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Formulation and Evaluation of Floating Microspheres of Lamotrigine

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ABSTRACT

Floating drug delivery systems are one of the innovative medication delivery technologies that are now available. Because the bulk density of a floating medication delivery system is lower than that of gastric fluids, it is able to maintain its buoyancy in the stomach without making a significant impact on the pace at which the stomach empties for an extended length of time. Ethyl cellulose and Eudragit S 100 were used as polymers in the process of manufacturing floating microspheres of lamotrigine. This was accomplished by the emulsion solvent evaporation mechanism. The micrometric features of the floating microspheres were investigated, including their particle size, % yield, in-vitro buoyancy, incorporation efficiency, drug polymer compatibility (infrared research), scanning electron microscopy, and in-vitro drug release. The results demonstrate that the particle size, percentage yield, in-vitro buoyancy, and in-vitro drug release of microspheres are all affected by the concentration of polymer, which rises as the concentration level increases. Additionally, it was discovered that the cumulative drug release using a distinct ethyl cellulose 3:1 A-5 drug:polymer ratio at 900 rpm speed was shown to be more effective than another ratio. It was discovered that the micromeritic property was satisfactory, and scanning electron microscopy revealed that the structure was hollow, with a smooth surface, and that the percentage of drug release was ninety percent over a period of twelve hours. The results of this investigation indicate that floating microspheres containing lamotrigine have the potential to provide prolonged drug delivery, which may result in a reduction in the number of times required to provide a dose.

Keywords: *Lamotrigine, Ethyl cellulose, Eudragit S100, Floating microspheres, antiepileptic study, gastric retention*

1. INTRODUCTION

When it comes to giving medications for systemic effects, the oral route of drug administration is the most essential way. Due to the fact that self-administration of medicine is either not practicable or not commonly employed, the parental route is not used. Just lately, the topical route of administration has been used for the purpose of delivering medications to the body in order to achieve systemic effects. The oral route of administration is likely to be responsible for the administration of at least ninety percent of all medications that are used to generate systemic effects. When a new medicine is developed, one of the first concerns that a pharmaceutical firm asks is whether or not the drug can be properly taken via the oral route in order to achieve the effect that was intended for it. In the event that it is not possible, the medicine is often administered in a medical facility or in the office of a physician. When it comes to medications that are taken orally, the most recommended category of product is the solid oral dose form. One is fully aware of the factors that contribute to this inclination.[1] Oral Controlled Drug Delivery: Drug absorption at the desired rate means, first, to reach the effective plasma level within an acceptable short time period; second, to avoid an overshoot in the case of rapidly absorbed drugs; and third, to maintain effective plasma levels over the desired time period over the course of the desired time period. It is true that the intensity of the pharmacological effect is related to the drug concentration at the site of action, which is in turn related to the plasma drug concentration; however, the ideal situation is achieved when the concentration is continuously maintained between the minimum effective level and the maximum safe level (Therapeutic Index). The usual dose forms of drugs always fail to sustain the drug's effectiveness.[2] Controlled release (CR) drug delivery systems (DDS) make an effort to maintain the blood concentration of the medication at levels that are efficient and reasonably consistent inside the body via the use of spatial placement or temporal delivery. As a result, CRDDS provide a number of benefits, including the reduction of variations in blood levels, the reduction of drug accumulation, the use of a lower total drug dose, the enhancement of patient compliance, and the reduction of both local and systemic adverse effects [3-4]. The purpose of the study that is being

described is to construct floating microspheres of lamotrigine by the use of the emulsion solvent evaporation process. Lamotrigine is a contender for a floating drug delivery system due to its physiochemical features and its short half-life. In order to facilitate the development of floating microspheres of lamotrigine, several grades of ethyl cellulose will be used as polymers

2. MATERIALS AND METHODS

Preparation of floating microspheres [5-6]

Floating microspheres were synthesized using the technique described by Kawashima et al. with minor changes. The floating microspheres were formulated in two categories: lamotrigine with ethyl cellulose (A1-A9) and lamotrigine with Eudragit S-100 (B1-B9), combined in a solvent combination of dichloromethane and ethanol (1:1). The resultant suspension was gradually introduced into a swirling 0.25% w/v solution of polyvinyl alcohol, totalling 400 ml, at room temperature from the bottom. The stirring was maintained for 2 hours at 900 rpm using a mechanical stirrer fitted with four-blade propellers to facilitate solvent evaporation, as shown in Table 1. Following the evaporation of the solvent, the microspheres were collected using filtering and then washed many times with water. The collected microspheres were desiccated at ambient temperature and preserved in desiccators.

