Research Paper

Ultrasound-induced Microencapsulation of Simvastatin for Gastric Retention and Controlled Delivery

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The objective of this study is to demonstrate an effective technique with potential for commercialization for microsphere production. Ultrasound-assisted ionic gelation of sodium alginate was used to encapsulate simvastatin. Chitosan was used as a mucoadhesive polymer for gastroretention of microsphere. Sodium alginate solution was sonicated using probe sonicator at a frequency of 20±3 KHz and ultrasonic power of 130 W with an input voltage range of 170-270 AC, 50 Hz, at a temperature of 50°. The influence of ultrasound waves on drug entrapment efficiency, yield and particle size dispersion was studied in comparison to mechanical stirring method. Mucoadhesiveness, release pattern and kinetics of drug release were also characterized. Ultrasound treatment caused small fissures and depressions on the surface of alginate as evidenced in SEM. Ultrasound of 20±3 KHz for 12 min duration was the optimum frequency and time in the experimental set up to obtain microspheres with uniform and smaller microparticles. The encapsulation efficiency of simvastatin was directly proportional to the sonication effect, concentration of alginate and extent of its cross linkage with calcium ions. DSC studies revealed that ultrasound treatment did not alter the structural integrity of the drug component. Formulation was found to be dissolution efficient and drug release pattern was concentration-dependent, which followed non-Fickian diffusion mechanism with an 'n' value of 0.8. Therefore, it could be concluded that ultrasound can be used as an efficient technology to develop drug-entrapped microsphere for controlled delivery.

Key words: Sonication, acoustic cavitation, microencapsulation, simvastatin, ionic gelation, drug release kinetics

In the present era, there is an immense need for the pharmaceutical industries to step forward, contrive novel effectual drug formulations and techniques to ameliorate the existing products. On the other hand, lack of scale up techniques and commercial procedures were the reason for the failure of the novel drug delivery system (DDS) to enter the market. Therefore, the pharmaceutical industries are in search of effective, reproducible and simple methods for producing DDS. A continuous search is on to find out better techniques for generating DDS, and to make a positive impact on the conventional techniques. Recently, ultrasound cavitation has gained importance due to its widespread use in a variety of processes i.e. physical, chemical and biological[1]. Research in ultrasound-activated novel delivery has emerged widely in the last two decades with the origination of gas bubbles[2]. High energy ultrasonic vibrations are tried for designing and formulating the various novel DDS[3]. Recently, in novel aspects, advantages of ultrasound technology in terms of intensification and low energy requests for microencapsulation are emphasized[4]. Generation of microspheres using cavitation approach is highly energy efficient and also flexible to control particle size over other conventional mechanical and high-pressure techniques[5]. The impact of process parameters such as the flow rate and liquid properties on the size distribution and effect of other equipment parameters like the operating frequency, power dissipation have also been evaluated over conventional methods[6].

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Review of literature emphasized that ultrasound-assisted microencapsulation, which is the scope of this research work appeared to be more competitive and attractive or even superior in terms of simplicity, reproducibility and energy efficiency compared to other conventional formulation approach[7,8]. In view of this, ultrasound-assisted microencapsulation has been proposed for the preparation of simvastatin microspheres in the current work.

Simvastatin is one of the widely used drugs in the treatment of hyperlipidemic condition and for the prophylactic treatment of obesity. It is highly effective in lowering the levels of low-density lipoprotein and triglycerides in the blood and for improving the lipid profile in hypercholesterolemic diabetic patients[9]. However, simvastatin has a few limitations for its conventional delivery. Simvastatin has a short half-life (<2 h) and therefore requires to be administered multiple times a day[10]. The bio-absorption of this drug is comparatively high in the upper portion of the GIT; therefore delivery of this drug by conventional methods result in variable and non-uniform absorption[11]. Lower duration of residence in the stomach and varying gastric emptying time may have a significant impact on the bioavailability of this drug[12]. Hence, a special delivery technique should be designed, which extends the gastric emptying time and deliver higher amount of drug in the stomach. Also, a formulation that would deliver the drug for a sustained span of time would be ideal. Drug-entrapped mucoadhesive microspheres have been designed for gastroretentive drug delivery[13]. These forms reduce the chances of dumping of dose and also inter-subject variability in absorption. Therefore the objective of this study is to investigate ultrasound waves for the production of simvastatin-entrapped microspheres.

MATERIALS AND METHODS

Simvastatin was obtained as a gift sample from Biocon, Bangalore, India. Sodium alginate and chitosan were purchased from Sigma-Aldrich, St. Louis, Missouri, United States. All other polymers, chemicals and reagents used were of analytical reagent grade.

