AMERICAN JOURNAL OF PHARMTECH RESEARCH
Journal home page: http://www.ajptr.com/

Development and Evaluation of Hydrophobic Carriers Based Sustained Release Diltiazem Hydrochloride Formulations by Various Techniques and Its Comparison

Sarada A[1*], Janaki Devi S[1], Pratyusha P V[2], Lohithasu D[3]
1. A. U. College of Pharmaceutical Sciences, Andhra University, Visakhapatnam-530003, Andhra Pradesh, India.
2. Maharajah's College of Pharmacy, Phoolbaugh, Vizianagaram, Andhra Pradesh, India.
3. GITAM institute of Pharmacy, GITAM University, Visakhapatnam, Andhra Pradesh, India.

ABSTRACT

The aim of present work is to study the release of diltiazem hydrochloride from tablets with ethyl cellulose (EC), eudragit RSPO and kollidon SR in different drug-to-polymer ratios were investigated with a view to develop twice-daily sustained release dosage form by polymeric dispersion (PD) technique. The polymeric dispersions containing ehtyl cellulose, eudragit RSPO or kollidon SR at drug-polymer ratios of 1:0.5, 1:1, 1:1.5, 1:2, with diltiazem hydrochloride were developed using solvent evaporation technique and co precipitation technique. The physical mixtures of drug and polymers were prepared by using simple mixing technique at the same ratio. The study of FTIR could not show significant interaction between diltiazem HCl and ethyl cellulose or kollidon SR or eudragit RSPO. Prepared tablets were evaluated for the release of diltiazem Hydrochloride over a period of 12 h in pH 7.4 phosphate buffer using US Pharmacopoeia type II dissolution apparatus. The *in vitro* drug release study revealed that the tablets prepared by dispersion technique have extended the release rate for 12 h whereas the tablets prepared by physical mixing technique at the same concentration have extended the release rate only up to 8 h. The *in vitro* release profile and the mathematical models indicate that release of diltiazem Hydrochloride can be effectively controlled from a tablet containing polymeric dispersion of eudragit RSPO.

Keywords: Diltiazem Hcl, Ethyl cellulose, Kollidon SR, Eudragit RSPO, FTIR studies.

*Corresponding Author Email: saradaanepu2014@gmail.com
Received 22 September 2015, Accepted 27 September 2015

Please cite this article as: Anepu S *et al*., Development and Evaluation of Hydrophobic Carriers Based Sustained Release Diltiazem Hydrochloride Formulations by Various Techniques and Its Comparison. American Journal of PharmTech Research 2015.

INTRODUCTION

The goal in designing sustained drug delivery system is to reduce the frequency of dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required, or providing uniform drug delivery. The multiple-dosing of conventional dosage form for long-acting therapy, leads to side effects or toxicities and poor patient compliance. These problems can be minimized by controlled-release drug delivery systems [1-3]. The design of a controlled release system depends on various factors such as the route of delivery, the type of drug delivery system, the disease being treated, the length of therapy, and the properties of the drug[4-7]. Diltiazem belongs to class I (high solubility and high permeability) of the Biopharmaceutical Classification System (BCS) [8]. It is a calcium channel blocker with peripheral and coronary vasodilator properties. It lowers blood pressure and has some effect on cardiac conduction. It is administered orally in the treatment of angina pectoris and management of antiarrythymia. Frequent administration results in an increased bioavailability due to the so called saturable first pass effect, a consequence of non linear pharmacokinetics of drug. Therefore development of a sustained release formulation helps in decreasing the frequency and overcoming this problem to some extent[9-13]. Polymeric dispersions (drug is dissolved at molecular level with the polymer) are not only applied for the improvement of the release rate and oral bioavailability but also improve the wetting behaviour of the hydrophobic drug as well as de-agglomeration and micellization of the drug with hydrophilic polymers. By judicious choice of the carrier it is also possible to delay or slow down the release pattern of drug by formulating it as a solid dispersion. A wide variety of polymers that are poorly soluble or which swell under aqueous conditions have potential as carriers for controlled release dosage forms[14-16]. The principal objective of the present work is the development and optimization of a sustained release formulation using hydrophobic carriers by polymeric dispersion technique and comparing this technique with physical mixing technique taking Diltiazem as the model drug. Development of formulations using hydrophobic carriers will be attempted using physical mixing technique. The same formulations will then be prepared by solvent evaporation technique and co precipitation technique. *In vitro* release of the drug from the matrix tablet is evaluated. The powder blend is also evaluated for its flow properties by calculating the angle of repose, carr's index, hausners ratio and the properties were compared with each excipient and the formulation having good flow properties is selected. In a similar fashion the tablets were evaluated for its hardness, friability, thickness, drug content to assess them as per IP.

The kinetics was also studied by fitting into various equations which depict the release mechanism of the drug from the tablet and the best fit in equation was selected.

MATERIALS AND METHOD

Diltiazem Hydrochloride and ethyl Cellulose gift sample Sigma Eldritch, USA, Eudragit RSPO and Kollidon SR purchased from BASF, Ludwigshafen, Germany. Standard graph of Diltiazem hydrochloride was done using pH 7.4 phosphate buffer and the absorbance of these samples was measured spectrophotometrically at 236 nm using UV- Visible spectrophotometer.

Construction of calibration curve

Preparation of working standard solution

Standard drug (100 mg) was accurately weighed and transferred into 100 ml volumetric flask. It was dissolved and make up to the mark with pH 7.4 phosphate buffer to obtained concentration of 1mg/ml. From this working standard solution, by using suitable dilutions, 2,4,6,8,10,15 and 20 µg/ml serial solutions were prepared. The absorbance of solutions containing drug was determined using uv range 100 to 400 nm. The absorbance maxima found to be 236 nm.

