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PREPARATION AND CHARACTERIZATION OF DILTIAZEM HYDROCHLORIDE TABLETS FOR CONTROLLED RELEASE

[1]Mohammad khaja, [2]Zeenath Ruhy
[1]Mother Teresa College of Pharmacy

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Abstract:
The aim of the present study was to prepare and characterize controlled-release matrix tablets of Diltiazem hydrochloride using various viscosity grades of hydrophilic polymers and hydrophobic polymers in three different proportions were prepared by wet granulation method and subjected to in vitro drug release studies. The studies shows that formulation of drug with polymers like hydrophilic HPMC K4M >HPMC K15M >HPMC K100M and hydrophobic polymers like Eudragit RL100 >Eudragit RS100> Ethyl cellulose showed the drug release in decreasing order. Among that D1C which containing HPMC K100M with ethyl cellulose in the ratio of 1:2 showed the best controlled release of diltiazem hydrochloride. Thus the above study clearly indicated that diltiazem HCl may be formulated as Controlled release tablets using HPMC K100M with ethyl cellulose by wet granulation method which will provide continuous release of drug at a predetermined rate and for a predetermined time.

Keywords: *Controlled release, Matrix tablets, Diltiazem hydrochloride, Wet granulation method.*

Corresponding author:
Mohammad khaja,
M. Pharmacy, Department of Pharmaceutics
Mother Teresa College of Pharmacy, Ghatkesar, NFC Nagar
Hyderabad, Telangana, India.
E-mail: khaja4242@gmail.com

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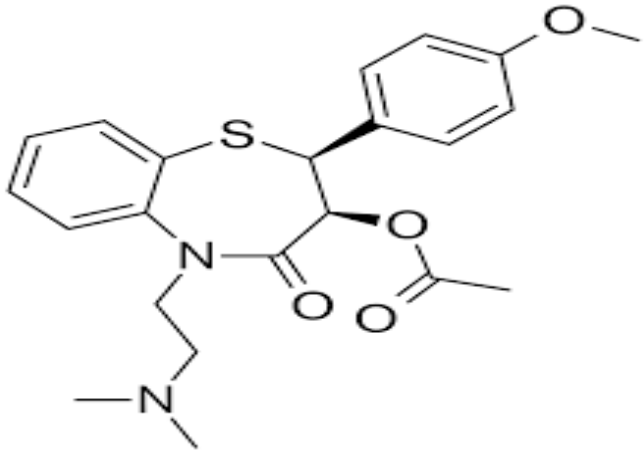
INTRODUCTION:

Oral route is the most preferred route for administration of drugs. Tablets are the most popular oral formulations available in the market and preferred by the patients and physicians alike. In long-term therapy for the treatment of chronic disease conditions, conventional formulations are required to be administered in multiple doses, and therefore have several disadvantages [1]. Controlled release (CR) tablet formulations are much desirable and preferred for such therapy because they offer better patient compliance, maintain uniform drug levels, reduce dose and side effects, and increase safety margin for high potency drugs [2]. Controlled release products are designed to maintain constant therapeutic plasma concentration of the drug within the therapeutic range of the drug over prolonged periods [3]. Matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e., hydrophilic polymers [4]. Matrix technologies have often proven popular among the oral controlled drug delivery technologies because of their simplicity, ease in manufacturing, high level of reproducibility, stability of the raw materials and dosage form and ease of scale-up and process validation [5]. Diltiazem hydrochloride is a widely used as a calcium channel blocking agent. It has a short biological half-life of 3-4.5 hrs and it is rapidly eliminated from the body. Its effects last only for few hours and hence it needs to be administered 3 to 4 times a day. Diltiazem is completely absorbed in gastrointestinal tract but exhibits very low oral bioavailability due to extensive first pass metabolism in the liver by the enzyme CYP3A of cytochrome P450 enzyme group. Hence there is every need for formulating a sustained release dosage form for Diltiazem hydrochloride to improve its therapeutic efficacy and patient compliance [6-9].

Figure 1: Chemical structure of Diltiazem



The aim of the present study was to prepare and characterize controlled-release matrix tablets of Diltiazem hydrochloride using various viscosity grades of hydrophilic polymers and hydrophobic polymers in three different proportions were prepared by wet granulation method and subjected to in vitro drug release studies.

MATERIALS:

Diltiazem hydrochloride Purchased from Dr.Reddy's (Hyderbad,India). HPMCK4M, HPMCK15M, HPMCK100M from Colorcon, Goa. EDGT RS 100, EDGT RL 100 from Evonik Degussa India Pvt Ltd, Mumbai. Lactose monohydrate, MCC from S.D. Fine Chem. Limited, Mumbai, India.

METHODOLOGY:

Determination of λ_{max} of Diltiazem Hydrochloride in distilled water:

Stock solution: Diltiazem Hydrochloride in distilled water **(**100 mg in 100 ml) **Scanning**: From the stock solution, a suitable concentration of Diltiazem Hydrochloride (10 µg / ml) was prepared in distilled water and UV scan was takenfor the above stock solutions between the wavelengths of 200- 400 nm.. The absorption maximum was found to be 236 nm and this wavelength was selected and utilized for further studies.