Construction of standard curve of simvastatin:

Simvastatin solution bearing a concentration of 1000 µg/ml was prepared in methanol[14]. Distilled water was used to further dilute the initial stock solution in methanol to obtain solutions with concentration ranging from 5-30 µg/ml. Simvastatin solutions of different concentration were scanned to detect the absorption maxima (λ_{max}), which was found to be 239 nm (fig. 1). Then, the standard curve of simvastatin was constructed at 239 nm using a spectrophotometer (UV-1800, Shimadzu, Kyoto-Japan). Standard curve was found to be linear at this wavelength and the correlation coefficient (r^2) value obtained was 0.999.

Fourier-transform infrared spectroscopy (FTIR) study:

FTIR study was employed to characterize and quantify the physicochemical compatibility between simvastatin and the polymers incorporated in the formulation. FTIR spectra were recorded for the mixture of drug and polymer at 1:1 ratio and for the drug separately. The spectra of the samples were obtained using an FTIR (Bruker Optics, model Tensor 27; Opus software) instrument. The sample was analysed in the ambit of 400-4000 cm^{-1}; wave number versus percent transmittance spectra was plotted.

Differential scanning calorimetry (DSC) analysis:

DSC analysis was performed on a differential thermal analyser 2100 (Dupont Co., Parkersburg, WV, USA) in an open pan system under stable atmospheric considerations. Initial DSC was obtained by an analyser, which was provided with data developing

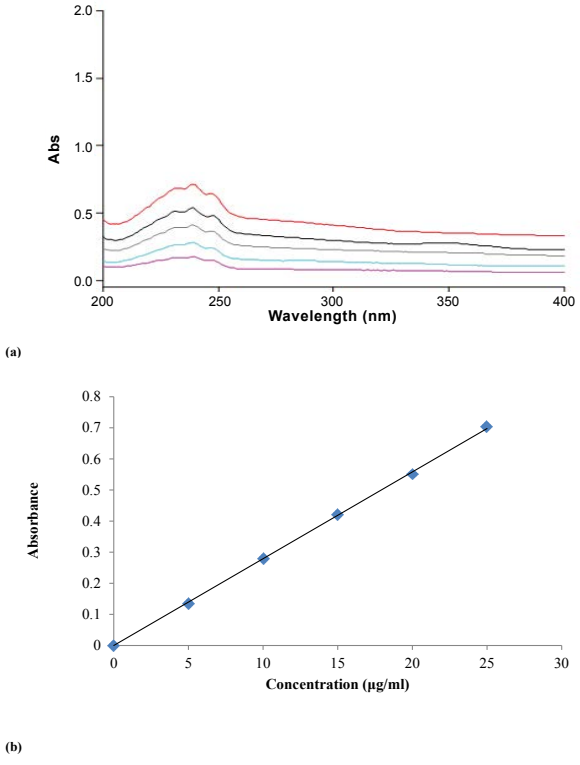

Fig. 1: UV spectra of simvastatin
UV spectra of (a) different concentrations of simvastatin and (b) standard curve of simvastatin with a slope of 0.027x

system. Alumina was used as the standard, which is inert in nature. The samples for analysis were packed in an aluminium pan and the thermal readings were observed at a room temperature of 160° at the rate of 10° min^{-1}. They were then cooled to room temperature. All samples were kept under nitrogen while cooling curves were recorded.

Scanning electron microscope (SEM) studies:

Sodium alginate solution was treated with ultrasound for 10 min at 50° using Sonoplus HD 2200 homogenizer (Bandelin Electronic, Berlin, Germany). Cavitation produced at a frequency of 20±3 KHz and ultrasonic power of 130 W with an input voltage range of 170-270 AC, 50 Hz were observed under SEM (Zeiss, IISc, Bangalore) at specified magnification (x5 and x10) in room temperature.

Formulation of gastroretentive microspheres:

Mucoadhesive gastroretentive microspheres entrapped with simvastatin were produced by ionic gelation method combined with ultrasonication[15]. Formulation composition and design of experiment has been shown in Table 1. The polymers tested in the formulation were chitosan and sodium alginate. The effect of ultrasound waves on drug entrapment efficiency, percent yield and particle size dispersion were studied in comparison to mechanical stirring method. Mucoadhesiveness, release pattern and kinetics of drug release were also characterized.

Preparation of polymer solution:

Simvastatin equivalent to 20 mg was dissolved in sufficient volume of ethanol on a magnetic stirrer by stirring at 300 rpm at room temperature. Simvastatin solution was incorporated in calcium chloride solution with uninterrupted stirring on a magnetic stirrer at a speed of 300 rpm to obtain homogenous solution. Sodium alginate solution was prepared in dilute HCl (pH 5.5) with continuous stirring for 8 h at a slow speed (100 to 300 rpm) on a magnetic stirrer to get a clear solution. Chitosan solution in 1 % acetic acid (pH 5.4) was prepared on a magnetic stirrer at a speed of 300 rpm[16].