Drug-excipient compatibility studies

Fourier Transform Infrared Spectroscopy

Compatibility with excipients was confirmed by carried out FTIR studies. The pure drug and its optimized formulations (SEET4, SEK4, SEEC4 and CPET4) were subjected to IR studies. IR spectroscopy was conducted using a PerkinElmer FTIR spectrophotometer and potassium bromide pellet method was employed and background spectrum was collected under identical conditions. The samples were analyzed between wave numbers of 4000 and 400 cm^{-1}.

Preparation of matrix tablets

Using different drug (Diltiazem hydrochloride) to polymer (Ethyl cellulose or Eudragit RSPO or Kollidon SR) ratios of 1:0.5, 1:1, 1:1.5, 1:2 were developed for twice-daily sustained release dosage form by polymeric dispersion (PD) technique, solvent evaporation (SE) technique and co precipitation technique. The physical mixtures of drug and polymers were prepared by using simple mixing technique at the same ratios (1:0.5, 1:1, 1:1.5 and 1:2). PMEC1, PMET1, PMK1, PMEC2, PMET2, PMK2, PMEC3, PMET3, PMK3, PMEC4, PMET4 and PMK4 prepared by polymeric dispersion (PD) technique. SEEC1, SEET1, SEK1, SEEC2, SEET2, SEK2, SEEC3, SEET3, SEK3, SEEC4, SEET4 and SEK4 prepared by solvent evaporation (SE) technique. CPET1, CPET2, CPET3 and CPET4 prepared by co precipitation (CP) technique. PMEC1, PMEC2, PMEC3, PMEC4, SEEC1, SEEC2, SEEC3 and SEEC4 prepared by using ethyl cellulose.

PMET1, PMET2, PMET3, PMET4, SEET1, SEET2, SEET3, SEET4, CPET1, CPET2, CPET3 and CPET4 prepared by using Eudragit RSPO. PMK1, PMK2, PMK3, PMK4, SEK1, SEK2, SEK3 and SEK4 prepared by using kollidon SR. Magnesium stearate used as lubricant. The dispersions or physical mixtures were compressed into tablets by direct compression method.

EVALUATION OF TABLETS

Evaluation of Powder Blend

Angle of repose

The angle of repose of powder blend was determined by the funnel method. The accurately weight powder blend were taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation[17].

Tan θ = h/r, Where, h and r are the height and radius of the powder cone.

Bulk density:

Both loose bulk density (LBD) and tapped bulk density (TBD) was determined. A quantity of 2 gms of powder blend from each formula, previously shaken to break any agglomerates formed, was introduced in to 10 ml measuring cylinder. After that the initial volume was noted and the cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5 cm at second intervals. Tapping was continued until no further change in volume was noted. LBD and TDB were calculated using the following equations.

LBD= Weight of the powder blend/Untapped Volume of the packing

TBD=Weight of the powder blend/Tapped Volume of the packing

Compressibility Index

The Compressibility Index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the LBD and TBD of a powder and the rate at which it packed down. The formula for Carr's Index is as below:

Carr's Index (%) = [(TBD-LBD) x100]/TBD

Total Porosity

Total porosity was determined by measuring the volume occupied by a selected weight of a powder (V_{bulk}) and the true volume of the powder blend (The space occupied by the powder exclusive of spaces greater than the intermolecular spaces, V).

Porosity (%) =V_{bulk}-V/V_{bulk} x 10

Evaluation of tablets

Weight variation test

To study weight variation twenty tablets of the formulation were weighed using a Essae electronic balance and the test was performed according to the official method. Twenty tablets were selected randomly from each batch and weighed individually to check for weight variation.

Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked and hardness of the tablets was determined.

Thickness

The thickness of the tablets was determined by using vernier calipers. Five tablets were used, and average values were calculated.

Friability Test

The friability of tablets was determined using Elico Friabilator. It is expressed in percentage (%). Ten tablets were initially weighed (W0) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W). The % friability was then calculated by:

$\% F = 100 (1-W_0/W)$; where % Friability of tablets less than 1% are considered acceptable.

Drug content

Five tablets were weighed individually and powdered. The powder equivalent to Average weight of tablets was weighed and drug was extracted in pH 7.4 phosphate buffer, the drug content was determined measuring the absorbance at 236 nm after suitable dilution using Agilent UV- Visible double beam spectrophotometer.

***In Vitro* dissolution studies**

Dissolution rate study of the tablets were performed by using the U.S. Pharmacopoeia (USP) model digital dissolution test apparatus type-II (Lab India, Mumbai) at the paddle rotation speed of 75 rpm using 900 ml of pH 7.4 phosphate buffer as dissolution media at 37 ± 0.5^oC. At particular time points (0.5, 1, 2,3,4,6,8,10 and 12h), 10 ml samples were withdrawn by using syringe filter (0.45µm) (Sepyrane, Mumbai) and then assayed for the drug content by measuring the absorbance at 236 nm using the UV-Visible spectrophotometer (Agilent) and the volume is adjusted with a fresh medium maintained at 37 ^oC after each sampling to maintain its constant volume throughout the test. Dissolution experiments were conducted in triplicate (n=3)[18].

