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A Study on Formulation of Multiparticulate Gastro Retentive Drug Delivery System of Curcumin

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ABSTRACT- The objective of our present study was to develop multiparticulate gastro retentive drug delivery system of Curcumin. The gastro retentive drug delivery system can be formulated to improve the absorption and bio-availability of curcumin by retaining the system into the stomach for prolonged period of time. The floating drug delivery system of curcumin was prepared by emulsion solvent diffusion method by using ethyl cellulose, Eudragit L100, Hydroxypropyl Methyl cellulose (HPMC), phyllium husk polymers in varying concentration. The formulations were evaluated for percent yield, particle size, entrapment efficiency, *in vitro* buoyancy as well as *in vitro* release studies. The optimized formulations were shown good buoyancy and *in vitro* controlled release of Curcumin.

Key-words: Ethyl cellulose, Eudragit L 100, Floating microsphere, Hydroxypropyl Methyl cellulose (HPMC), Phyllium husk

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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 identify- cation). 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 micro spheres are characteristically free-flowing powders having a size < 199 µm and remains buoyant over gastric contents for a prolonged period.

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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 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 *C. longa* L. plant (Family: Zingiberaceae) is India country. Curcumin is a potent phytomolecule with a wide range of biological activities and shows low absorption [5]. It was selected for this study because it's 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 M and short half-life (28 min) limit its use via the oral route [6].

To develop a drug delivery system for oral administration, the preferred route of administration, it is necessary to optimize not only the release rate from the system but also the residence time of the system in gastrointestinal tract organ [7]. Various oral delivery systems have been developed including polymeric matrices, osmotic tablets,

and microcapsules. However, limited number of approaches has been pursued to extend the residence time of the delivery system within the GIT. Hydrodynamically Balanced System (HBS) or Floating drug delivery system (FDDS) is among the numerous approaches that have been developed in order to increase the gastric residence time (GRT) of dosage forms [8]. Development of floating delivery system involves use of many low density polymers. EC, HPMC, and Eudragit L and Phyllium husk are such low density polymers. Many controlled release dosage forms utilize hydrophilic polymers for retarding drug release. The mechanism of drug release is dependent on the swelling as well as dissolution process. In this case the early part of the release process is marked by the swelling due to the conversion of the polymer from a glassy to a rubbery state due to water penetration.

The floating microspheres beneficially alter the absorption of a drug, thus enhancing its bioavailability. They are 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. Floating microspheres are gastro-retentive drug delivery systems based on a non-effervescent approach. These micro-spheres are characteristically free-flowing powders having a size <199 µm and remain buoyant over gastric contents for a prolonged period. As the system floats over gastric contents, the drug is released slowly at desired rate, resulting in increased gastric retention with reduced fluctuations in plasma drug concentration.

Curcumin is a potent phytomolecule with wide range of biological activity [9-10] possess a low absorption [11]. It is poorly absorbed in the lower GIT and has short elimination half life ~0.39 hour. The aim of the present investigation was to formulate the floating microspheres of curcumin in order to achieve a prolonged retention in the upper GIT, which may result in enhanced absorption and thereby improved bioavailability. The prepared microspheres were evaluated for yield, *in vitro* release, size, and buoyancy and incorporation efficiency. The effect of various formulation variables on the size and drug release was studied.

MATERIALS AND METHODS

The curcumin was purchased from Aushadhi Herbal, Delhi, Ethyl Cellulose from Central drug house, New Delhi, Eudragit L100 and N.K.B.R. from college of pharmacy, Meerut. Whereas, Phyllium husk purchased from Herbo-pharma Meerut, HPMC also from N.K.B.R. Meerut, India.

Preparation of floating microspheres

Floating microspheres were prepared by emulsion solvent diffusion method [11]. The drug and polymer blends were mixed in the solvent (ethanol/dichloride-methane, 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 & stirred at 750 rpm with a mechanical stirrer for 1 hour at room temp. The floating micro-spheres were collected by decantation, washed thrice with n-hexane, dried overnight in an oven at 40±2^{O}C, and stored in a desiccator containing calcium chloride as desiccant.