Table 1: Formulation table of floating microspheres

S. No	Batch	Polymer	Drug polymer ratio (mg)
1	A-1	Ethyl Cellulose	01:01
2	A-2	Ethyl Cellulose	01:02
3	A-3	Ethyl Cellulose	01:03
4	A-4	Ethyl Cellulose	02:01
5	A-5	Ethyl Cellulose	03:01
6	B-1	Eudragit S-100	01:01
7	B-2	Eudragit S-100	01:02
8	B-3	Eudragit S-100	01:03
9	B-4	Eudragit S-100	02:01
10	B-5	Eudragit S-100	03:01

Characterization of floating microspheres:

Micromeritic evaluation:

Bulk density: Bulk density= Bulk/mass volume

Tapped density: Tapped density= Tapped/mass volume

A. Percent Compressibility Index

Carr_Index = (ρtapped - ρbulk) / ρtapped * 100

ρtapped: Tapped bulk density of the material (kg/m3)

ρbulk : Bulk density of the material (kg/m3)

B. Angle of repose:

Tan θ = h/r

Where, h= height of pile, r = radius of the base of pile on the graph paper.

C. Hausner's Ratio: Hausner's ratio is an indirect index of ease of measuring the powder flow. It was calculated by the following formula (Sinko, P.J. 2006; Chein, Y.W. 1992; Liberman, H.A. et al., 1990).

Hausner's ratio = Tapped density/Bulk density.

Particle size: The dimensions of the particles in both the blank and drug-loaded microspheres were assessed using optical microscopy using a compound microscope (Olympus India) fitted with ocular and calibrated stage micrometres. Following the calibration of an ocular micrometre by positioning the ocular lens and concentrating on the item for measurement to ascertain its size in ocular units, samples are then placed on a slide for the measurement of microsphere dimensions [7].

Scanning electron microscopy (SEM): Dry floating microspheres were affixed to a gold-coated electron microscope using ion sputtering. The arbitrary examination of a stub observed the microsphere. The microspheres investigation was performed with a JEOL JSM-670F from Japan. The microspheres were introduced at an accelerated voltage of 3.0 [8].

Percentage yield: The percentage yield of microspheres is the ratio of the weight of collected microspheres to the total weight of all solid ingredients used. The collected dry microspheres were weighed to evaluate recovery.

Determination of drug loading of microspheres: Twenty milligrams of floating microsphere samples were dissolved at ambient temperature using ultrasonication in 50 mL of ethanol to ascertain the loading. The liquid was further filtered using a Millipore filter (0.45 µm). An ultraviolet (UV)-visible sensor (UV 1700-1800) from Shanghai Phoenix Optical Instrument Co., Ltd., Shanghai, China, was used to ascertain drug concentrations at 271 nm.

Drug entrapment efficiency: The efficacy of the microspheres in trapping was evaluated by extracting the medicine from them. According to conventional practice, 50 mg of desiccated microspheres was ground using a pestle and mortar, thereafter dissolving the fine microspheres in several milliliters of ethanol and diluting with 50 mL of 0.1 N HCl for 24 hours. After 24 hours, the solution was filtered through a 0.45 µm filter. The lamotrigine in the filtrate was evaluated spectrophotometrically at 271 nm using a UV-visible spectrophotometer (Shimadzu, UV-1800, Japan), employing 0.1 N HCl as the blank [9].

***In vitro* buoyancy:** Floating microspheres were evaluated for their in vitro floating characteristics using a USP dissolving apparatus 2 (paddle type). Fifty individual microspheres were immersed in a 500 mL jar of simulated gastric fluid from each formulation. The paddle rotates at 50 rpm, with the temperature maintained at 37 ± 0.5°C. The quantity of floating microspheres was quantified at hourly intervals during a duration of eight hours. In vitro buoyancy was expressed as a percentage, and the subsequent equation was established [10].

***In vitro* release study:** 100 milligrams of floating microspheres of lamotrigine were precisely weighed, and dissolving investigations were performed using 900 mL of enzyme-free simulated gastric fluid (SGF) at a temperature of 37 ± 0.5°C using a USP type II equipment. The rotational velocity was sustained at 100 revolutions per minute. An aliquot of 5 mL of dissolving media was extracted at regular intervals for a duration of 12 hours and replaced with fresh medium. The gabapentin microsphere content was quantified using a UV spectrophotometer (Spectro UV-2080, double beam, Analytical Technologies, India) at 210 nm, using simulated gastric fluid as the blank [11-12].

