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Development, Formulation and Evaluation of Eudragit RS/ RL Based Multiparticulate System

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Abstract : The purpose of this present work was to develop sustained release multiparticulate system as microspheres of freely water-soluble diltiazem hydrochloride by using with eudragit RS 100 or eudragit RS/RL 100 combination which are biocompatible and non-biodegradable polymer and use as encapsulating material for the sustained release of pharmaceuticals. Microspheres of diltiazem hydrochloride with various polymers drug ratios have been prepared by solvent-evaporation technique to get the optimum release of the drug for a prolonged period. The prepared microspheres were characterized by entrapment efficiency, particle size, micromeritic properties, in-vitro release behavior, scanning electron microscopy etc. Drug loaded microspheres should high entrapment efficiency (86.87%). The *in-vitro* drug release was done by using U.S.P.dissolution rate test basket type apparatus. The release of drug was prolonged upto 12 hrs. by increasing the polymer concentration.
Key words : multiparticulate system; eudragit RS/RL combination; solvent-evaporation technique; diltiazem hydrochloride.

Introduction

The sustained release dosage forms, single unit or multiple unit doses, help to provide optimum treatment by better patient's compliance and steady state plasma drug concentrations for the desired period time. However, multiple unit formulations like multiparticulate system for oral use allow the administration of much smaller drug amounts than single unit, by modifying the rate of dissolution of drug providing a method of releasing the active ingredients at a desired rate[1].

The polymethacrylates like, eudragit RS 100, eudragit RL 100, being a biocompatible and non-biodegradable polymer, are studied extensively as encapsulating material for the sustained or controlled release of pharmaceuticals. Eudragit RL and eudragit RS, also referred to as aminomethacrylate synthesized from acrylic acid and methacrylic acid esters with eudragit RL having 10% of functional quaternary ammonium groups and eudragit RS having 5% functional quaternary ammonium groups[2]. Microspheres with various polymers with drug ratios have been prepared to get the optimum release of the drug for a prolonged period.

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Diltiazem hydrochloride, a benzothiazepine calcium-channel blocker, is used alone or with an angiotensin-converting enzyme inhibitor, to treat hypertension, chronic stable angina pectoris, and Prinzmetal's variant angina[3]. In spite of its favorable clinical response and short biological half life near about 3.5 to 4 hrs. Over dosage with deltiazem hydrochloride may be associated with bradycardia, with or without atrioventricular conduction defects and hypotension. Therefore, there are continued efforts to improve the pharmaceutical formulation of diltiazem hydrochloride in order to achieve an optimal therapy.

The Solvent evaporation is the most commonly used method for microencapsulation of the drugs that are soluble or suspended in the organic phase. In this method, a solution or suspension of drug in an organic solvent containing dissolved polymer is emulsified to form w/o or o/w dispersion, possibly with the aid of a surfactant. The organic phase is then evaporated by heating or applying vacuum, leaving microspheres.

The present study is to develop the sustained release deltiazem hydrochloride microspheres as multiparticulate system by using different drug-polymer ratio with which maintain more uniform drug plasma concentration with reduce dosing frequency.

Materials and Methods

Materials

Diltiazem hydrochloride was obtained as a gift sample from Dr. Reddy's Laboratories Ltd., Hyderabad and eudragit RS-100, eudragit RL-100 were purchased from Roehm Pharma, Germany and others reagents were of analytical grade.

Methods

Preparation method for microsphere : Diltiazem microspheres were prepared by solvent evaporation technique. Different amounts of eudragit RS/ RL combinations were dissolved in 8.5 ml acetone separately by using a magnetic stirrer. The core material, diltiazem hydrochloride, was added to the polymer solution and mixed for 15 minutes, followed by addition of magnesium stearate (10% w/w of polymer weight) and then mixed thoroughly. The resulting dispersion was added in a thin stream to a mixture of 135 ml light liquid paraffin and 15 ml n-hexane contained in a 250 ml beaker with constant stirring at 700 rpm using a mechanical stirrer .Stirring was continued for 3 hr. until the acetone evaporated completely.