Table 1: Composition of batches of floating micro spheres of Curcumin

Batch	Curcumin (mg)	Ethyl Cellulose (mg)	HPMC	Eudragit L 100	Psylliyum Husk
F-1	100	200	–	–	–
F-2	100	400	–	–	–
F-3	100	800	–	–	–
F-4	100	100	100	–	–
F-5	100	200	200	–	–
F-6	100	100	400	–	200
F-7	100	–	–	100	100
F-8	100	–	–	200	200
F-9	100	–	–	400	200

In-vitro evaluation of floating microspheres of Curcumin determination of percent yield

Thoroughly dried microspheres were collected as well as weighed accurately. Then the percentage yield was calculated.

Determination of entrapment efficiency

The drug content of Curcumin loaded microspheres was determined by dispersing 100 mg microspheres in 10 ml of ethanol, which was stirred with a magnetic bead for 8 hours to extract the drug. The samples were diluted and analyzed spectrophotometrically at 421 nm and the percentage drug entrapment was calculated.

Particle size analysis

Particle size of prepared microspheres was measured using an optical microscope, and the mean particle size was calculated by measuring 100 particles with the help of a calibrated ocular micrometer [12].

Floating behaviour (Buoyancy)

50 mg of the microspheres were placed in 100 ml of simulated gastric fluid (pH 1.2) containing 0.02% w/v tween 20. The mixture w as stirred at 100 rpm on a magnetic stirrer. After 4 h, the layer of buoyant microspheres was pipette and seprated by filtration particle in the sinking particulate layer were also seprated by filtration. Particles of both types were dried in desiccators. Both the fractions of microspheres were weighed and buoyancy was determined by the weight ratio of floating particles to the sum of floating and sinking particles [13].

Characterization of Microspheres by Scanning Electron Microscopy (SEM)

The surface topography and internal textures of the microspheres was observed by scanning electron

microscopy [14].

In- vitro dissolution studies in 0.1N HCl

The *in- vitro* dissolution studies were carried out by using USP XXI V paddle type dissolution apparatus. Weighed amount of drug loaded floating microspheres was introduced into 900 ml 0.1 N HCl, used as a dissolution medium, maintained at 37±0.5°C at a rotation speed of 100 rpm. The samples were withdrawn at predetermined time intervals. First two samples were withdrawn at 30 min. Interval and next 11 samples were withdrawn at 1 hour interval. The samples were analyzed spectrophotometrically at 430 nm to determine the concentrations of drug present [15].

RESULTS AND DISCUSSION

Percent yield

All batches find a percentage yield of greater than 70%, whereas five batches showed a yield of more than 80%. Percentage yield was found to be higher with formulation of the high amount of polymer. Results show that percentage yield increases with an increase in the amount of polymer.

Entrapment efficiency

All batches find percent entrapment more than 50 % and it is found that entrapment of drug increases with an increase in the amount of the polymer. For emulation F-6 shows maximum entrapment, whereas formulation F-7 shows minimum entrapment of the curcumin.

Particle size analysis

Results show that the particle size of prepared microspheres was in the range of 130±20 μm to 226±25 μm. It was concluded that with the increase in polymer concentration.

Study of Scanning Electron Microscopy

Results show that ethyl cellulose microspheres of ketorolac trometamol were predominantly spherical in shape with smooth surface. The porous nature and characteristic internal structure of the microspheres, a hollow cavity inside enclosed with the rigid shell constructed with drug and polymer was clearly evident. Ethyl cellulose, Phyllium husk and HPMC based floating microspheres were found to be much more elongated in nature than microspheres prepared by using Phyllium husk and Eudragit L100. The porous nature and cavity formed in the microspheres would dictate the floating behaviour of microspheres of Curcumin as shown in Fig 1.

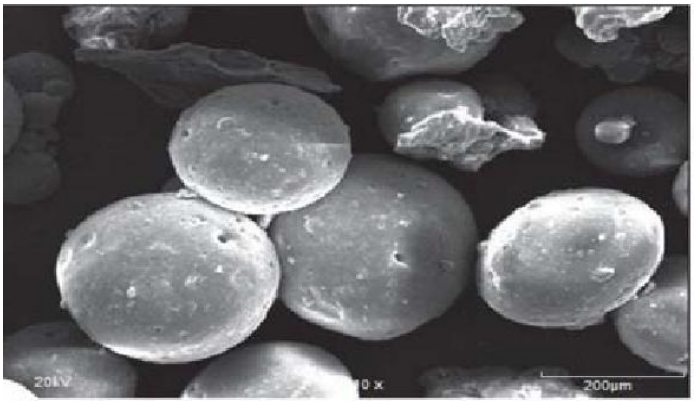

Fig. 1: SEM photomicrographs of batch F-6

Floating ability (Percent buoyancy)

The formulated batches of floating microspheres of curcumin showed average buoyancy more than 53%.Amongst the batches of prepared microspheres, batch F-6 showed highest buoyancy (72.53%). Further it was observed that in case of ethyl cellulose, Phyllium husk and HPMC based microspheres, buoyancy was high, as compared with only ethyl cellulose based microspheres (Table 2).

