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DESIGN AND CHARACTERIZATION OF HOLLOW MICROSPHERE OF DILTIAZEM HCL

Rathod Utsav C*, Anandkumar. K Patel, Utkarsh.M. Trivedi, Ritesh D. Ghasadiya

APMC College of Pharmaceutical Education And Research, Himatnagar, Gujarat-383001, India

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For Correspondence:

Rathod Utsav C

APMC College of Pharmaceutical Education And Research, Himatnagar, Gujarat-383001, India

E-mail:

ucrathod@gmail.com

ABSTRACT

The purpose of this research was to prepare a Gastro Retentive drug delivery system (GRDDS) of Diltiazem HCl. In the present study, preparation of Diltiazem HCl Hollow microspheres, in-vitro evaluation of Floating Drug Delivery System (FDDS), prediction of the drug release, and polymers concentration to match target release profile was investigated. Hollow microspheres were prepared by non aqueous emulsion solvent evaporation technique using Eudragit RS100 (ERS) and Eudragit RL100 (ERL) as the rate controlling polymer. Particle size analysis, drug encapsulation efficiency, buoyancy percentage and release studies were performed. Results showed that the polymer concentration and stirring speed affected the size, incorporation efficiency and drug release of microspheres (> 12 h) and its floating time (> 10 hr). The mean particle size of prepared hollow microspheres increased but the drug release rate from the microspheres decreased as the polymer concentration increased. The developed floating microspheres of Diltiazem HCl may be used in prolonged drug release in stomach for 12 h, thereby improving the bioavailability.

INTRODUCTION

The prolongation of the gastric residence time (GRT) of delivery system could be achieved by design of pharmaceutical formulation which depends on the physiological state of stomach and maintaining them in buoyant fashion in gastric juice.Gastrointestinal targeting dosage forms, including intragastric floating, high density, bioadhesive, swelling, magnetic systems.[1,2]

Diltiazem HCl, a benzodiazepine, voltage sensitive ca^{2+} channel blocker with a high therapeutic potential but with a very short biological half life was encapsulated within microsphere.Diltiazem is a calcium ion influx inhibitor (calcium entry blocker or calcium ion antagonist). The antihypertensive, antianginal and antiarrhythmic effects of diltiazem is believed to be related to its specific cellular action of selectively inhibiting transmembrane influx of calcium in cardiac muscle, coronary arteries, and systemic arteries and in cells of the intra cardiac conduction system.[3] Given orally, 90–100% of diltiazem is absorbed, but due to high first pass metabolism, bioavailability is much lower (40–60%), half life is 4-5 hours (with chronic dosages) and not cleared by hemodialysis.[4]

The Eudragits are biocompatible copolymers which were synthesized from acrylic and methacrylic acid esters. These polymers are well tolerated by the skin and have been used in the formulation of dosage forms especially matrix tablets for oral sustained release[5,6] and in tablet coating. They have also been used in the microencapsulation of drugs [7,8,9].

MATERIAL AND METHOD

Diltiazem HCl was obtained as a gift sample from Lincoln Pharmaceutical Ltd, Kalol, gujarat Eudragit RS100 (ERS) and Eudragit RL100 (ERL) were obtained from Crystal Chemical Pvt. Ltd, Himatnagar (Gujarat) All other chemicals / reagents used were of analytical grade available commercially.

Characterization of Drug (Diltiazem HCl):

The IR spectrum of Diltiazem HCl was taken using Shimadzu FTIR spectroscope. The spectrum was compared with the reference spectrum given in Brittain HG. [10].

Drug Excipient compatability study:

Diltiazem HCl (DTZ) and two grades of Eudragits were subjected to drug-excipients compatibility studies. The drug and polymer were mixed physically in 1:1 ratio and the mixtures were placed in sealed vials for 3 months at room temperature. FTIR measurements of drug, individual polymer and drug-polymer mixtures were obtained on Shimadzu FTIR. Samples were prepared by mixing with KBr and placing in the sample holder. The spectra were scanned over the wave number range of 4000-400 cm^{-1} at the ambient temperature.

