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Original Article

Design and Evaluation of Hollow Microspheres Containing Aceclofenac by Using Eudragit RS 100 With HPMC

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ABSTRACT

The present study hollow microsphere of Aceclofenac was prepared by emulsion–solvent diffusion method by using Eudragit RS100 and HPMC as a polymer. Mean particle size range for all formulation was varied from 613.74 to 869.1µm, due to change in drug and polymer ratio. Drug entrapment of all formulation were found in range of 60.14 to 75.12% w/w and its efficiency slightly decrease with increasing the HPMC content. True density, tapped density values for all formulation were less than that of gastric fluid (1.004gm/cm3), suggested that it exhibit good buoyancy. Angle of repose (<40) for all formulation showed excellent flowability. Shape of the hollow microsphere was found to be spherical by SEM study, small cavity was present on surface, which may due to solvent evaporation during drying process. It is responsible for floating property. In FTIR study, all characteristic peaks were appeared in hollow microsphere spectra with out any remarkable change in the position after successful encapsulation, indicated no chemical interaction and stability of drug during microencapsulation process. Ideal property of hollow microspheres include high buoyancy and sufficient release of drug in pH 6.8. Percent drug release rate of F 1, F2, F3 formulations (45.80%, 66.69%, 81.89%) in 12 hours, which is slow and incomplete drug release. In order to increases the percent drug release rate, the ratio of Eudragit and HPMC is decreased and increased respectively. F5, F6 formulations showed high release rate (97.85%, 98.89%) in 10 hours and F7, F8 formulations showed high release rate (98.20%, 99.24%) in 9 hours, with less buoyancy. F4 formulation showed appropriate balance between buoyancy and drug release rate 94.68% in 12 hours, it may considered as a best formulation. The *in-vitro* release data was applied to various kinetic models to predict the drug release kinetic mechanism. The zero order plots for all formulation were found linear in both dissolution medium. Result shows that, drug release rate may follow zero order mechanism. Higuchi and Peppas plot was found good linear, which indicates diffusion may be the mechanism of drug release and n>0.5, that indicated drug release may follow anomalous diffusion.

Keywords:

1. INTRODUCTION

Drugs that have narrow absorption window in upper part of GI tract i.e. stomach and small intestine, which

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is due to short transit time of dosage form. Formulation of these drug leave upper part of GI tract and reaches to non-absorbing distal regiment, resulting lesser bioavailability. Floating drug delivery systems are prolong the drug release rate from formulation in stomach and upper part of small intestine until all the drug is released for the desired period of time.Rheumatoid arthritis (RA) is a chronic inflammatory disease of joint space which involve synovial proliferation and cartelage distruction. Non-steroidal anti-inflammatory drugs (NSAIDs) are considered to first line drug. Aceclofenac is a new NSAIDs, which enhibit good analgesic, anti-inflammatory, antipyretic for acute and chronic inflammation with better gastric tolerance. It was chosen as a model drug since it has short half life (3-4 hrs) and two-third (70-80%) of dose is excreted by renal transport. The objective of present study was to develop a hollow microsphere (microballoon) of Aceclofenac in order to achieve an extended retention in upper GIT, which may result in enhanced absorption and thereby improves bioavailability. [1-4]

2. MATERIALS AND METHODS

Aceclofenac were procured from Cipla,Mumbai and Eudragit Rs 100 was purchased from Rohm Pharma, HPMC was purchased from Loba chemic Pvt. Ltd., Mumbai.

2.1 Experimental Methodology

Preparation of Standard Curve of Aceclofenac with 0.1 N HCI /Phosphate Buffer pH 6.8:

100 mg of aceclofenac was accurately weighed and dissolved in a small portion of 0.1 N HCI/ Phosphate Buffer pH 6.8 and make the volume to 100 ml volumetric flask then the volume was made up to 100 ml. This was the primary stock solution, contained concentration of 1000 μ g/ml. From this primary stock solution 10 ml was accurately pipetted out and transferred in to a 100 ml volumetric flask and volume was made up to 100 ml with 0.1 N HCl which contained the concentration of 100 μ g/ml. From the second stock solution again 10 ml was pipette out and diluted up to 100 ml with 0.1 N HCl to get concentration of 10 μ g/ml. From third stock solution aliquots equivalent to 1-10 μ g were pipetted out in to a series of 10 ml volumetric flask and volume was made up to 10 ml with 0.1 N HCI. The absorbance of these solutions were measured against the 0.1 N HCI as blank at 275 nm using UV Visible double beam spectrophotometer.

