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DEVELOPMENT AND EVALUATION OF EUDRAGIT FLOATING MICROSPHERES CONTAINING EZETIMIBE

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ABSTRACT

The purpose of this research work was to formulate and evaluate the floating microspheres of poorly water-soluble drug, ezetimibe by emulsion solvent diffusion evaporation technique using eudragit RS 100 and eudragit RL 100. The formulated microspheres were characterized for various parameters. The microspheres with Eudragit RS 100 showed drug loading of 20.9 to 81.8% and the particle size of 2.631 to 7.254 µmand the microspheres with Eudragit RL 100 showed drug loading of 63.5 to 73.6%, the particle size distribution of 1.549 to 5.962 µm. The prepared microspheres were white, free-flowing and virtually spherical in shape.The drug release was extended up to 10 h and its release mechanism from formulations followed the super case-II transport which indicated that drug release from floating microspheres by diffusion controlled polymeric relaxation.

Keywords: Ezetimibe; Eudragit RS100;Eudragit RL100; Floating microspheres; Anti-hyperlipidemic

1. INTRODUCTION

Floating microspheres are free-flowing comprising polymers that are biodegradable. It mainly delivers the drug into the targeted site of action and maintains the required concentration without any untoward effects and also protects the GIT from the irritation caused by the drug [1, 2]. The important reasons to formulate microspheres are to overcome the negative aspect and limitations of conventional dosage forms and also to improve the rate of bioavailability of insoluble hydrophobic drugs. These floating drug delivery systems immediately float upon interacting with the gastric liquids and they provide an excellent increase in absorption window and bioavailability of the drug in the upper small intestine. The floating drug delivery systems have less density than the gastric fluids and stay in the stomach as floating for a longer duration of time and do not influence the rate of gastric emptying. The drug release from the floating microspheres is at a controlled or sustained rate[3,4,5]

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The ideal requirement for a floating drug delivery system is that:

- It must discharge substance gradually to fill in as a supply
- It ought to keep up explicit gravity lower than gastric substance [6]

Hyperlipidemia is a health disorder that has troubled humankind for ages. In 2002 coronary heart epidemiological confirmations emphatically upheld a positive connection between hyperlipidemia, blood lipids and its inconveniences. The heart's blood supply is blocked completely due to higher deposition of lipoproteins and thus heart attack occurs, scientifically called myocardial infraction [7]. Hyperlipidemia refers to an acquired genetic disorder that results in elevating the lipid levels coursing in the blood. These lipids enter blood vessels and increment the danger of getting atherosclerosis which may prompt stroke, heart attack and they need to be amputated. The incidence of atherosclerosis is higher if a person is already suffering from high blood pressure, kidney failure, or diabetes. It's a condition where high levels of lipids, fatty substances are found in blood and is a significant reason for coronary supply route infection [8].

The main objective of the floating drug delivery system is to overcome some physiological difficulties like the inability of the dosage form to retain in the GIT region and the variable nature of gastric emptying rate which is unpredictable and reduced bioavailability. In this study, Ezetimibe is used as a model drug (Figure 1). It is a cholesterol absorption inhibitor and is considered a BCS class II drug. Ezetimibe has poor solubility, high permeability and low bioavailability with a half-life of 22 h [9]. The purpose of the current investigation was to build up a gastro retentive particulate medication for the controlled release of drug and to enhance the oral bioavailability of poorly water-soluble drugs for the treatment of hyperlipidemia.

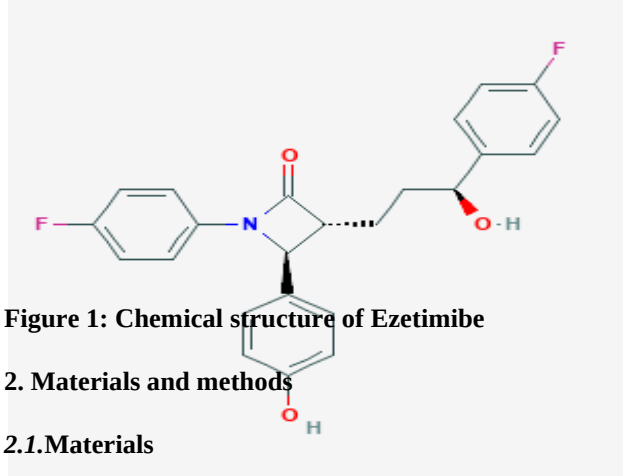

Figure 1: Chemical structure of Ezetimibe

2. Materials and methods

*2.1.*Materials

Ezetimibe was received as a gift sample from Jig chemical Ahmedabad, Gujarat, Eudragit RS100 from Roehm Pharma, Germany, Eudragit RL100 was purchased from Yarrow chem products, Dichloromethane and n-butanol were obtained from S.D fine chemical Ltd. All the synthetic substances and reagents utilized were of analytical grade.

