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Formulation and Evaluation of Floating Microspheres of Edoxaban

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ABSTRACT: The aim of the present study is formulation and characterization of floating microspheres using Edoxaban, an oral anticoagulant for the prevention of stroke and non central nervous system embolism. Floating microspheres were prepared by a solvent evaporation method using a biodegradable and non-biodegradable polymer viz. Gelatin and Ethyl cellulose as release retarding polymers. The formulation were subjected to various evaluation parameters like % practical yield, particle size distributions, flow properties, actual drug content, entrapment efficiency, invitro release studies and stability studies. The prepared microspheres had smooth surface with free flowing and almost spherical in shape. The drug loaded microspheres show 67.0 to 81.5 % drug entrapment, angle of repose was in the range of "19.75 ^{o} to 30.56 ^{o}". Bulk and tapped densities showed good packability and Carr's index ranges from 14.37 to 19.96. Most of the isolated microspheres were of particle size range 113 to 655mm. The drug loaded in Gelatin and Ethyl cellulose microspheres was stable and compatible, as confirmed by FTIR studies. In vitro drug release studies were carried out up to 8 h in two different pH media i.e. acid buffer (pH 1.2) and phosphate buffer (pH 7.4) and the effect of the variation in polymer ratio on drug dissolution was evaluated according to dissolution test results. The release of Edoxaban was influenced by polymer concentration and size of microspheres. The dissolution data were plotted according to the four different kinetic models. In vitro dissolution studies showed that zero-order, Hixson-crowell and Higuchi model release characteristics were exhibited. The stability studies of formulation F2 and F7 indicates that 25^{o}C is a suitable.

Key words: Microspheres**,** Solvent evaporation, Controlled release, Edoxaban, Gelatin, and Ethyl cellulose

I. INTRODUCTION:

Floating microspheres are gastroretentive drug delivery systems based on non-effervescent approach. They are spherical empty particles without core. These microspheres are characteristically free flowing powders consisting of protein or synthetic polymers with diameters 1 µm to 1000 µm. Hydro dynamically controlled drug delivery systems (Floating drug delivery system) are low density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. The sustained release of drug from floating systems improves the gastric retention of drugs and reduces the fluctuations in plasma drug concentration. Commonly used polymers to prepare floating microspheres include polycarbonate, HPMC, cellulose acetate, calcium alginate, Eudragit S, chitosan etc. Thus floating microspheres are considered as one of most promising buoyant systems. They possess the unique advantages of multiple unit systems and in addition better floating properties. The general techniques involved in their preparation include emulsion solvent evaporation and emulsion solvent diffusion. The drug release and better floating properties mainly depend on the type of polymer, plasticizer and the solvent employed for the preparation[1,2].

Edoxaban is used as an oral anticoagulant for the prevention of stroke and non central nervous system embolism. Edoxaban inhibit free factor Xa and prothormbinase activity and inhibits thrombin induced platelet aggregation[3].

Microspheres encapsulated with Edoxaban, increase the effectiveness and release of drug in control manner from polymer membrane and thereby maintain its concentration for longer duration. Due to short acting action, fast clearance, enzymatic stability and absorption throughout GIT make Edoxaban, a suitable target for developing floating dosage form. The main objective of the

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present study was undertaken to prepare and evaluation of Edoxaban using natural biodegradable and synthetic non biodegradable polymer as carrier for oral administration in view to achieve oral controlled release of the drugs.

II. MATERIALS AND METHODS:

1. MATERIALS:

Edoxabanwas purchased from Cipla Pharmaceuticals, Bombay. EthylcelluloseS.D. Fine Chem. Ltd., Mumbai.andGelatin powder Bacto were purchased from S.D. Fine Chem. Ltd., Mumbai. Analytical grade ethanol, dichloromethane, tween-80 were purchased from S.D. Fine Chem. Ltd., Mumbai.All other chemicals used were of analytical grade.

2. METHODS:

2.1 Preformulation studies:

Preformulation studies are the first step in the rational development of dosage forms of a drug. It can be defined as the determination of physical, chemical and mechanical properties of a new drug substance alone and when combined with excipients. The overall objective of preformulation studies is to generate information useful in developing stable and bioavailable and sustained release dosage forms which can be mass produced.