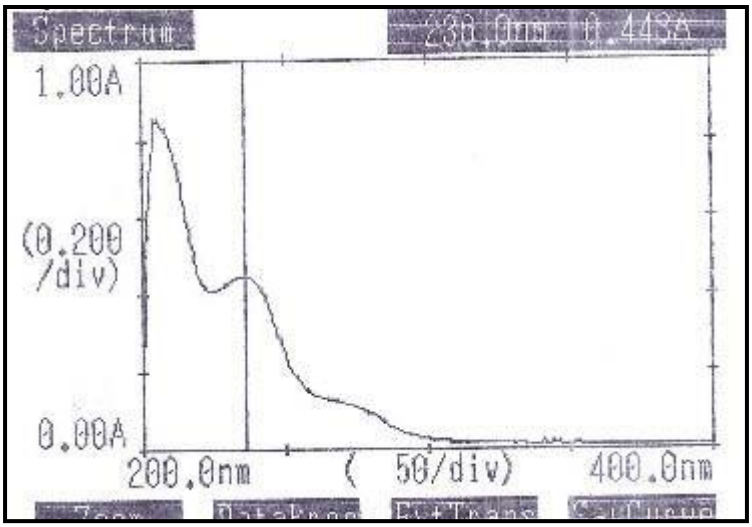


Figure 2: UV spectrum of Diltiazem Hydrochloride in distilled water.Preparation of Calibration Curve of Diltiazem HydrochlorideConstruction of Calibration Curve:

Spectrophotometric Method for the Estimation of Diltiazem Hydrochloride:

The standard curve of diltiazem HCl was prepared in distilled water.

Procedure:
Standard Solution: Accurately weighed 100 mg of diltiazem hydrochloride was dissolved in 100 ml of distilled water to give a concentration of 1 mg/ ml.

Stock Solution: From the standard solution, a stock solution was prepared to give a concentration of 100 mcg/ ml in distilled water. Aliquots of 0.3, 0.6, 0.9, 1.2 and 1.5 ml were pipetted out into 10 ml volumetric flask. The volume was made up to the mark with distilled water. These dilutions give 3, 6, 19, 12, 15 mcg/ ml. Concentration of diltiazem hydrochloride respectively. The absorbance of prepared solutions of diltiazem hydrochloride in distilled water were measured at 236 nm respectively in Shimadzu UV- 1700 spectrophotometer against appropriate blank.
The absorbance data for standard calibration curves are given in table-4.3. Thestandard calibration curve yields a straight line, which shows that the drug follows Beer's law in the concentration range at 3 to 15 mcg/ ml.

Table 1: Standard graph of Diltiazem Hydrochloride in distilled water

Conc. in µg/ml	**Absorbance mean ± SD***
0	0
3	0.132±0.004
6	0.276±0.002
9	0.409±0.001
12	0.545±0.000
15	0.672±0.001

*** Standard deviation n = 3**

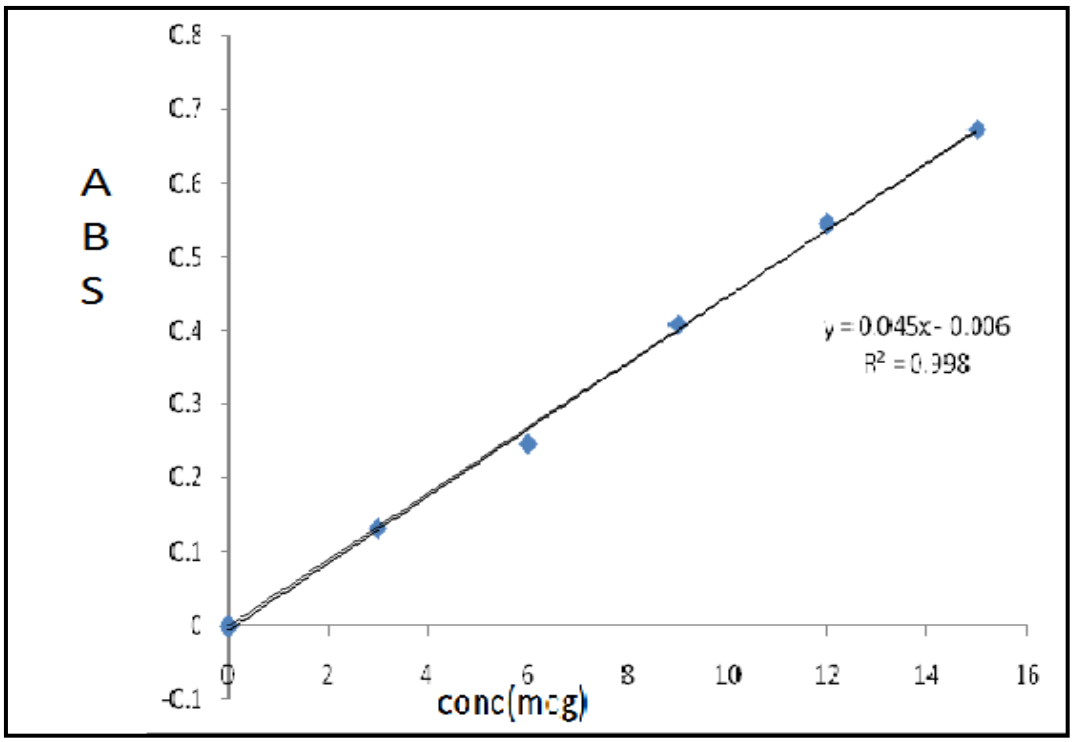


Figure 3: Calibration curve of Diltiazem Hydrochloride in distilled water.

Preparation of matrix tablets:

In the present work, wet granulation method has been used to prepare matrix tablets of Diltiazem hydrochloride in different ratios of both hydrophilic and hydrophobic polymers along with drug and other excipients like lactose , microcrystalline cellulose and IPA as solvent used in granulation. Magnesium stearateused as glidant and lubricant.

All the weighed ingredients were passed through 80 mesh sieve ,separately weighed quantity of diltiazem hydrochloride and the all excipients as given in table except lubricants were mixed geometrically with mortor and pestle.

The mixed powder is converted into damp mass by using IPA as granulating agent, the obtained mass is passed through 22 mesh sieve and the obtained granules were kept in hot air oven for drying. After dried granules were again passed through 44 sieve , to obtaining uniform granules, and finally magnesium stearate was added and mixed.

