

Research Article

Development and Evaluation of Floating Microspheres of Curcumin

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Abstract

Purpose: To prepare and evaluate floating microspheres of curcumin for prolonged gastric residence time and increased drug bioavailability.

Methods: Floating microsphere were prepared by emulsion solvent diffusion method, using hydroxypropyl methylcellulose (HPMC), ethyl cellulose (EC), Eudragit S 100 polymer in varying ratios. Ethanol/dichloromethane blend was used as solvent in a ratio of 1:1. The floating microspheres were evaluated for flow properties, particle size, incorporation efficiency, as well as in-vitro floatability and drug release. The shape and surface morphology of the microspheres were characterised by optical and scanning electron microscopy.

Result: The floating microspheres showed particle size, buoyancy, drug entrapment efficiency and yield in the ranges of 251 - 387 μ m, 74.6 - 90.6 %, and 72.6 - 83.5 %, and 45.5 - 82.0 %, respectively. Maximum drug release after 20 h was 47.1, 55.7, 69.4 and 81.3 % for formulations F1, F2, F3 and F4, respectively. Scanning electron micrographs indicate pores both on the surface and interior of the microspheres.

Conclusion: The developed curcumin microsphere system is a promising floating drug delivery system for oral sustained administration of curcumin.

Keywords: Gastro-retentive, Sustained release, Curcumin, Floating microspheres; Ethyl cellulose, Hydroxypropyl methylcellulose, Eudragit

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INTRODUCTION

In the past, herbal drugs did not attract researchers' interest for the development of novel drug delivery systems due to difficulties in processing (including standardization, extraction and identification). Recently however, with the advances in technology, new doors have been opened for the development of herbal drug delivery systems [1].

The floating microspheres beneficially alter the absorption of a drug, thus enhancing its bioavailability. They prolong dosing intervals which would allow development of once a day formulations and thereby increase patient compliance beyond the level of existing dosage forms by achieving control over gastric residence time [2-3]. Floating microspheres are gastro-retentive drug delivery systems based on a non-effervescent approach. These microspheres are characteristically free-flowing powders having a size $< 199 \mu\text{m}$ and remain buoyant over gastric contents for a prolonged period. As the system floats over gastric contents, the drug is released slowly at the desired rate, resulting in increased gastric retention with reduced fluctuations in plasma drug concentration [4].

Studies have revealed that curcumin has broad range of therapeutic activities, including anti-inflammatory, antibacterial, antifungal, anticancer, antispasmodic and antioxidant [5]. Curcumin (isolated from *Curcuma longa*) is the active ingredient of the spice, turmeric, used in cooking in India and other regions of Asia. The origin of the plant, *Curcuma longa* L. (which belongs to Zingiberaceae family) is India. Curcumin is a potent phytochemical with a wide range of biological activities and shows low absorption [5]. It was selected for this study because it is poorly absorbed in the lower GIT and has a short elimination half-life of 0.39 h. The poor bioavailability ($< 1\%$) of the molecule owing to its insolubility at gastric pH and degradation at alkaline pH of intestine in the humans, has severely limited its clinical

application. High oral doses (8 g/day) in humans result in C_{max} of $< 2 \mu\text{M}$, and short half life (28 min) limit its use via the oral route [6].

EXPERIMENTAL

Curcumin was a gift sample from Krish Entepizes, Mumbai, India. HPMC and Eudragit S 100 were received as a gift samples from Glukem Pharmaceuticals (P) Ltd, India. All other chemicals used were of analytical grade.

Preparation of floating microspheres

Floating microspheres were prepared by emulsion solvent diffusion method [7]. Briefly, the drug and polymer blends were mixed in the solvent (ethanol/dichloromethane, 1:1) as per the composition in Table 1. The resulting slurry was introduced into a 250 ml beaker containing 200 ml 0.2 % sodium lauryl sulfate SLS and stirred at 750 rpm with a mechanical stirrer for 1 h at room temperature. The floating microspheres were collected by decantation, washed thrice with n-hexane, dried overnight in an oven at $40 \pm 2 \text{ }^\circ\text{C}$, and stored in a desiccator containing calcium chloride as desiccant.

