ISSN: 0975-766X
CODEN: IJPTFI
Available Online through
www.ijptonline.com
Research Article

FORMULATION AND IN VITRO EVALUATION OF FLOATING MICROSPHERES OF PROPRANOLOL

Kiran Kumar P.V[1*], Murali Krishna Ranga[1]
[1]Department of Pharmaceutics, Krishna Teja Pharmacy College, Chadalawadanagar, Reniguntla Road, Tirupathi- 517506, A.P., India.
Email: pvk.kirankumar@gmail.com

Received on 22-03-2012 *Accepted on 08-04-2012*

Abstract

The aim of present work is to prepare floating microspheres of Propranolol using Eudragit S 100 and Eudragit L 100 as polymer. Floating drug delivery system have a bulk density less than gastric fluids and so remains buoyant in the stomach without affecting gastric emptying rate for a

prolonged period of time. Propranolol is nonsteroidal antiinflammatory drug with short elimination half life 1-3 hours. The short half life of Propranolol and multiple administration dose make Propranolol a very good candidate for formulation of floating drug delivery system. Floating microspheres of Propranolol were prepared by emulsion solvent diffusion method using Eudragit S 100 and Eudragit L 100 as polymer. The floating microspheres was evaluated such as micromeritic properties, particle size, percentage yield, in vitro buoyancy, incorporation efficiency, drug polymer compatibility (IR study), scanning electron microscopy and drug release of microspheres. The micromeritic properties was found to be good and scanning electron microscopy confirmed their hollow structure with smooth surface. Formulation PM2 prepared with Eudragit S 100 drug:polymer ratio (1:2) which exhibited excellent micromeritic properties, percentage yield, in vitro buoyancy, incorporation efficiency and percentage drug release 92.26 % for a period of 12 hrs. Results show that as increase in drug:polymer ratio affects the particle size, percentage yield, in vitro buoyancy and drug release of microspheres. The data obtained in this study thus suggest that a floating microspheres of Propranolol are promising for sustained drug delivery which can reduce dosing frequency.

Keywords: Propranolol, Eudragit S 100, Eudragit L 100, Floating microspheres.

Introduction

To develop oral drug delivery systems, it is necessary to optimize both the residence time of system within the gastrointestinal tract and release of drug from the system. Drugs that are easily absorbed from the gastrointestinal tract and have a short half life are eliminated quickly from the blood circulation and require frequent dosing. To avoid this problems, the oral controlled release formulations have been developed in an attempt to release the drug slowly into the gastrointestinal tract and maintain a constant drug concentration in the serum for a longer period of time. Such oral drug delivery devices have a restriction due to the gastric retention time (GRT), a physiological limitation. Therefore prolonged gastric retention is important in acheiving control over the GRT because this helps to retain the controlled release system in the stomach for a longer time in a predictable manner[1]. Various attempts have been made to prolong the residence time of the dosage forms within the stomach. The prolongatoion of the GRT of delivery devices could be acheived by adhesion to the mucous membranes, by preventing their passage through the pylorus or by maintaining them in buoyant fashion in gastric juice. Unfortunately floating devices administered in a single unit form (tablet) such as hydrodynamically balanced systems are unreliable in prolonging the GRT owing to their "all or none" emptying process and thus, they may cause high variability in bioavailibility and local irritation due to a large amount of drug delivered at a particular site of GIT. In contrast, multiple unit particulate dosage form (e.g.microspheres) have the advantages that they pass uniformly through the git to avoid the vagaries of gastric emptying and provide an adjustable release, thereby reducing intersubject variability in absorption and risk of local irritation[2]. Propranolol is an important analgesic and nonsteroidal anti inflammatory drug, also with antipyretic properties, whose mechanism of action is the inhibition of prostaglandin synthetase. This drug is used in therapy of rheumatic disorder and its plasma elimination half life is 1 to 3 hours, and in order to maintain therapeutic plasma level drug must be administered at least thrice a day[3]. On the other hand, eudragit (methacrylate copolymers) have been recently received increased attention for preparing modified dosage forms because of their inertness, solubility, in relatively non toxic solvents of resins with different properties. The aim of present study was to develop and evaluate floating microspheres of Propranolol using Eudragit S-100 & Eudragit

L-100 as polymer and emulsion solvent diffusion as a method of preparation. Propranolol whose physicochemical properties and short half life make it suitable candidate for floating drug delivery system.