The desired amount of blend was compressed into tablets by using tablet compression machine (Rimek tablet machine , minipress) equipped with 8.4 mm tooling of plain face on lower punch and a center break line on upper punch. Before compression , the surfaces of the die and punch were lubricated with magnesium stearate. All the preparations were stored in airtight container at room temperature for further study.

Table 2: Formulation code in matrix tablets of Diltiazem hydrochloride :polymer(1:1) ratio.

System	Formulation code
DH : HPMCM K4M + EC	S1A
DH: HPMC K4M + EGT RS100	S2A
DH : HPMC K4M + EGT RL100	S3A
DH : HPMC K15M + EC	M1A
DH: HPMC K15M + EGT RS100	M2A
DH : HPMC K15M + EGT RL100	M3A
DH : HPMC K100M + EC	D1A
DH: HPMC K100M + EGT RS100	D2A
DH: HPMC K100M + EGT RL100	D3A

Table 3: Formulation code in matrix tablets of Diltiazem hydrochloride : polymer(1:1.5) ratio

System	Formulation code
DH : HPMCM K4M + EC	S1B
DH: HPMC K4M + EGT RS100	S2B
DH : HPMC K4M + EGT RL100	S3B
DH : HPMC K15M + EC	M1B
DH: HPMC K15M + EGT RS100	M2B
DH : HPMC K15M + EGT RL100	M3B
DH : HPMC K100M + EC	D1B
DH: HPMC K100M + EGT RS100	D2B
DH: HPMC K100M + EGT RL100	D3B

Table 4: Formulation code in matrix tablets of Diltiazem hydrochloride : polymer(1:2) ratio.

System	Formulation code
DH : HPMCM K4M + EC	S1C
DH: HPMC K4M + EGT RS100	S2C
DH : HPMC K4M + EGT RL100	S3C
DH : HPMC K15M + EC	M1C
DH: HPMC K15M + EGT RS100	M2C
DH : HPMC K15M + EGT RL100	M3C
DH : HPMC K100M + EC	D1C
DH: HPMC K100M + EGT RS100	D2C
DH: HPMC K100M + EGT RL100	D3C

Table 5: Composition of matrix tablets of Diltiazem hydrochloride : polymer in(1:1) ratio.(Total weight of each tablet 300 mg)

Ingredient	Formulation code								
	S1A	S2A	S3A	M1A	M2A	M3A	D1A	D2A	D3A
HPMC K4M	45	45	45	-	-	-	-	-	-
HPMC K15M	-	-	-	45	45	45	-	-	-
HPMCK100M	-	-	-	-	-	-	45	45	45
EC	45	-	-	45	-	-	45	-	-
EGT RS 100	-	45	-	-	45	-	-	45	-
EGT RL 100	-	-	45	-	-	45	-	-	45
Lactose	110	110	110	110	110	110	110	110	110
MCC	5	5	5	5	5	5	5	5	5
IPA	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Mg St	5	5	5	5	5	5	5	5	5

Table 6: Composition of matrix tablets of Diltiazem hydrochloride : polymer in(1:1.5) ratio.(Total weight of each tablet 300 mg)

Ingredient	Formulation code								
	S1B	S2B	S3B	M1B	M2B	M3B	D1B	D2B	D3B
HPMCK4M	67.5	67.5	67.5	-	-	-	-	-	-
HPMC K15M	-	-	-	67.5	67.5	67.5	-	-	-
HPMCK100M	-	-	-	-	-	-	67.5	67.5	67.5
EC	67.5	-	-	67.5	-	-	67.5	-	-
EGT RS 100	-	67.5	-	-	67.5	-	-	67.5	-
EGT RL 100	-	-	67.5	-	-	67.5	-	-	67.5
Lactose	65	65	65	65	65	65	65	65	65
MCC	5	5	5	5	5	5	5	5	5
IPA	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Mg St	5	5	5	5	5	5	5	5	5

Table 7: Composition of matrix tablets of Diltiazem hydrochloride : polymer in(1:2) ratio.(Total weight of each tablet 300 mg)

Ingredient	Formulation code								
	S1C	S2C	S3C	M1C	M2C	M3C	D1C	D2C	D3C
HPMC K4M	90	90	90	-	-	-	-	-	-
HPMC K15 M	-	-	-	90	90	90	-	-	--
HPMC K100M	-	-	-	-	-	-	90	90	90
EC	90	-	-	90	-	-	90	-	--
EGT RS 100	-	90	-	-	90	-	-	90	-
EGT RL 100	-	-	90	-	-	90	-	-	90
Lactose	20	20	20	20	20	20	20	20	20
MCC	5	5	5	5	5	5	5	5	5
IPA	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Mg St	5	5	5	5	5	5	5	5	5

RESULTS AND DISCUSSION:

Analysis of drug:

Description: Visual inspection of drug revealed that drug is done

property	observation
Organoleptic properties	A white, odorless, crystalline powder andhas a bitter taste

Melting point: It was found to be 212^0c

Fourier Transformed Infrared (FT-IR) Spectroscopic Analysis:

Figure 4: IR specta of pure diltiazem hydrochloride

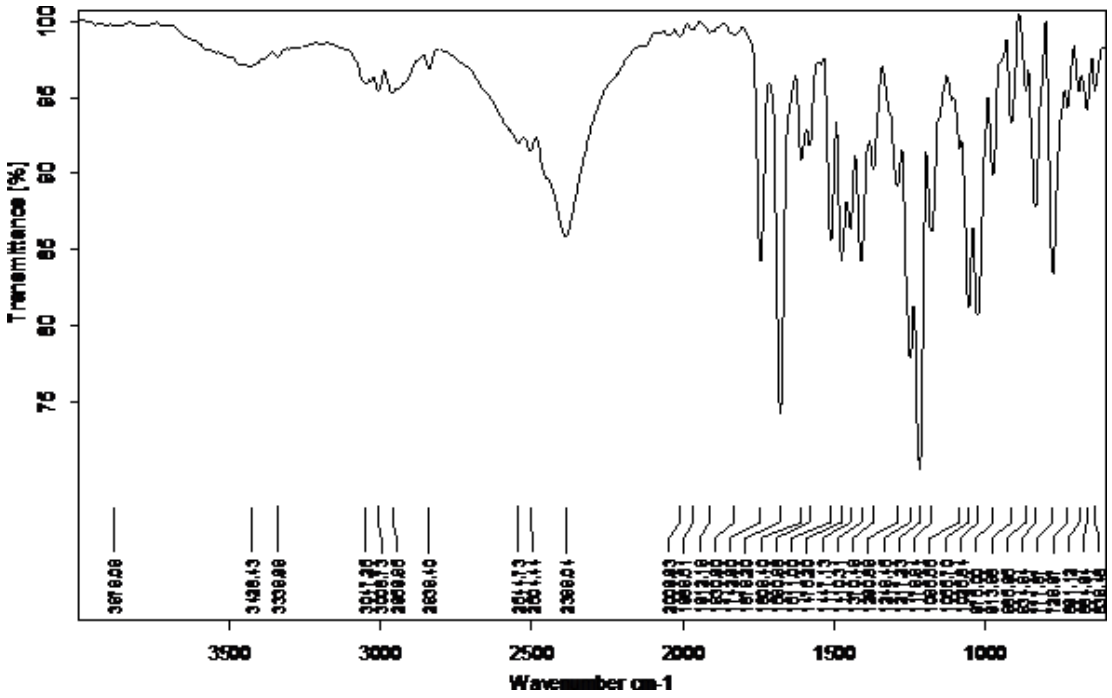


Table 8: Evaluation of pre-compression parameters of matrix tablets of Drug:polymer(1:1) ratio.

Code	Bulk density (g/ml)	Tapped density(g/ml)	Bulkiness untapped(ml/g)	Bulkinesstapped (ml/g)	Carr's index (%)	Angle of repose ( )
S1A	0.5403	0.6385	1.8500	1.5660	15.37	29.24
S2A	0.4368	0.4992	2.2893	2.0032	12.50	33.11
S3A	0.4482	0.5122	2.2311	1.9523	12.49	27.47
M1A	0.4511	0.5552	2.2100	1.8000	18.75	24.62
M2A	0.5147	0.6005	1.9420	1.6650	14.28	27.64
M3A	0.5200	0.6066	1.9230	1.6485	14.27	36.46
D1A	0.4481	0.5121	2.2316	1.9527	12.49	29.24
D2A	0.5155	0.6015	1.9398	1.6625	14.29	32.47
D3A	0.4095	0.4336	2.4420	2.3062	5.55	29.98

Table 9*: In-vitro* drug release from formulation S1A

Time (Hrs.)	Square Root of time	Log time	Cumulative drug release	Cumulative Percentage Drug release	Cumulative Percentage drug remain	Log Cumulative Percentage drug release	Log Cumulative Percentage Drug remain
1	1.0000	0.0000	20.0948	22.3251	77.6749	1.3487	1.8902
2	1.4142	0.3010	21.8246	24.2443	75.7557	1.3846	1.8794
3	1.7320	0.4771	24.5474	27.2667	72.7333	1.4419	1.8617
4	2.0000	0.6020	30.3085	33.6642	66.3358	1.5277	1.8217
5	2.2360	0.6989	32.9925	36.6424	63.3576	1.5639	1.8017
6	2.4494	0.7781	42.4678	47.1652	52.8348	1.6736	1.7729
7	2.6457	0.8450	48.4295	53.7833	46.2167	1.7306	1.6647

8	2.8284	0.9030	58.6213	65.1003	34.8997	1.8135	1.5428
9	3.0000	0.9542	65.7961	73.0642	26.9358	1.8637	1.4303
10	3.1622	1.0000	75.6920	84.0503	15.9497	1.9245	1.2027
11	3.3166	1.0413	81.6772	90.6904	9.3096	1.9575	0.9687
12	3.4641	1.0791	87.6631	97.3306	2.6694	1.9882	0.4264

Table 10*: In-vitro* drug release from formulation M1A

Time (Hrs.)	Square Root of time	Log time	Cumulative drug release	Cumulative Percentage drug release	Cumulative Percentage Drug remain	Log Cumulative Percentage drug release	Log Cumulative Percentage drug remain
1	1.0000	0.0000	18.88582	20.98191	79.01809	1.321845	1.897727
2	1.4142	0.3010	20.95082	23.27377	76.72623	1.366867	1.884944
3	1.7320	0.4771	22.74024	25.25921	74.74079	1.40242	1.873558
4	2.0000	0.6020	27.58778	30.64196	69.35804	1.486317	1.841097
5	2.2360	0.6989	30.07292	33.39951	66.60049	1.52374	1.823477
6	2.4494	0.7781	37.95933	42.15751	57.84249	1.624875	1.762247
7	2.6457	0.8450	42.21286	46.87845	53.12155	1.670973	1.725271
8	2.8284	0.9030	50.55732	56.14383	43.85617	1.749302	1.642031
9	3.0000	0.9542	61.82163	68.65211	31.34789	1.836654	1.496208
10	3.1622	1.0000	70.44627	78.22634	21.77366	1.893353	1.337931
11	3.3166	1.0413	79.15128	87.88882	12.11118	1.943934	1.083187
12	3.4641	1.0791	85.67304	95.12464	4.875358	1.978293	0.688007