Table 1: Composition of the formulations

Material (mg)	F1	F2	F3	F4
Eudragit S100	250	500	750	-
Ethyl cellulose	-	-	250	500
HPMC	-	-	250	250

Note: Each formulation contained 250 mg of curcumin; The ingredients were dissolved in 10 ml of a solvent system, dichloromethane:ethanol (1:1)

Measurement of particle size

Particle size was measured by microscopic technique. In this method, a suspension of floating microspheres was prepared using castor oil. A drop of the suspension was mounted on a slide and observed under

optical microscope; about 600 particles were measured with the aid of an eye-piece micrometer. All the microspheres in a field were counted [8].

Measurement of bulk density

Bulk density is determined by pouring pre-sieved microspheres into a graduated cylinder via a large funnel and measure the volume and weight.

Measurement of tapped density

A known weight of the microspheres was transferred to a measuring cylinder, tapped manually 100 times, and the ratio of weight to volume of the microspheres gives the tapped density [9].

Determination of Carr's index (Compressibility)

This parameter was computed from tapped (DT) and bulk density (DB) data of the microspheres as in Eq 1 [10]

$$\text{Carr's index} = \{(DT - DB)/DT\}100 \dots\dots\dots(1)$$

Determination of Hausner ratio

The Hausner ratio of the microspheres was determined from the ration of tapped density to bulk density.

Evaluation of angle of repose

The angle of repose of the microspheres, which measures the resistance to particle flow, was determined by the fixed funnel method. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the heap of the blends. An accurately weighed sample of the microspheres was allowed to pass through the funnel freely on to a flat surface. The height (h) and radius (r) of the powder cone were measured and the angle of repose (θ) calculated using Eq 2 [11].

$$\theta = \tan^{-1} \frac{h}{r} \dots\dots\dots(2)$$

Scanning electron microscopy

Scanning electron microscopy was carried out on formulations F5. The dry microspheres were placed on a brass stub coated with gold in an ion sputter and scanned using JEOL – 6360A scanning electron microscope at an accelerating voltage of 20KV [12].

Drug entrapment efficiency (DEE)

The amount of drug entrapped in 50 mg of microspheres was evaluated by crushing the microspheres and extracting with aliquots of 0.1N HCl and 0.2 % sodium lauryl sulfate (SLS) repeatedly as curcumin is soluble in SLS. The extract was transferred to a 100 ml volumetric flask and the volume was made up using 0.1N HCl. The solution was filtered by Whatman filter paper of pore size 0.02 μm and the absorbance measured spectrophotometrically (Shimadzu 1700) at 254 nm. The drug entrapped (DEE, %) in the microspheres was calculated using Eq 3.

$$\text{DEE} = (AA/TA)100 \dots\dots\dots(3)$$

where AA is the actual amount present in the microspheres and TA is the theoretical amount.

Determination of microsphere yield

Microspheres with a size range of 251-388 μm were prepared and weighed. The ratio of the weight to the total weight of all the non-volatile ingredients used for the preparation of the microspheres, expressed as a percentage, was taken as the yield.

Assessment of *in-vitro* buoyancy

Microspheres (300 mg) were spread over the surface of a USP XXIV dissolution apparatus type II filled with 900 ml of 0.1N

hydrochloric acid containing 0.02 % Tween 80. The medium was agitated with a paddle rotating at 100 rpm for 12 h. The floating and the settled fractions of microspheres were recovered separately, dried and weighed. Buoyancy (%) was calculated as the ratio of the mass of the microspheres that remained floating to the total mass of the microspheres, expressed as a percentage [13].

In-vitro drug release studies

A modified USP XXIV dissolution apparatus type I (basket) was used to study *in vitro* drug release from the microspheres. The test was carried out separately at 100 rpm in distilled water and 1M HCl (pH 1.2) as dissolution media (900 ml) maintained at 37 ± 1 °C. Samples (2ml each) were withdrawn at intervals and analyzed spectrophotometrically at 254 nm. The release medium was replenished with the same amount of fresh medium to maintain sink conditions. All experiments were performed in triplicate. Cumulative drug release (%) was calculated from a standard curve [14].

