodium starch glycolate as superdisintegrant was observed compared to croscarmellose sodium as given in Table 3. The significant longer disintegration time for sodium starch glycolate containing spheroids can be attributed to its disintegration mechanism, which acts by swelling on contact with aqueous medium, which is further accompanied by gelling, which could possibly occlude the pores in the spheroids prolonging further disintegration of spheroids.[24,25] Unlike sodium starch glycolate, the croscarmellose sodium has a dual functional mechanism of disintegration i.e., water wicking and rapid swelling, leading to superior disintegration characteristics than sodium starch glycolate. This is the rate limiting step for dissolution of drug. The sodium bicarbonate was included as stabilizer in all the above IR Atorvastatin calcium spheroid formulations, to maintain the drug stability during storage. It also acts as buffering agent which helps to increase the pH of gastric environment, leading to improved efficacy of the dosage form to impart its action. The comparative *in-vitro* dissolution profile of 1% w/w locust bean gum (Formulation FR-14) and 1% w/w PVP K-30 (Formulation FR-15) as binders used in the formulation of IR Atorvastatin calcium spheroids is shown in Figure 4. The results indicated that the spheroids prepared using 1%

w/w locust bean gum as binder showed faster drug release (89.23±2.40 %) compared to 1% w/w PVP K-30 (86.07±2.18 %) in 30 min of time interval. All other parameters for spheroids prepared with PVP K-30 binder like average size, angle of repose, granule density, tapped density, carr's index, friability, yield and disintegration time were commensurate and analogous to optimized formulation FR-14.

Table 4: Entrapment efficiency of different IR Atorvastatin calcium spheroid formulations

Formulation	Drug loading (%)	Entrapment efficiency (%)
FR-1	3.06±0.18	92.21±1.24
FR-2	3.48±0.24	87.00±0.96
FR-3	3.54±0.15	88.51±1.88
FR-4	3.78±0.26	94.24±1.23
FR-5	3.59±0.25	89.67±1.84
FR-6	3.49±0.18	87.15±1.62
FR-7	3.62±0.24	90.46±1.48
FR-8	3.77±0.25	94.08±1.12
FR-9	3.80±0.31	95.19±1.76
FR-10	3.68±0.24	91.93±1.83
FR-11	3.57±0.20	89.34±1.52
FR-12	3.72±0.24	92.81±1.40
FR-13	3.63±0.26	90.54±1.07
FR-14	3.75±0.21	93.70±1.61
FR-15	3.66±0.29	91.38±1.93

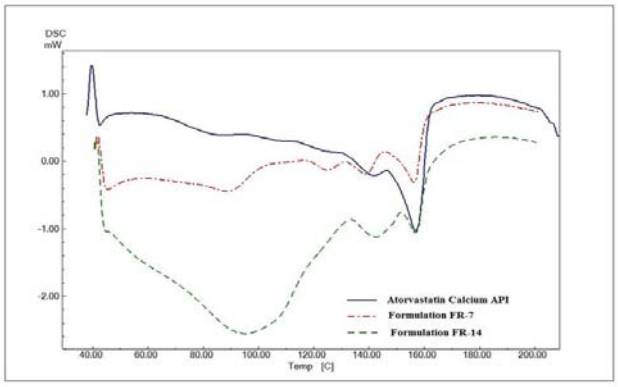

Figure 2: DSC thermogram of Atorvastatin calcium API and its drug loaded formulations i.e., FR-7 and FR-14.

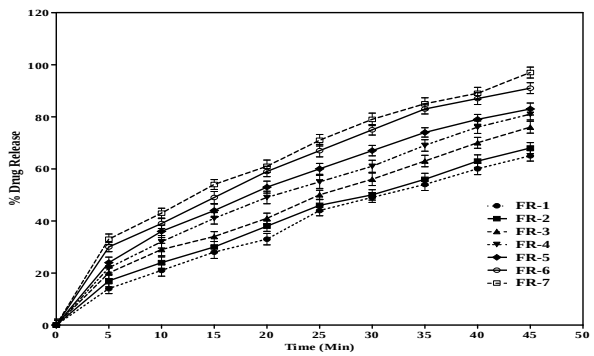

Figure 3: *In vitro* dissolution profile of IR Atorvastatin calcium spheroids prepared with different concentration of sodium starch glycolate (Formulations FR-1 – FR-7).