RESULTS AND DISCUSSION

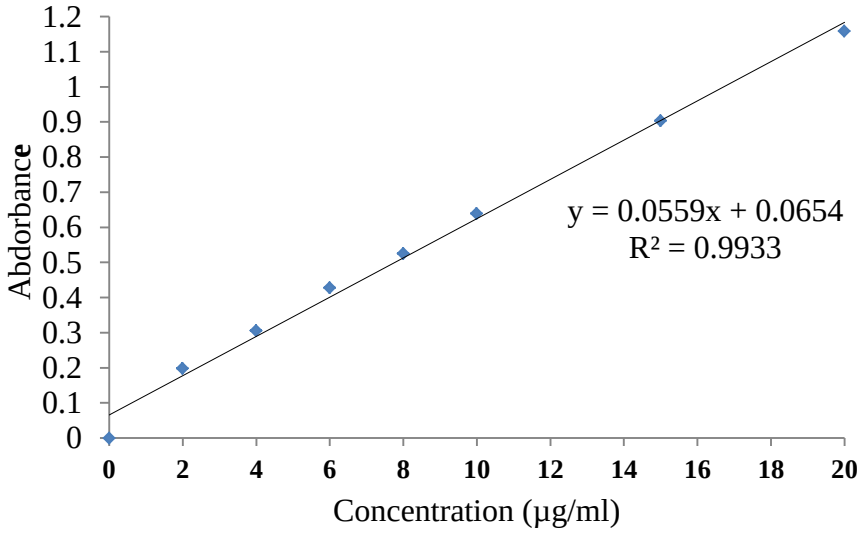


Figure 1: Standard curve of Diltiazem hydrochloride

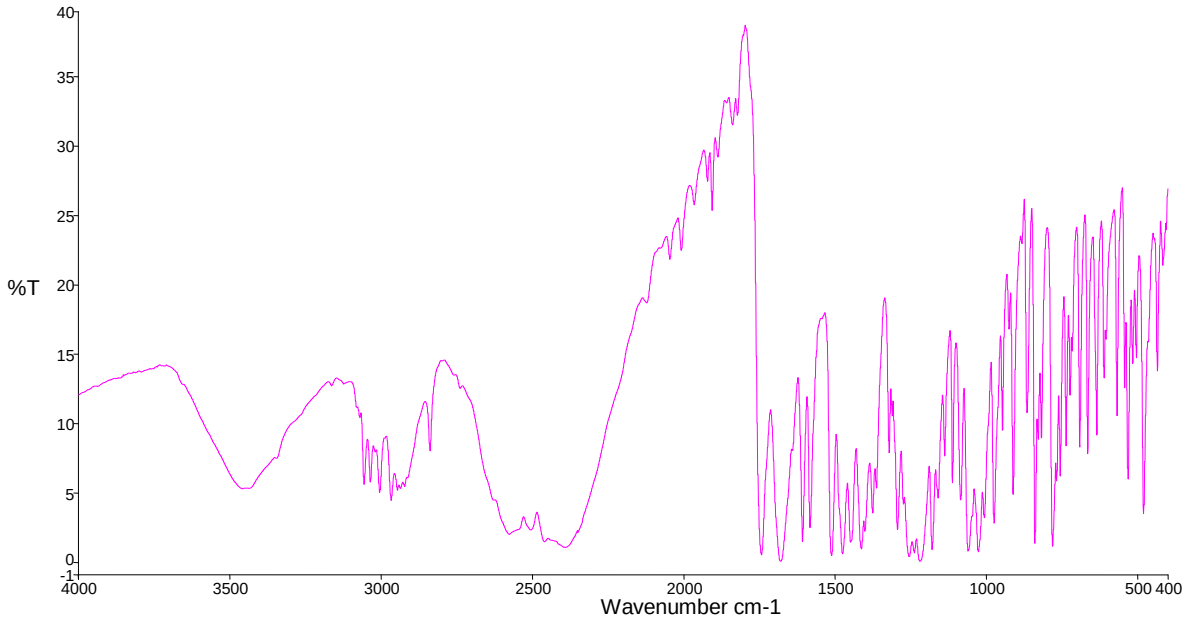
Fourier Transform Infrared Spectroscopy

The FTIR spectra were shown in figure 2. In figure 2. a). the peak at 3427.43 cm^{-1} is the characteristic of the heterocyclic amine N-H stretch, the peak at 1742.90 cm^{-1} characteristic of C=O stretch, the peak at 1055.70 cm^{-1} characteristic of C-O stretch, the peak at 777.67 cm^{-1} characteristic of Ar-H stretch and the peak at 2959.85 cm^{-1} is the characteristic of the -CH-stretch in the drug (Diltiazem HCl).From figure-2, b). SEET4; c). SEK4; d.) SEEC4; e). CPET4, optimized formulations shown that indicates no interaction between drug and other excipients which are used in the formulation. The surface characteristics of optimized formulations were determined by Scanning Electron Microscopy (SEM) analysis. The SEM photographs of the optimized formulations shown in figure 9.