2.1.1 Solubility studies:

Solubility analysis was done to select a suitable solvent system to dissolve the drug and also to test its solubility in the dissolution medium which was to be used. Drug solubility study was performed by taking an excess quantity of drug in different solvents like water, ethanol, methanol, acetone and buffers[4].

2.1.2 Melting point:

Melting point determination of the drug sample was done by open capillary method using melting point apparatus. Drug was taken in glass capillary tube whose one end was sealed by means of flame. The capillary tube was placed in a melting point apparatus attached to a thermometer to measure the melting point. The sample holder was heated gradually and the temperature at which drug melts was recorded. Melting point of a drug sample is a first indication of purity of sample.

2.1.3 Preparation of standard calibration curve by using UV spectroscopy:

Preparation of 0.1 N HCl: 8.5 ml of HCl was dissolved in distilled water and volume was made up to 1000 ml to make 0.1 N HCl.

2.2 Preparation of pH7.4 phosphate buffer: -

28.80 g of di-sodium hydrogen phosphate & 11.45 g of potassium hydrogen phosphate were dissolved in water & volume was made up to 1000 ml.

Preparation of stock solution- Accurately weighed 100 mg of Edoxaban was dissolved in 10ml of methanol in a 100ml of volumetric flask and make up the volume with pH1.2 buffer solution.10ml of this solution was taken in a 100ml of volumetric flask and make up the volume with pH 1.2 buffer solutions to get working stock solution having concentration 100 µg/ml.

From this stock solution aliquots 1ml, 2ml, 3ml, 4ml and 5ml were pipette out into a series of 50ml volumetric flasks and volume was made up to the mark 100 ml with buffer solution pH 1.2 was scanned in the range of 200-400nm in UV-Visible spectrophotometer and 245 nm was selected as a wave length for determination. Fig 1. The absorbance of the resulting solutions was then measured at 245 nm using UV spectrometer against respective parent solvent as a blank.

2.3 Preparation of microspheres of Edoxaban: [5,8]

Edoxaban Microspheres were prepared by Solvent Evaporation technique.

Sl.No	Batch Code	Drug: Ethyl cellulose: Gelatin
1.	F1	1: 1: 0
2.	F2	1: 2: 0
3.	F3	1: 3: 0
4.	F4	1: 4: 0
5.	F5	1: 0: 1
6.	F6	1: 0: 2
7.	F7	1: 0: 3
8.	F8	1: 0: 4

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2.4 Evaluation of prepared floating microspheres:

2.4.1. Percentage yield (%):

Percentage yield of floating microspheres was calculated by dividing actual weight of product to total amount of all non-volatile components that are used in the preparation of floating microspheres and is represented by following formula.

% yield= (weight of floating microspheres /weight of drug and polymer) X100 Eq.(1)

2.4.2. Particle size analysis:

Particle size and shape of the microspheres was determined by optical microscopy. The freshly prepared microspheres were examined on an optical microscope and the size of microspheres was measured by precalibrated ocular micrometer and stage micrometer. About 100 particles of each formulation were observed and measured.

2.4.3. Micromeritic properties:

The prepared microspheres are characterized by their micrometric properties, such as microsphere size (mean particle size), Bulk density, Tapped density, Carr's compressibility index, Hausner's ratio and angle of repose.

2.4.3.1. Bulk and Tapped density: Bulk and tapped densities were measured by using 50 ml of graduated cylinder. Accurately weighed amount of 5g of sample passed through a glass funnel. The sample poured in cylinder was tapped mechanically for 3 times and 100 times for calculating bulk volume (Vb) and tapped volume (Vt) respectively. Then tapped volume was noted down and bulk density and tapped density were calculated. It was expressed in g/cm^3.

$$\text{Bulk density } (\rho_b) = \frac{\text{Mass of microspheres (M)}}{\text{Volume of microspheres after tapping } (V_b)} \quad \text{Eq. (2)}$$

$$\text{Tapped density } (\rho_t) = \frac{\text{Mass of microspheres (M)}}{\text{Volume of microspheres after tapping } (V_t)} \quad \text{Eq. (3)}$$

2.4.3.2. Carr's Compressibility Index: Compressibility index (C.I.) or Carr's index value of microspheres was calculated according to the following equation

$$\%\ \text{Compressibility index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100 \quad \text{Eq. (4)}$$

The value given below 15% indicates a powder with usually give rise to good flow characteristics, whereas above 25% indicate poor flow ability.