The microspheres were filtered by using whatman filter paper. The residue was washed 4-5 times with 50 ml portions of n-hexane. The product was then dried at room temperature for 24 hours.

Particle Size Analysis : Microspheres were separated into different size fraction by sieving for 10 minutes using a mechanical shaker containing standard sieves having aperture of 590µm, 250µm, 149µm, 111µm, 88µm. The particle size distributions of the microspheres for all the formulations were determined and mean particle size of microspheres were calculated by using the following formula**.**

Mean particle size = ∑(mean particle size of the fraction × weight fraction) / ∑ (weight fraction) [4, 5, 6, 7]**.**

Drug Entrapment Efficiency, Drug Loading and Percentage Yield : The amount of diltiazem hydrochloride (DTZ)present in the eudragit microspheres was determined by taking the known amount of microspheres in which 10mg drug should be present theoretically. Then the microspheres were crushed and the powdered microspheres were taken and extracted in 100 ml of distilled water and stirred for 15 minutes at 1500 rpm. Then the solution was filtered and diluted 10 times. Then the absorbance was measured spectrophotometrically at 236 nm against distilled water as blank and concentrations were determined by employing simultaneous equation method.

Drug entrapment efficiency (DEE) percentage (%) = [Experimental drug Content/ Initial Drug Content into the Formulation] ×100 [8].

Drug Loading percentage (%) = [Q_m / W_m] × 100 [9] Where, Wm = Weight of the microspheres; Q_m = Quantity of the drug present in W_m microspheres.

Yield Percentage (%) = [Weight of Microspheres / Total Expected Weight of Drug and Polymers] ×100 [10]

Surface morphology : The samples for the scanning electron microscope (SEM) analysis were prepared by sprinkling the microspheres on one side of an adhesive stub. The microspheres ware then coated with gold. Finally the microspheres were then observed with the scanning electron microscope (Model-FEI Quanta 200 MK2, Netherlands).

FTIR studies : The infrared spectra were recorded by using a FTIR spectrophotometer (Model- Perkin Elmer, Spectrum-100, UK) by the KBr pellet method. The spectra obtained for diltiazem hydrochloride and physical mixtures of diltiazem hydrochloride (DTZ) with polymers were compared to check compatibility of drug with polymers[9].

Angle of Repose : Angle of repose of different formulations was measured according to fixed funnel standing method $\theta = \tan^{-1} h/ r$ where, θ = angle of repose, r = the radius of the base of the pile and h = height of the pile.

Bulk Density and Tapped Density : Bulk density and tapped density were measured by using 10 ml of graduated cylinder. The sample poured in cylinder was tapped mechanically for 100 times, and then tapped volume was noted down. Bulk density and tapped density were calculated. Each experiment for micromeritic properties were performed in triplicate manner[10].

Carr's Index : Compressibility index (Ci) or Carr's index value of microsphere was computed according to the following equation: Carr (%) = [(Tapped density – Bulk Density) / Tapped Density] × 100 [10].

Hausner Ratio : Hausner ratio of microparticles was determined by comparing the tapped density to the bulk density using the equation: Hausner Ratio = Tapped density / Bulk Density[10].

In vitro drug release study : In vitro release profile of Diltiazem hydrochloride from the preparation was examined in pH 1.2 buffer from 0 to 2 hr., in pH 4.5 phosphate buffer from 2 to 4 hr. and in phosphate buffer pH 6.8 from 4 to 12 hr. by using the rotating basket method specified in USP XXI at 100 rpm. [9)] Microspheres equivalent to 90 mg of drug was placed in the basket and the medium was maintained at 37±0.5°C. An aliquot of 5 ml were withdrawn periodically at intervals of 1 hr. and the same volume of fresh medium was replaced. The concentration of the drug released at different time intervals was determined by measuring the absorbance at 236 nm against appropriate blank. Three trials were carried out for all formulations. The percentage of drug release was calculated and plotted against the function of time to study the pattern of drug release.

In vitro Drug Release Kinetics : Drug release data were fitted to kinetic model including the zero order, first order, Higuchi matrix and Korsmeyer-Peppas release equations to find the equation with the best fit[11, 12, 13].