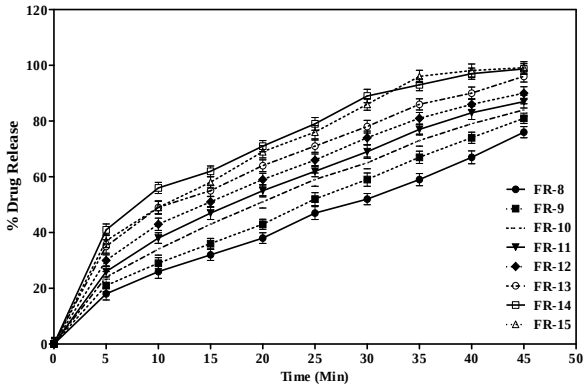

Figure 4: *In vitro* dissolution profile of IR Atorvastatin calcium spheroids prepared with different concentration of croscarmellose sodium (Formulations FR-7 – FR-15).

CONCLUSION

The employed method is economical, simple and rapid. The polysaccharide isolated from the seeds of the carob tree, was found to be suitable as spheronization aid in the formulation of IR Atorvastatin calcium spheroids for fixed dose combination drug delivery system by extrusion/spheronization. The results of friability, micromeritic properties and Hausner's ratio were within the limit. The drug loaded spheroids were orbicular in shape as evidenced in SEM photomicrographs, resulting in good flow properties. From the DSC studies, it was confirmed that, no chemical interaction exists between the drugs and polymer's used, indicating the stability of Atorvastatin calcium with locust bean gum. The IR Atorvastatin calcium formulation containing 1% w/w locust bean gum suspension as a binder and 7% croscarmellose sodium showed fast disintegration of spheroids resulting in a fast dissolution of drug with excellent physico-mechanical properties of spheroids. The above study suggests that the locust bean gum is a promising spheronization aid with high potential.

Acknowledgments: Mr. Rohan D. Deshpande, wish to express his gratitude to Government of India {Council of Scientific and Industrial Research (CSIR), New Delhi}, for providing financial assistance for this project in the form of Senior Research Fellowship (File No:8/484 (0009)/2013-EMR-I).

REFERENCES

1. Bechgaard H, Nielsen H, Controlled Release multiple units and single unit doses, Drug Development and Industrial Pharmacy, 4, 1978, 53–67.
2. Sriamornsak P, Nunthanid J, Luangtana-anan M, Puttipipatkhachorn S, Alginate-based pellets prepared by extrusion/spheronization: A preliminary study on the effect of additive in granulating liquid, European Journal of Pharmaceutics and Biopharmaceutics, 67, 2007, 227–235.
3. Ghebre-Sellassie I, Multi particulate Oral Drug Delivery, Marcel Dekker, New York, 1994.