Sodium alginate solution, 150 ml per batch was sonicated in a glass beaker of 250 ml capacity and a diameter of 7 cm. Probe sonicator at a frequency of 20±3 KHz and ultrasonic power of 130 W with an input voltage range of 170-270 AC, 50 Hz was used (fig. 2). Probe of diameter 2 cm and immersed in the suspension to a depth of 3 cm in a beaker 2 cm away from the bottom. Sonication was in continuous mode with temperature control to 50°. During the sonication, simvastatin dispersed in calcium chloride solution was added drop-wise to sodium alginate solution.

Another set of microencapsulation was also carried out for selected formulation composition (Table 1) using similar procedure mentioned above but without sonication. At the time of addition of simvastatin-dispersed calcium chloride solution, sodium alginate solution was stirred at a speed of 900 to 1100 rpm on a magnetic stirrer.

Chitosan coating:

Immediately after cross linking of alginate dispersion, it was placed over magnetic stirrer and chitosan solution was added drop-wise at a stirring speed of

TABLE 1: FORMULATION OF SIMVASTATIN MICROSPHERES

Formulation code	Sodium alginate and chitosan solution		Calcium chloride solution	Sodium alginate, chitosan and calcium chloride solution (volume ratio)	Sonication time period (min)
	Conc. (% w/v)	Conc. ratio	Conc. (% w/v)		
F1	0.2:0.4	1:2	0.5	10:4:2	04
F2	0.3:0.4	1.5:2	0.5	10:4:2	08
F3	0.4:0.4	2:2	0.5	10:4:2	12
F4	0.5:0.4	2.5:2	0.5	10:4:2	16
F5	0.2:0.6	1:3	0.5	10:4:2	04
F6	0.3:0.6	1.5:3	0.5	10:4:2	08
F7	0.4:0.6	2:3	0.5	10:4:2	12
F8	0.5:0.6	2.5:3	0.5	10:4:2	16
F9	0.2:0.8	1:4	0.5	10:4:2	04
F10	0.3:0.8	1.5:4	0.5	10:4:2	08
F11	0.5:0.8	2.5:4	0.5	10:4:2	12
Encapsulation without sonication					
F12	0.4: 0.4	2:2	0.5	10:4:2	10
F13	0.5: 0.6	2.5:3	0.5	10:4:2	10
F14	0.5: 0.8	2.5:4	0.5	10:4:2	10

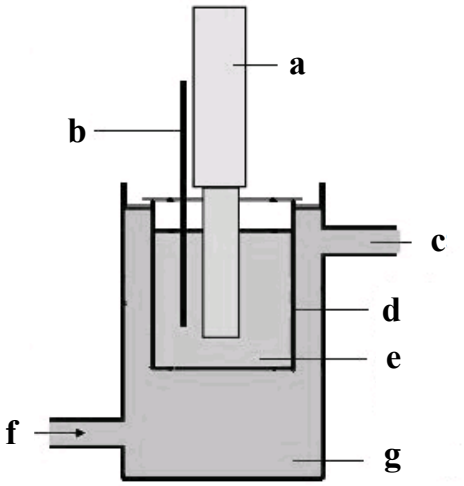

Fig. 2: Ultrasound instrumentation set up for microsphere production
a. Ultrasonic probe; b. thermostat; c. water out; d. sample holder; e. sample solution; f. water in (50°); g. water jacket

300 rpm. Preparation was kept overnight, filtered and dried at 50° to collect free flowing microspheres[17].

Entrapment efficiency:

Entrapment efficiency was conducted to quantitatively estimate the amount of drug present in microspheres. Microspheres were crushed in a clean dry mortar. A sufficient volume of methanol was added to it in order to dissolve the drug. The solutions were sonicated to obtain homogenous solution. The resultant solution was strained through a membrane filter (0.45 µ). Clear filtrate of the drug extract was diluted appropriately with methanol and subsequently with distilled water. Drug concentration was measured spectrophotometrically on a UV/Vis instrument at 239 nm[18]. The product yield was determined for all the formulations using the following Eqn., % yield = (practical yield/theoretical yield)×100. The percent encapsulation efficiency was calculated from the following Eqn., % encapsulation efficiency = (amount of encapsulated drug/amount of added drug)×100.

Particle size distribution study:

Standard USP procedure (method I) for size analysis was followed to understand the size dispersion of microspheres. A set of seven standard sieves (0.15-1.18 mm) were used in the study, sieves were arranged such that course sieve to the top and finest sieve to the bottom. Entire sieves array was mounted on the sieve shaker. Dried sample of microspheres weighing accurately 100 g was placed on the top (coarse) sieve. The sieve shaker was operated for 10 min. The samples retained on each sieve was then collected and processed for analysis. Homogeneity of the formulation was determined by plotting % retained weight vs. sieve size[19]. Assessment of size distribution was made with the help of a grading curve, i.e. log sieve size versus % fines. D_{30}, D_{60} and D_{90} values were ascertained from the grading curve, which corresponded to 30, 60 and 90 % fines[20]. To check the spread of the range of the particle sizes the coefficient of uniformity (C_U) and coefficient of curvature (C_C) was also calculated using the Eqn., $C_U = D_{60}/D_{10}$; $C_C = [D_{30}]^2/D_{10}D_{60}$.