*2.2.*Preparation of floating microspheres

Emulsion solvent diffusion evaporation technique was employed for the development of microspheres. Ezetimibe and polymer (Eudragit RS & RL100) are mixed in the ratio as mentioned in Table 1 and dissolved in the mixture containing 8:5:2 ratio of ethanol, dichloromethane and n-butanol. Required quantity of distilled water and polyvinyl alcohol were mixed in a beaker. Drug polymer mixture was added as a thin stream into water containing polyvinyl alcohol and stirred at 300 rpm using a mechanical stirrer for 20 min at room temperature. The mixture is allowed to

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sediment and the supernatant layer is separated. The sediment is collected and allowed to dry to get microspheres [10] (Figure 2).

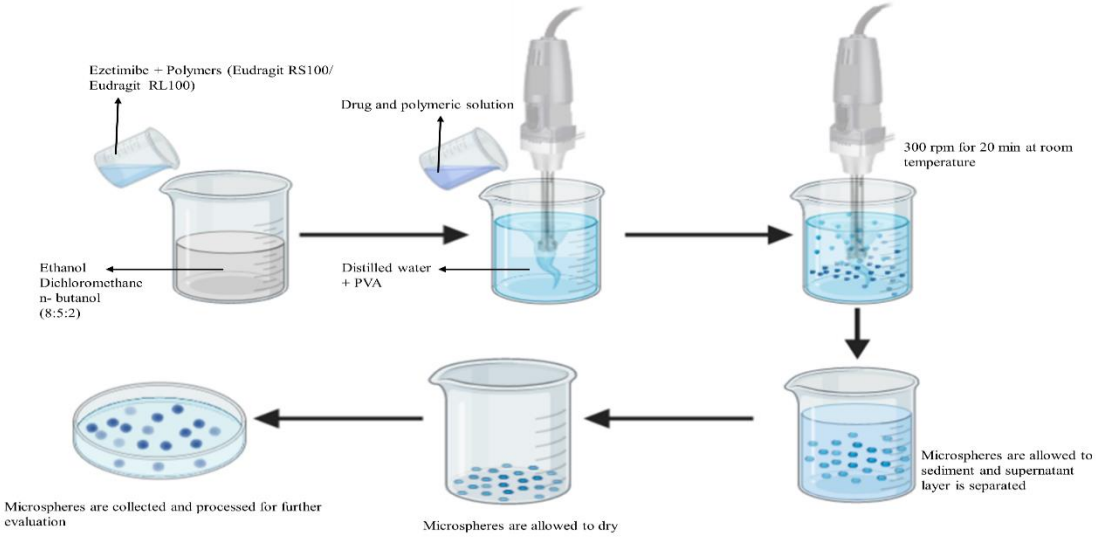

Figure 2: Process of preparing floating microspheres

The formulation prepared by using Eudragit RS100 was assigned a batch code of A1- A5 and with Eudragit RL100 as B1-B5.

Table 1: Formula for preparation of Ezetimibe microspheres

Sl. no.	Ezetimibe: Eudragit RS 100	Ezetimibe: Eudragit RL 100
1	1:1	1:1
2	1:2	1:2
3	1:3	1:3
4	1:4	1:4
5	1:5	1:5

2.3. Characterization of Microspheres

2.3.1. Drug-polymer compatibility

The drug-polymer compatibility was analyzed using an FTIR spectrophotometer. In this technique ezetimibe and polymer with potassium bromide were ground finely utilizing mortar and pestle. This blend was set in a pressure-

driven press packed at 10 kg/cm3 for the formation of thin transparent pellets which were placed in the sample holder and analyzed. The values were recorded between 400-4000 cm-1.

The drug and polymer were subjected to differential scanning calorimetry to know their physical compatibility. The drug, polymer and microsphere formulations were put in an aluminum container and were fixed thematically by heating at 10°C per minute using nitrogen. The DSC instrument was balanced for temperature using indium. Also, for enthalpy adjustment indium was fixed in aluminum dish with a fixed void container as a reference [11].

2.3.2. Determination of process yield and drug loading

The percentage yield of the floating microspheres of all the ten batches was calculated by taking the final weight of the product after drying in contrast to the total weight of drug and polymer used in the preparation of floating microspheres [12]. The % yield of microspheres was determined by using the equation (1).

$$\text{Yield } (\%) = \frac{\text{weight of microspheres}}{\text{Total weight of drug and polymer}} \text{ x } 100 \qquad (1)$$

Drug loading was determined by weighing 5mg of microspheres, which was dissolved in 10ml of ethanol, later the extract was filtered. The absorbance for the filtered solution after dilution was estimated at 232 nm against blank [13]. The amount of ezetimibe present in the floating microspheres was determined by the equation (2).

$$\% \text{ Drug loading} = \frac{\text{Amount of drug actually present}}{\text{Theoretical drug load}} \text{ x } 100 \qquad (2)$$

2.3.3. Determination of particle size

The optical microscopic method was used to determine the size of microspheres. The size was counted using a calibrated optical microscope and the average particle size of the microsphere was calculated after measuring the diameter of 100 particles [14].