2.4.3.3. Hausner ratio:

Hausner's ratio of microspheres was determined by comparing the tapped density to the bulk density using the equation.

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \times 100 \quad \text{Eq. (5)}$$

2.4.3.4. Angle of repose:

The maximum angle which is formed between the surface of a pile of powder and horizontal surface is called the angle of repose.

Tan θ = h/r Eq. (6)

Where □ =angle of repose h = height of the circle formed by the powder heap r = radius of heap

2.4.4. Percentage floating:

Floating microspheres of about (200 mg) was weighed and placed in simulated gastric fluid (pH 1.2, 100 ml) containing 0.02 w/v % Tween 80. The mixture was stirred at 100 r/min in a magnetic stirrer. After 12 h, the layer of buoyant microparticles was pipetted and separated by filtration. Particles in the sinking particulate layer were separated by filtration. Particles of both types were dried in a desiccator until constant weight. 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.

% Buoyancy of microspheres = [Wf/(Wf+Ws)] x 100 Eq. (7)

Where Wf and WS are the weight of floating and settled particles, respectively

2.4.5. Floating time:

It is defined as the time taken by floating microspheres to remain buoyant in the medium. The floating microspheres were placed in the beaker containing 200 ml of 0.1N HCl and examined for the duration of time till they float.

2.4.6. Drug content:

The floating microspheres equivalent to 50 mg of nateglinide were weighed accurately and crushed. The powdered microspheres were placed in 100 ml volumetric flask and the volume was made up using pH 6.8 phosphate buffer and kept for 24 h. The solution was then filtered through whatman filter paper No. 44. The solution was diluted with fresh solvent and absorbance was measured at 210 nm using UV spectrophotometer (Shimadzu-1601) and the percent drug content was calculated[9].

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2.4.7. Drug entrapment efficiency: The percent drug entrapped was calculated as follows

% Entrapment efficiency=Calculated drug content/Theoretical drug content x100

2.4.8. Surface morphology: The surface morphology was measured by using scanning electron microscope (SEM).

2.4.9. In-vitro drug release study:

The in-vitro drug release studies of formulations were carried out in 0.1 N HCl (pH 1.2) for 2 h and in pH 6.8 buffer for 10 h. The drug release rate from floating microspheres was determined using paddle type eight station dissolution test apparatus (Electrolab). A weighed amount of floating microspheres equivalent to 100 mg drug was kept in 0.1 N HCl (1.2 pH) maintained at 37± 0.5 ºC at a rotation speed of 100 r/min. Sink condition was maintained during the study. 5 ml sample was withdrawn at 60 min time interval, the initial volume of the dissolution fluid was maintained by adding 5 ml of fresh dissolution fluid after each withdrawal, passed through 5 □ m membrane filter and analyzedspectrophotometrically at 210 nm. The same process was repeated using pH 6.8 as dissolution medium[10].

2.4.10. Release kinetics study:

The drug release kinetics was studied by various kinetic models such as Korsmeyer-peppas, Higuchi plot, First order plot and Zero order plot. To study the release kinetics, data obtained from In-vitro drug release studies were plotted in various kinetic models. Zero order as cumulative amount of drug released Vs time, First order as log cumulative percentage of drug remaining Vs time, and Higuchi's model as cumulative percentage of drug released Vs square root of time. The best fit model was confirmed by the value of correlation coefficient near to 1. The data was presented for the most appropriate model. If n value is 0.45 or less, the release mechanism follows "Fickian diffusion" and higher values of 0.45 to 0.89 for mass transfer follow a non-fickian model (anomalous transport). The drug release follows Higuchi model of drug release and case II transport if the n value is 0.89. For the values of n higher than 0.89, the mechanism of drug release is regarded as super case II transport[11,12].