Kinetics of drug release: The release of the medication from diverse controlled-release formulations is often assessed using four kinetic models. The data acquired from the in vitro drug release were analyzed using five models to determine the most appropriate one. Zero-order kinetics is a drug-release process independent of drug concentration.

The zero-order release equation is:

Zero-order kinetics: Ft= K0t

Here, F indicates the drug fraction released in time t and K0 denotes the zero-order release constant.

First-order kinetics: “Ln (1 - F) = -K1t”

Here F shows the drug release fraction in time t and K1denotes the Ist order release constant

Higuchi model: F= K2 t1/2

Here F signifies drug release fraction in period t &K2 denotes the “Higuchi constant”.

Korsmeyer-Peppas model: Mt/M∞= K3tn

Here Mt denotes the drug amount released in time t, M∞ signifies the drug amount release at time infinity, K3 denotes the kinetic constant and n indicates the exponent defining the swelling mechanism. [13-15].

3. DISCUSSION

The floating medication delivery system has a bulk density inferior to that of gastric fluids, allowing it to stay buoyant in the stomach without influencing the gastric emptying rate for an extended duration. As the system remains buoyant in the stomach contents, the medicine is gradually discharged at the specified pace from the system. Subsequent to the drug's administration, the leftover system is evacuated from the stomach. This leads to an extended stomach residence duration and improved regulation of plasma medication concentration fluctuations. Single unit formulations (floating tablets) are prone to issues such as adhesion or obstruction inside the gastrointestinal system, which may provide a risk of discomfort. Conversely, a floating system composed of several unit forms (floating microspheres) has distinct advantages over a single unit formulation. Floating microspheres provide a sustained therapeutic impact, hence decreasing the frequency of dose. The objective of the current work was to create floating microspheres of Lamotrigine using the emulsion solvent evaporation technique with Ethyl cellulose and Eudragit S100 as polymers.

The average particle size of the microsphere formulations A1 to A5, which comprise ethyl cellulose, ranges from 125.70±1.15 to 165.35±0.21, respectively. The findings for formulations B1 to B5 ranged from 105.62±1.12 to 142.33±0.25, respectively. The influence of polymer content on the particle size of microspheres was assessed. The average particle size of the microspheres was shown to rise with a reduction in ethyl cellulose. The viscosity of the medium escalates with

increased concentrations of ethyl cellulose or Eudragit S 100, leading to heightened interfacial tension. Shearing efficiency is reduced with elevated viscosities. This leads to the creation of bigger particles. The bulk density, tapped density, and Hausner's ratio of formulations A1 to A5 and B1 to B5, which include varying concentrations of the drugs ethyl-cellulose or Eudragit S 100, were calculated. The values of Carr's index and angle of repose suggest good flow qualities.

Table 2: Micrometrics properties of floating microspheres

Batch Code	Mean Particle Size [a] (µm)	True Density[b] (g/cm^3)	Tapped Density[b] (gm/cm^3)	Compressibility Index[b] (%)	Angle of Repose[b] (θ)
A-1	125.70±1.15	0.198±0.032	0.246±0.012	19.52±0.26	33.86±1.45
A-2	136.23±2.10	0.165±0.056	0.199±0.004	17.09±0.13	31.72±2.32
A-3	152.41±0.12	0.159±0.034	0.188±0.013	15.42±0.25	30.63±1.63
A-4	162.46±3.32	0.148±0.017	0.171±0.005	13.45±0.17	32.32±1.34
A-5	165.35±0.21	0.135±0.045	0.154±0.015	12.33±0.35	25.45±0.65
B-1	105.62±1.12	0.174±0.022	0.221±0.022	21.26±0.23	41.22±0.54
B-2	114.35±0.45	0.168±0.051	0.207±0.032	18.84±0.15	28.54±0.65
B-3	126.78±1.32	0.162±0.074	0.201±0.043	19.41±0.54	27.18±0.33
B-4	134.57±2.43	0.151±0.052	0.174±0.053	13.21±0.23	26.87±0.29
B-5	142.33±0.25	0.145±0.041	0.163±0.011	11.04±0.52	21.15±0.65