2.3.4. In vitro floating behavior

In vitro floating behavior of ezetimibe loaded microspheres to ascertain the floating behavior was carried out by transferring 10 mg of microspheres in a beaker containing 100 ml of 1.2 pH buffer containing 0.02% of tween 80 and stirred at 100 rpm using a magnetic stirrer. The layer of floated microspheres on the surface of the medium was collected after 12 h, particles in the sinking particulate layer were collected by filtration.

Both parts of floated and sediment particles were dried to a constant weight [15]. The percentage of buoyancy was calculated by using the equation (3).

$$\% \text{ Buoyancy} = \frac{\text{Weight of floating microsphere after 12h}}{\text{Initial weight of floating microspheres}} \text{ x } 100 \qquad (3)$$

2.3.5. In vitro drug release studies

The dissolution rate of ezetimibe from the formulated microspheres was studied using USP Type II basket type dissolution test apparatus. Microparticles equivalent to 50mg were weighed, filled in capsule and placed in the basket. The dissolution media used was simulated gastric fluid (SGF) pH 1.2, and was maintained at a temperature

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of 37 ± 50 C. The rotation speed of the basket maintained was 100 rpm and 5ml of aliquots were withdrawn at programmed time intervals for 12h and drug release was studied by UV spectrophotometer at the wavelength of 232 nm. The volume withdrawn was supplanted with an equivalent volume of fresh 5mL of SGF.

*2.4.*Evaluation of optimized formulation

2.4.1. Scanning electron microscopy

Scanning electron microscopy was carried out to portray the shape and surface morphology of the microspheres. The samples were sprinkled on the adhesive tape stuck onto a stub prepared by using a sputter cutter coated with gold. The study was carried out at 20kv. The coated microspheres were scanned and their photographs were taken [16].

2.4.2. Study of release kinetics

The data obtained from *in vitro* studies was fitted to several kinetic models such as zero order, first order, Higuchi and Korsmeyer-Peppasto expressthe mechanism of ezetimibe release from the formulated microspheres and rate constants for the respective models was calculated[17].

3. Results and Discussion

3.1. Preparation and characterization of floating microspheres

Ten different batches of floating microspheres with different polymers were prepared by emulsion solvent diffusion evaporation technique. Ethanol was used here as a solvent, as both drug and excipients are freely soluble in it. The floating microspheres prepared by using Eudragit RS100 were assigned a batch code of A1- A5 and with Eudragit RL100 as B1-B5.

3.2. Characterization of microspheres

3.2.1. Drug- polymer compatibility

The results demonstrated that there was no change in spectra of Ezetimibe with Eudragit RS100 and RL100 (Figure 3 and 4). Thus, indicating the compatibility of the drug with the polymer.

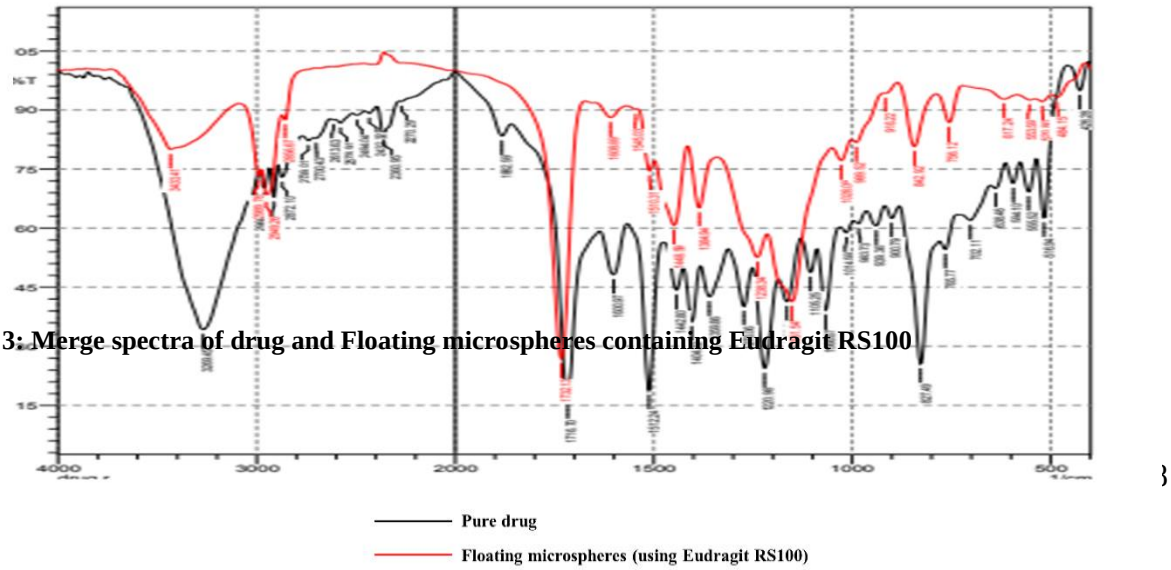

Figure 3: Merge spectra of drug and Floating microspheres containing Eudragit RS100