Preparation of Hollow microsphere:

Microspheres containing highly water-soluble Diltiazem HCl were prepared by non-aqueous emulsion solvent evaporation method using two structurally different poly(trimethyl ammonioethyl methacrylate) copolymers: Eudragit RL100 and RS100. Polymers were used separately. In this case polymers, weighed quantities of Eudragit RL100 and RS100 were completely dissolved in Dichloromethane and ethanol (1:1), Magnesium stearate and DTZ were then added and stirred using a magnetic stirrer (10 min). Camphor is added as pore forming agent(1%). Especially with 10% magnesium stearate, the microspheres were nearly uniform. The drug polymer mixture was then slowly introduced into liquid paraffin(100 ml) previously emulsified with 1% Span 80, while stirring at 400 rpm held by the mechanical stirrer (Remi, Mumbai) equipped with a three-blade propeller, at room temperature. The whole system was stirred for 2hr to allow the complete evaporation of organic solvent. The oil layer was decanted and microspheres were washed with n-hexane(10times×20ml). The method is pictorially represented in fig.1. The representative formulations are given in Table 1.

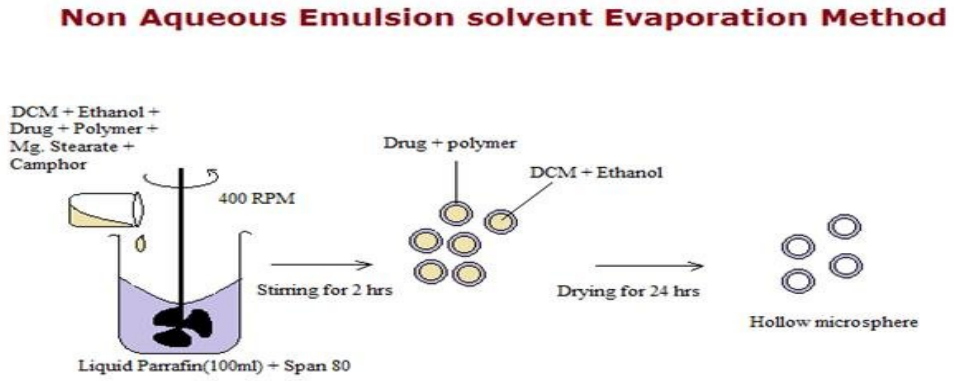

Fig. 1 Preparation of Hollow Microsphere

Table: 1 Composition of Hollow Microsphere formulations

Batch→	**ERS1**	**ERS2**	**ERS3**	**ERL1**	**ERL2**	**ERL3**
Ingredient↓						
Diltiazem HCl (mg)	120	120	120	120	120	120
Eudragit RS 100(mg)	120	180	240	----	----	----
Eudragit RL 100(mg)	----	----	----	120	180	240
DCM: Ethanol	1:1	1:1	1:1	1:1	1:1	1:1
Liquid Paraffin(ml)	100	100	100	100	100	100
Span 80 (%)	1%	1%	1%	1%	1%	1%
Camphor(mg)	100	100	100	100	100	100
Magnesium stearate(%)	10%	10%	10%	10%	10%	10%

Determination of percent yield:

Thoroughly dried microspheres were collected and weighed accurately. The percentage yield was then calculated. [11]

$$\% \text{ Yield} = \frac{\textit{Total weight of microspheres obtained}}{\textit{Total weight of drug ,polymer and non volatile solids}} \times 100$$

Particle size analysis

Particle size of prepared microspheres was measured using an optical microscope, and the mean particle size was calculated by measuring 200 particles with the help of a calibrated ocular microscope. [12]

Loading efficiency and encapsulation efficiency:

The DTZ content in the microspheres was determined by pulverizing the DTZ-loaded microspheres (10 mg) followed by immersing them in 100 ml simulated gastric fluid (SGF) (with pH 1.2 and without enzymes) with agitating at room temperature for 12 h .After filtration through a 0.45 m membrane filter (Millipore), The drug concentration was determined by UV spectroscopy at the wavelength of 236 nm. The filtered solution from the empty microspheres (without DTZ) was taken as blank. All samples were analyzed in triplicate and the drug loading (DL) and encapsulation efficiency (EE) was calculated according to the following equation: [11]

$$(\%)\ DL = \frac{WD}{WT} \times 100$$

Where,
DL: drug loading
WD: the wt. of the drug loaded in the microspheres
WT: Total wt. of the microspheres

$$(\%)\ EE = \frac{WA}{WT} \times 100$$

Where,
EE: Encapsulation Efficiency
WA: Amount of actual drug present
WT: Theoretical drug content