Materials and Methods

Materials:

Propranolol was received as gift sample from Ciron Drugs and Pharmaceutical Pvt. Ltd. Mumbai (India), Eudragit S 100 and Eudragit L 100 was received as gift sample from Deggusa india pvt. Ltd., Mumbai. ethanol, methanol, dichloromethane, tween 20 was obtained from SD fine chemicals Ltd., Mumbai (India). All other chemical and reagent used in this study were of analytical grade.

Method of preparation[4]

Floating micropsheres were prepared by emulsion solvent diffusion method. Weighed amount (as shown in table 1) of Propranolol was mixed with Eudragit S 100 and Eudragit L 100 rug:polymer ratio (1:1, 1:2, 1:3) in a solution of ethanol :dichloromethane (1:1) at room temperature. The resulting drug polymer solution was poured slowly using glass tube into 200 ml of water containing 0.75 % w/v polyvinyl alcohol, maintained at constant temperature of 400 c and preparation was stirred at 300 rpm for 1 hr. The finely developed floating microspheres were then filtered, washed with water and seived between 50 and 30 mesh size and dried overnight at 400 C.

Table: 1 Formulation table of floating microspheres of Propranolol.

SI.No	Ingredients	Formulation code					
		PM1	PM2	PM3	PM4	PM5	PM 6
1	Propranolol	0.500	0.500	0.500	0.500	0.500	0.500
2	Edragit S 100	------	-------	-------	1.500	0.500	1.000
3	Edragit L 100	1.500	1.000	1.500	------	-----	-----
4	Ethanol	8	8	8	8	8	8
5	Dichloromethane	8	8	8	8	8	8

Evaluation of floating microspheres

Yield of Floating microspheres:

The prepared floating microspheres with a size range of 102 - 192 μm were collected and weighed. The measured weight was divided by total amount of all non-volatile components which were used for the preparation of microspheres[5].

% yield = (Actual weight of product / Total weight of excipient and

drug) x 100

In vitro Buoyancy

Floating microspheres (equivalent to 100 mg) were dispersed in 900ml of 0.1 N hydrochloric acid solution (pH 1.2) containing tween 20 (0.02 W/V%) to simulate gastric fluid at 37°. The mixture was stirred with a paddle at 100 rpm and after 12 hr, the layer of buoyant microspheres (Wf) was pipetted and separated by filtration simultaneously sinking microspheres (Ws) was also separated. Both microspheres type were dried at 40°C overneight. Each weight was measured and buoyancy was determined by the weight ratio of the floating microsphers to the sum of floating and sinking microsphers[6].

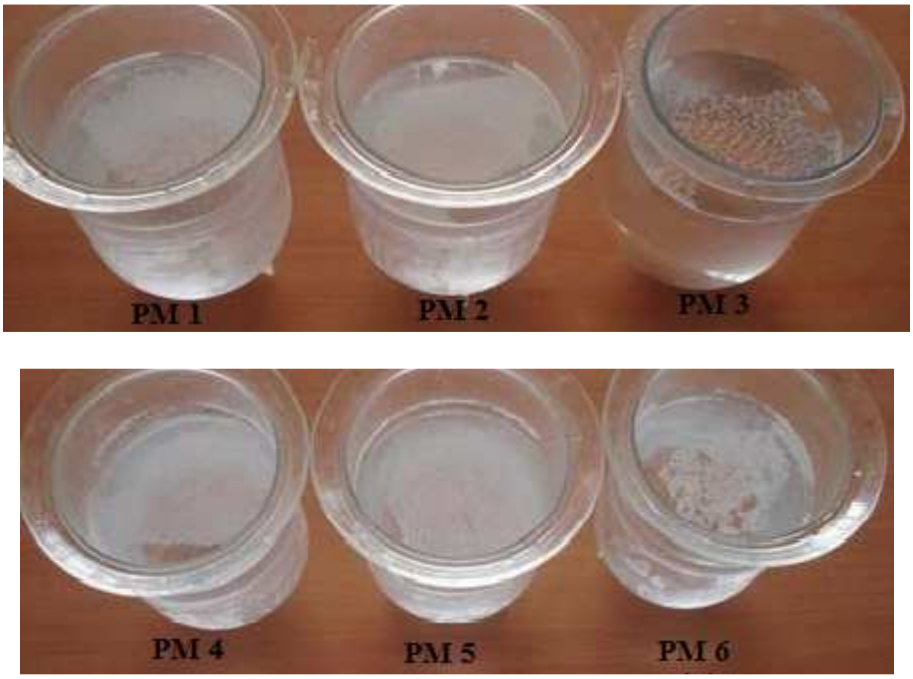


Fig. 2 In vitro buoyancy of floating microspheres of Propranolol.