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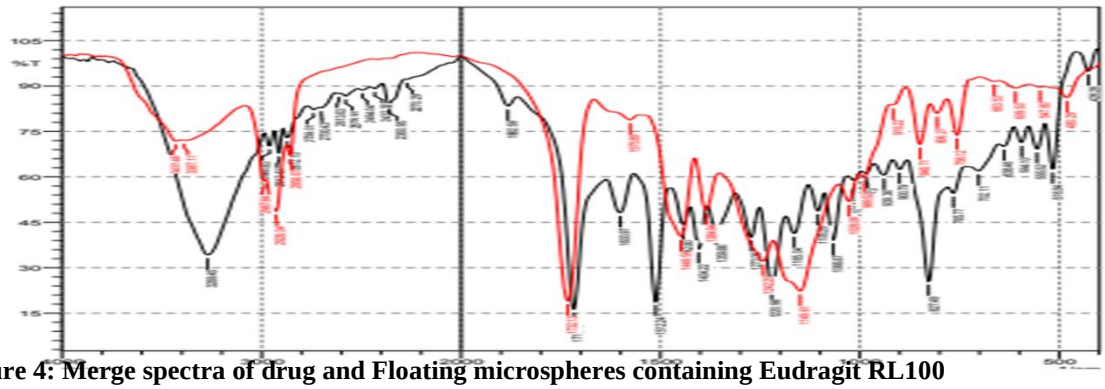

Figure 4: Merge spectra of drug and Floating microspheres containing Eudragit RL100

DSC images of Ezetimibe demonstrated a sharp endothermic peak at 163.59°C (Figure 5). Thermographs of Ezetimibe-loaded floating microspheres with Eudragit RS100 microspheres showed the same endothermic peak at 140.14°C and RL100 microspheres at 186.62°C (Figure 6 and 7). This confirms that there is no interaction between drug and polymer.