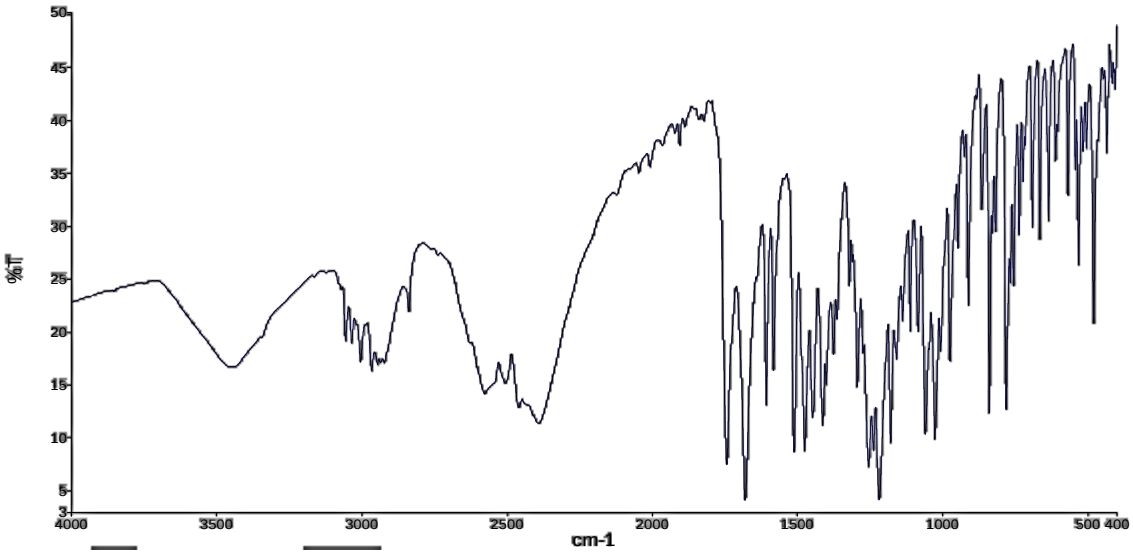
Table 1: Pre Compression parameters for formulations of SEEC4, SEET4, SLK4 and CPET4)

Property	SEEC4	SEET4	SEK4	CPET4
Loose bulk Density (LBD)	0.123	0.112	0.092	0.113
Tapped Bulk Density (TBD)	0.145	0.128	0.108	0.132
Compressibility Index	15.17	15.69	17.81	17.39
Hausner's Ratio	1.17	1.14	1.2	1.16
Angle of Repose	27.47	27.62	22.25	20.62

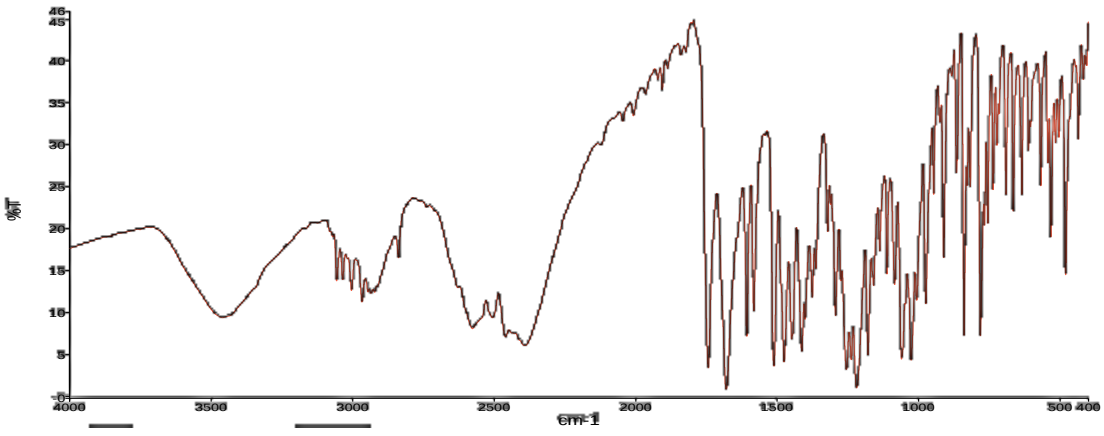
a)



b)



c)