***In vitro* mucoadhesion test:**

This study was performed in the simulated gastric fluid. The scraped gastric mucosal layers were obtained freshly from goat and mounted on the wooden piece (6×1.5 cm). Microspheres (100 mg) were placed on the mounted tissue and incubated for duration of 5 min and placed in the cylindrical tubes of a disintegration test apparatus containing simulated gastric fluid (900 ml). Then the disintegration apparatus was operated. The tissue specimen was given a slow, up and down movements in the test fluid at 37°, at a speed of 31 dips/min. After every 1 h time interval the fluid was filtered and number of micro particles that falls out of the tissue was counted and the procedure was continued for 12 h[21,22].

***In vitro* drug release study:**

This study of release pattern for the selected formulations (F3, F8, F11) were carried out using an amber-coloured USP XXIV dissolution apparatus (TDT-08T, Electrolab) type-II (paddle) method for 12 h. Drug-entrapped microspheres (100 mg) were placed in 0.1 N HCl (900 ml, pH 1.2) solution maintained at 37±0.5° and stirred at 75 rpm. A known volume of dissolution sample was withdrawn each time and was replenished with the same volume of pre-warmed fresh dissolution media. The amount of simvastatin released was analysed in a UV/Vis spectrophotometer at 239 nm. The experiments were performed in triplicate.

Drug release kinetics were analysed with various mathematical models such as Higuchi, Korsemeyer-Peppas and zero order kinetics. The correlation coefficient values (r^2) were used to determine how well it fits in a model and also evaluation of the drug release pattern[23,24].

Dissolution efficiency (DE):

DE of a pharmaceutical dosage form is defined as the area under the dissolution curve between defined time points[25]. DE was used to compare the dissolution

profiles of three formulations F3, F8 and F11, considering the amount of drug dissolved in 12 h as the maximum. The following equation was used to characterize the % DE. % DE = $(\int_o^t y.dt/y_{100}.t)\times 100$.

RESULTS AND DISCUSSION

The rationale of this work was to improve the therapeutic efficacy of simvastatin through preparing gastroretentive mucoadhesive microspheres. A gastroretentive mucoadhesive microspheres entrapped with simvastatin was developed by ultra-sonication combined with ionic gelation of sodium alginate. Ultrasound frequency of 20±3 KHz (130 W) with an input voltage range of 170-270 AC, 50 Hz, was applied to fabricate simvastatin-entrapped microsphere[26]. Biocompatible polymer, chitosan was employed to impart mucoadhesive character to the microspheres, thereby these could be retained in the stomach by adhesion to the mucosal wall. Drug release from these microspheres then would be continuous to mucosal tissues and eventually to get absorbed in to the systemic circulation. Simvastatin microspheres cross-linked with calcium ions help in the delivery of the drug for a prolonged period of time[4].

Many variables control the characteristics of drug-entrapped microspheres. The impact of ultrasound waves on drug encapsulation efficiency, yield and particle size of microspheres was investigated in comparison to mechanical stirring method. The mucoadhesiveness and drug release kinetics from the microspheres were also characterized to understand efficiency of DDS[27].

Drug compatibility was explored using the FTIR method, and simvastatin was found to be stable in the presence of formulation ingredients (fig. 3). Frequencies of the functional groups were within the standard range (Table 2). Further, treatment with ultrasound waves did not modify the integrity of the drug substance; as was clearly evident from the DSC studies (fig. 4).

Initially, in order to standardize the ultrasound frequency required to produce cavities in the polymeric structure, many trials were run employing ultrasound at the frequencies ranging from 20 to 33 KHz and at a fixed concentration of alginate solution. Ultrasound at the frequencies of 20±3 KHz produced small fissures and depressions on the surface of the sodium alginate solution (fig. 5). This effect enabled the polymeric structure to develop cavities[28]. Intense shock waves caused cavitation bubble to collapse violently inwards in the liquid leading to the formation of liquid jets of high speed. This resulted in the formation of numerous cracks and scratches on the polymer which in turn helped in the formation of mean droplet sizes in the range of micrometres[29]. The power required to disperse a liquid phase in to small droplets was rendered by the high, intensive ultrasound. Formation of cavities inside the polymeric structure enabled the microspheres to be uniform (fig. 6) and observed with highest drug entrapment. Therefore, the frequency of 20±3 KHz was chosen for further investigation.