Buoyancy percentage:

Microballoons (100 mg) were spread over the surface of dissolution apparatus (type II-paddle type) filled with 900 mL 0.1 mol L^{-1} HCl containing 0.02% Tween 20. The medium was agitated with a paddle rotating at 100 rpm for 10 hr. The floating and the settled hollow microspheres were recovered separately. The hollow microspheres were dried and weighed. Buoyancy percentage was calculated as the ratio of the mass of the hollow microspheres that remained floating and the total mass of the hollow microspheres. [13]

% Buoyancy = [Wf / (Wf + Ws)] x 100

where

Wf- weights of the floating microspheres

Ws-weights of the floating settled microspheres

In vitro drug release studies:

The in vitro release of Diltiazem HCl from the different formulations of hollow microspheres was examined using the rotating basket method dissolution testing apparatus 1. The 20 mg of hollow Microspheres were wrapped in muslin cloth and kept in baskets. Simulated gastric fluid with set up pH 1.2, without enzymes and adjust to 900 ml which was used as the dissolution medium and maintained at 37 ± 0.5^{o}C at a rotation speed of 100 rpm.[6] An aliquot of 10 ml of the solution was withdrawn at initially 30 min then 1h intervals and replaced by 10 ml of fresh dissolution medium. Samples were assayed spectrophotometrically at 236 nm after filtration through a 0.45µm membrane filter(Millipore). All experiments were performed in triplicate. [14]

Morphology:

For morphology and surface characteristics, the surface morphology of the microsphere was then studied by ocular microscope Particle size analysis. (Fig.6)

RESULTS AND DISCUSSION

1. Characterization of Drug (Diltiazem HCl):

The drug Diltiazem HCl was characterized by IR spectroscopy. The IR spectrum shown in fig.2 was compared with the reference spectrum given in Brittain HG.[10] It showed the characteristic peaks for O-CH_3 C-H stretch stretching, amine HCI N-H stretch acetate C=O stretch ,lactam C = O stretch as shown in figure.2 and The characteristic peaks are shown in the table 2.

Table: 2 Characteristic IR peaks of Diltiazem HCl [10]

Sr no	IR frequency	Functional Group Assignment
1	2837	O=CH_3 C-H stretch
2	2393	Amine HCl N=H stretch
3	1743	Acetate C=O stretch
4	1639	Lactam C=O stretch

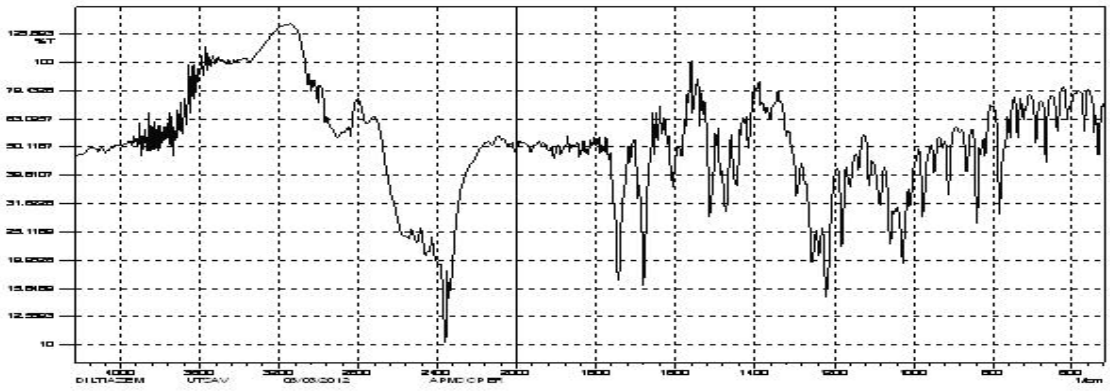

Fig.2: IR spectrum of Diltiazem HCl

2. Drug-Excipients Compatibility Studies:

The study carried out at room temperature, Eudragit RS 100, Eudragit RL 100 and final preparation. The result shows broad characteristic groups such O-CH_3 C-H stretch stretching, amine HCI N-H stretch acetate C=O stretch lactam C = O stretch indicating that they are compatible with the drug. (Fig.3,4,5)