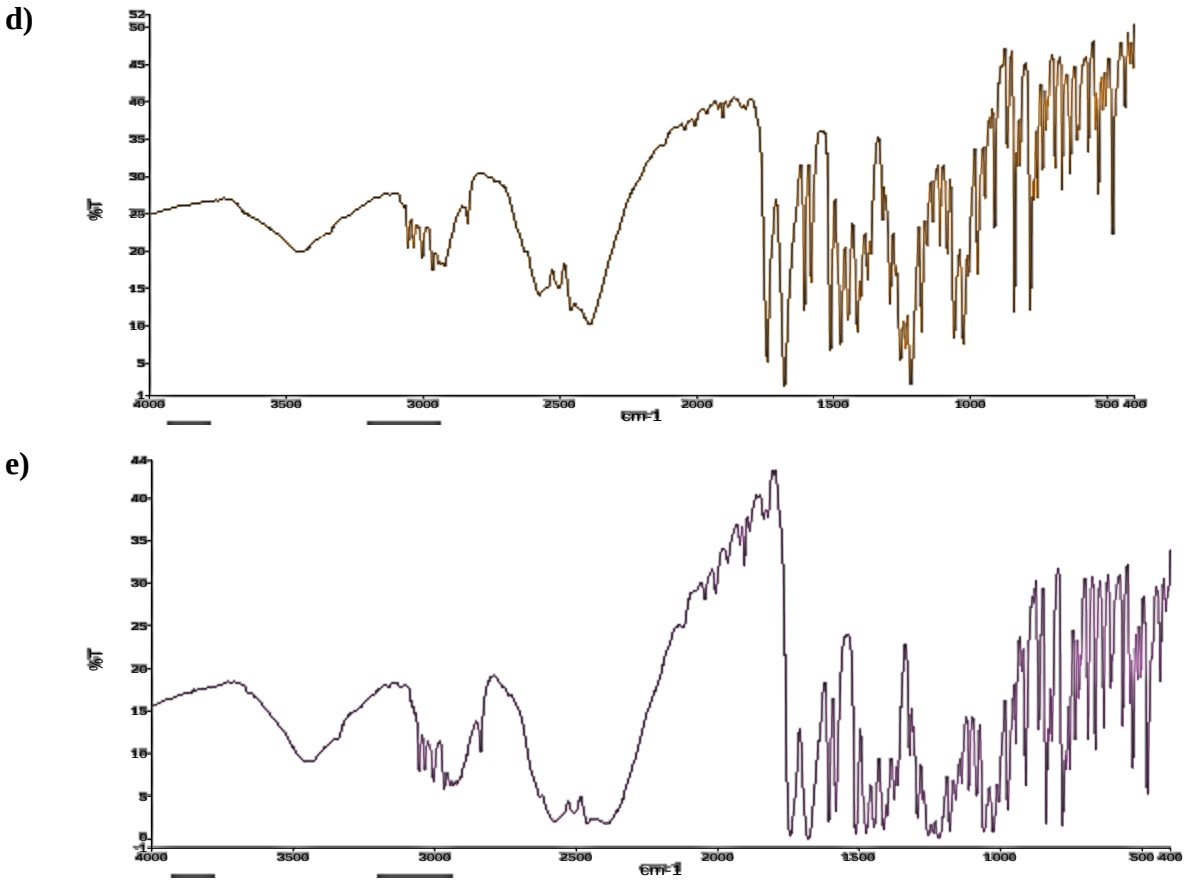


Figure 2: Fourier Transform Infrared Spectroscopy of optimized formulations a) Pure drug; b) SEET4; c) SEK4; d) SEEC4; e) CPET4.

Table 2: Post compression parameters of formulation containing Drug to Polymer ratio is 1:0.5

Formulation Code	Weight variation	Thickness	Hardness	Friability	Drug Content
PMEC1	±5.2	1.98±.01	5.8±.0.10	0.52±0.04	92.02
PMET1	±5.6	1.92±.03	5.9±0.07	0.61±.01	97.24
PMK1	±5.8	2.01±.05	5.4±0.03	0.55±0.02	93.49
SEEC1	±7.9	2.05±.04	7.2±0.10	1.13±0.02	97 .98
SEET1	±7.7	2.1±.06	5.2±0.40	1.17±0.03	93.44
SEK1	±7.4	1.9±.07	7.8±0.20	1.15±0.04	97.23
CPET1	±7.2	2.1±.05	5.3±0.30	1.03±.0.02	97.54

Table 3: Post compression parameters of formulation containing Drug to Polymer ratio is 1:1

Formulation Code	Weight variation	Thickness	Hardness	Friability	Drug Content
PMEC2	±5.3	2.08±.01	7.2±0.6	0.42±0.04	93.66
PMET2	±7.7	2.01±.03	7.8±0.4	0.6±.0.10	97.01
PMK2	±7.2	2.01±.05	7.2±0.8	0.53±0.02	91.64
SEEC2	±3.9	2.05±.04	5.4±0.9	1.10±0.02	98.48
SEET2	±3.3	2.1±.06	7.3±0.7	1.07±0.03	98.23
SEK2	±3.7	2.2±.07	5.8±0.4	1.18±0.04	97.87
CPET2	±2.9	2.1±.05	7.2±0.3	1.05±.0.02	98.46

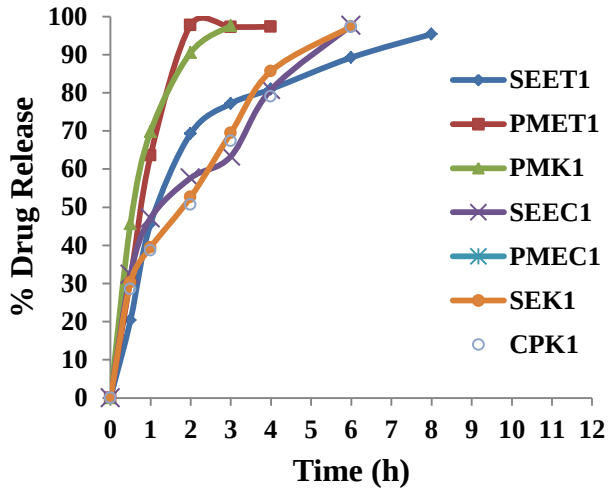


Figure 3: % Drug release profiles of formulations (Drug: Polymer ratio= 1: 0.5)

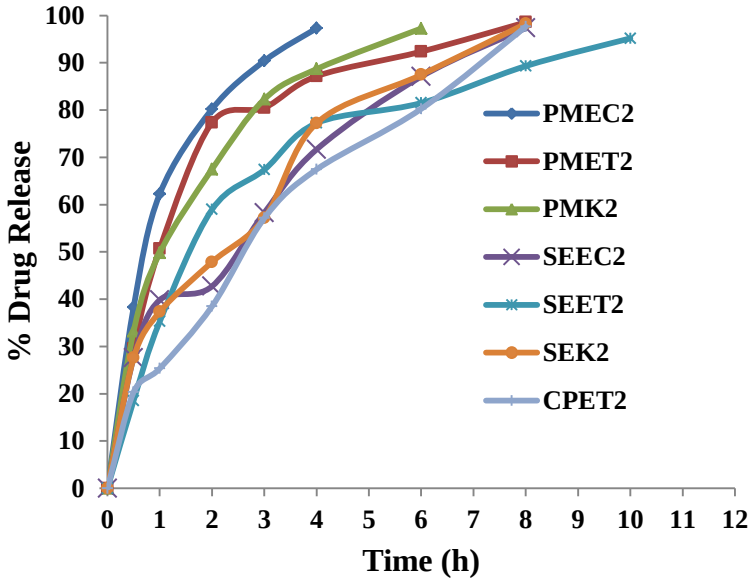


Figure 4: % Drug release profiles of formulations (Drug: Polymer ratio= 1: 1)