Incorporation efficiency

Floating microspheres were dissolved in a minimum amount of methanol and drug was extracted into suitable aqueous media (0.1 N hydrochloric acid) by evaporating methanol. The solution was filtered through whatman filter paper, diluted suitably and analyzed for drug content spectrophotometrically at 290 nm using 0.1N hydrochloric acid as blank[7].

Micromeritic properties

The floating microspheres were characterized by their micromeritic properties such as particle size, bulk density,tapped density, hausners ratio, carr's index and angle of repose[8].

Drug release

Drug release from Floating microspheres having a size range between 102 - 192 μm and floating microspheres equivalent to 150 mg of drug was carried out using paddle method at 100 rpm.

Table-2: Percentages Yield, invitro buoyancy and incorporation efficiency of floating microspheres of Propranolol

Formulation code	Percentage Yield	In Vitro buoyancy	Incorporation efficiency
PM1	81.08±1.91	87.00±1.00	61.59±1.59
PM2	77.73±1.51	83.00±1.02	81.70±2.01
PM3	62.14±0.13	80.66±1.08	61.59±1.57
PM 4	85.89±2.13	90.33±1.52	79.03±2.00
PM5	89.19±1.59	71.66±4.04	81.70±2.02
PM6	86.13±2.00	87.00±4.04	81.70±2.02

Table: 3 Micrometric properties of floating microspheres of Propranolol.

SI. No	Formulation code	Mean Particle size	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Hausners ratio	Carr's Index	Angle of repose
1	PM1	125.33±15.27	0.622±0.03	0.173±0.01	1.75±0.01	1.09±1.61	16.01±2.81
2	PM2	182.33±26.30	0.674±0.03	0.692±0.07	1.06±0.02	10.1±1.05	17.07±1.61
3	PM3	0.722±0.001	0.591±0.05	0.652±0.05	1.16±0.03	5.00±2.34	14.01±2.15
4	PM4	0.658±0.003	0.655±0.03	0.707±0.02	1.04±0.02	9.16±0.81	15.27±1.52
5	PM5	102.22±2.750	0.722±0.01	0.773±0.01	1.10±0.01	4.73±2.73	16.77±1.42
6	PM6	161.33±11.01	0.632±0.02	0.684±0.03	1.07±0.03	7.63±2.66	19.11±2.42

Results and Discussion

Method of introducing polymer solution

The high surface tension of water caused the solidification and aggregation of Eudragit S100 and Eudragit L 100 on the surface of aqueous phase. To minimize the contact of polymer solution with the air - water interface and to develop a continuous process for preparing microspheres, a new method of introducing the polymer solution into aqueous phase was developed. The method involves the use of a glass tube immersed in an aqueous phase and the

introduction of the polymer solution through the glass tube without contacting the surface of water[9]. This method improved the yield of microspheres and reduced the extent of aggregate formation and made it possible to make microspheres continuously. As the polymer solution is continuously introduced into the main vessel, it will overflow from the top of the vessel together with the prepared microspheres, since most of the formed microspheres will float on the top of the aqueous phase.

Yield of microspheres

The percentage yield of microspheres was in range of 62.14± 0.13 to 89.19 ± 1.59 (as shown in table 2). To observe the effect of polymer concentration on the percentage yield of the resulting microspheres formulation were prepared using varying drug: polymer ratio of first 2 hrs in pH 1.2 with tween 20 (0.02 W/V%) to simulate gastric fluid and 10 hrs in phosphate buffer pH 7.4. with tween 20 (0.02 W/V%) to simulate gastric fluid. Each time 5 ml of samples were withdrawn at different time intervals and replaced with fresh phosphate buffer, the amount of drug release was analyzed at 290 nm using shimadzu UV visible spectrophotometer. Eudragit S 100 and Eudragit L 100. The percentage yield of the microspheres was found to be increased with increasing Eudragit S100 and Eudragit L 100 concentration[10].