The morphology of microspheres was analyzed using scanning electron microscopy. The observation of the microspheres revealed a hollow spherical architecture with a smooth surface shape (Fig 1). Certain microspheres had a dented surface morphology but demonstrated excellent buoyancy on the medium's surface, suggesting an undamaged exterior. The external surface of the microspheres was smooth and dense, but the inside surface was porous. The microsphere shell exhibited a porous structure. The phenomenon may result from the evaporation of solvent confined inside the microsphere shell after the formation of a smooth and thick outer layer. The percentage yield of floating microsphere formulations A1 to A5 examines the influence of polymer concentration on the production of the floating microspheres, using formulations created at different concentrations of ethyl cellulose. The yield of the floating microspheres augmented with increased polymer concentration. At low concentrations of ethyl cellulose, a portion of the polymer solution aggregated into a fibrous structure, solidifying before droplet formation, or transitory droplets ruptured before full solidification owing to inadequate mechanical strength, leading to a low yield (Table 2).

Figure 1: Scanning electron microphotograph of floating microsphere of batch A-5

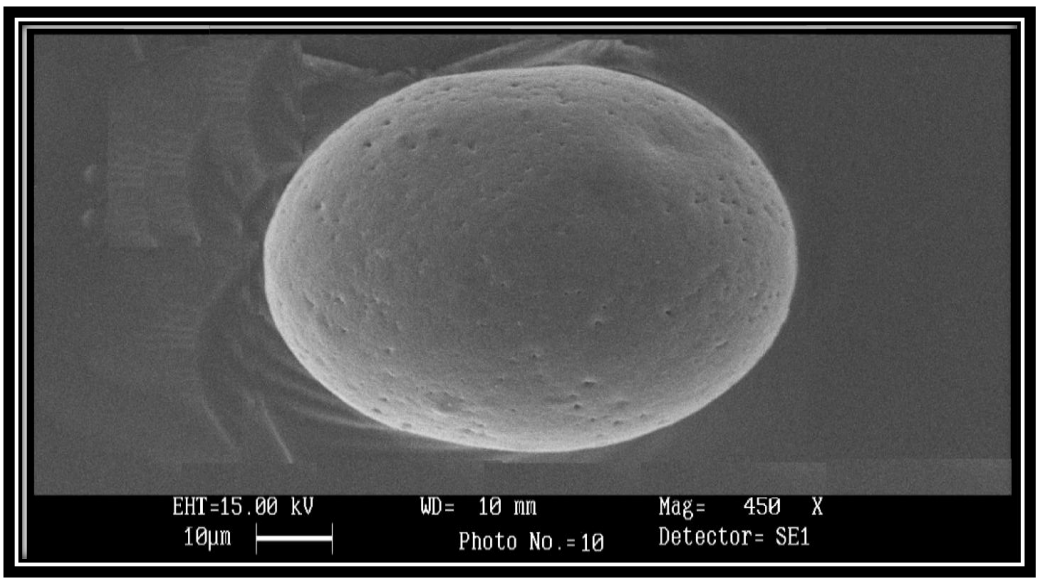
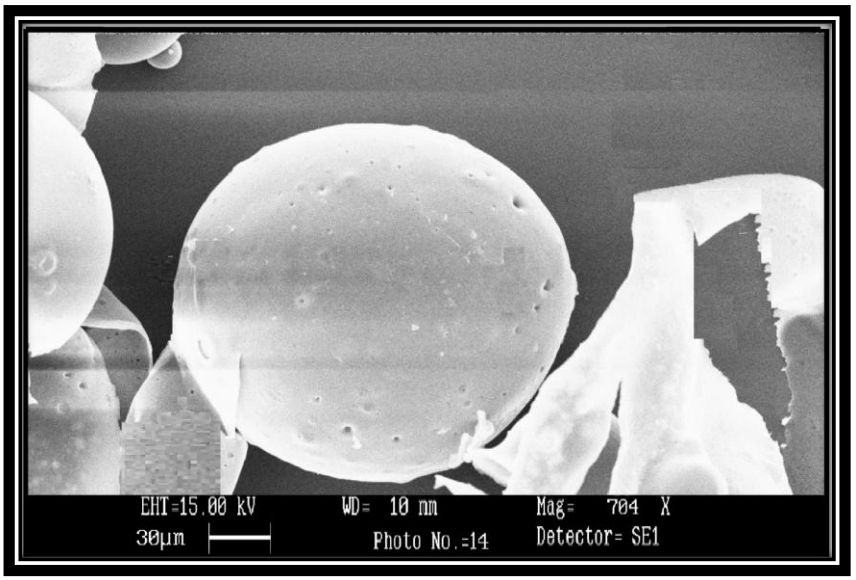


Figure 2: Scanning electron microphotograph of floating microsphere of batch B-5.