Results and Discussions

Evaluation of preparation method : In this project attempts have been made to prepare by the eudragit RS-100 or combination with eudragit RS/RL-100 microspheres bearing diltiazem hydrochloride through solvent evaporation technique. Here, the formulations were prepared by using the polymers such as, eudragit RS-100 and magnesium stearate with a specific drug- polymer ratio which coded as F1, F2, F3, F4 and F5 respectively, while the formulation with a eudragit RS and RL combinations coded with S1, S2 and S3. All batches were prepared in triplicate.

Particle Size Analysis : Particle size can be determined by sieve analysis method. The mean diameter of microspheres increased from 212 ± 3.00 µm to 241 ± 2.00 µm. The average particle size of microspheres can describe by Fig.1.

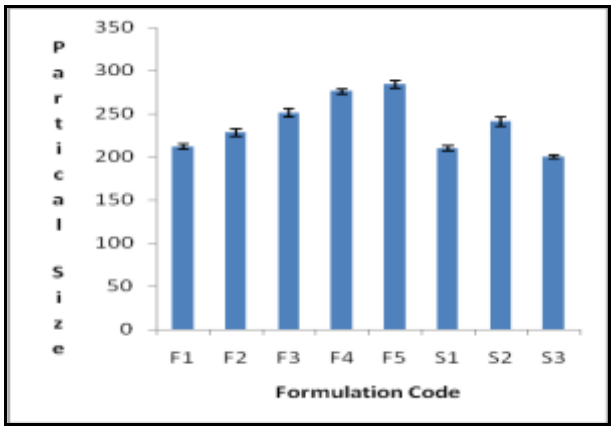

Fig. No. 1. Histogram Diagram of Mean Partical Size (µm)

Drug Entrapment Efficiency, Drug Loading and Percentage Yield : The drug entrapment efficiency was increased up to 86.87% with increasing polymer concentration of eudragit RS100 and combination with eudragit RS100/ RL100 which described by Fig.2.

The results of drug loading increased from 13.38 ± 0.66 % to 24.31 ± 0.47 % of microsphere with decreasing the amount of polymer which explain by Fig.3

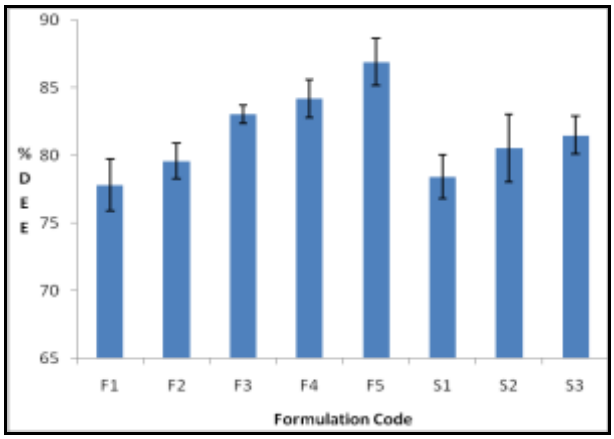

Fig. No. 2. Histogram Diagram of % Drug Efficiency (DEE)