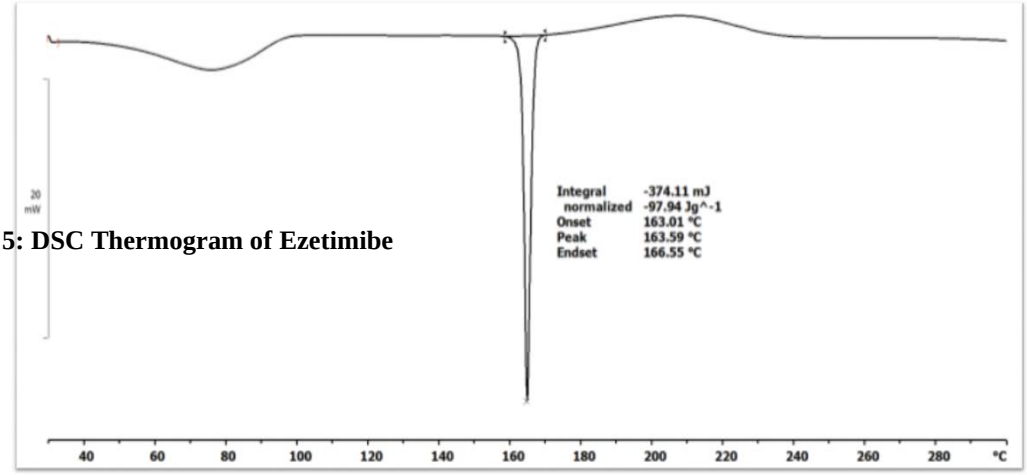

Figure 5: DSC Thermogram of Ezetimibe

Figure 6: DSC Thermogram of Ezetimibe loaded microspheres using Eudragit RS100

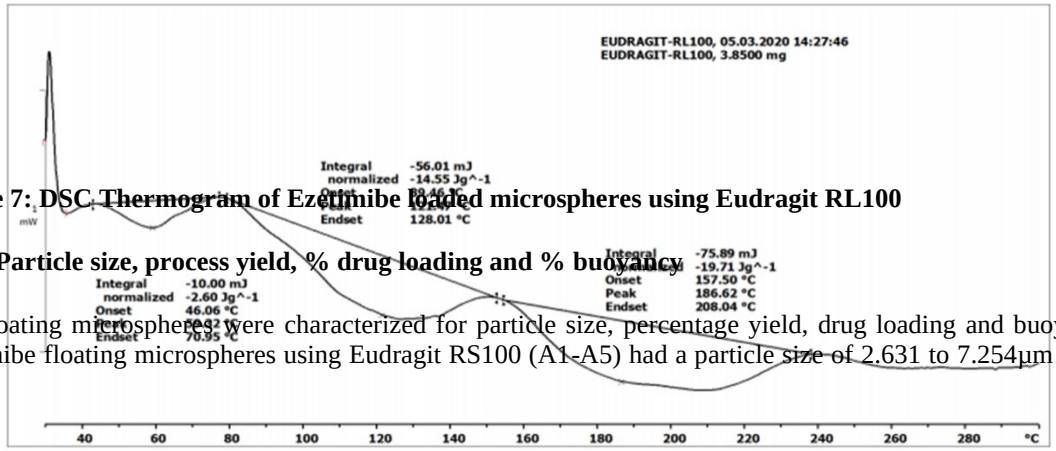

Figure 7: DSC Thermogram of Ezetimibe loaded microspheres using Eudragit RL100

3.2.2. Particle size, process yield, % drug loading and % buoyancy

The floating microspheres were characterized for particle size, percentage yield, drug loading and buoyancy. The Ezetimibe floating microspheres using Eudragit RS100 (A1-A5) had a particle size of 2.631 to 7.254µm (Figure 8),

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percentage yield in the range of 70.5 to 86.16%, drug loading of 70.9 to 81.8% and buoyancy of 69.13 to 85.21% (Table-2)

Table 2: Results of particle size, process yield, % drug loading and % buoyancy for Ezetimibe floating microspheres with polymer Eudragit RS 100 (A1-A5)

Batches	Drug-polymer ratio	Particle size (µm)	Process yield (%)	% Drug loading	% Buoyancy
A1	1:1	2.631±2.31	70.5	74.5±2.98	69.13±0.9
A2	1:2	4.178±1.22	73.3	70.9±1.86	73.67±1.2
A3	1:3	4.267±2.04	80	81.8±4.66	85.21±1.6
A4	1:4	4.552±1.64	82.72	78.18±3.64	79.55±1.8
A5	1:5	7.254±2.98	86.16	80±2.58	75.55±1.4

The formulations using Eudragit RL100 (B1-B5) was found to have a particle size in the range of 1.549 to 5.962µm (Figure 9), process yield of 69 to 80%, drug loading of 63.5 to 73.6% and buoyancy of 66.5 to 79.90% (Table-3)

Table 3: Results of particle size, process yield, % drug loading and % buoyancy for Ezetimibe floating microspheres with polymer Eudragit RS 100 (B1-B5)

Batches	Drug-polymer ratio	Particle size (µm)	Process yield (%)	% Drug loading	Buoyancy (%)
B1	1:1	1.549±2.44	69	69.5±2.98	66.5±0.4
B2	1:2	1.936±2.11	71.93	71.3±1.86	68.55±0.6
B3	1:3	4.178±1.99	72.5	63.5±4.66	71.90±1.2
B4	1:4	4.552±2.36	76	73.6±3.64	79.90±1.8
B5	1:5	5.962±2.66	80	64.5±2.58	70±1.6

Eudragit RS100 and Eudragit RL100 concentration affected both particle size and process yield of microspheres. From the results, it was observed that as the concentration of polymer increased the particle size and process yield also increased (Table. 2 and 3). It might be due to an increase in viscosity of the polymer in drug-polymer solution, which leads to the formation of outsized emulsion droplets leading to the increased size and weight of the microspheres [18, 19]. The formed large-sized particles need more energy to break down into smaller particles.

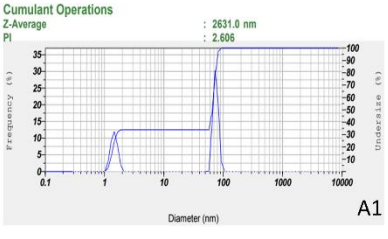

Fig. 8(a): Particle size of formulation A1

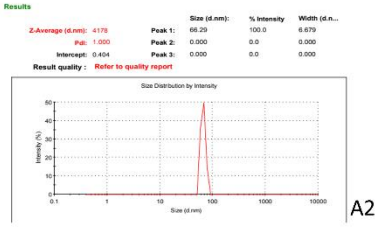

Fig. 8(b): Particle size of formulation A2

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Figure 8: Particle size of formulations A1 to A5