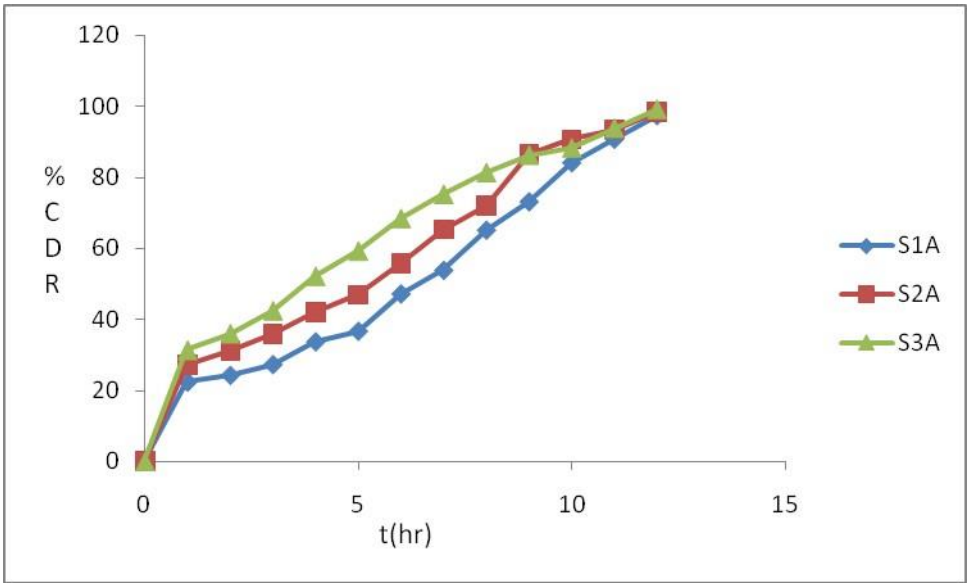


Figure 5: Cumulative percentage drug release of Diltiazem hydrochloride from formulation S1A, S2A and S3A.

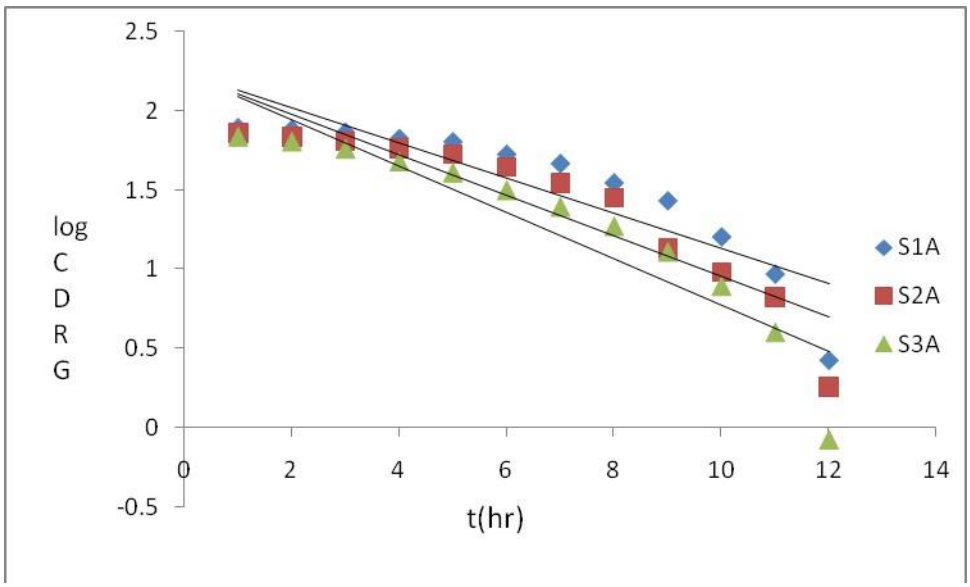


Figure 6: First order plots of Diltiazem hydrochloride from formulation S1A, S2A and S3A.

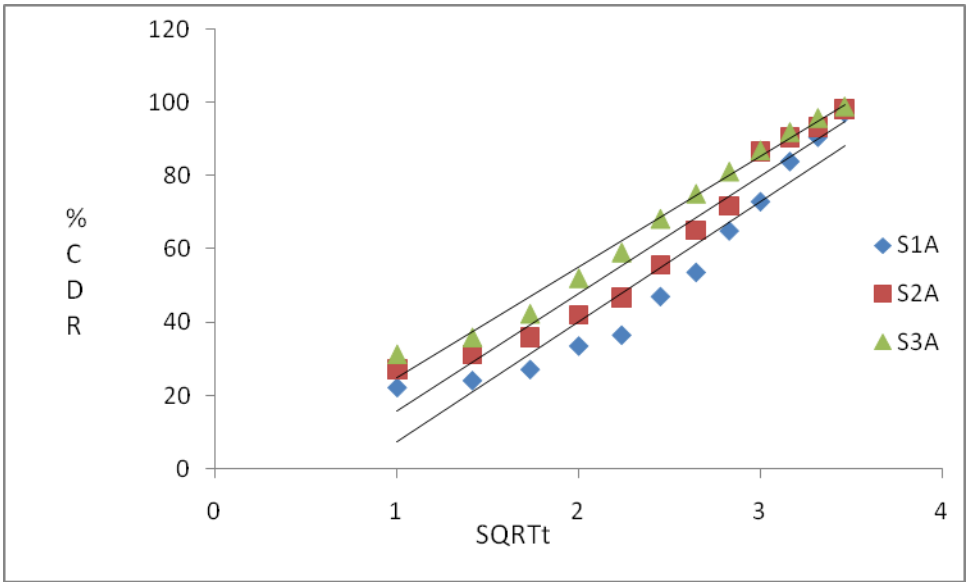


Figure 7: Huguchi order plots of Diltiazem hydrochloride formulation S1A, S2A and S3A