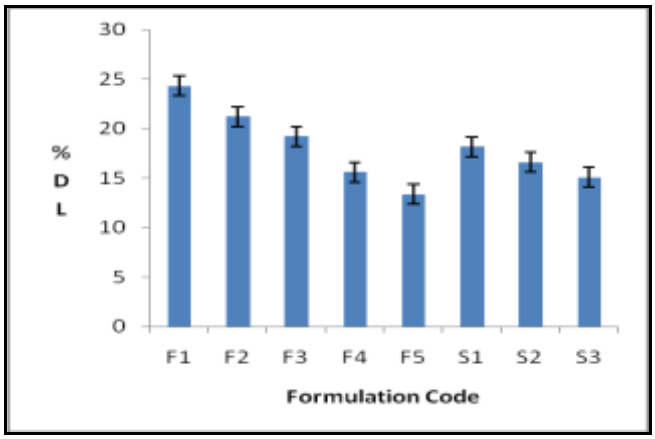

Fig.No.3 Histogram Diagram of % Drug Entrapment Loading (DL

The percentage yield was increased up to 89.52 % which described by Fig.4

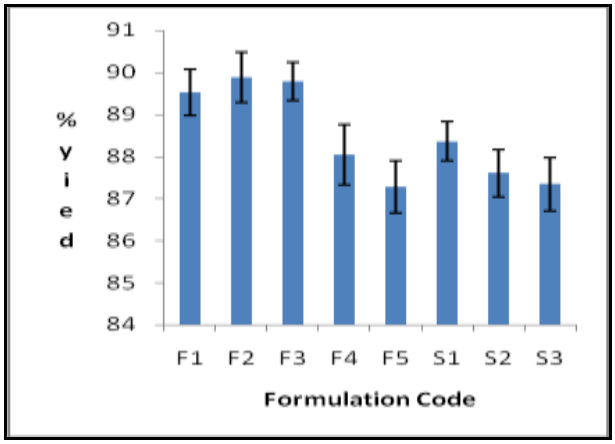

Fig.No.4 Histogram Diagram of % Yield

Surface morphology : Finally, the microspheres were observed with the scanning electron microscope (Model-FEI Quanta 200 MK2, Netherlands) for the surface morphology of eudragit based multiparticulate system with drug before dissolution study and after dissolution study described by Fig. 5 and 6.

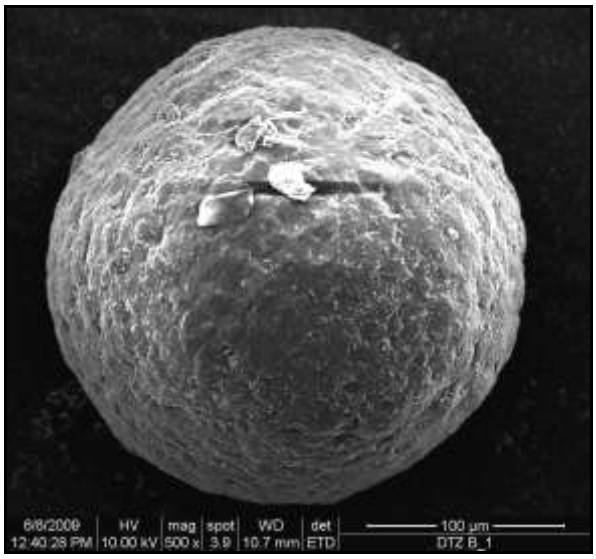

Fig. No. 5. SEM of Diltiazem Hydrochloride Microspheres before Dissolution Study

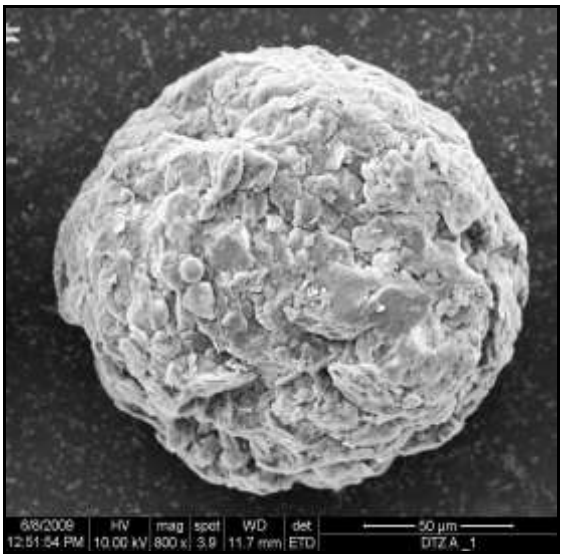

Fig.No.6. SEM of Diltiazem Hychloride Microspheres after Dissolution Study

FTIR studies : The FTIR spectra analysis of diltiazem hydrochloride and the physical mixtures shows that there was no significant interaction between drug and polymers as shown in Fig. 7, 8, 9 and 10.