4. Ananymous, Preparing Modified Release Multi particulate Dosage Forms With Eudragit Polymers, Pharma Polymers News, 9, 2002, 2-3.
5. Deshpande RD, Gowda DV, Mahammed N, Design of Pistacia lentiscus (mastic gum) controlled release spheroids and investigating the influence of roll compaction, Industrial Crops and Products, 44, 2013, 603-610.
6. Nakano M, Ogata A, Examination of natural gums as matrices for sustained release of Theophylline, Chem Pharm Bull (Tokyo), 32, 1984, 782-785.
7. Kulkarni GT, Gowthamarajan K, Brahmajirao G, Suresh B, Evaluation of binding properties of selected natural mucilages, Journal of Scientific and Industrial Research, 61, 2002, 529-532.
8. Baveja SK, Rangarao KV, Arora J, Examination of natural gums and mucilages as sustaining materials in tablet dosage forms, Indian Journal of Pharmaceutical Sciences, 50, 1988, 89-92.
9. Kulkarni GT, Gowthamarajan K, Dhobe RR, Yohanan F, Suresh B, Development of Controlled Release Spheriods using Natural Polysaccharide as Release Modifier, Drug Delivery, 12, 2005, 201-206.
10. Dey P. Sa B, Maiti S. Carboxymethyl ethers of locust bean gum—A review, International Journal of Pharmacy and Pharmaceutical Sciences, 3, 2011, 4–7.
11. Bashardoust N, Leno Jenita JJ, Zakeri–Milani P, Physicochemical Characterization and Dissolution Study of Ibuprofen Compression-Coated Tablets Using Locust Bean Gum. Dissolution Technology, 2013, 38-43.
12. Shah N, Shah T, Amin A, Polysaccharides: a targeting strategy for colonic drug delivery. Expert Opinion on Drug Delivery, 8, 2011, 779–796.
13. Jain SK, Jain A, Target-specific drug release to the colon. Expert Opinion on Drug Delivery, 5, 2008, 83–498.
14. Chourasia MK, Jain SK, Pharmaceutical approaches to colon targeted drug delivery systems. Journal of Pharmacy and Pharmaceutical Sciences, 6, 2003, 33–66.
15. Sinha VR, Kumria R, Microbially triggered drug delivery to the colon. European Journal of Pharmaceutical Sciences, 8, 2003, 3–18.
16. Wong TW, Chan LW, Lee HY, Heng PW, Release characteristics of pectin microspheres prepared by an emulsification technique, Journal Micro encapsultion, 19, 2002, 511–522.
17. Cosijins A, Nizet D, Nikolokakis I, Porous pellets as drug delivery system, Drug Development and Industrial Pharmacy, 35, 2009, 655–662.
18. Du Pasquier A, Disma F, Bowmer T, Gozdz AS, Amatucci G, Tarascon JM, Differential scanning calorimetry studies of lithium ion and the reactivity of carbon anodes in plastic lithium ion batteries, Journal of the Electrochemical Society, 145, 1998, 472–477.
19. Chaudhari MP, Chaudhari DP. Formulation and evaluation of multiparticulate system for chronotherapeutic delivery of salbutamol sulphate. Journal of Pharmacy and Bioallied Sciences, 4, 2012, S71–S73.
20. Wei H, Qing D, De-Ying C, Bai X, Li-Fang F, *In-vitro* and in-vivo studies of pectin/ethylcellulose film-coated pellets of 5-fluorouracil for colonic targeting, Journal of pharmacy and pharmacology, 60, 2008, 35–44.
21. Chatchawalsaisin J, Podczeck F, Newton JM, The influence of chitosan and sodium alginate and formulation variables on the formation and drug release from pellets prepared by extrusion/spheronization, International Journal of Pharmaceutics, 275, 2004, 41–60.
22. Sriamornsak P, Nunthanid J, Luangtana-anan M, Weerapol Y, Puttipipatkhachorn S, Alginate-based pellets prepared by extrusion/spheronization: Effect of the amount and type of sodium alginate and calcium salts, European Journal of Pharmaceutics and Biopharmaceutics, 69, 2008, 274–284.
23. Fell JT, Surface and interfacial phenomenon. In Pharmaceutics- The Science of Dosage Form Design. Ed. M. E. Aulton. New York: Churchill Livingstone, 1988, 50–61.
24. Gowthamarajan K, G. Kumar KP, Gaikwad NB, Suresh B, Preliminary study of *Anacardium occidentale* gum as binder in formulation of paracetamol tablets, Carbohydrate Polymers, 83, 2011, 506–511.
25. Yuasa H, Takashima Y, Kanaya Y, Studies on the development of intra gastric floating and sustained release preparation. I. Application of calcium silicate as a floating carrier, Chemical and Pharmaceutical Bulletin, 44, 1996, 1361–1366.

Source of Support: Nil, **Conflict of Interest:** None.