The objective of manufacturing floating microspheres was to prolong the stomach retention duration of a medication. The buoyancy test was conducted to assess the floatability of the produced microspheres. The microspheres were distributed on the surface of a simulated stomach fluid, and the proportion of buoyant vs settled microspheres was quantified over time. The in-vitro buoyancy of formulations A1 to A5 and B1 to B5, which comprise varying drug-to-polymer ratios, was shown to exceed 90%. The findings indicated a correlation wherein greater particle sizes corresponded to extended floating durations of up to 12 hours (Table 2).

The incorporation efficiency of formulations A1 to A5 and B1 to B5, which comprise variants of drug polymers, indicated that an increase in polymer concentration enhanced drug entrapment. The drug entrapment efficiency was deemed satisfactory across all formulations (Table 2).

It was noticed that when the concentration of ethyl cellulose or Eudragit S 100 rose, the percentage release of lamotrigine decreased. The elevation in polymer concentration results in a heightened density of the polymer matrix within the microspheres, therefore extending the diffusional route length. This may reduce the total medication release from the polymer matrix. Additionally, smaller microspheres are produced at reduced polymer concentrations, resulting in a greater surface area exposed to the dissolving liquid (Table 2). The release of lamotrigine from the formulated floating hollow microspheres was examined in 0.1N HCl (pH 1.2) during a duration of 12 hours. The cumulative percentage of medication release for group α microspheres ranged from 81% to 98%. Due to the insolubility of ethyl cellulose in acidic media, the microspheres maintained their structural integrity throughout in-vitro dissolution experiments. The cumulative percentage of medication release for formulations containing Eudragit S 100 floating microspheres ranged from 74% to 98%. In formulations A-5 and B-5, the cumulative percentage of drug release was determined to be 81.2±1.13 and 81.02±1.22, respectively. It was observed that when the polymer ratio increased, the cumulative percentage of medication release rapidly decreased. This may be attributed to the enhanced partitioning of the medication inside the polymer (ethyl cellulose or Eudragit S-100). It was revealed that for both groups, the release of lamotrigine considerably reduced ($p<0.05$) with an increase in the quantity of polymers. A significant enhancement in drug release was seen with an increase in the stirring rate. The increase in surface area of microspheres may be attributed to their decreased size. In formulations A-4 and B-3, the cumulative percentage of drug release was determined to be 82.1±0.33 and 90.37±0.78, respectively.

Increasing the amount of dichloromethane in the solvent phase resulted in an enhanced release. Conversely, an increase in the amount of ethanol resulted in a reduction in drug release. The underlying cause may be the size of microspheres, which enlarges with a rise in ethanol volume. The cumulative percentage of drug release in formulations A-9, A-10, and B-8, B-9, B-10 was determined to be 81.23±1.21, 98.25±0.42, and 74.32±1.22, 81.23±0.33, and 97.6±0.13, respectively (Figures 3 and 4). The drug release from floating hollow microsphere batches adhered to Korsmeyer-Peppas model, with a 'n' value above 0.5, indicating a supercase II transport mechanism.

Figure 3: *in-vitro* drug release study (Zero-order kinetics) of floating microsphere of batches (A-1 to A-5)

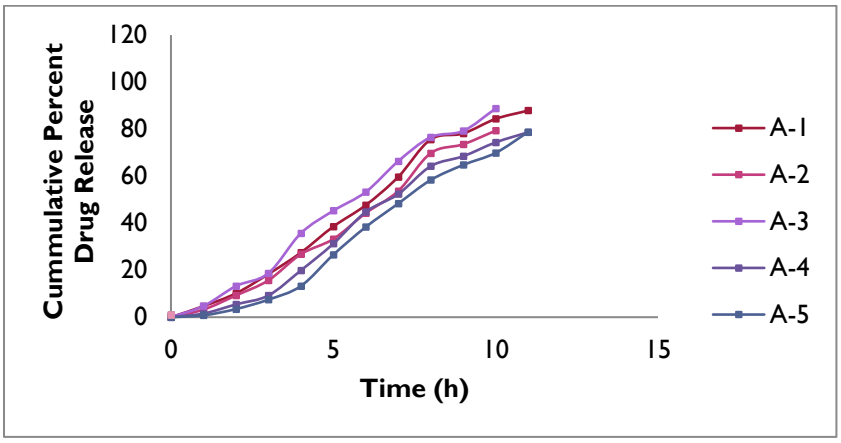


Figure 4: *in-vitro* drug release study (Zero-order kinetics) of floating microsphere of batches (B-1 to B-5)