Another investigation of this study was to understand the effect of duration of ultrasound waves on the properties of microspheres (Table 3). The microspheres were produced with varying the sonication time from 4 to 16 min and also varying the concentration of alginate. The production yield was largest (78.61± 2.07 %) when formulation was sonicated for 10 min. The lowest yield (55.23±1.25) was observed when sonicated for 4 min. The yield of the formulations F3, F8 and F11 was 70 % when sonicated for a period of 12 min. Because, ultrasound provided the local molecular vibration to disentangle polymer chains and slight reduction of molecular weight, both of which improved drug dispersion. Increasing the ultrasound power level increased the local power density in the polymer matrix and resulted in a more mechanochemical degradation that provided a greater reduction in tensile strength[30]. As a result the yield and encapsulation efficiency was significantly higher. Whereas, mechanical stirring failed to disentangle the polymeric chains and did not induce fissures and depressions on the surface of the polymer. It did not cause any local molecular vibrations and therefore failed to disentangle polymer chains. As a result, the yield and entrapment efficiency was found to be less in the case of F12, F13 and F14.

The drug encapsulation efficiency was found to be highest at an alginate concentration of 0.5 % w/v. Higher viscosity of the polymer solution owing to the increased polymer concentration decreased the drug on the external surface resulting in higher encapsulation efficiency[5] (Table 3). The encapsulation efficiency of simvastatin was found to be directly proportional to the concentration of the alginate, extent of its cross linkage with calcium ions and ultrasound time. Lower alginate concentrations reduced the viscosity of the mixture which lead to lower encapsulation. There was no appreciable increase in encapsulation efficiency upon

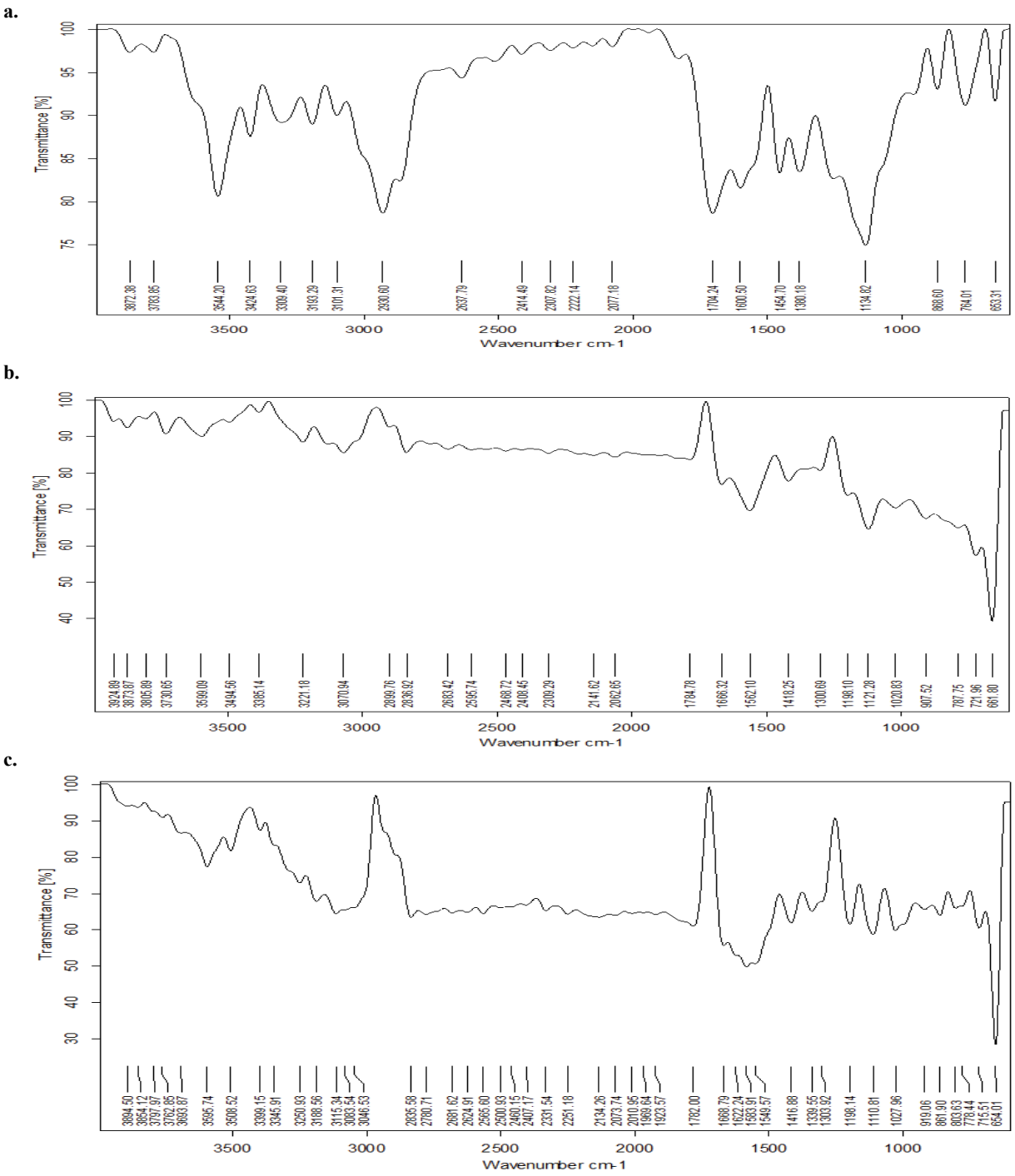

Fig. 3: Physical compatibility study
FTIR Spectra of (a) simvastatin, (b) physical mixture of simvastatin and sodium alginate and (c) physical mixture of simvastatin and chitosan