2.2 Preparation of Hollow Microsphere Of Aceclofenac Sodium

Hollow microsphere containing aceclofenac were prepared using emulsion solvent diffusion technique. The drug to polymer ratio used to prepare the different formulations was 1:7. The polymer content was a mixture of Eudragit RS 100 (ES 100) Hydroxypropylmethylcellulose (HPMC) as shown in table. The drug polymer mixture dissolved in a mixture of ethanol (8 ml) and dichloromethane (8 ml) was dropped in to 0.75% polyvinyl alcohol solution (200 ml). The solution was stirred with a propeller-type agitator at 40^{o}C temperature for 1 hour at 300 RPM. The formed hollow microsphere were passed through sieve no.12 and washed with water and dried at room temperature in a desiccator. The various batches of hollow microsphere were prepared as follows. [5, 6]

2.3 Evaluation of Microspheres

***Particle size analysis*:** Particle size analysis plays an important role in determining the release characteristics and floating property. The sizes of hollow microspheres were measured by using a set of standard sieves ranging from 14, 16, 18, 22, 30 and pan. The sieves were arranged in increasing order from top to bottom. The hollow microspheres were passed through the set of sieves and amount retained on each sieve was weighed and calculate the % weight of hollow

microspheres retained by each sieve. Mean particle size for all formulation was determined by dividing the total weight size of formulation to % total weight of hollow microspheres. [7, 8]

***Floating Property of Hollow microsphere*:** 100 mg of the hollow microsphere were placed in 0.1 N HCI (300 ml) containing 0.02% Tween 20. The mixture was stirred with paddle at 100rpm. The layer of buoyant microballoons was pipetted and separated by filtration at 1, 2, 4 and 6 hours. The collected microballoons were dried in a desiccator over night. The percentage of microballoons was calculated by the following equation :

$$\% \text{ hollow microsphere} = \frac{\text{Weight of hollow microsphere}}{\text{Initial weight of hollow microsphere}} \times 100$$

***Drug Entrapment*:** The various formulations of the hollow microspheres were subjected for drug content. 50 mg of hollow microspheres from all batches were accurately weighed and crushed. The powdered of microspheres were dissolved with 10ml ethanol in 100ml volumetric flask and makeup the volume with 0.1 N HCl. This resulting solution is than filtered through whatmann filter paper No. 44. After filtration, from this solution 10 ml was taken out and diluted up to 100 ml with 0.1 N HCl. Again from this solution 2 ml was taken out and diluted up to 10 m1 with 0.1 N HCI and the absorbance was measured at 275 nm against 0.1 N HCI as a blank. [9]

The percentage drug entrapment was calculatedas follows.

$$\% \text{ Drug entrapment} = \frac{\text{Calculated drug concentration}}{\text{Theoretical drug concentration}} \times 100$$

***Determination of True Density*:** The true density of hollow microspheres was determined by liquid displacement method using n-hexane as solvent. A pycnometer was used to determine true density. First of all, weight of pycnometer (a) was noted than 25 ml of n-hexane was added and weight (b) was noted. The pycnometer was emptied and weight amount of hollow microspheres was added not weight (c) was noted. Now n-hexane was added to occupy the void spaces within the hollow microspheres until and hollow microspheres n-hexane together occupied the volume i.e. 25ml. Again weight (d) was noted than true density was calculated according to following formula.

$$\text{Density of liquid (p)} = {}^{b-a}/_{25}$$

$$\text{True density} = \frac{c-a}{25-[a-a/\rho]}$$

***Determination of Tapped Density*:** It is the ratio between a given mass of hollow microspheres and it's volume after tapping. Tapped density of hollow microspheres was determined by the tapping method. Accurately weighed quantity of hollow microspheres was transferred in to a 10 ml measuring cylinder. After observing the initial volume of floating micro spheres, the tapping was continued on a hard surface until no further change in volume was noted and the tapped density was calculated according to following formula.

$$\text{Tapped density} = \frac{\text{Mass of hollow microspheres}}{\text{Volume of hollow microspheres after tapping}}$$