In vitro buoyancy

The in vitro buoyancy test was carried out to investigate buoyancy of prepared microspheres. The microspheres formulations PM1to PM 6 showed good floating ability range from 80.66 ± 1.08 to 90.33 ± 1.52.(as shown in table 2). The results also showed a tendency that, larger the particle size longer the floating time[11].

Incorporation efficiency

The incorporation efficiency of formulation PM 1 to PM 6 was carried out and found to be in a range 61.59 ± 1.57 to 81.70 ± 2.02 (as shown in table 2.)

Micromeritic properties

The mean particle size of floating microspheres formulation PM 1 to PM 6 was found to be 0.658 ± 0.03 to 182.33 ± 26.50 (as shown in table 3). The effect of polymer concentration on the particle size of floating microspheres was determined. The mean particle size of the icrospheres was found to be increase with increasing Eudragit

concentration (as shown in table 1). The viscosity of medium increases at a higher Eudragit concentration resulting in enhanced nterfacial tension. Shearing effieincy is also diminished at higher viscosities. This results in the formation of larger particles. The bulk density, tapped density, hausners ratio of formulation PM 1 to PM 6 ranges from 0.591 ± 0.05 to 0.722 ± 0.01gm/cm³, 0.652 ± 0.05 to 0.773 ± 0.001gm/cm³, 1.04 ± 0.02 to 1.75 ±0.01 respectively[12]. The carr's index ranges between 1.09 ± 1.61 to 10.01± 1.05 %. The angle of repose of microspheres ranges from 14.0 ± 2.15 to 19.11 ± 2.42 (as shown in table 3). The values of carr's index and angle of repose indicate excellent flow properties.

Infrared spectroscopy

This was compared with standard functional group frequencies of Propranolol as shown in Table 5. From FTIR study, the characteristic peaks of drug such as of OH (3130), CH Stretching Aromatic (3003 cm^{-1}), CH Stretching Aliphatic (2963 cm^{-1}), C=O(1749 cm^{-1}), Al-CH-bend(1454 cm^{-1}), Ar-CH In plane Bending(1091 cm^{-1}), The Eudragit S 100 the peak contain OH (3140 cm^{-1}), CH Stretching Aromatic (3020 cm^{-1}), CH Stretching Aliphatic (2862 cm^{-1}), C=O(1630 cm^{-1}), Al-CH-bend(1334 cm^{-1}), Ar-CH In plane Bending(1082 cm^{-1}). The Eudragit L 100 OH (3170), CH Stretching Aromatic (3067 cm^{-1}), CH Stretching Aliphatic (2954 cm^{-1}), C=O(1598 cm^{-1}), Al-CH-bend(1672 cm^{-1}), Ar-CH In plane Bending(1134 cm^{-1}), remaining peaks also either shifted or replaced in the IR spectrum of formulation shown in Fig. 6 & 8.

Table: 5 IR Interpretations for Pure drug and Polymer.

Functional groups	**Propranolol**	**Eudragit S 100**	**Eudragit L 100**
OH	3130	3140	3170
CH Stretching (Aromatic)	3003	3020	3067
CH Stretching (Aliphatic)	2963	2862	2954
C=O	1749	1630	1598
C=C	1600	1560	1672
Al-CH-bend	1454	1334	1289
Ar-CH (In plane Bending)	1091	1082	1134

Fig No. 6: FT – IR of Propranolol.