III. RESULTS AND DISCUSSION:

3.1. Preformulation studies Solubility analysis:

Sample of Edoxaban was found to be soluble in ethanol, methanol, dichloromethane and chloroform and insoluble in water. Melting point determination: The melting point of drug sample was found to be 167º C. Preparation of calibration curve by using UV spectroscopy. The results were showed in table no 1 and figure no 1.

Table 1: Absorbance value of Edoxaban in 0.1 N HCl

Sl.No	Concentration (µg/ml)	Absorbance
1	2	0.025
2	4	0.052
3	6	0.074
4	8	0.104
5	10	0.127
6	12	0.148
7	14	0.178

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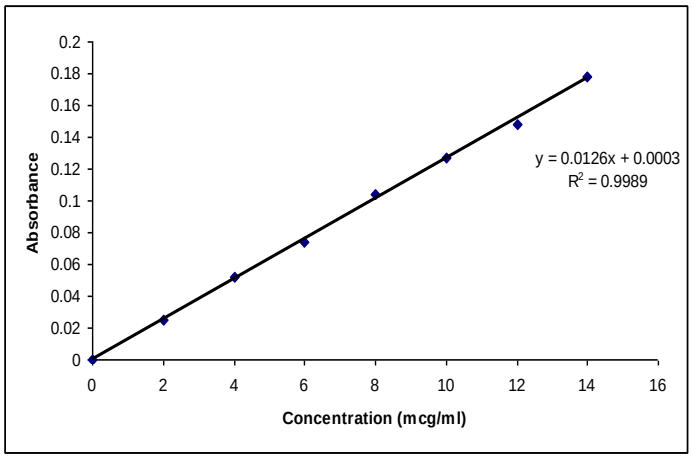
Figure No. 1: Standard Calibration Curve of Microspheres of Edoxaban in pH 1.2 at 245 nm



3.2. Percentage yield:

The Percentage yields of floating microspheres were found in the range of 84–92.2 %. It was observed that with the increase in the polymer concentration (i.e. decrease in drug to polymer ratio) in the formulation, the product yield increased. It was found that average percentage yield was greater than 50 % for all the batches which shows the suitability of this method for preparation of microspheres. The results were showed in table 2.

Table No. 2. %Practical Yield of Different Formulations of Edoxaban Loaded Microspheres

Formulation code	Total amount of ingredients (g)	Practical yield (g)	Percentage yield (%)
F1	1.0	0.843	84.30
F2	1.5	1.291	86.06
F3	2.0	1.770	88.50
F4	2.5	2.241	89.64
F5	1.0	0.871	87.10
F6	1.5	1.341	89.40
F7	2.0	1.826	91.30
F8	2.5	2.305	92.20

3.3. Particle size:

The average particle size range for formulations F1, F2, F3 and F4 was found to be 44.598 µm, 66 µm, 80 µm, 85 µm respectively and for formulations F5, F6, F7 and F8 was found to be 70 µm, 60 µm, 120 µm, 80 µm respectively. The results were showed in table 3. The particle size of the microspheres increases with increase in polymer concentration respectively. This is because the viscosity of polymer solution increases with increasing polymer concentration resulting in enhanced interfacial tension, which in turn decreases the stirring efficiency, which results in increased particle size.

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3.4. Micromeritic properties:

The results of micromeritic properties were showed in table 3. The tapped density values obtained in the range from 0.116-0.168 gm/cm.3 and bulk density values obtained in the range from 0.106-0.154 gm/cm3 .for all the formulations. For the prepared formulations angle of repose ranged between (25º- 30º), the compressibility index ranged between 6.89 %-13.81 % and Hausner's ratio ranged between (1.07-1.16), confirmed good flow properties of the microspheres. Thus the floating microspheres showed better flow property and were non-aggregated.

Table no 3. Micromeritic Properties of Different Formulation of Edoxaban Loaded Microspheres.