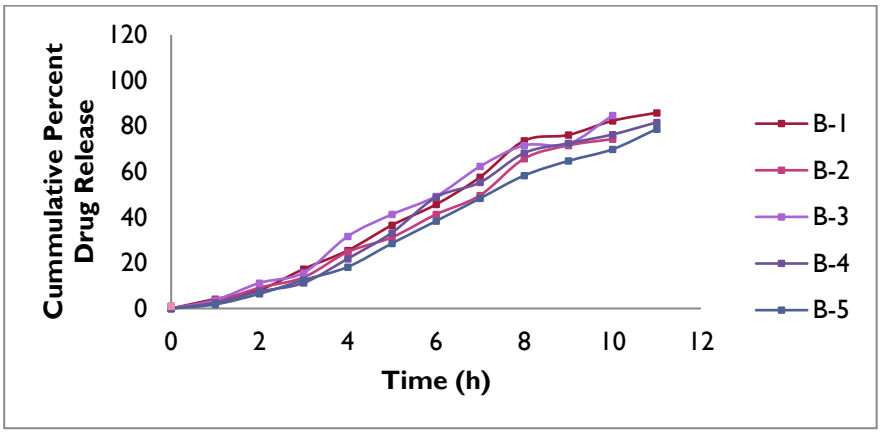


Table 2: Physical parameters of prepared floating microspheres

Batch code	Yield[a] (%)	Incorporation efficiency[a] (%)	Buoyancy [a] (%)	Floating lag times (sec)	Total floating time (hrs)
A-1	65.43±0.12	56.32±0.72	62.33±0.45	110	>12
A-2	71.54±0.35	61.95±0.78	66.54±0.12	115	>12
A-3	79.85±0.44	67.42±0.61	71.23±0.65	121	>12
A-4	85.85±1.75	71.54±1.42	84.31±0.94	123	>12
A-5	94.32±0.65	74.95±0.85	92.25±0.64	115	>12
B-1	67.23±0.45	51.12±0.76	59.25±0.72	122	>12
B-2	73.12±1.18	55.11±0.34	68.32±0.22	126	>12
B-3	81.64±0.33	60.33±1.03	81.54±0.75	124	>12
B-4	88.45±0.21	64.56±0.21	89.11±0.78	126	>12
B-5	96.33±0.66	73.23±0.75	94.14±0.65	125	>12

4. CONCLUSION

The data acquired from the research may be effectively synthesized using Ethyl cellulose and Eudragit S 100 as polymers by emulsion solvent evaporation. The percent yield of all floating microsphere formulations exceeded 75%, indicating that the encapsulation techniques used were successful. The % yield markedly improved with the augmentation of polymer quantity in each preparation procedure. The entrapment efficiency was satisfactory in all instances. This indicated that optimal settings were used in the preparation technique. The in-vitro buoyancy exceeded 90% after 12 hours, indicating good performance of the suggested formulations. The percentage of buoyancy markedly rose with the augmentation of polymer in each

production procedure. The average particle size of microspheres varied according on the kind of polymer used. The particle size markedly increased as the polymer quantity decreased. The flow characteristics of all the manufactured microspheres were satisfactory, indicating that the created microspheres were non-aggregated. The in-vitro release of floating microspheres of lamotrigine indicated that formulation A-5 and B-5 was optimal, as it demonstrated sustained release in a consistent way over a prolonged duration (beyond 12 hours). In-vitro release data analyzed using several kinetic models indicate that the release followed mixed-order kinetics, the Higuchi diffusion mechanism, and non-Fickian control (anomalous diffusion) accompanied with swelling. Ultimately, it was determined that the formulated floating microspheres of lamotrigine may serve as a viable option for safe and effective sustained drug administration over a prolonged duration, hence decreasing dose frequency.

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