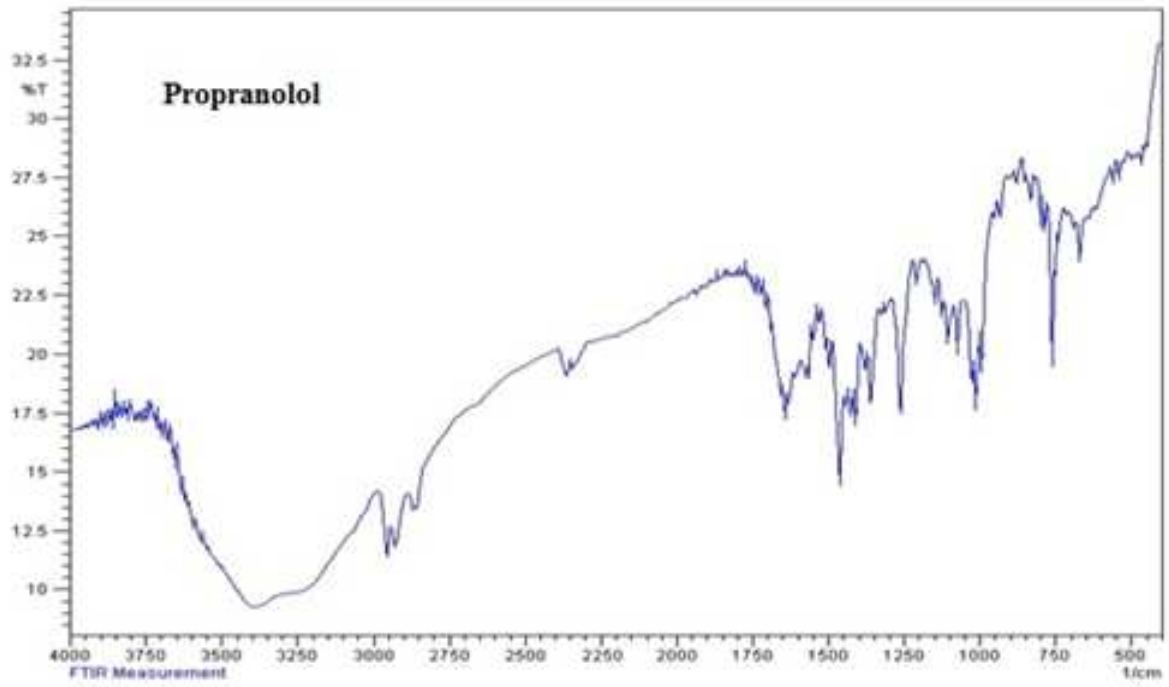


Fig No-7: FT – IR of Eudragit S 100.