S.No.	Formulation code	Particle size	Angle of Repose Mean ± SD*	Bulk Density (g/ml) Mean ± SD*	Tapped Density (g/ml) Mean ± SD*	Carr's Index (%) Mean ± SD*	Hausner ratio
1	F1	44.598 µm	24º 55" ± 0.367	0.424± 0.0065	0.496± 0.0072	14.43 ± 0.195	1.01
2	F2	66.54 µm	23º 85"± 0.411	0.478± 0.0069	0.570± 0.0069	16.13± 0.168	1.12
3	F3	80.32 µm	23º 10"± 0.466	0.507± 0.0077	0.619± 0.0095	18.07± 0.057	1.30
4	F4	85.52 µm	19º 75" ± 0.519	0.526± 0.0043	0.657± 0.0055	19.96± 0.076	1.10
5	F5	70.36 µm	25º 97"± 0.176	0.391± 0.0080	0.470± 0.0088	16.26± 0.329	1.09
6	F6	60.52 µm	27º 36"± 0.211	0.418± 0.0032	0.489± 0.0031	14.37± 0.115	1.13
7	F7	120.42 µm	29º 07"± 0.096	0.451± 0.0066	0.536± 0.0066	15.81± 0.200	1.07
8	F8	80.44 µm	30º 56"± 0.128	0.482± 0.0052	0.577± 0.0049	16.40± 0.199	1.02

*All the values are expressed as mean± S.D of three readings

3.5. Percentage floating:

Excellent buoyancy was shown by prepared microspheres because of their hollow nature, which can be retained for a longer period of time in the upper part of gastrointestinal tract (GIT) in order to increase gastric residence time of the drug. Buoyancy of prepared microspheres was investigated by in-vitro buoyancy test and the buoyancy of all the formulations were found to be in the range of 66 - 88%, the results were showed in table 4. Formulation F5 showed least percentage buoyancy of 66%, while F7 showed highest buoyancy of 88%. The formulations prepared with the various drug and polymer ratios were evaluated for floating time. In the test of floating time, more than 80% microspheres remained floating for more than 12 hour. The good buoyancy behavior of the microspheres may be attributed to the hollow nature of the microspheres. As the concentration of polymers increases, buoyancy also increases. Formulation F7 gave the best floating ability (88%) in SGF. Smaller the microspheres lesser was the floating ability, while larger the size, floating

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ability was found to be more and sustained was the release of drug.

Table 4: Evaluation of floating microparticulated drug delivery systems

Formulation code	Percentage floating (%)	Floating time (hours)	Drug content (%)	Drug entrapment efficiency (%)
F1	83	12	68.32	70.48
F2	74	13	72.30	85.93
F3	84	16	80.79	87.91
F4	72	11	71.65	91.10
F5	88	12	71.63	74.48
F6	76	13	73.87	75.76
F7	66	11	85.22	82.81
F8	73	15	85.29	89.25

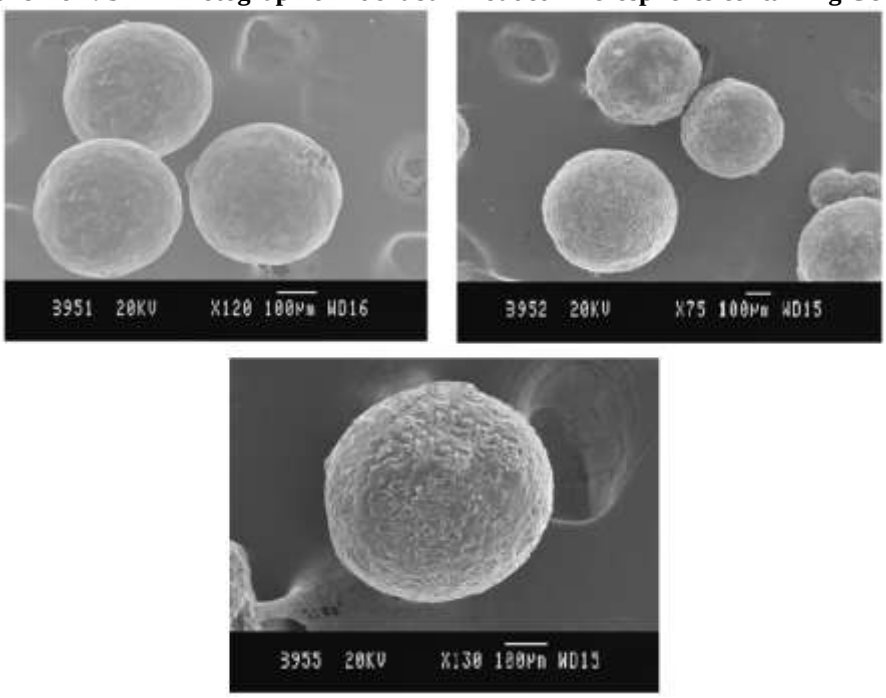
3.6. Drug content and entrapment efficiency:

The drug entrapment efficiency of all formulations was found to be in the range between 70.48 to 91.2% and the drug content was found to be in the range of 64.35 to 88.2%, the results were showed in table 4. With the increase in polymer concentration, increased entrapment efficiency was seen because with increasing polymer content, more particles of drug would be coated leading to higher encapsulation efficiency as can be seen from Table 4. An increase in polymer concentration in the internal phase shows increase in drug loading. This may be due to increase in viscosity of internal phase which reduces the migration of drug in aqueous phase, thus entrapping greater amount of drug.

3.7. Surface morphology using SEM:

Morphology of floating microspheres was examined by scanning electron microscopy. The SEM images of prepared formulations were showed by figure 2. SEM analysis showed that the prepared floating microspheres were having size in micrometers and the particles were nearly spherical.

Figure No 2. SEM Photograph of Edoxaban –loaded Microspheres containing Gelatin



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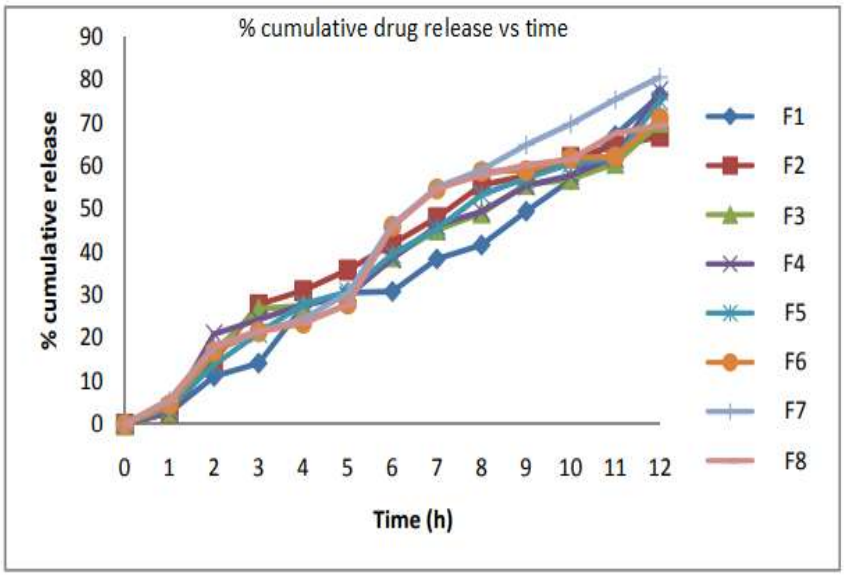
3.8. In vitro drug release:

In-vitro drug release studies were performed in 0.1 N HCl for 2 h and in pH 6.8 buffer for 10 h. The results of cumulative drug release were showed in table no. 5. The graph was plotted between cumulative drug release and time and showed in figure no 3. The cumulative release of drug significantly decreased with increase in polymer concentration. The increased density of polymer matrix at higher concentration resulted in an increased diffusion path length. This may decrease the overall drug release from the polymer matrix. And it was found that as the polymer concentration was increased the release rate decreases. The selected formulation percentage of drug released was found to be initially 5.39% at 1 h and 80.67% up to 12h.