***Percentage Compressibility Index*:** The same tapping method was used to determine percentage compressibility index. The percentage compressibility index was calculated according to following formula.

$$\% \text{ Compressibility index} = \left[1 - \frac{V}{V0}\right] \times 100$$

, Where V and V0 are the volumes of the sample after and before

the standard tapping respectively. Each determination was made in triplicate. [10]

***Percentage Yield* :** The percentage yield of different formulations was determined by weighing the hollow microspheres after drying. The percentage yield was calculated as follows.

$$\% \text{ Yield} = \frac{\text{Total weight of hollow microspheres}}{\text{Total weight of drug and polymer}} \times 100$$

***Angle of Repose*:** Flow property of hollow microspheres is usually assessed by determining angle of repose of the floating micro spheres. It is the maximum angle that can be obtained between the free floating surface of floating micro balloons heap and the horizontal plane. The angle of repose of hollow microspheres was determined by fixed funnel method. The hollow microspheres were allowed to fall freely through a funnel until apex of conical pile just touched the tip of the funnel. The angle of repose φ was determined according to the following formula

$\varphi = \tan^{-1} h/r$ Where, h = height of pile r = radius of the pile formed by the hollow microspheres.

***Shape and Surface Characterization by Scanning Electron Microscopy*:** From the formulated batches of hollow microspheres, formulation (F4) which showed an appropriate balance between the buoyancy and the percentage release were examined for surface morphology and shape using scanning electron microscope Hitachi, Japan. Sample was fixed on carbon tape and fine gold sputtering was applied in a high vacuum evaporator. The acceleration voltage was set at 20KV during scanning. Microphotographs were taken on different magnification and higher magnification (200X) was used for surface morphology.

***Fourier Transform Infra-red Spectroscopy (FT-IR) Analysis*:** The Fourier transform infra-red analysis was conducted for the analysis of drug polymer interaction and stability of drug during microencapsulation process. Fourier transform infra-red spectrum of pure aceclofenac, Eudragit RS 100, HPMC and hollow microspheres were recorded. [11]

***In vitro* Release Studies:** The drug release rate from floating micro spheres was carried out using the USP dissolution paddle assembly. A weighed amount of floating micro spheres equivalent to 100 mg drug were dispersed in 900 ml of 0.1 N HCI (pH 1.2) maintained at 37 ± 0.5°C and stirred at 100 rpm. At preselected time intervals one ml sample was withdrawn and replaced with equal amount of 0.1 N HCI (pH 1.2). The collected samples were suitably diluted with 0.1 N HCI and analyzed spectrophotometrically at 275 nm to determine the concentration of drug present in the dissolution medium. The dissolution studies were repeated using phosphate buffer pH 6.8 as dissolution medium. [12]

***Stability Study*:** From the prepared hollow microspheres F4 which showed appropriate balance between the buoyancy and the percentage release was selected for stability studies. The prepared formulation (F4) were placed in borosilicate screw capped glass containers and stored at room temperature (27 ± 2° C), oven temperature (42±2° C) and in refrigerator (5-8° C) for a period of 45 days. The samples were assayed for drug content at regular intervals of two week. [13]

3. RESULT AND DISCUSSION

Evaluation of Hollow Microspheres:

***Particle size analysis*:** Particle size was determined by siveing method it plays important role in floating ability and release corrected of drug from microballoon. If size of microballoons less than 500 mm so release rate of drug will be high and floating ability will reduce, while microballoons range between 500mm - 1000mm, floating ability will be more and release rate will be in sustained manner. The mean

particle size of hollow microsphere was in range 613. - 869. mm .

***Floating Property of hollow microsphere*:** Hollow Microsphere were dispersed in 0.1 NHCl containing tween 20 (0.02% w/v) to simulate gastric fluid. Floating ability of different formulation were found to be differed according to Eudragit and HPMC ratio. F1-F4 formulations showed best floating ability (90.47-72.17%) in 6 hours. F5-F8 formulation showed less floating ability (60.12-26.18%). The floating ability of microsphere decreased by increased the HPMC ratio.

***Drug Entrapment* :** The drug entrapment efficacy of different formulations were in range of 43.14 - 74.12 % w/w as shown in Table No-10. Drug entrapment efficacy slightly decrease with increases HPMC content and decreases Eudragit ratio in microballoons. This is due to the permeation characteristics of HPMC, that could facilitate the diffusion of part of entrapped drug to surrounding medium during preparation of hollow microspheres.