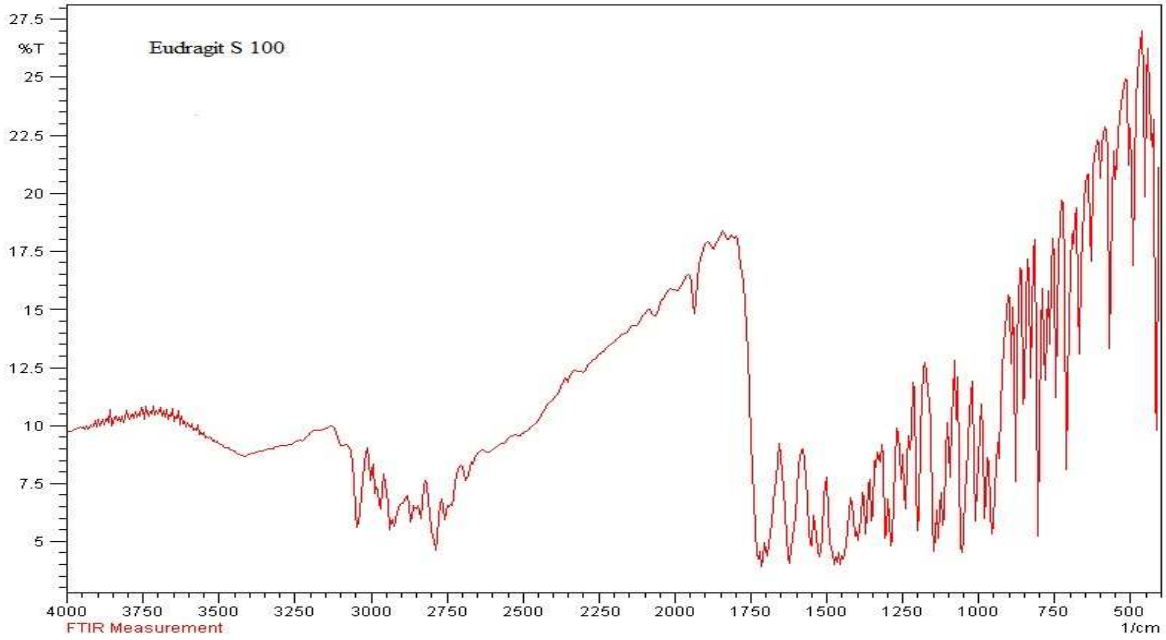
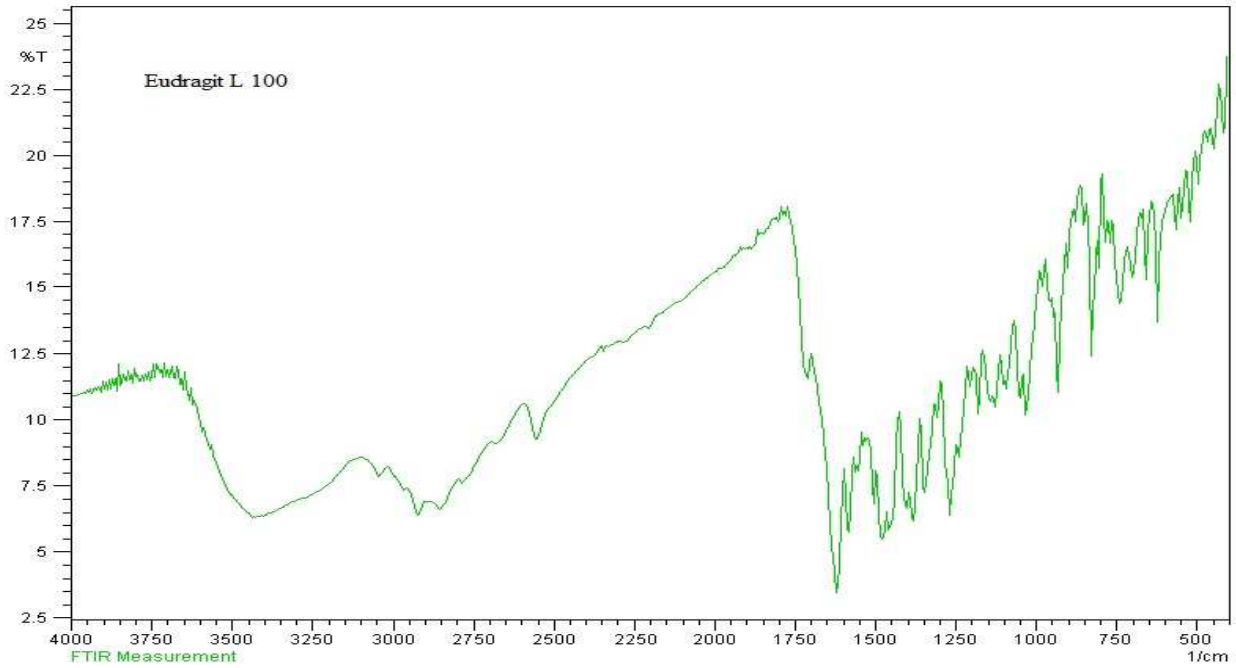


Fig No-8: FT – IR of Eudragit L 100.



Scanning electron microscopy (SEM)

Morphology of floating microspheres was examined by scanning electron microscopy. The view of the microspheres showed hollow structure with a smooth surface morphology exhibited range of sizes within each batch. The outer surface of microspheres was smooth and dense, while the internal surface was porous [13]. The shell of microspheres also showed some porous structure it may be caused by evaporation of solvent entrapped within the shell of microsphere after forming smooth and dense layer.