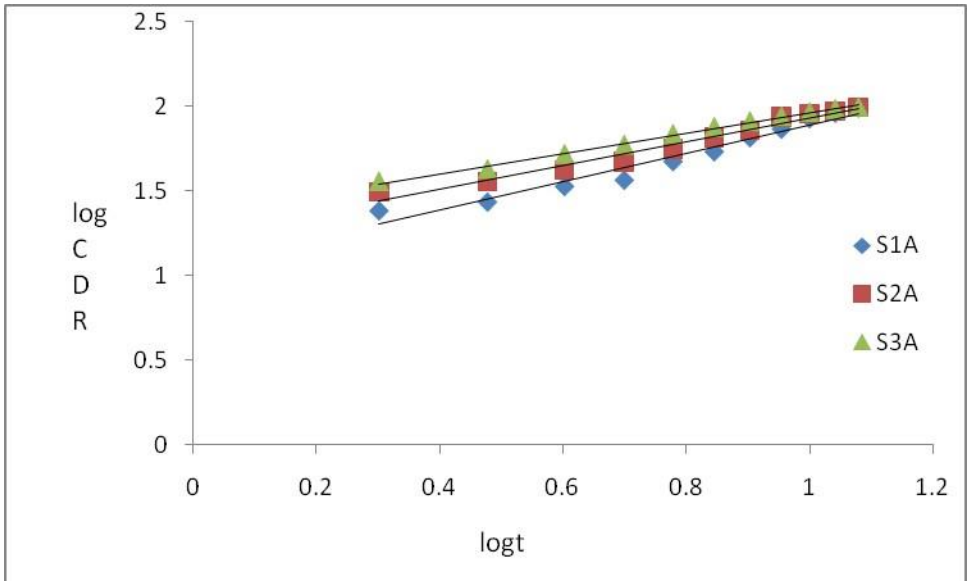


Figure 8: Peppas order plots of Diltiazem hydrochloride formulation S1A, S2A and S3A

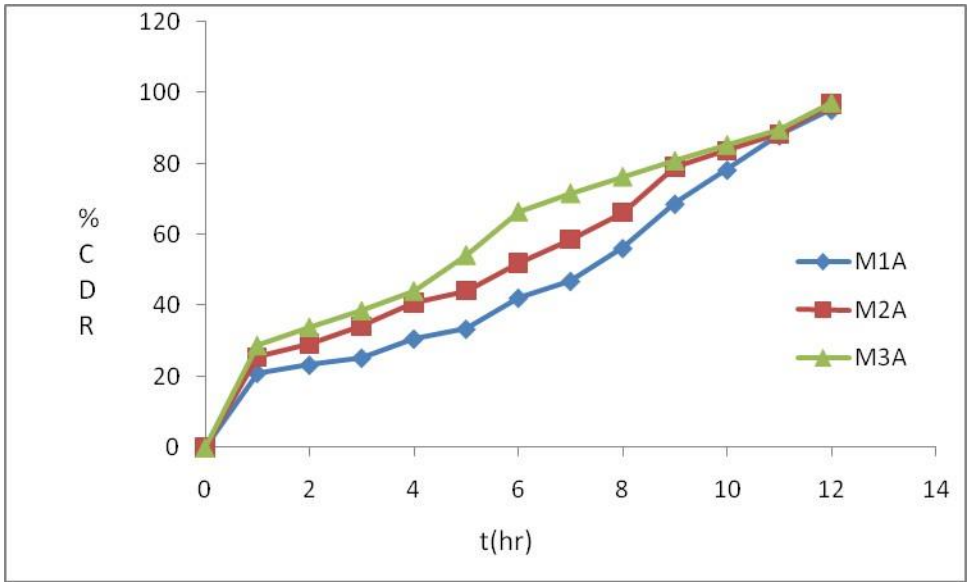


Figure 9: Cumulative percentage drug release of Diltiazem hydrochloride from formulation M1A, M2A and M3A.

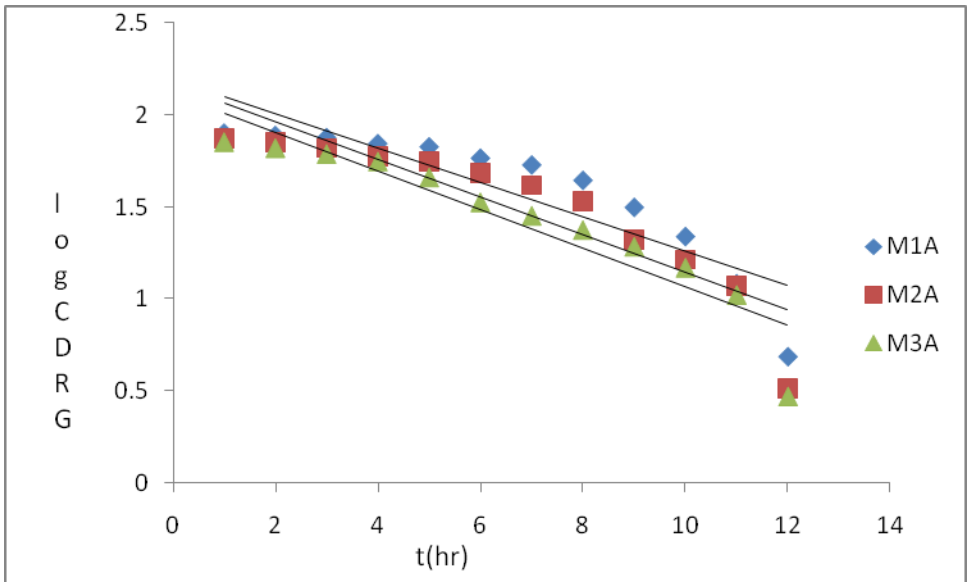


Figure 10: Frist order plots of Diltiazem hydrochloride from formulation M1A, M2A and M3A.