***Percentage Yield*:** Percentage yield of different formulation was determined by weighing the microballoons after drying. The percentage yield of different formulation were in range of 55.10 - 84.67% .

***True density*:** It is determined by liquid displacement method using n-hexane as solvent. The true density value of hollow microsphere range from 0.482-0.916 gm/cm3. The true density of hollow microsphere were less than of gastric fluid (1.004 gm/cm3) will suggest that it will exhibit good floating property.

***Tapped density*:** Tapped density was determined by tapping method. The tapped density value of different microballoons range from 0.201 - 0.405gm/cm3. The density value of microballoons were less than the density of gastric fluid (-1.004 g/cm3) thereby, it will have good buoyancy property in stomach.

***Percentage Compressibility index* :** It is determined by same tapping method and its range is 8.34 ± 0.641 - 17.45 ± 1.01 %. The percentage compressibility value less than 20 for all formulation suggested excellent flow property.

***Angle of repose*:** Angle of repose of microballoons was determined by fixed funnel method. Angle repose of microballoons was in range of 24°.09' - 38°.12'. All formulation shown excellent flow ability as represented in term of angle of repose (<40°).

***Scanning Electronic Microscopy*:** Shape and surface characteristic of hollow microspheres examine by Scanning Electronic Microscopy analysis as shown in Fig. Surface morphology of F4 formulation examine at to different magnification 40X and 200X, which illustrate the smooth surface of floating microballoons and small hollow cavity present in microsphere which is responsible for floating property.

FT-IR Spectrum of Aceclofenac :

FT-IR Spectra of Aceclofenac, Eudragit RS 100, HPMC, physical mixture of drug polymer and F4 formulation were recorded. The aceclofenic present in the formulation F4 was conformed by FTIR spectra. The characteristic peaks due to pure Aceclofenac at 667.32, 1291.25 1717.49, 1771.50, 1291 for C-H bending, C-N Stretching, C= O Str., due to polynuclear aromatic ring, secondary aromatic, carboxylic group, esters to group respectively, which us shown in Table-16. All these peaks have appeared in formulation and physical mixture, indicating no chemical interaction between aceclofenac and polymer. It also confirmed that the stability of drug during microencapsulation process.

***In-Vitro Drug release study* :** *In-vitro* drug release study of microballoons was evaluated in 0.1 N HCl phosphate buffer pH 6.8. Eudragit RS100 which is present in all formulation, have low permeability in acid medium. Since Eudragit is less soluble in acidic pH, release of drug in 0.1 N HCl was generally low compared to phosphate buffer 6.8. Release rate of F1,

F2, F3 formulations were found to be slow and incomplete in both dissolution medium. In order to increase the release rate of drug the ratio of Eudragit and HPMC is decreased and increased respectively. F5, F6, F7, F8 formulations showed high release rate with less floating property. F 4 formulation showed best appropriate balance between buoyancy and drug release rate. Release data for all formulation.

Table 1: Formulation of The Floating Microspheres Prepared

S.No	Formulation Code	Aceclofenac(gm)	Eudragit Rs 100 (gm)	HPMC(gm)	Monostearin
1	F1	0.1	0.9	0.1	0.5
2	F2	0.1	0.8	0.1	0.5
3	F3	0.1	0.7	0.1	0.5
4	F4	0.1	0.6	0.1	0.5
5	F5	0.1	0.5	0.1	0.5
6	F6	0.1	0.4	0.1	0.5
7	F7	0.1	0.5	0.1	0.5
8	F8	0.1	0.4	0.3	0.5

Table 2: Percentage Buoyancy for Different Formulation

Formulation	1 hour	2 hours	4 hours	6 hours
F1	99.14	98.08	94.23	90.47
F2	99.1	96.52	93.17	88.69
F3	99.54	94.67	83.34	75.45
F4	99.65	92.44	80.52	72.17
F5	99.72	90.95	71.49	60.12
F6	99.45	86.62	60.14	53.76
F7	89.34	76.41	50.04	35.09
F8	80.51	69.23	42.2	26.18