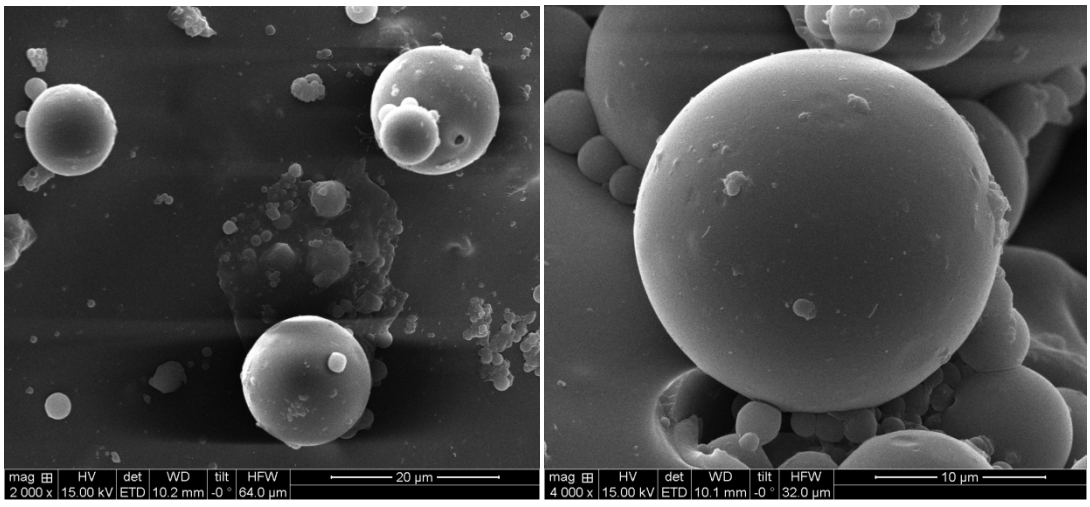
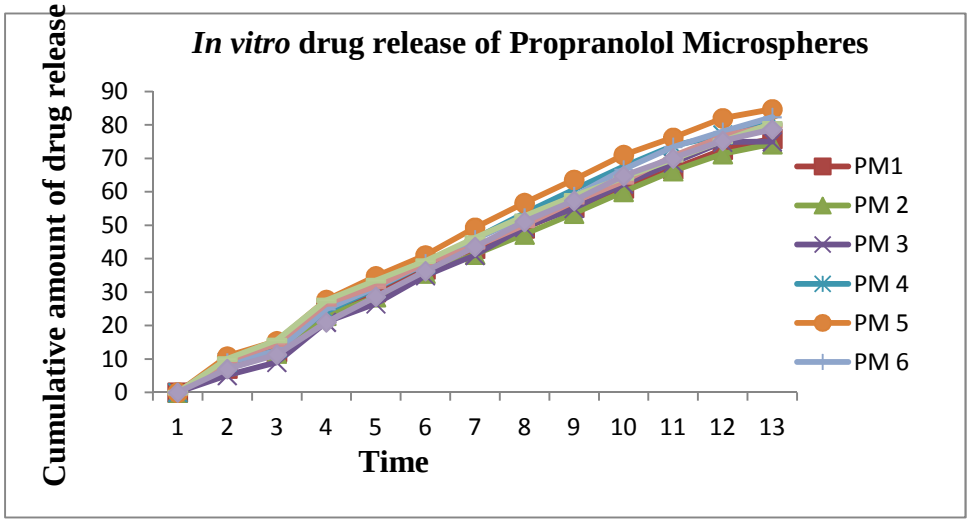


Figure-9: Sem of Propranolol Microspheres.

Drug release

The drug release from formulation PM1 to PM 6 was as follows the percentage drug release 80.12 ± 0.17 to 93.31 ± 1.81 at end of 12 hour and formulation PM 2 and PM 6 show percent drug release 80.12 ± 0.17 to 93.31 ± 1.81 at end of 12 hr. Among all formulation PM 2 was found to be the best formulation as it release Propranolol in a sustained manner with constant fashion over extended period of time (after 12 hr). it was observed as the concentration of Eudragit S 100 and Eudragit L 100 was increased percent release of Propranolol decreases. The increase in Eudragit S 100 and Eudragit L 100 concentration leads to the increased density of polymer matrix into the microspheres which result in an increased diffusional path length. This may decrease the overall drug release from polymer matrix[14]. Furthermore smaller microspheres are formed at lower polymer concentration and have larger surface area exposed to dissolution medium.



Conclusion

Floating microspheres of Propranolol with enteric acrylic polymers such as Eudragit S 100 and Eudragit L 100 were successfully prepared by the emulsion solvent diffusion method. The formulation PM2 with drug:polymer ratio (1:2) was found to be satisfactory in terms of excellent micromeritic properties, yield of microspheres (89.19 %), incorporation efficiency (81.70 %), in vitro buoyancy (90.33 %) and highest in vitro drug release of 92.26 % in sustained manner with constant fashion over extended period of time for 12 hrs. From the results it was observed

that Drug: Polymer ratio influences the particle size, in vitro buoyancy, as well as drug release pattern of floating microspheres.

Acknowledgements

The authors are thankful to the Management, Krishna Teja Pharmacy College, Tirupati for providing necessary facilities to carry out this work.

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Corresponding Author:

Kiran Kumar P.V [1*],

Email: *pvk.kirankumar@gmail.com*