Statistical analysis

To ascertain drug release mechanism and release rate, the data were model fitted to various release models - zero order (Eq 4),

first order (Eq 5), Higuchi (Eq 6) and Korsmeyer-Peppas (Eq 7) using PCP Disso V3.0 dissolution software [15].

$$\text{Release rate} = k \dots\dots\dots (4)$$

$$\text{Release rate} = k[A] \dots\dots\dots (5)$$

$$\text{Release rate} = kt^{0.5} \dots\dots\dots (6)$$

$$\text{Release} = kt^n \dots\dots\dots (7)$$

where k is a constant, A is concentration of reactant, n is the release exponent, t is time.

RESULTS

Physicochemical characteristics of microspheres

The physicochemical characteristics of the floating microspheres are shown in Tables 2 and 3 as well as Fig 1. The microspheres were discrete and free flowing. The mean arithmetic diameter varied between 251 and 388 μm .

The yield of floating microspheres was in the range of 45.5 - 82.0 which indicates the percentage yield increased with increasing the polymer concentration while drug entrapment efficiency ranged from 72.6 to 83.5 %. It was found that the entrapment efficiency increased with increasing amount of polymers in the hollow microspheres i.e. batch F3 and F4.

Table 2: Characteristics of floating curcumin microspheres

Formulation	Yield (%)	Entrapment efficiency (%)	Angle of repose (°)	Buoyancy (%)
F1	45.46±0.158	72.6±0.1	18.5±0.0	74.6±0.2
F2	62.12±0.147	78.3±0.1	19.5±0.0	80.3±0.3
F3	75.56±0.085	80.2±0.1	21.9±0.1	83.6±0.3
F4	82.02±0.079	83.5±0.1	23.0±0.7	90.6±0.2

Table 3: Micromeritic properties of curcumin floating microspheres

Formulation	Particle size (μm)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Hausner ratio	Carr's index
F1	251±2	0.150±0.040	0.166±0.253	1.11±0.03	9.64±0.04
F2	266±4	0.168±0.004	0.216±0.030	1.29±0.01	22.58±0.53
F3	325±6	0.166±0.005	0.214±0.016	1.29±0.01	22.43±0.00
F4	388±8	0.176±0.009	0.200±0.536	1.14±0.14	12.0±0.01

SEM indicates that the microspheres were spherical with a smooth surface; distinct pores were evident on the surface of microspheres, which will be responsible for the release. The photomicrographs also showed the presence of loose crystals of drug on the surface of a few microspheres

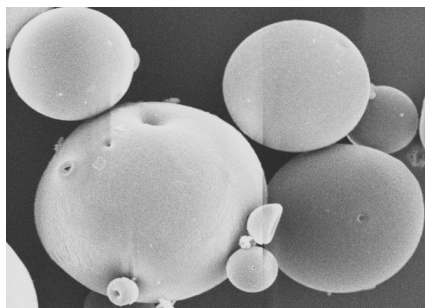


Figure 1: SEM of prepared floating microsphere formulation F4

Drug release

Cumulative drug release after 20 h for formulation F4, F1, F2 and F3 was 81.3, 47.1, 55.7 and 69.4 %, respectively. Eudragit S100 (an anionic copolymer of methacrylic acid and methyl methacrylate containing free

carboxylic and ester groups [16]) is insoluble in acidic medium and also exhibits low permeability.