Table 3: Evaluation studies of different Formulation

Formulation	Drug Entrapment (% w/w)	Percent Yield* (%)	True density* (gm/cm3)	Tapped density (gm/cm3)	% Compressibility index	Angle of Repose*	Mean particle size* (mm)
F1	74.12	84.67	0.482	0.201	8.34	24°.09’	869
F2	71.56	81.53	0.513	0.220	9.67	26°.22’	826
F3	67.23	76.89	0.584	0.256	10.56	27°.98’	800
F4	64.76	72.56	0.647	0.279	11.23	29°.38’	790
F5	60.01	70.34	0.672	0.301	13.89	32°.09’	762
F6	55.38	68.03	0.710	0.356	12.87	35°.61’	758
F7	49.47	59.44	0.852	0.378	16.23	36°.34’	664
F8	43.14	55.10	0.916	0.405	17.45	38°.12’	613

Table 4: Release Kinetics Of Hollow Microsphere In 0.1 N HCl

Formulation	Zero Order		Higuchi Equation		Peppas Equation	
	r2	K_0	r2	K_H	r2	n
F1	0.950	1.81	0.974	6.946	0.937	0.776
F2	0.954	2.08	0.998	8.141	0.817	0.795
F3	0.963	2.86	0.994	11.04	0.872	0.746
F4	0.948	3.49	0.991	13.66	0.835	0.693
F5	0.930	4.03	0.993	16.09	0.752	0.610
F6	0.964	4.68	0.996	18.08	0.822	0.614
F7	0.956	5.80	0.998	22.42	0.833	0.572
F8	0.954	5.85	0.997	22.86	0.759	0.573

Table 5: Release Kinetics Of Hollow Microsphere In Phosphate Buffer PH 6.8

Formulation	Zero Order		Higuchi Equation		Peppas Equation	
	r2	K_0	r2	K_H	r2	n
F1	0.997	3.761	0.978	13.73	0.920	0.776
F2	0.982	5.92	0.973	21.84	0.937	0.795
F3	0.984	7.65	0.965	27.69	0.941	0.746
F4	0.991	8.29	0.982	30.54	0.890	0.693
F5	0.969	8.84	0.987	33.49	0.843	0.610
F6	0.950	8.67	0.988	33.04	0.794	0.614
F7	0.955	8.31	0.992	32.43	0.784	0.572
F8	0.937	8.44	0.985	33.02	0.771	0.572

Table 6: Stability Study Data for F4 Formulation

S.No	Days	% Drug Remaining 5-8°C	% Drug Remaining 27± 2°C	% Drug Remaining 42± 2°C
1	0	100 ± 00	100 ± 00	100 ± 00
2	14	99.6 ± 0.015	99.9 ± 0.003	99.4 ± 0.041
3	28	99.5 ± 0.013	99.8 ± 0.027	99.2 ± 0.036
4	45	99.4 ± 0.15	99.6 ± 0.012	99.1 ± 0.02

***Release Kinetics*:** Drug release pattern was evaluated in 0.1 N HCl and phosphate buffer pH 6.8. Release rate of F1, F2, F3 formulations were found to be slow and incomplete in both dissolution medium. It was found that drug release rate increased by decreasing and insreasing the ratio of Eudragit and the HPMC respectively. Kinetics and mechanism of drug release from all formulation was evaluated on the basis of zero order, Higuchi equation and Pappas model. Correlation coefficient (r2) and slop value for each equation was

calculated from Microsoft excel. Zero order plot for all formulations were found to be linear in both dissolution medium. That indicates it may follow zero order mechanism. Higuchi plot was found to be linear, which indicates diffusion may be the mechanism of drug release for each formulation. Peppas plot was found good linear, n > 0.5 for all formulations, indicated that drug release may follow anomalous diffusion. Zero order plot for F4 formulation was found to be linear in both dissolution medium, it considered as a best fit for drug release.