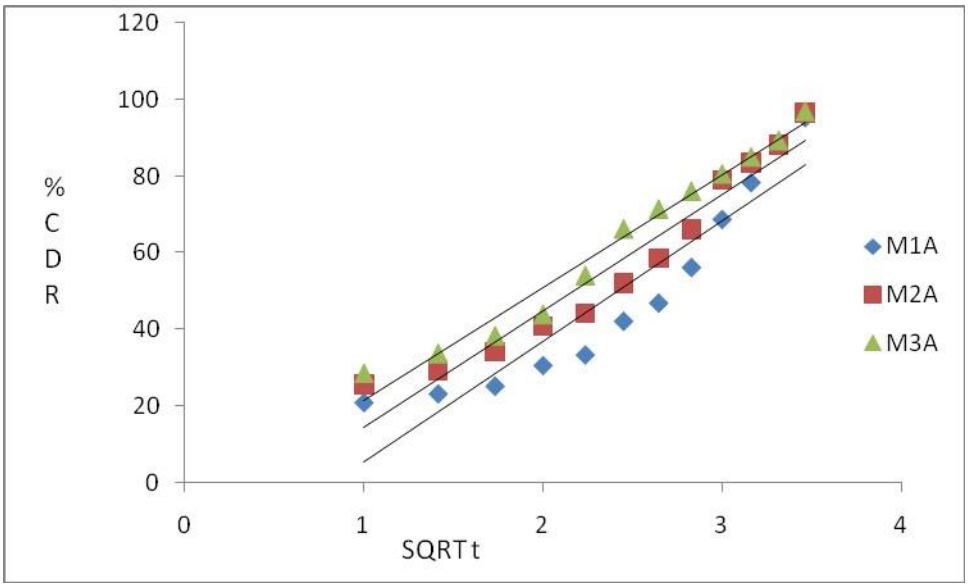


Figure 11: Hihuchi order plots of Diltiazem hydrochloride from formulation M1A, M2A and M3A.

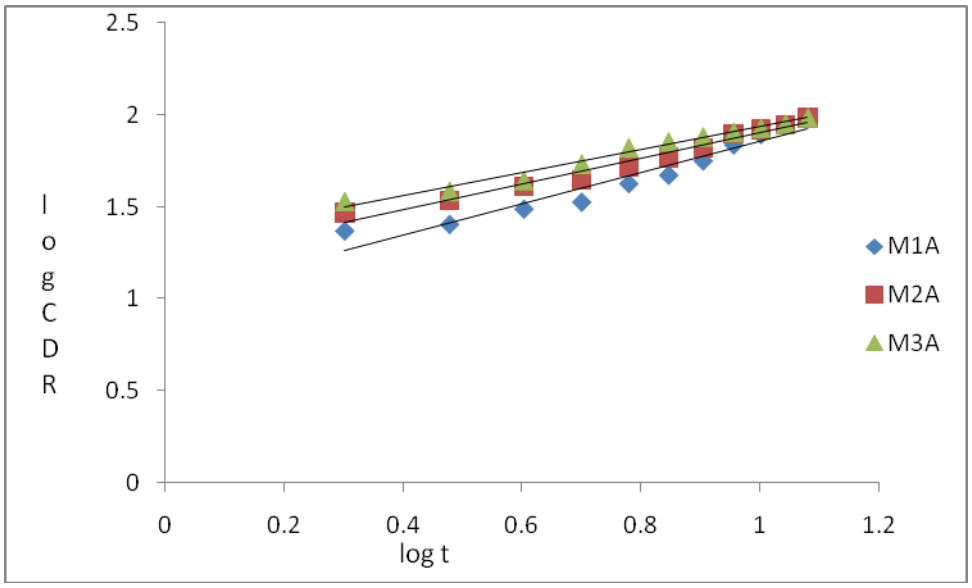


Figure 12: Peppas order plots of Diltiazem hydrochloride formulation M1A, M2A and M3A

In the present work , an attempt has been made to prepare controlled release matrix tablets of diltiazem hydrochloride , a calcium channel blocking agent using hydrophilic polymers like various grades of HPMC (K4M, K15M, K100M) and hydrophobic polymers of EC, EGT RS100 and EGT RL100 along with diluents lactose, microcrystalline cellulose, magnesium stearate as glidant and IPA as granulating agent by wet granulation method. The prepared tablets were tested for physical parameters like, hardness, weight variation, thickness, friability, drug content, in-vitro drug release study. Hardness of the tablets was found to be in the range of 8.0 to 9.5 kg/cm2 . The friability of all the formulations was found to be 0.05 %(not more than 1%) given.Drug content estimation data for all formulations are given in the table no: 11 to 13.It was found to be in the range of 97.13 to 99.38% with low values of standard