Table 4: Post compression parameters of formulation containing Drug to Polymer ratio is 1:1.5

Formulation Code	Weight variation	Thickness	Hardness	Friability	Drug Content
PMEC3	±7.2	2.28±.01	7.6 ± 0.4	0.32±0.04	97.34
PMET3	±7.6	2.39±.03	7.1±0.07	0.48±.01	99.28
PMK3	±7.4	2.31±.05	7.2±0.03	0.35±0.02	97.48
SEEC3	±3.8	2.25±.04	7.8±0.10	1.01±0.02	97.24
SEET3	±7.3	2.31±.06	7.6±0.40	1.03±0.03	97.59
SEK3	±7.7	2.29±.07	7.3±0.20	1.11±0.04	98.63
CPET3	±7.5	2.31±.05	7.4±0.30	0.95±.0.02	98.28

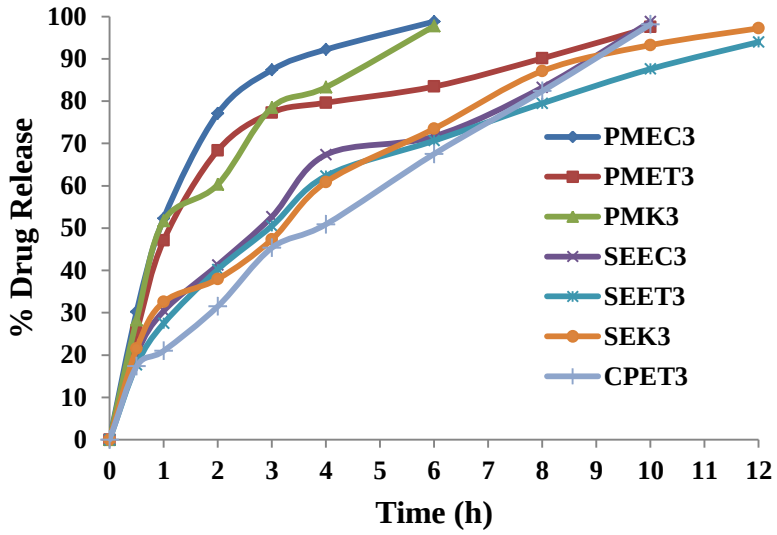


Figure 5: % Drug release profiles of formulations (Drug: Polymer ratio= 1: 1.5)

Table 5: Post compression parameters of formulation containing Drug to Polymer ratio is 1:2

Formulation Code	Weight variation	Thickness	Hardness	Friability	Drug Content
PMEC4	±3.1	2.38±.01	8.6±0.07	0.12±0.04	98.49
PMET4	±3.7	2.49±.03	8.4±0.03	0.11±.01	97.37
PMK4	±3.4	2.41±.05	8.9±0.10	0.15±0.02	99.21
SEEC4	±3.7	2.35±.04	8.6±0.40	0.7±0.02	98.48
SEET4	±2.8	2.41±.06	8.2±0.20	0.95±0.03	97.57
SEK4	±3.6	2.39±.07	7.9±0.30	0.92±0.04	98.31
CPET4	±3.1	2.41±.05	8.1±0.40	0.13±.0.02	99.47

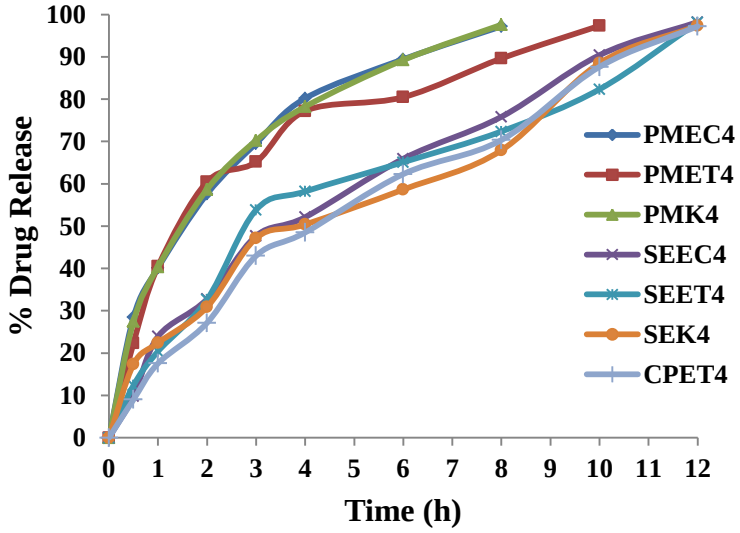


Figure 6: % Drug release profiles of formulations (Drug: Polymer ratio= 1: 2)