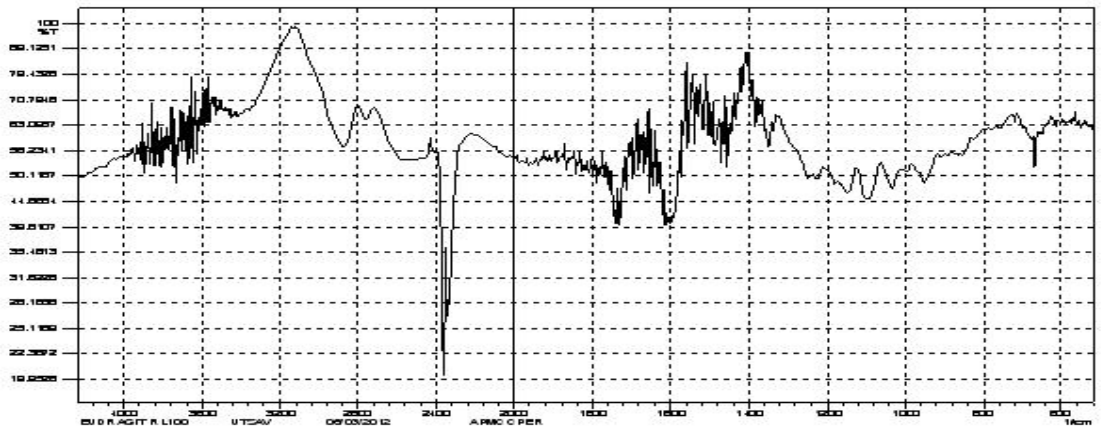

Fig.3: IR spectrum of Eudragit RL 100

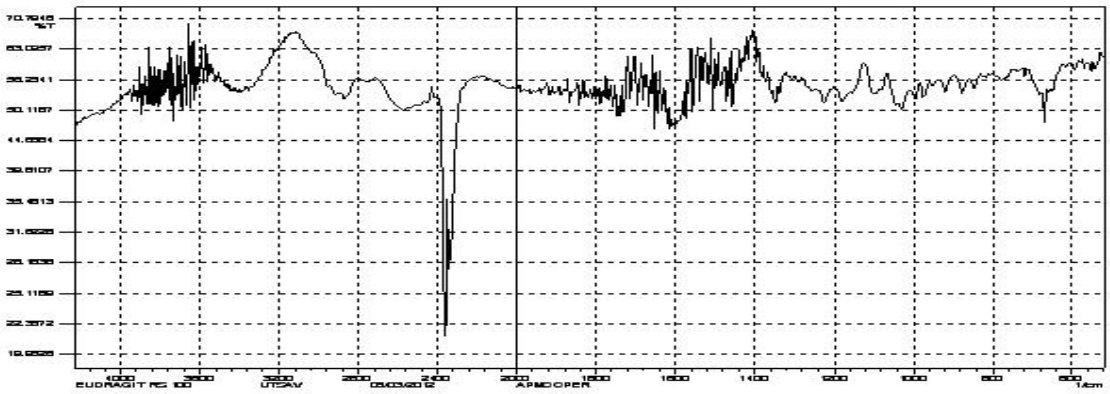

Fig.4: IR spectrum of Eudragit RS 100

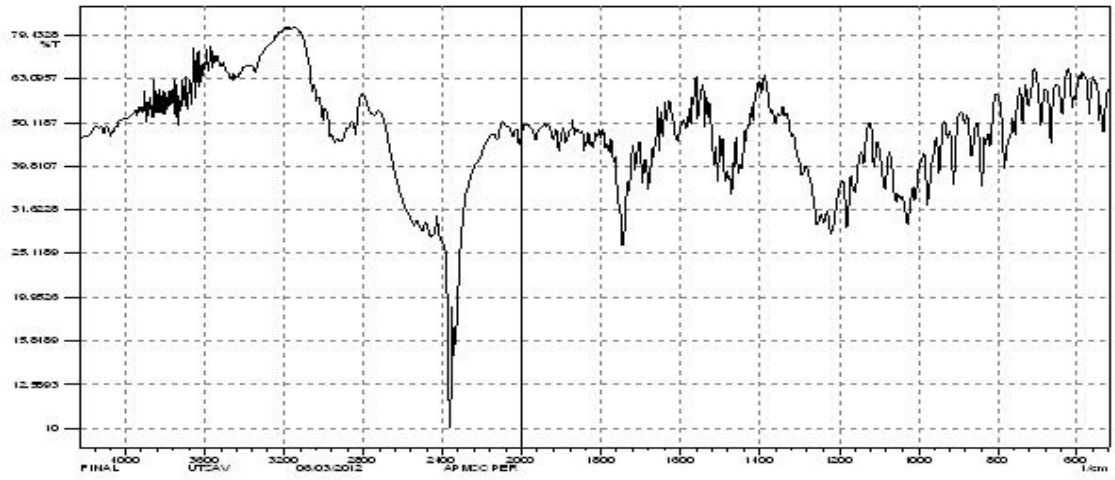

Fig.5: IR spectrum of final preparation

Table.3 Micromeritics Property:

Batch	Weight (mg)	Particles size (µm)	Bulk Density gm/cm^3	Tapped Density gm/cm^3	Hausner's Ratio	% Carr's index	Angle of repose(θ)
ERS1	500	233±11.32	0.72±0.02	0.84±0.01	1.16±0.01	14.28±2.1	$35^{o}4'$
ERS2	690	240±8.41	0.77±0.01	0.86±0.04	1.11±0.03	10.5±1.1	$40^{o}12'$
ERS3	898	246±13.43	0.78±0.04	0.810±0.03	1.03±0.02	3.70±1.6	$43^{o}16'$
ERL1	480	239±9.11	0.73±0.02	0.899±0.01	1.21±0.01	17.97±0.5	$33^{o}21'$
ERL2	695	246±11.14	0.850±0.02	0.949±0.02	1.10±0.03	9.57±2.1	$38^{o}29'$
ERL3	910	248±13.22	0.79±0.01	0.808±0.03	1.01±0.02	1.25±0.9	$42^{o}15'$

Table. 4 Encapsulation, drug loading, % yield

Batch	% Entrapment efficiency	%Drug loading	% Yield	% Buoyancy (After 12 hr)
ERS1	70±0.27	74	67	68.65
ERS2	72±0.42	78	66.67	65.18
ERS3	78±0.24	84	72	70.12
ERL1	61±0.55	76	67.5	67.21
ERL2	65±0.26	80	60.84	64.30
ERL3	68±0.16	82	68.34	61.46

3. Morphology:

Microsphere appeared to be hollow presumably because of the rapid escape of the volatile solvent from the polymeric matrix. This hollow nature responsible for prolong gastric retention by floating in gastric fluid. (fig.6)