Table 5: In-vitro dissolution studies of floating microspheres of Edoxaban Cumulative % drug release for different batches of microspheres formulations

S. No.	Time (h)	Percent cumulative drug release for different batches of microspheres formulations							
		F1	F2	F3	F4	F5	F6	F7	F8
1	0	0	0	0	0	0	0	0	0
2	1	2.63	2.44	2.63	2.87	3.43	4.54	5.65	5.87
3	2	11.02	14.03	16.02	20.04	12.06	16.08	17.04	18.07
4	3	12.00	13.11	12.21	12.30	12.17	12.13	13.24	13.15
5	4	24.20	34.02	27.12	24.32	24.08	24.15	34.14	32.10
6	5	31.24	32.14	28.52	27.33	31.72	34.52	32.24	30.14
7	6	30.13	40.23	31.12	34.22	33.16	28.13	42.22	41.63
8	7	38.02	47.52	45.72	48.02	44.43	52.42	55.22	53.31
9	8	42.53	51.33	48.62	48.03	51.73	55.62	56.44	53.23
10	9	48.28	55.08	57.23	50.11	58.18	54.22	64.21	60.27
11	10	56.44	62.73	54.41	56.98	61.32	62.30	69.28	61.24
12	11	67.15	67.15	67.15	67.15	67.15	67.15	67.15	67.15
13	12	77.33	65.32	71.32	73.25	75.14	71.54	80.63	69.04

Figure 3: Graph showing % cumulative drug release vs time of the prepared formulations



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3.9. Release kinetic study:

The in-vitro release data were substituted in various models such as zero order, first order, higuchi plot and korsmeyerpeppas kinetics models. Model fitting release profiles of formulation were showed in table 6. The highest regression (0.947) was obtained for higuchi equation. To explain the mechanism of drug release, korsmeyer-peppas equation was used. Value of slope (n) was calculated and found to be (0.713) which is less than 0.89 which indicates anomalous non-fickian diffusion i.e. coupling of diffusion and erosion, which indicates that the drug release is sustained by more than one process. From the above parameters the best selected formulation was found to be F7 having, 88.2% yield, 88% buoyancy, 85.2% drug content, 91.2% entrapment efficiency and 80.67% drug release.

Table 6: Model fitting release profile of formulations F1 to F8

Formulation	Zero order (r2)	First order (r2)	Higuchi (r2)	Korsmeyer-Peppas	
				(r2)	n value
F1	0.918	0.976	0.974	0.885	0.836
F2	0.746	0.857	0.916	0.773	0.752
F3	0.812	0.926	0.949	0.791	0.727
F4	0.834	0.946	0.958	0.789	0.715
F5	0.837	0.939	0.958	0.874	0.735
F6	0.747	0.830	0.897	0.856	0.703
F7	0.827	0.944	0.947	0.904	0.713
F8	0.754	0.837	0.905	0.88	0.659

IV. CONCLUSION:

Floating microspheres of Edoxaban,were prepared by novel oil-in-water emulsion solvent evaporation technique, using various biodegradable polymers such as ethyl cellulose and eudragit S-100 in order to retain drug in body for longer period of time. Edoxaban, is insoluble in water and has short half life of 1.5 h. It requires frequent dosing before meals due to short half life and thereby imposing side effects. The drug requires a novel gastroretentive drug delivery system which can provide an extended period of time in stomach and improve oral bioavailability. Floating microspheres were characterized for floating ability, compatibility study, particle size and shape, drug content, in vitro drug release, entrapment efficiency. Due to their low density, these multi particulate drug delivery systems showed good floating ability and remained in gastric environment for more than 12 h. Eudragit S-100 based microspheres showed its buoyancy for more than 15 h, required for sustained therapeutic activity in comparison to Ethyl cellulose based microspheres. Major advantages of the system include ease of preparation, good floating ability, high encapsulation efficiency and sustained drug release over several hours. From this study it was concluded that formulation of floating microspheres of Edoxaban, offers prolonged gastric residence time and continuous release of the medication over an extended period of time thus oral bioavailability of the drug and subsequent efficacy is improved.

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