TABLE 2: FTIR SPECTRA OF SIMVASTATIN AND PHYSICAL MIXTURES WITH FORMULATION INGREDIENTS

Functional Group	IR Standard Range (cm^{-1})	Simvastatin (cm^{-1})	Simvastatin with sodium alginate (cm^{-1})	Simvastatin with chitosan (cm^{-1})
C=O stretch	1760-1665	1704	1666	1666
O-H stretch(H-bonded)	3500-3300	3424	3397	3385
C-H stretch	3000-2850	2893	2833	2899
C=C stretch	3100-3010	3101	3083	3070
C-O bend	1150-1050	1134	1114	1121

Readings are mean of 3 observations

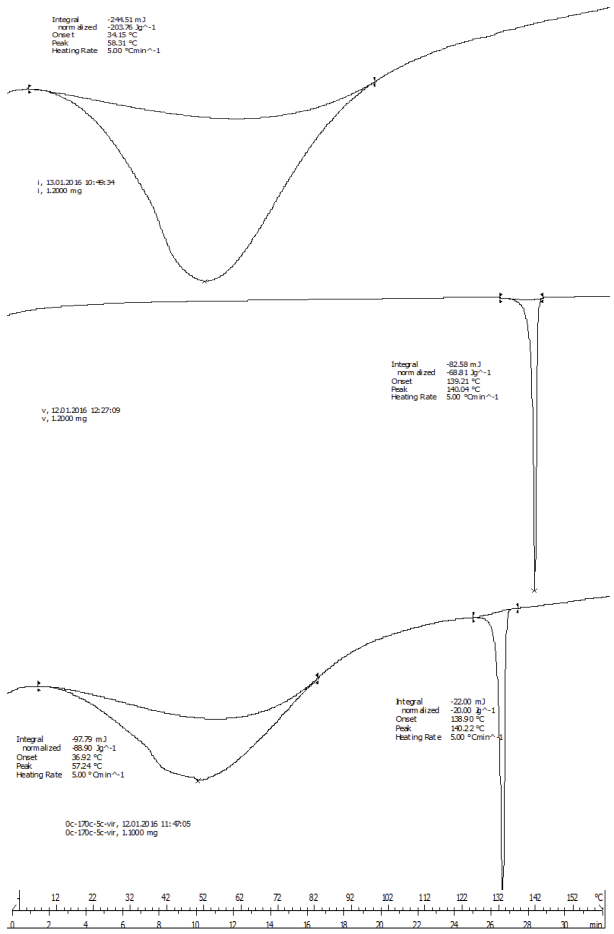

Fig. 4: DSC spectra of sodium alginate, simvastatin and formulation F11
Simvastatin showing endotherm at 140.04

increase in chitosan concentration as chitosan did not undergo ionic gelation.

The mucoadhesiveness of the microspheres also increased as the concentration of chitosan increased. The mucoadhesiveness of all the formulations was found to be above 60 % and lasted for more than 12 h. Mucoadhesiveness of the formulations with highest concentration of chitosan (F9, F10, and F11) was above 75 %. Therefore, the concentration of chitosan appeared to be of great significance in retaining microspheres in the upper gastric environment (Table 3).

Bulk flow, size distribution, surface properties were reported to directly affect the dissolution and drug release properties[31,32]. Therefore, to understand the effect of sonication and mechanical stirring on the micromeritic properties, formulations F3, F8, F11, F12, F13 and F14 were examined by deriving D_{10}, D_{30}, D_{60}, D_{90} values and coefficients such as C_U and C_C (Table 4). The ultrasound has an appreciable effect on the size of the microspheres. Increased sonication frequency and time duration resulted in smooth and smaller sized particles. Lower alginate concentration in combination with increased sonication time (16 min) produced smaller and smoother microspheres. The combination of lower sonication time (4 min) and higher alginate concentration resulted in large-sized, irregular and rough-surfaced microspheres. The percent fines obtained was significantly increased with increasing the sonication time. The size and surface characteristics of F3, F8 and F11 formulations were found to be smaller and smoother in comparison to F12, F13 and F14 as shown by the size distribution pattern in fig. 6.