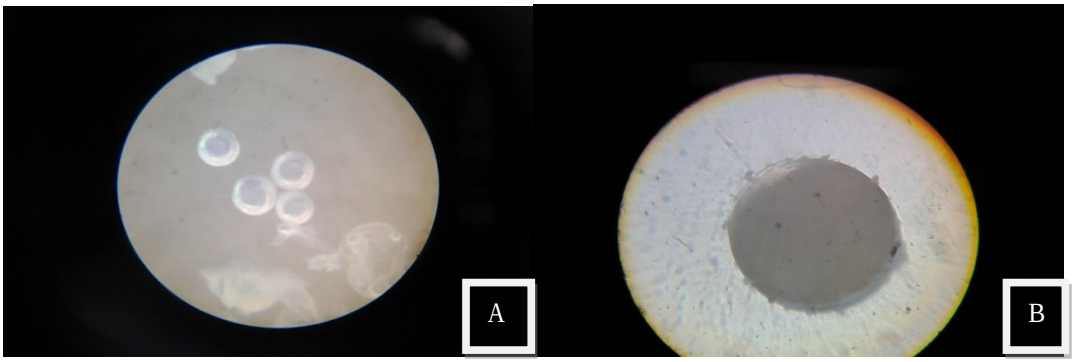

Fig. 6: Optical microphotographs (A) 10× and (B) 45×

4. Various processing conditions and variables on the microsphere formualtion

The highly water soluble drug Diltiazem HCl was successfully incorporated into eudragit polymers using Non aqueous emulsion solvent evaporation method. In this method, drug polymer mixtures were dispersed into an immiscible vehicle to form an emulsion. As the solvent is evaporated, the droplets become gradually concentrated and the nucleation takes place to produce microspheres. It was observed that when the speed of mechanical stirrer was below 400 rpm, there was no formation of spherical microspheres and lumping of the solvent phase. At high speed microspheres adhesion to the container wall, resulting in decreased mean particle size so increase release because increase the surface area.

Flocculation was recognized when no magnesium stearate was added. Especially with 10% magnesium stearate, The microspheres were nearly uniform and free-flowing with good reproducibility. This is because magnesium stearate reduces the interfacial tension and prevents electrification and flocculation during the preparation of microspheres.

5. Particle Size:

The result indicated that the mean particle size or average diameter of microsphere was in the range of 200 to 250 µm. (Table.1) There was formation of microspheres with larger sizes due to an increase in solution viscosity with increase polymer concentration.

6. Buoyancy percentage:

The % buoyancy of formulation ERS1-ERS3 at the end of 12hr were found to be 68.65%, 65.18%, 70.12% and for formulation ERL1-ERL3 at the end of of 12hr were found to be 67.21%, 64.30%, 61.46%. The result indicate that with an increase concentration of polymers increase the percentage buoyancy. (Table.3)

7. Drug entrapment efficiency:

The drug content of all formulation was determined spectrophotometrically. The entrapment efficiency depends upon its solubility in the solvent and continuous phase. An increase in the concentration of polymer in fixed volume of organic phase resulted in increase entrapment efficiency. It is also evident that the entrapment efficiency of Eudragit RS 100 microsphere was higher than that of Eudragit RL 100 microsphere. The entrapment efficiency of formulation were 61 to 72 % (Table.3)The result show that Eudragit containing microsphere showed desirable high drug content and entrapment efficiency.

8. In vitro drug release:

The release of Diltiazem HCl from microspheres made of Eudragit RL100 and RS100 polymers depended on the polymer concentration used. The cumulative drug release of ERS1-ERS3 at the end of 12h were 78.33%, 75.05%nd 76.98% and ERL1-ERL3 were 82.24%,79% and 81.75% This indicates that the drug release rate decreases with increasing amount of the polymer. It was also observed that the release rate of drug from Eudragit RL100 microspheres was a little higher than that of Eudragit RS 100 microspheres because Eudragit RL100 contains higher amount of quaternary ammonium groups, which renders it more permeable and accelerates the drug release as reported by Obeidat and Price.[15]