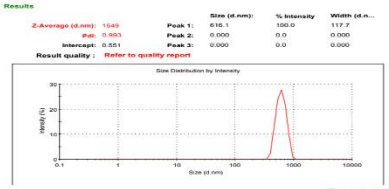

Fig. 9(a): Particle size of formulation B1

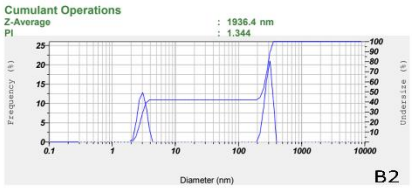

Fig. 9(b): Particle size of formulation B2

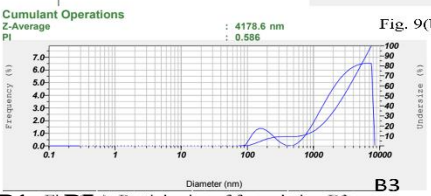

Fig. 9(c): Particle size of formulation B3

Figure 9: Particle size of formulations B1 to B5

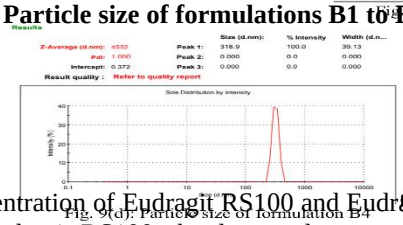

Fig. 9(d): Particle size of formulation B4

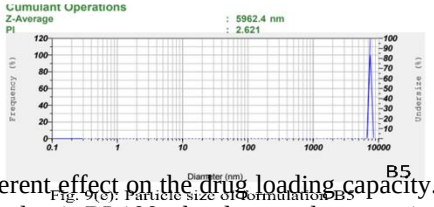

Fig. 9(e): Particle size of formulation B5

The concentration of Eudragit RS100 and Eudragit RL100 had a different effect on the drug loading capacity. In the case of Eudragit RS100, the drug: polymer ratio of 1:3 and with Eudragit RL100, the drug: polymer ratio of 1:4 showed greater drug loading. When the results for both the polymers were compared, it was witnessed that the microspheres prepared by using Eudragit RS100 showed greater drug loading. This is due to the presence of quaternary ammonium groups. Eudragit RS100 has less amount of the quaternary ammonium groups, they form a thick polymeric surface around the drug, avoiding the drug to enter the surrounding media, whereas Eudragit RL100 has a large number of quaternary ammonium groups which enables the process of diffusion during the preparation of microspheres, leading the drug to move out into the surrounding medium[20].

The % buoyancy of the microspheres decreased with an increase in polymer concentration. The drug: polymer ratio of 1:3 in the case of Eudragit RS100 and 1:4 in the case of Eudragit RL100 showed increased buoyancy. Further increase in polymer concentration led to the reduction of the % buoyancy. This might be due to the formation of a porous structure, which allows the media to enter the microsphere system. The vacant space present in the microspheres is filled with the surrounding media. This leads to an increase in the weight of the microspheres, which further sinks and reduces the % buoyancy [21].

3.2.3. In-vitro drug release studies

The data from the *in-vitro* drug release profile of Eudragit RS100 was plotted in Figure 10, and for Eudragit RL100 was plotted in Figure 11. The *in-vitro* release of the floating microspheres at 12hrs for Eudragit RS100 ranged from 64.44 % ±0.60 to 90.4±0.53 and for 58.33 % ±0.52 to 91.71 % ±0.51. To determine the mechanism of *in-vitro* drug release and release kinetics of drug from the dosage form, the results of optimized formulation were fitted to various mathematical models like zero order, first order, Higuchi and Korsmeyer-Peppas model (Table 4 and 5). In the case of Eudragit RS100, formulation A3 and Eudragit RL100, formulation B4 were best fitted with zero-order kinetics with the highest regression values of 0.9876 and 0.997 respectively. The 'n' values for A3 and B4 were 1.181 and 1.588 respectively and were obtained from the Korsmeyer-Peppas model. The formulations followed the super case-II transport which indicated that drug release from floating microspheres by diffusion-controlled polymeric relaxation.

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Figure 10:% CDR profile of Ezetimibe floating microspheres of A1-A5

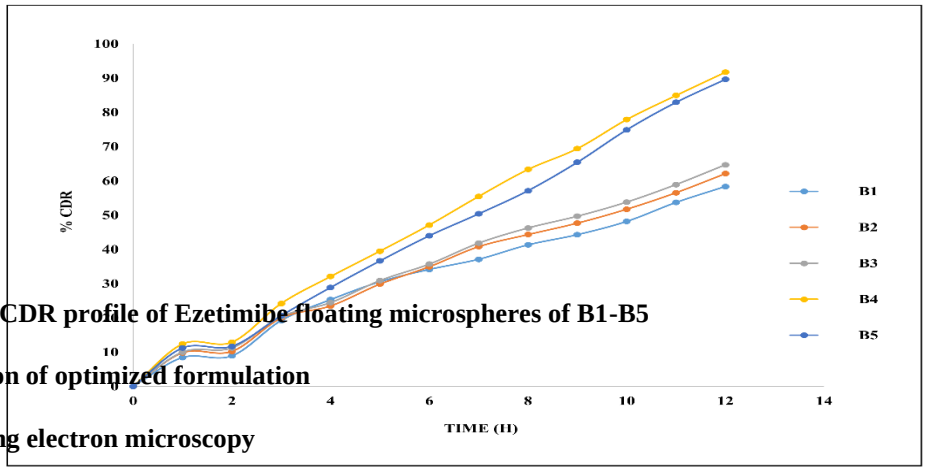

Figure 11:% CDR profile of Ezetimibe floating microspheres of B1-B5

3.3. Evaluation of optimized formulation

3.3.1. Scanning electron microscopy

The morphology of the optimized formulations A3 and B4 was examined by scanning electron microscopy. The SEM photographs of the optimized formulations are shown in Figures 12 and 13. The photographs of microspheres showed spherical shapes.