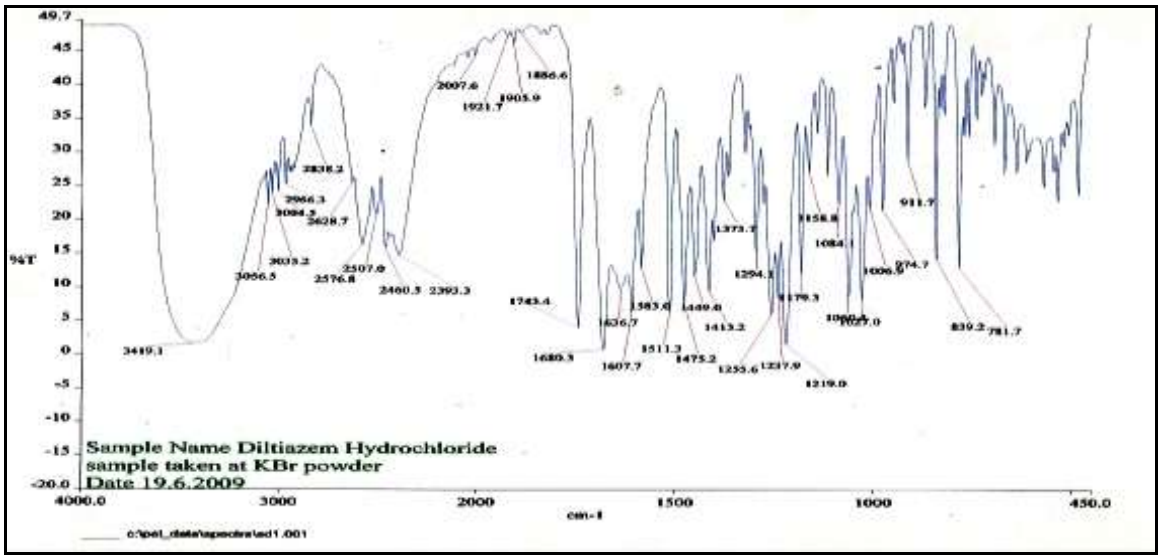

Fig. No. 7. FTIR Spectra of Diltiazem Hydrochloride

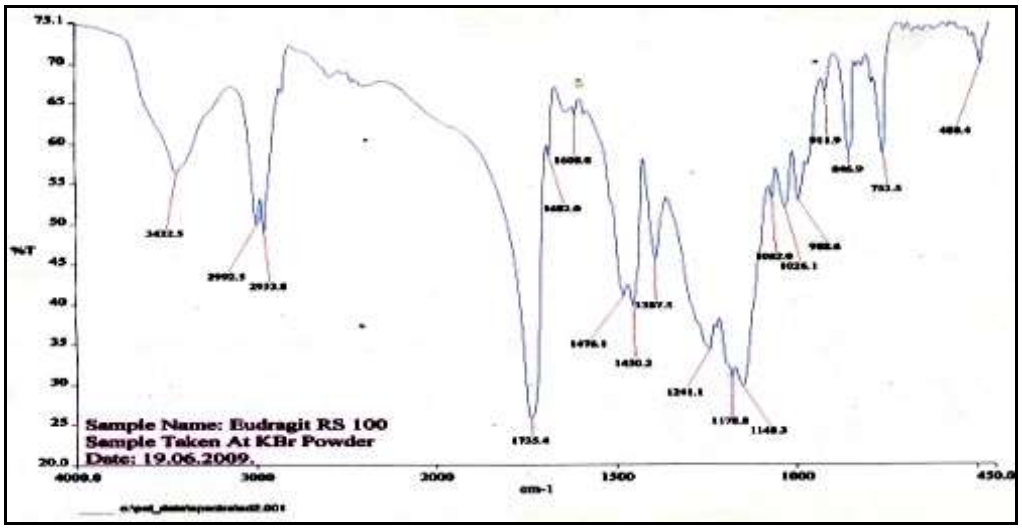

Fig. No. 8. FTIR Spectra of Eudragit RS 100

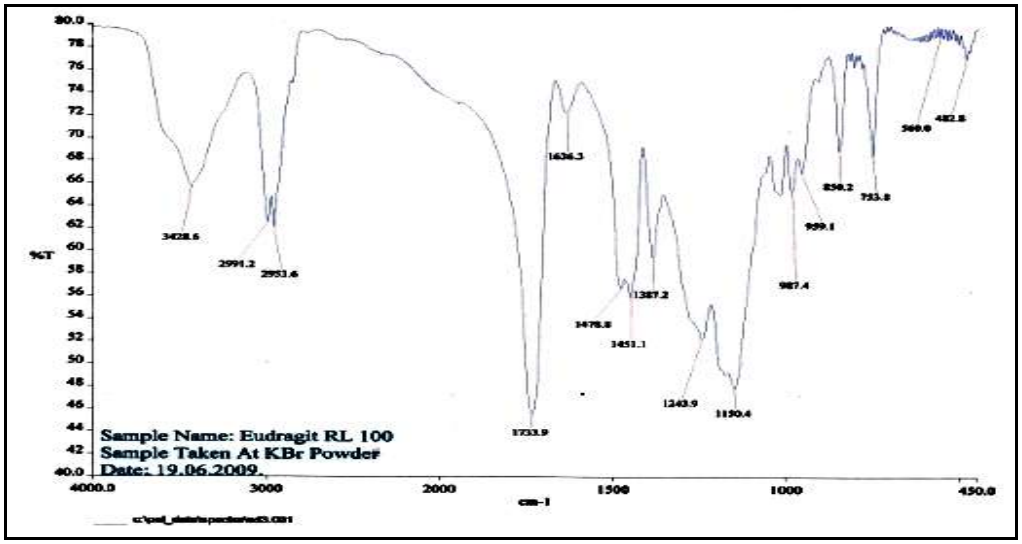

Fig. No. 9. FTIR Spectra of Eudragit RL 100

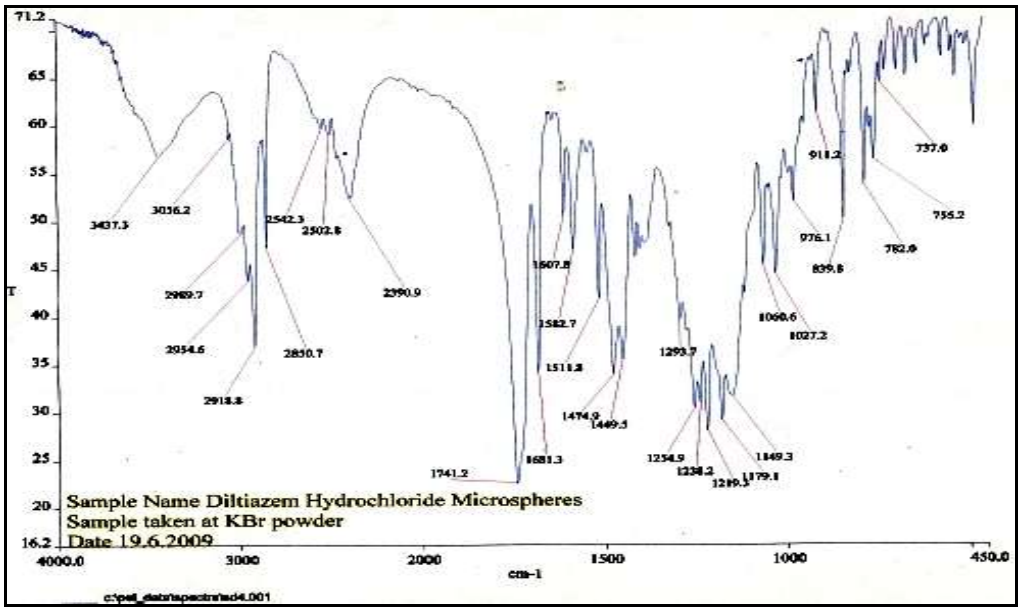

Fig. No. 10. FTIR Spectra of Diltiazem Hydrochloride Microsphere with Eudragit RS and RL 100

Micromeritic properties : The value of angle of repose of formulation within the range of 25˚, indicating very good flow properties for the microspheres. The tapped density values ranged between 0.757 to 0.774 gm /cm^3. The result of Carr's index range from 5.880 to 11.255 %, which suggests excellent flow characteristics of the microspheres. Hausner ratio range from 1.102 to 1.113%, which indicates good flow property of microspheres.