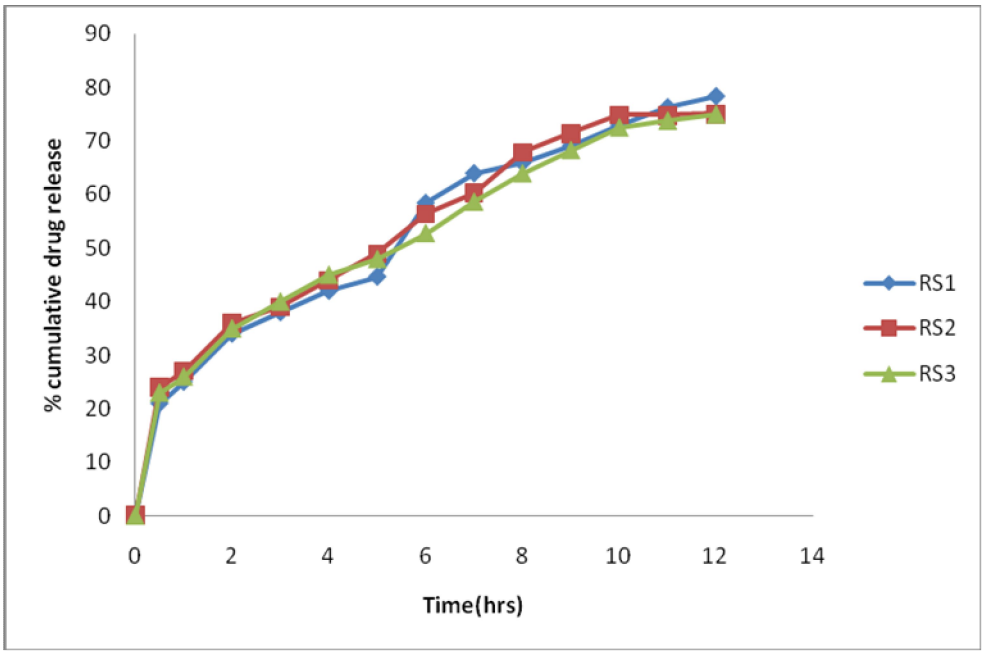

Fig. 7: Dissolution profile of Diltiazem HCl loaded Eudragit RS 100 Microsphere

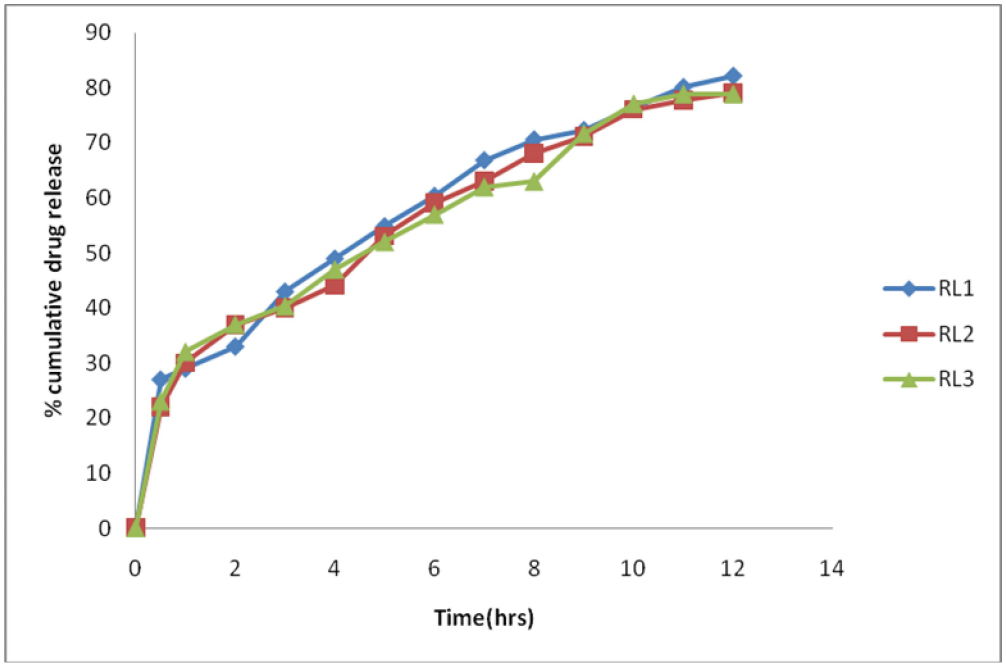

Fig.8: Dissolution profile of Diltiazem HCl loaded Eudragit RL 100 Microsphere

CONCLUSION

In this study, Diltiazem HCl was successfully encapsulated into two structurally different Eudragit polymers. By using an optimal proportion of magnesium stearate as droplet stabilizer, uniform and reproducible microspheres could be prepared. The surface structure of the microsphere was spherical and smooth. The encapsulation efficiencies were successfully increased with eudragit polymers which range 61-72 % and the mean size was between 200-250µm. The release rate of Eudragit RS100 microspheres exhibit a lag time at the initial release and the best release was observed with formulation ERL1.

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