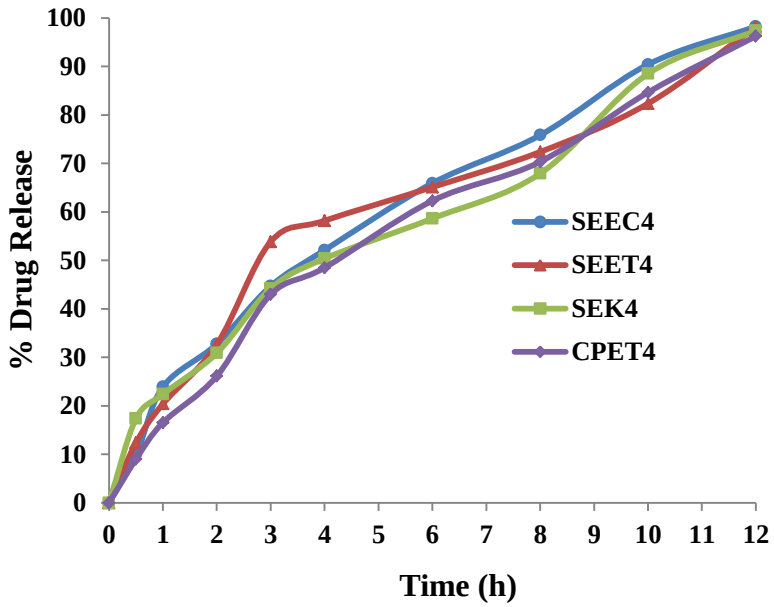


Figure 7: % Drug release profiles of optimized (SEEC4, SEET4, SEK4 and CPET4) formulations

Kinetic studies

Table 6: Kinetics data for matrix tablets with Drug to Polymer ratio is 1:0.5

	PMEC1	PMET1	PMK1	SEEC1	SEET1	SEK1	CPET1
Zero Order	0.900	0.777	0.815	0.880	0.753	0.908	0.922
First Order	0.968	0.917	0.998	0.901	0.979	0.952	0.938
Higuchi model	0.998	0.930	0.977	0.985	0.934	0.992	0.996
Hixon crowell	0.997	0.880	0.977	0.961	0.927	0.982	0.984
Peppas model	0.998	0.877	0.961	0.975	0.884	0.986	0.992
‘ n’ Value	0.503	0.543	0.426	0.419	0.516	0.489	0.413

Table 7: Kinetics data for matrix tablets with Drug to Polymer ratio is 1:1

	PMEC2	PMET2	PMK2	SEEC2	SEET2	SEK2	CPET2
Zero Order	0.816	0.708	0.808	0.903	0.792	0.913	0.953
First Order	0.995	0.967	0.997	0.958	0.982	0.924	0.890
Higuchi model	0.974	0.918	0.974	0.988	0.954	0.993	0.986
Hixon crowell	0.969	0.928	0.967	0.985	0.948	0.984	0.971
Peppas model	0.956	0.907	0.979	0.970	0.987	0.985	0.985
‘n’ Value	0.434	0.414	0.436	0.461	0.539	0.480	0.593

Table 8: Kinetics data for matrix tablets with Drug to Polymer ratio is 1:1.5

	PMEC3	PMET3	PMK3	SEEC3	SEET3	SEK3	CPET3
Zero Order	0.781	0.707	0.823	0.919	0.890	0.910	0.974
First Order	0.987	0.953	0.986	0.826	0.983	0.977	0.830
Higuchi model	0.957	0.911	0.974	0.995	0.991	0.991	0.977
Hixon crowell	0.973	0.903	0.965	0.942	0.983	0.993	0.940
Peppas model	0.940	0.898	0.949	0.995	0.987	0.986	0.983
‘n’ Value	0.474	0.406	0.465	0.515	0.539	0.486	0.596

Table 9: Kinetics data for matrix tablets with Drug to Polymer ratio is 1:2

	PMEC4	PMET4	PMK4	SEEC4	SEET4	SEK4	CPET4
Zero Order	0.840	0.798	0.838	0.951	0.908	0.958	0.962
First Order	0.984	0.954	0.975	0.891	0.824	0.867	0.905
Higuchi model	0.975	0.961	0.982	0.991	0.978	0.981	0.922
Hixon crowell	0.955	0.957	0.983	0.974	0.926	0.948	0.972
Peppas model	0.975	0.943	0.975	0.975	0.972	0.986	0.990
'n' Value	0.518	0.455	0.492	0.676	0.632	0.548	0.734

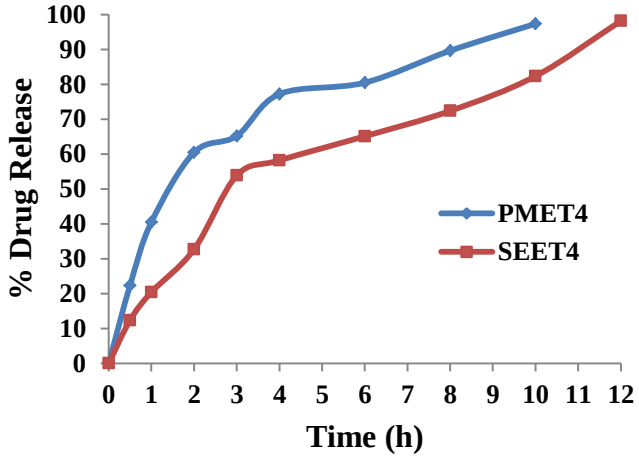
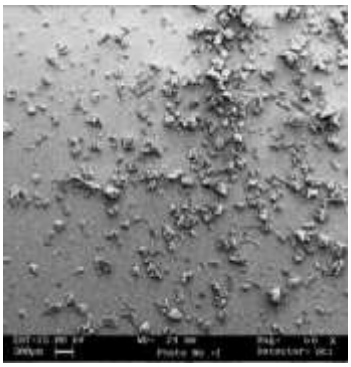