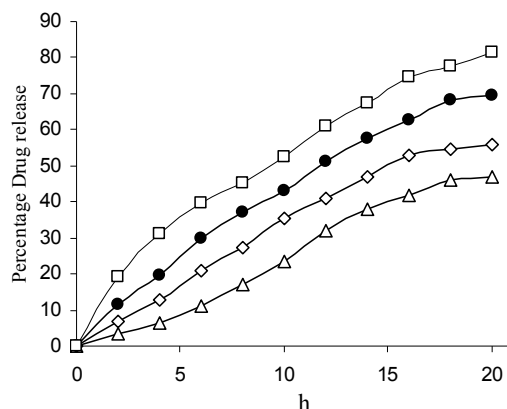


Figure 2: Drug release profiles of curcumin from floating microspheres (**Note:** F1 = Δ , F2 = \diamond , F3 = \bullet , F4 = \square)

In all the cases, the best-fit model was found to be Korsmeyer-Peppas with 'n' value between 0.65 to 0.73 (Table 4) suggesting a non-Fickian (anomalous) release mechanism ($0.5 < n < 1$) for the drug, i.e., erosion followed by diffusion controlled release.

Table 4: *In-vitro* drug release kinetics of the formulations

Batch code	Zero order model		First order model		Higuchi model		Korsmeyer-Peppas model		
	R	K	R	K	R	K	Slope (n)	R	K
F1	0.8361	1.13	0.9850	-0.07	0.9623	10.03	0.6761	0.9651	5.01
F2	0.8024	1.16	0.9821	-0.03	0.9553	8.72	0.6855	0.9688	5.09
F3	0.9152	1.25	0.9823	-0.02	0.9838	10.06	0.6671	0.9752	4.08
F4	0.9021	1.38	0.9862	-0.01	0.9827	10.00	0.6746	0.9651	6.15

DISCUSSION

In the present study four different batches of floating microspheres of curcumin were formulated using different polymer i.e. eudragit S 100, ethyl cellulose and HPMC by emulsion solvent diffusion method. The physical characterization, floating behavior and in vitro release studies were studied.

Angle of repose, Hausner ratio, and Carr's index can be used to predict flowability. The higher the Hausner ratio the greater the cohesion between particles while the higher the Carr's index of the greater the tendency to form bridges between particles.

Floating microspheres of batch F4 were spherical in shape. The porous nature of the floating microspheres and the spherical shape of the microspheres are evident from their SEM photomicrographs (Figure 1).

Buoyancy for all the formulations was $\geq 74\%$ after 12 h. The nature of the polymer influenced the floating behavior of the microspheres. Microspheres of batch F1 containing eudragit RS 100 were least buoyant. In general with increase in the amount of polymers there is an increase in the buoyancy percentage. The increase in the buoyancy percentage may be attributed to air which caused swelling because of increased amount of the polymers present. The good buoyancy behavior of the microspheres may be attributed to the hollow nature of the microspheres.

Formulations containing larger amount of polymer i.e. batch F3 and F4 shows more entrapment efficiency. Due their floating nature, the microspheres were forcibly immersed into the dissolution medium to avoid adherence to the surface of the jar, thus leading to nonparticipation in the dissolution process. The drug release was extended to 20 h. Microspheres prepared with ethyl cellulose and HPMC, (F3 and F4) showed more release in comparison to those prepared with eudragit S 100 this may be attributed to poor water solubility of eudragit S 100.

The data obtained for in vitro release were fitted into equations for the zero-order, first order, Korsmeyer Peppas and Higuchi release models. The interpretation of data was based on the value of the resulting regression coefficients. The in vitro drug release showed the highest regression coefficient values for Korsmeyer Peppas model. It indicates that non-fickian diffusion is the mechanism of drug release.

In a previous study Rahman *et al* developed a floating microspheres of curcumin using HPMC K100 and poloxamer 188 using

emulsion/solvent evaporation method [17]. Studies conclude that curcumin loaded floating microspheres can be used as a drug delivery system to improve the absorption kinetics of curcumin.

CONCLUSION

Curcumin floating microspheres were successfully developed using emulsion solvent diffusion method. The microspheres had good yield and showed high, drug entrapment efficiency. The flow properties of microspheres were within the acceptable range and therefore would be easily filled into capsules. Release properties were satisfactory and the formulations hold promise for further development into drug delivery systems for oral administration of curcumin.

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