***In-vitro* drug release study** : In the *in-vitro* release profile of diltiazem hydrochloride from the preparations was examined in pH 1.2 buffers from 0 to 2 h, in pH 4.5 phosphate buffers from 2 to 4 h and in phosphate buffer pH 6.8 from 4 to 12 h using the rotating basket method specified in USP XXI at 100 rpm. The effect of variation in drug to polymer ratio on drug release was studied on diltiazem microspheres. Different drug to polymer ratios were taken. Increase in polymer concentration resulted in a decrease of drugs release rate. Sustained release up to 12 hours was achieved when drug: polymer ratio was taken up to 1:3.The in-*vitro* drug release study of diltiazem microspheres are shown in Fig. 11 and 12.

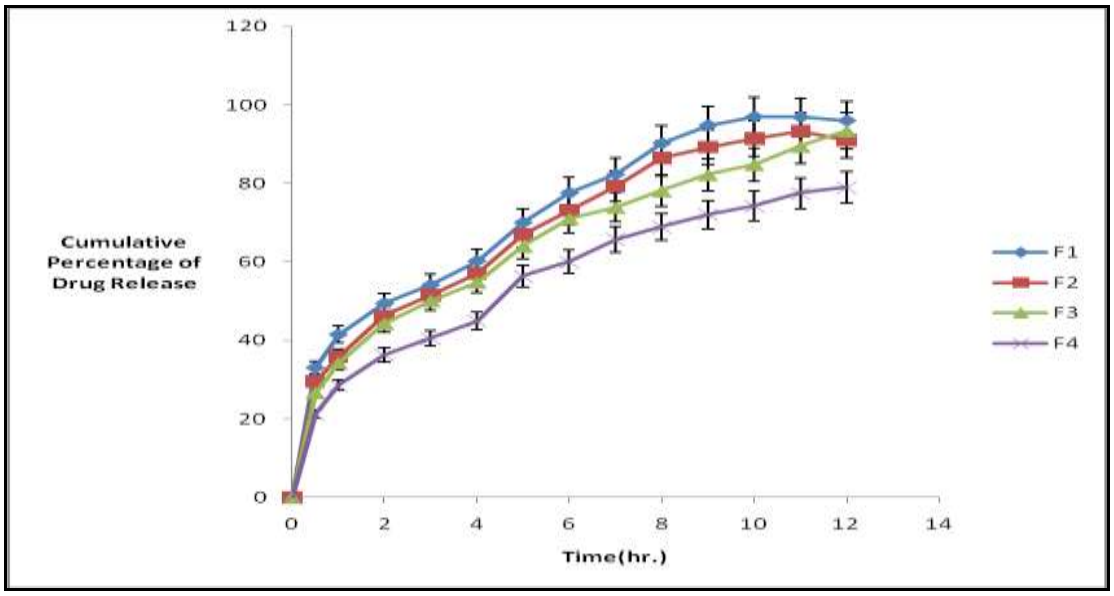

Fig. No. 11. *In-Vitro* Drug Release Studies for F1, F2, F3, and F4 Formulations

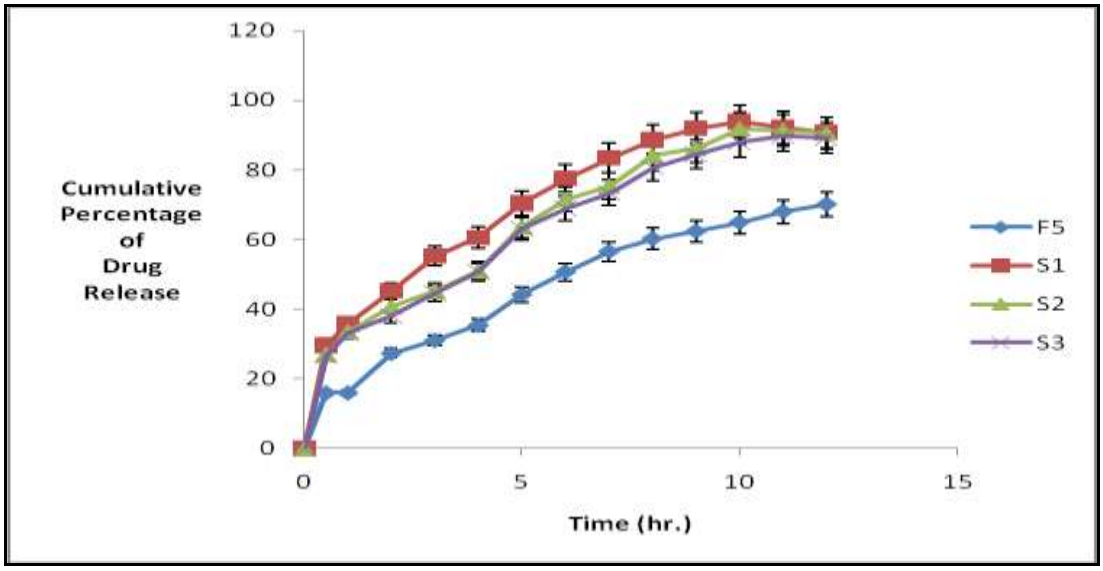

Fig. No. 12. *In-Vitro* Drug Release Studies for F5, S1, S2, and S3 Formulations

Drug release kinetics : The drug release kinetics profile was best fit in Higuchi matrix model kinetics followed by first order kinetics and zero order kinetics. It was found that the mechanism of drug release from microspheres was Diffusion controlled. The formulations made with eudragit RL100 and eudragit RS100

combinations showed faster drug diffusion than that of eudragit RS 100. This diffusion can be attributed to the greater permeable nature of RL 100 polymer, which is due to higher content of hydrophilic quaternary ammonium groups than RS 100 polymer. The n value in korsmeyer-peppas model was found to be less than 0.5, which means prepared microspheres follow Fickian diffusion.

The release kinetic parameters are shown in the Table 1.