D_{10} referred to 10 % of the particles are finer and 90 % of the particles are coarser than that particular particle size D_{10}. Similarly, D_{60} means diameter of the microparticles for which 60 % of the particles are finer and 40 % of the particles are coarser than D60. Hence in the present investigation, D_{10}, D_{30}, D_{60} and D_{90} values were used as measures of gradation. The D_{10}, D_{30}, D_{60}, and D_{90} values obtained were within satisfactory range indicating that the % fines obtained were not to a greater extent. Therefore, the ultrasound of 20±3 KHz for 12 min duration was the optimum frequency and

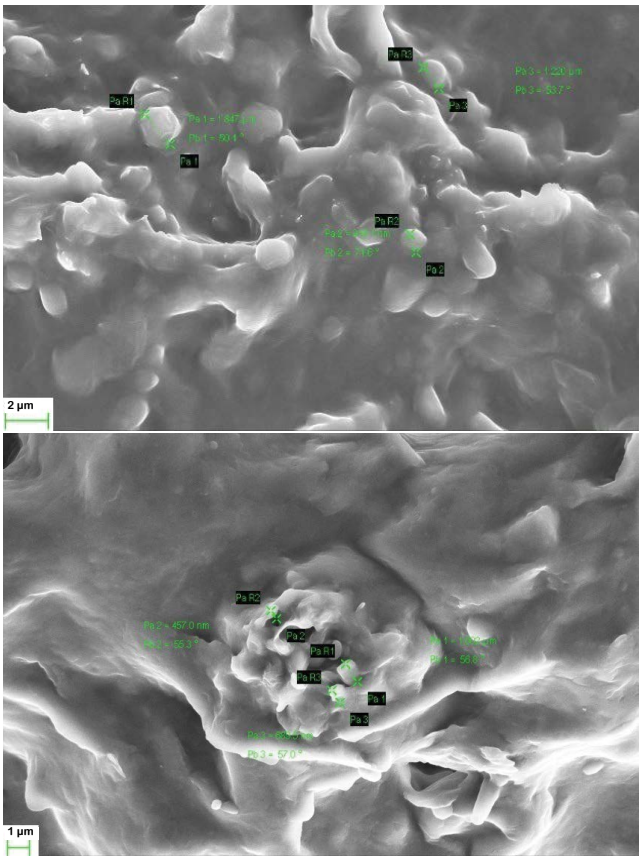

Fig. 5: Ultrasounds action and surface modification of drug entrapped sodium alginate

time to obtain microspheres with uniform and smaller sized microparticles.

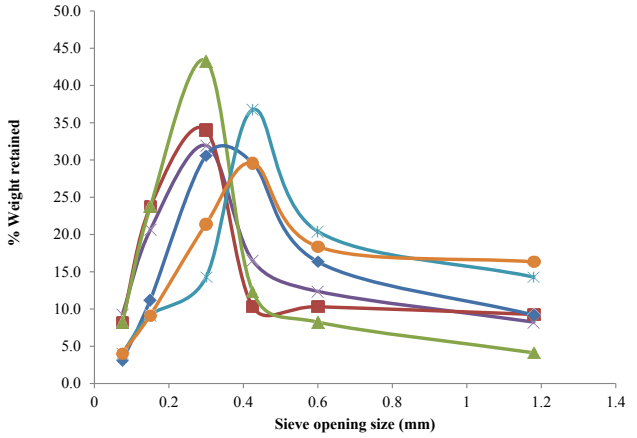

Fig. 6: Size distribution of microspheres from selected formulations

F3; F8; F11; F12; F13; F14

Further, to ascertain the size distribution, the C_U and C_C values were verified. When the C_U was less than 4, the microspheres were considered to be uniform in size or monodisperse. If the value of C_U was greater than 4, then the microspheres were said to be graded or polydisperse. Another coefficient to measure size distribution is coefficient of gradation or coefficient of curvature (C_C)[33]. For the particles to be monodisperse, the value of C_U has to be smaller than 4 and C_C should be around 1. C_U and C_C values were less than 4 and around 1, respectively, for the formulations F3, F8 and F11 indicating that they were monodisperse in nature.