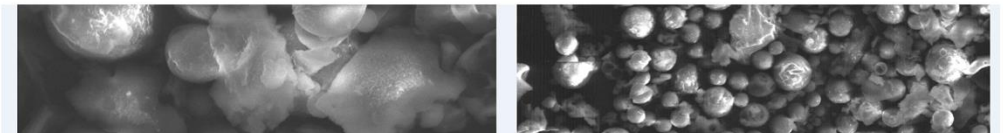

Figure 12: SEM images of Ezetimibe loaded Eudragit RS 100 microspheres of A3

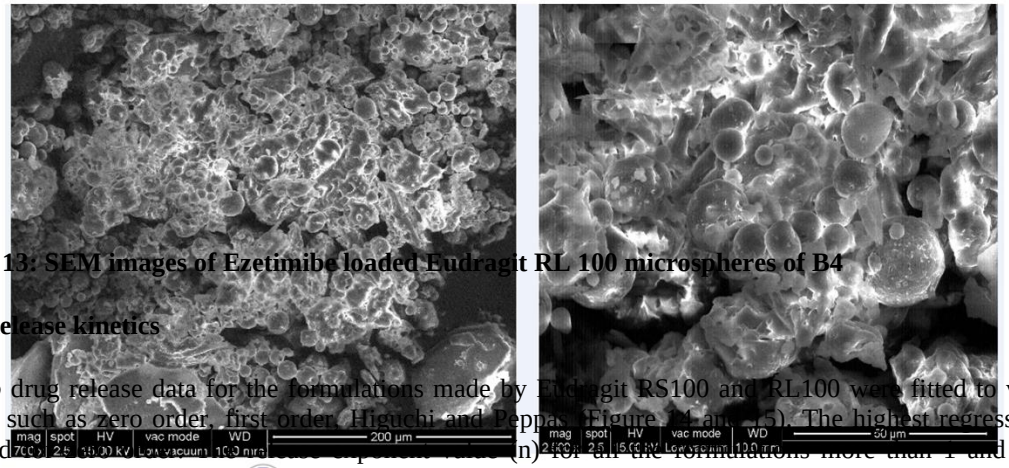

Figure 13: SEM images of Ezetimibe loaded Eudragit RL 100 microspheres of B4

*3.3.2.*Release kinetics

In-vitro drug release data for the formulations made by Eudragit RS100 and RL100 were fitted to various kinetic models such as zero order, first order, Higuchi and Peppas (Figure 14 and 15). The highest regression value was obtained [illegible] for all the formulations more than 1 and suggests non-

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Fickian diffusion – super case-II transport as the release mechanism (Table 4 and 5). This indicates that the drug is released by the diffusion process and is released in a controlled manner. The mechanism of drug transport is due to the relaxation of the polymer matrix. First, the drug shows slow diffusion and dissolution process, followed by a controlled release pattern.

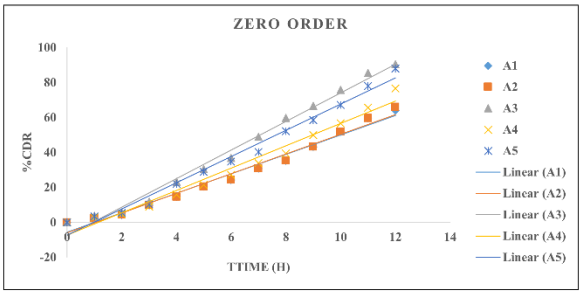


Fig. 14(a): Zero order release kinetics

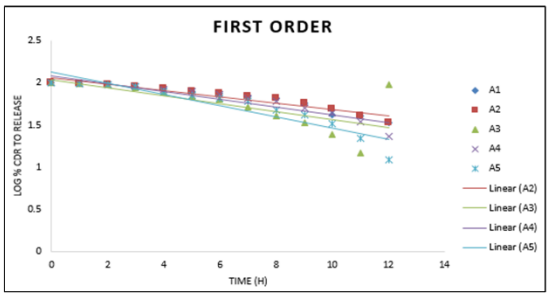
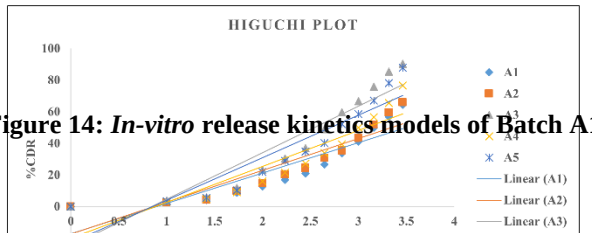