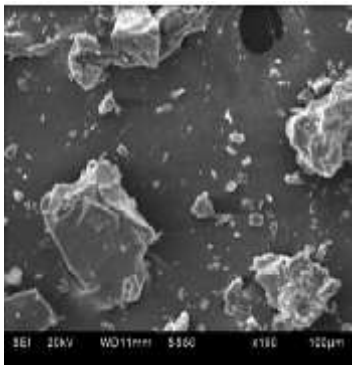
Figure 8: % Drug release profiles of optimized formulations (PMET4 and SEET4)

a)

b)



c)



d)

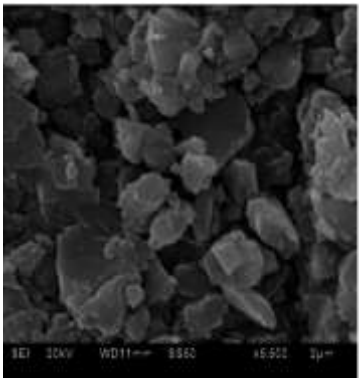


Figure 9: SEM Images of a) Pure Diltiazem b) Pure Eudragit and optimized formulations c) PMET4; d) SEET4

CONCLUSION

The *in vitro* drug release study revealed that the tablets prepared by dispersion technique have extended the release rate for 12 h whereas the tablets prepared by physical mixing technique at the same concentration have extended the release rate only up to 8 h. The *in vitro* release profile and the mathematical models indicate that release of diltiazem Hydrochloride can be effectively controlled from a tablet containing polymeric dispersion of Eudragit RSPO.

REFERENCES

1. Sahoo J, Murthy PN, Biswal S, Manik. Formulation of Sustained-Release Dosage Form of Verapamil Hydrochloride by Solid Dispersion Technique Using Eudragit RLPO or Kollidon®SR. AAPS PharmSciTech, 2009;10(1), 27-33.
2. Elliott WJ. Circadian variation in the timing of stroke onset. A meta-analysis. Stroke. 1998; 29:992–996.
3. Gallerani M, Manfredini R, Ricci L, Grandi E, Cappato R, Calò G, Pareschi PL, Fersini C. Sudden death from pulmonary thromboembolism: chrono biological aspects. Eur Heart J 1992; 6:305–323.
4. Navin D, Sheo Dutt M, Bhanu Sagar PS. Sustained release drug delivery system. Indian J Res Pharm Biotechno 2013; 1(3):305-310.
5. Sandeep Singh T. Formulation and Evaluation Of Sustain Release Matrix Tablets of Levosulpiride. Res J Pharma Biological Chemical Sci 2013; 4(2):1326-1335.
6. Hareesh Reddy M, Sambasiva Rao A. A review of oral matrix type controlled drug delivery system. Indo Am J Pharma Sci 2015; 2(5):937-946.
7. Manish JC, Satish Patel A. A Concise Review on Sustained Drug Delivery System and Its Opportunities. Am. J. PharmTech Res., 2012; 2(2):227-238.
8. Milind PW, Jatin SP. Biopharmaceutical classification system: scientific basis for biowaiver extensions. Int J Pharm Pharma Sci 2010; 2(1):12-19.
9. Diltiazem HCl in: Therapeutic Drugs, Vol. I, Sir Collin Dollery (Eds.), Churchill Livingstone, London, 1991; 143-147.
10. Chaffman M, Brogden RN. Diltiazem- a review of its pharmacological properties and therapeutic efficacy, Drugs. 1985; 29, 387-454.
11. Siddiqui AI, Bakde BV, Tappar KK. Floating strategy for low absorption window diltiazem hydrochloride. Int J Pharm Technology. 2011; 3(1): 1893-1903.

12. Suraj SK , Meghana SK , Omkar RM , Varsha GB, Pravin PA, Pravin DC , Ashok V. Bhosale. Optimization of floating osmotic drug delivery system of diltiazem hydrochloride using 3^2 factorial designs. . Indo Am J Pharma Res 2013:3(6):4585-4593.
13. Raghukiran CVS, Vamshi Krishna J. Preparation & evaluation of cellulose matrices for sustained release of diltiazem Hcl. Indo Am J Pharma Res 2014; 4 (6):2799-2808.
14. Joshi HN, Tejwani RW, Davidovich M, Sahasrabudhe VP, Jemal M, Bathala MS, Varia SA, Serajuddin ATM. Bioavailability enhancement of a poorly water soluble drug by solid dispersion in polyethylene glycol-polysorbate 80 mixture. Int J Pharm, 2004; 269(1):251-258.
15. Dannenfelser RM, He H, Joshi Y, Bateman S, Serajuddin ATM. Development of clinical dosage forms for a poorly water soluble drug I: application of polyethylene glycol-polysorbate 80 solid dispersion carrier system. J Pharm Sci, 2004; 93(5):1165-1175.
16. Kennedy M, Hu J, Gao P, Li L, Ali-Reynolds A, Chal B, Gupta V, Ma C, Mahajan N, Akrami A, Surapaneni S. Enhanced Bioavailability of a Poorly Soluble VR1 Antagonist Using an Amorphous Solid Dispersion Approach: A Case Study. Mol Pharm, 2008; 5(6):981-993.
17. Harsha INS, Lohithasu D ,Manohar Babu K, Madhu G , Lavanya K, Krishna Swaroop K. Formulation and characterization of piroxicam liquisolid technique for solubility enhancement. World J Pharm Pharma Sci 2014; 3(3):1393-1404.
18. Lakshmana Prabu S, Shirwaikar AA, Shirwaikar A, Ravikumar G, Kumar A, Jacob A. Formulation and evaluation of oral sustained release of Diltiazem Hydrochloride using rosin as matrix forming material. Ars Pharm, 2009; 50(1):32-42.