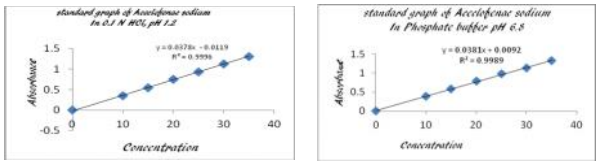

Fig 1: Standard graph of Aceclofenac sodium in 0.1n Hcl, and Phosphate buffer PH 6.8

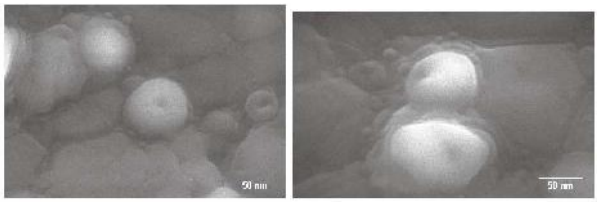

Fig 2: Micro Photographs of Formulation F4

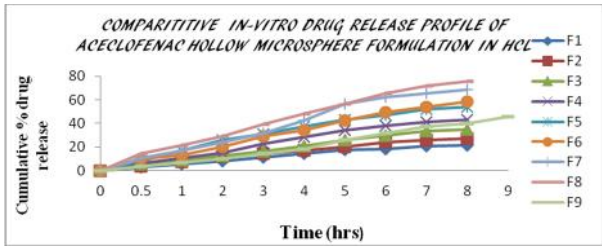

Fig 3: Comparititive In-Vitro Drug Release Profile Of Formulation in HCl

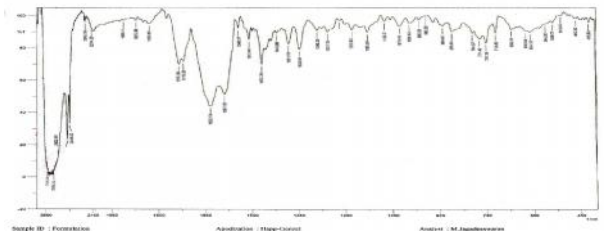

Fig 4: FTIR Spectrum of Formulation F4

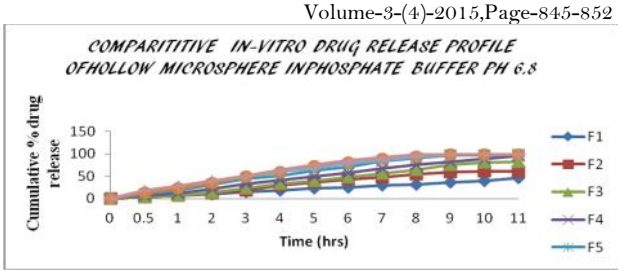

Fig 5: Comparititive In-Vitro Drug Release Profile Of Formulation in Phosphate Buffer

***Stability Study*:** Stability study was carried out for the F4 formulation by exposing it to different temperature 5-8°C, 27°C and 42°C for 45 days. The sample was analysed for drug content at the regular interwals. It was found that no remarkable change in the drug content of F4 formulation. This indicate that F4 was stable for following temperature.

4. CONCLUSION

Hollow microspheres of Aceclofenac were prepared by emulsion– diffusion technique and performances of this formulation were evaluated. It increases the bioavailability of dosage form with prolong effect hence improves the patients compliances. Mean particle size for all formulations were varied, due to change in drug and polymer ratio. Drug entrapment efficiency slightly decreases with increasing the HPMC content. True density, Tapped density values for all formulation were less than of that of gastric fluid (1.004gm/cm3), suggested that it exhibit good buoyancy. Angle of repose (<40) for all formulation showed excellent flowability. Drug release pattern was evaluated in 0.1 N HCl and phosphate buffer pH 6.8. Release rate of F1,F2,F3 formulations were found to be slow and incomplete in both dissolution medium. In order to increase the release rate of drug the ratio of Eudragit and the HPMC is decreased and increased respectively. Ideal property of hollow microsphere includes high buoyancy and sufficient release of drug in pH 6.8. It is necessary to select an appropriate balance between buoyancy and drug release rate from all developing hollow microsphere. F4 formulation

showed best appropriate balance between buoyancy and drug release rate, it considered as a best fit for drug release. Zero order plot for F4 formulation was found to be linear in dissolution medium, that indicates it may follow zero order mechanism. The design system F4 might be able to float in the stomach. This phenomenon could prolong the gastric residence time (GRT) consequently, it provides sustained action. In addition, hollow microspheres enabled increased drug absorption rate, as it gradually sank in the stomach and arrived at the absorption site. The developed formulation overcomes the drawbacks and limitations of sustained release preparations. Therefore multiple unit floating system, i.e., hollow microsphere will be possibly beneficial with subject to sustain action.

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