Release studies were conducted for formulations F3, F8 and F11 in simulated gastric media for 12 h. Drug release from all of these formulations was observed to be sustained as shown in fig. 7. The pattern of drug release for formulation F11 was linear and satisfactory in comparison to F3 and F8. Interpretation of

TABLE 3: FORMULATION PROPERTIES OF SIMVASTATIN MICROSPHERES

Formulation Code	% Yield	Encapsulation efficiency	% Particles retained on tissue after 12 h	AUC	DE (%)
F1	55.23±1.25	48.08±2.05	56.25±1.25	450.21±3.01	66.59±1.14
F2	62.47±0.15	54.26±2.12	55.27±2.02	600.14±2.11	76.73±1.16
F3	71.56±2.16	61.26±1.78	69.24±0.15	702.00±3.04	83.66±0.88
F4	74.56±1.85	62.21±3.01	71.43±0.35	779.00±6.54	89.49±2.13
F5	58.45±2.05	51.24±2.85	61.34±1.01	526.31±6.17	71.60±1.1
F6	65.24±3.08	56.24±2.45	59.24±1.23	565.21±3.73	74.12±1.12
F7	67.13±2.54	64.51±2.22	79.32±0.15	711.31±3.06	77.70±2.11
F8	77.03±1.58	65.52±1.09	72.45±1.15	709.58±4.11	73.52±2.12
F9	70.31±1.27	52.18±3.12	76.54±0.34	760.21±6.04	75.85±2.20
F10	74.05±2.65	62.51±3.54	69.47±1.23	821.04±3.21	92.17±2.14
F11	78.61±2.07	71.58±0.12	76.23±1.07	920.41±3.31	96.88±2.22
F12	63.26±0.15	46.22±1.25	73.42±2.07	483.05±3.28	69.86±2.09
F13	65.12±0.05	49.25±1.55	76.34±1.13	503.12±4.07	69.25±2.10
F14	66.05±1.41	53.36±1.32	75.72±1.12	523.31±6.08	69.80±1.12

Readings are mean of 3 observations±SD

TABLE 4: SIZE DISTRIBUTION OF MICROSPHERE OF SELECTED FORMULATIONS

Formulation code	Parameter*					
	D_{10}	D_{30}	D_{60}	D_{90}	C_U	C_C
F3	2.10±0.04	2.40±0.12	2.6±0.01	2.95±0.28	1.23±0.08	1.05±0.24
F8	2.05±0.11	2.35±0.12	2.55±0.24	3.0±0.17	1.24±0.14	1.06±0.26
F11	2.15±0.13	2.40±0.26	2.50±0.24	2.80±0.16	1.16±0.14	1.07±0.04
F12	2.01±0.35	2.24±0.06	2.68±0.05	2.81±0.26	1.33±0.22	0.92±0.08
F13	2.09±0.06	2.3±0.12	2.54±0.32	2.79±0.28	1.21±0.26	1.0±0.16
F14	2.0±0.01	2.27±0.14	2.59±0.17	2.88±0.22	1.29±0.16	0.99±0.14

*Values are average of 3 readings±SD

TABLE 5: RESULTS OF KINETIC MODELING OF DRUG RELEASE STUDIES

Formulation code	Zero order		First order		Higuchi model		Peppa's model	
	Slope	r^2	Slope	r^2	Slope	r^2	n	r^2
F3	4.632	0.73	-0.033	0.909	0.799	0.976	0.699	0.875
F8	4.526	0.755	-0.031	0.926	0.819	0.991	0.619	0.885
F11	5.147	0.736	-0.044	0.939	0.892	0.975	0.792	0.821
F12	5.483	0.553	-0.022	0.951	16.65	0.964	0.416	0.980
F13	5.746	0.478	-0.022	0.935	17.53	0.944	0.401	0.968
F14	6.024	0.522	-0.025	0.955	18.33	0.958	0.401	0.982

Values are average of 3 readings

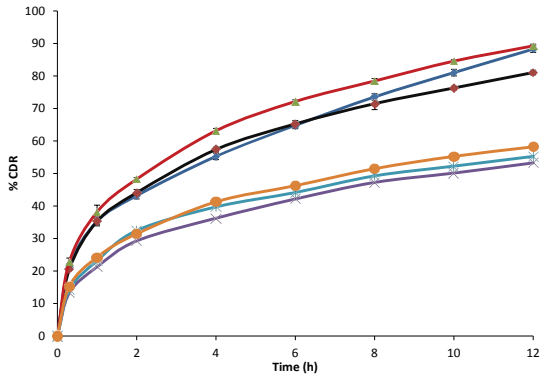

Fig. 7: Drug release pattern of selected formulations
F3; F8; F11; F12; F13; F14

dissolution data through mathematical models showed that the drug release followed first order kinetics, which indicated that the release was concentration-dependent. Further interpretation of results using Higuchi model indicated non-Fickian diffusion to be the predominant mechanism of drug release with 'n' value at around 0.8 (Table 5). % DE was also found to be highest for formulation F11.

Therefore, from the results obtained it could be concluded that the production of microspheres using ultrasound waves was found to be efficient in terms of simplicity, reproducibility and process time. Ultrasound exerted a great impact on the properties of the prepared microspheres. Scale up procedure and commercialization would be possible if ultrasound technique is employed for the production of microspheres. Simvastatin microspheres formulated with a simultaneous ultrasound effect and ionic gelation of the polymer showed a desirable drug content, good micromeritic properties, and adequate release characteristics.

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Conflicts of interest:

The authors have no conflict of interest.

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