Fig. 14(b): First order release kinetics



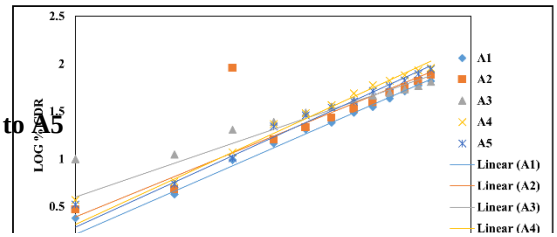


Figure 14: *In-vitro* release kinetics models of Batch A1 to A5

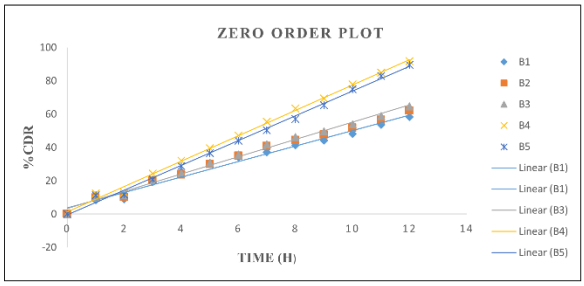


Fig. 15(a): Zero order release kinetics

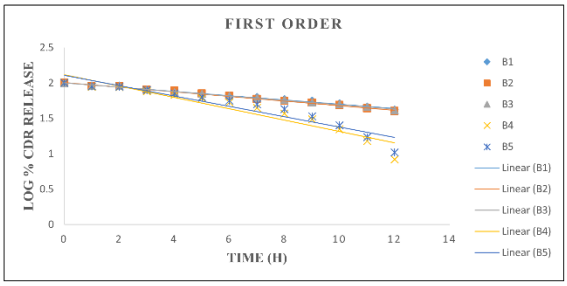
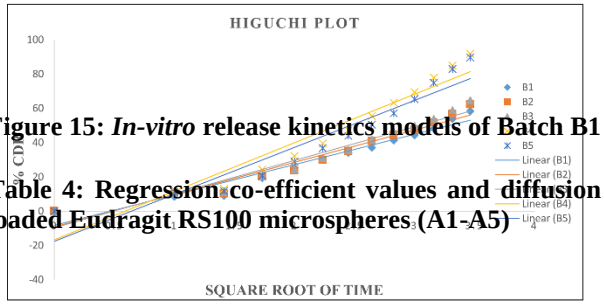


Fig. 15(b): First order release kinetics



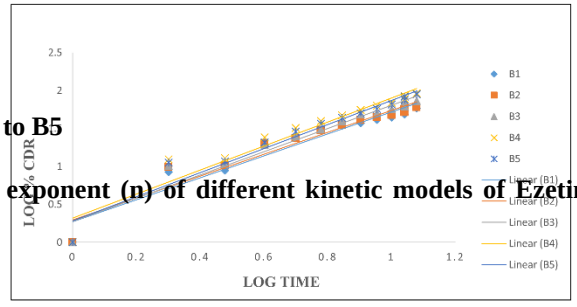


Figure 15: *In-vitro* release kinetics models of Batch B1 to B5

Fig. 15(c): Higuchi model release kinetics

Fig.15(d): Korsmeyer- Peppas model release kinetics

Table 4: Regression co-efficient values and diffusion exponent (n) of different kinetic models of Ezetimibe loaded Eudragit RS100 microspheres (A1-A5)

Sl.no	Formulation Code	Drug release kinetics Correlation coefficients (r^2)			Korsmeyer-Peppas	
		Zero order	First order	Higuchi	r^2	N

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1	A1	0.983	0.900	0.810	0.978	1.511
2	A2	0.9791	0.972	0.838	0.770	1.411
3	A3	0.9876	0.850	0.861	0.802	1.181
4	A4	0.976	0.884	0.826	0.957	1.527
5	A5	0.9839	0.860	0.850	0.962	1.573

Table 5: Regression co-efficient values and diffusion exponent (n) of different kinetic models of Ezetimibe loaded Eudragit RS100 microspheres (B1-B5)

Sl.no	**Formulation Code**	**Drug release kinetics Correlation coefficients (r^2)**			**Korsmeyer-Peppas**	
		Zero order	**First order**	**Higuchi**	**r^2**	**n**
1	B1	0.982	0.9907	0.953	0.934	1.445
2	B2	0.963	0.995	0.948	0.929	1.441
3	B3	0.992	0.9953	0.9482	0.944	1.532
4	B4	0.997	0.906	0.924	0.933	1.588
5	B5	0.996	0.898	0.906	0.944	1.584

Conclusion

The present study reported the development of Ezetimibe (Anti-Hyperlipidemic drug) loaded floating microspheres by using polymers Eudragit RS 100 and RL 100. From the outcome of the results, it can be concluded that the floating microsphere (A3) and (B4) formulations can be used for reducing the dosing frequency, improving the bioavailability and effectiveness of the drug. The floating microspheres with both the polymers showed floating ability over 12h, thereby reducing the dosing frequency and increased residence time in the stomach. The data obtained by this study can be used to study the *in-vivo* effectiveness. This method of preparing floating microspheres can be used for different medications with a short half-life and low bioavailability.

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Conflict of interest

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There are no conflicts of interest

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