Table 2: Characterization of various batches of floating microspheres of Curcumin

Formulation code	Production yield (%)	Entrapment efficiency (%)	Buoyancy age (%)	Mean particle size (μm)
F-1	82.8	54.12	65.75	10
F-2	84.6	66.42	62.54	17
F-3	85.9	73.12	69.45	24
F-4	77.5	63.25	60.23	30
F-5	80.8	73.67	70.22	35
F-6	82.6	80.45	72.53	41
F-7	72.3	50.64	53.86	47
F-8	75.7	60.76	55.14	53
F-9	77.6	77.61	58.65	60

Table 3: Dissolution profiles of batches of Floating microspheres of Curcumin

Time (mins)	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
0	0	0	0	0	0	0	0	0	0
30	14.57	11.75	10.97	10.34	7.65	6.89	15.78	14.12	11.78
60	21.50	19.20	16.76	15.67	13.45	11.67	22.54	20.67	18.98
120	29.12	27.12	24.22	25.67	21.34	17.54	31.34	29.67	26.56
180	35.16	33.47	31.97	30.77	26.55	24.65	37.16	34.78	32.76
240	41.15	39.21	37.67	36.88	32.56	30.76	43.67	41.34	38.65
300	48.30	44.12	41.34	43.45	39.56	34.67	49.56	47.45	44.87
360	54.12	48.24	46.34	50.34	44.67	39.76	55.76	53.34	50.78
420	59.45	54.32	52.34	54.76	50.78	44.74	61.56	59.65	56.45
480	64.23	61.72	59.67	60.87	55.78	50.45	65.35	63.55	60.45
540	71.22	65.43	63.23	63.45	60.67	56.34	73.23	71.45	63.78
600	75.23	69.78	67.91	67.34	65.87	60.23	76.56	73.67	67.63
660	80.23	74.26	70.67	70.67	70.65	65.45	82.56	79.67	70.45
720	86.43	78.23	74.23	74.53	75.56	70.12	89.67	82.76	74.87

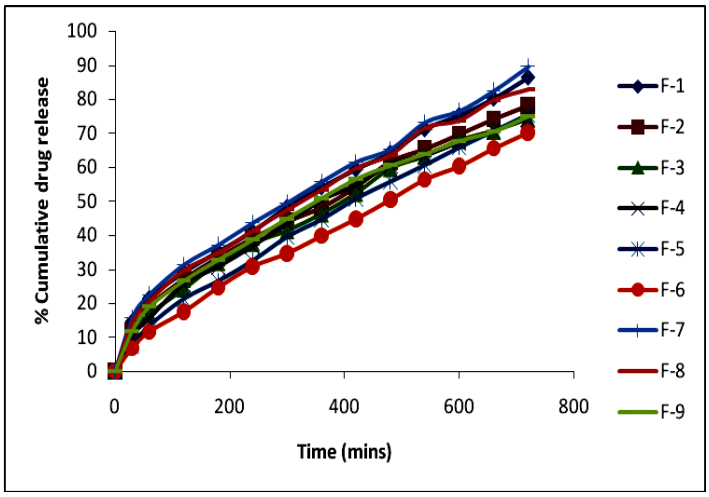

Fig. 1: Shows effect of different polymer on dissolution profiles

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 co-efficient values for Korsmeyer Peppas model. It indicates that non-fickcian diffusion is the mechanism of drug released.

In a previous study Rahman *et al.* [16] developed floating microspheres of curcumin using HPMC K100 and poloxamer 188 using emulsion/solvent evaporation method. Studies concluded that curcumin loaded floating microspheres can be used as a drug delivery system to improve the absorption kinetics of curcumin.

CONCLUSIONS

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 the oral administration of curcumin.

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