Table 1. *In-Vitro* Release Kinetic Parameters for Diltiazem Hydrochloride Microspheres

Formulation Code	Zero- Order Model		First-Order Model		Higuchi Model		Korsmeyer-Peppas Model	
	r^2	k_0	r^2	k_1	r^2	k_h	r^2	K_{kp}
F1	0.870	6.785	0.946	-0.128	0.977	27.45	0.976	0.363
F2	0.878	6.588	0.970	-0.094	0.982	26.61	0.984	0.388
F3	0.896	6.366	0.973	-0.083	0.992	25.57	0.994	0.397
F4	0.903	5.664	0.985	-0.053	0.991	22.65	0.987	0.425
F5	0.939	5.261	0.986	-0.041	0.989	20.62	0.978	0.485
S1	0.852	6.64	0.945	-0.098	0.974	27.11	0.983	0.394
S2	0.907	6.781	0.968	-0.091	0.982	26.94	0.967	0.42
S3	0.911	6.605	0.982	-0.082	0.985	26.22	0.967	0.417

r^2, indicates correlation coefficient; k_0, k_1, and $k_{h\ a}$ are constant of release kinetics; K_{kp}, indicates diffusional exponent (n).

Conclusion

In the present study, an attempt was made to deliver a novel anti hypertensive and chronic stable anti angina pectoris drug. The multiparticulate system was meant to deliver through oral route as capsules. Microspheres were prepared by using both polymers eudragit RS 100 and eudragit RL 100 and also eudragit RS 100 alone microspheres which were found to be satisfactory. Drug release was sustained up to 12 hrs. The drug dissolution profile was also found to follow higuchi matrix kinetics. The microspheres were spherical, discrete, compact and free flowing character. The drug–polymer interaction results suggested no interaction between drug and polymers were observed. Based on the in vitro characterization, it was concluded that diltiazem hydrochloride could be administered orally as multiparticulate system used for sustained release dosage form.

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