deviation, indicates uniform drug content in the prepared tablets. Drug excipients interactions were characterized by IR spectroscopy studies, the IR spectrum of diltiazem hydrochloride and drug with polymers mixture. The IR spectrum of diltiazem hydrochloride shows that characteristics peaks at 1055.70 cm-1 is due to alkyl aryl ether linkage, peak at 1742.90 cm-1 is due to c = o stretching of ester structure, confirms the drug structure. The drug is in the form of hydrochloride salt.IR specrum of diltiazem hydrochloride pure, physical mixture of polymers were taken , the IR spectras obtained indicates good compatability between drug and polymers. Effect of different type, grade and level of polymer on release profile of drug. Effect of HPMC on release rate of drug. HPMC, which is commomly used in hydrophyllic matrix drug delivery systems, is mixed alkyl hydroxyl alkyl cellulose either containing methoxyl and hydroxyl propyl groups. The hydration rate of HPMC depends on the nature of the these substituents, specifically ,the hydration rate of HPMC increases with increase in the hydroxyl propyl content. The solubility of HPMC is PH independent. In-vitro dissolution of matrix Diltiazem hydrochloride tablets containing HPMC of various viscosities. The Prepared tablets did not disintegrate, however a gel layer was formed on surface of the tablet due to swelling of HPMC in presence of water. Here concentration of each type of HPMC (K4M, K15M and K100M) was kept (15%, 22.5% , 30%).Formulations containing HPMCK100M showed delayed release as compared to those containing HPMC K4M, HPMCK15M. This revealed that as viscosity of HPMC increased release rate of drug was decreased. HPMC K100M tablets exhibited significant effect on drug release , this might due to more viscosity and high molecular weight of HPMC K100M in addition to its slower rate of erosion and more swelling than HPMC K4M, HPMC K15M . Different ratios of HPMC K4M, HPMC K15M,HPMC K100M with hydrophobic polymers like EC, EGT RS100 and EGT RL100 in the ratios 1:1, 1:1.5, 1:2, with respect to the drug release was retarted with HPMC K100M in concentration of 1:2 up to 90% drug released in 12hrs. The overall drug release is affected by the rate of water uptake and diffusion rate of the drug through the swollen gel being formed. This gel increases the diffusion path length of the drug. Its viscous nature also affects the diffusion coeffient of the drug. As a result reduction in drug release rate is obtained .Drug release from HPMC matrices showed that ,viscosity of polymer plays Important rolein the Retardation of drug release in the following order. HPMCK100M> HPMCK15M> HPMCK4M. Effect of ethyl cellulose, EGT RS100 and EGT RL100 with HPMC on release rate of drug. Drug release studies were observed in case of Ethylcellulose and combination with various viscosity grades of HPMC like K4M, K15M and K100M in the ratio of 1:1, 1:1.5 and 1:2. In an attempt to prolong the release of drug, the concentration of HPMC was increased did not significantly prolong the drug release, faster release of the drug from the hydrophilic matix was probably due to faster dissolution of the highly water soluble drug from the core and its diffusion out of the matrix forming the pores for entry of solvent molecules. Further EC was incorporated in hydrophilic matrix, the matrix could release the drug up to 12hrs only. Incorporation of EC was found to control the drug release to some extent, which could be attributed to the decreased penetration of the solvent molecules, in the presence of hydrophobic polymer leading to decreased diffusion of the drug from the matrix. Combinations of drug and EC with HPMC in different ratio were tried. Ratio of HPMC:EC kept as 1:1, 1:1.5, 1:2. Combination of drug: EC +HPMC K4M kept in the ratio of 1:1, 1:1.5, 1:2, the release was found in the formulations of S1A, S1B, S1C is 97.33%, 95.03% and 92.40% of diltiazem hydrochloride in 12hrs. Combination of drug: EC +HPMC K15M kept in the ratio of 1:1, 1:1.5, 1:2, the release was found in the formulations of M1A, M1B, M1C is 95.12%, 92.91% and 90.49% of diltiazem hydrochloride in 12hrs. Combination of drug: EC +HPMC K100M kept in the ratio of 1:1, 1:1.5, 1:2, the release was found in the formulations of D1A, D1B, D1C is 93.93%, 91.61% and 90.99% of diltiazem hydrochloride in 12hrs. In order to retard drug release the amount of EC was increased .The drug release was decreased up to (1:2) ratios of HPMC : EC. This was found to give the desired controlled release profile for a period of 12 hrs . Hydrophobic polymers , which are capable of forming insoluble or skeleton matrices, have been widely used for controlling the release of drugs due to their inertness and drug embedding ability. Liquid penetration in to the matrix is rate – controlling step in such systems, unless channeling agents are used, eg: EGT RS100 and EGT RL 100. Eudragits (poly methyl methacrylates) are extensively used as release controlling agents. The drug release is slow down in EGT RS100 than in EGT RL100 due to 5% of functional quaternary ammonium groups present in EGT RS 100 and it is low permeability and pH independent. But in case of EGT RL 100 presence of 10% of functional quaternary ammonium groups, high permeability and pH independent.Combinations of drug and EGT RS 100 with HPMC in different ratio were tried. Ratios of HPMC:EGT RS100 up to1:1, 1:1.5, 1:2. Combination of drug: EGT RS100 +HPMC K4M in the ratios of 1:1, 1:1.5, 1:2, the

release was found in the formulations of S2A, S2B, S2C is 98.21%, 97.65% and 95.32% of diltiazem hydrochloride in 12hrs. Combination of drug: EGT RS100 +HPMC K15M in the ratios of 1:1, 1:1.5, 1:2, the release was found in the formulations of M2A, M2B, M2C is 96.73%, 94.71% and 92.87% of diltiazem hydrochloride in 12hrs. Combination of drug: EGT RS100 +HPMC K100M in the ratios of 1:1, 1:1.5, 1:2, the release was found in the formulations of D2A, D2B, D2C is 95.98%, 92.91% and 91.74% of diltiazem hydrochloride in 12hrs Combination of drug: EGT RL100 +HPMC K4M in the ratios of 1:1, 1:1.5, 1:2, the release was found in the formulations of S3A, S3B, S3C is 99.16%, 98.34% and 96.75% of diltiazem hydrochloride in 12hrs.s Combination of drug: EGT RL100 +HPMC K15M in the ratios of 1:1, 1:1.5, 1:2, the release was found in the formulations of M3A, M3B, M3C is 97.02%, 95.08% and 93.75% of diltiazem hydrochloride in 12hrs.Combination of drug: EGT RL100 +HPMC K100M in the ratios of 1:1, 1:1.5, 1:2, the release was found in the formulations of D3A, D3B, D3C is 96.18%, 94.08% and 92.63% of diltiazem hydrochloride in 12hrs.

During dissolution process, it was observed that increase in the amount of hydrophilic polymer in the tablets resulted in a reduction in the drug release rate, all the tablets showed swelling the extent of swelling increased with the increase in the amount of polymer. Drug release from hydrophobic matrices showed that type of polymers plays important role . Retardation of drug release was in the following order. EC> EGT RS 100> EGT RL 100. The in-vitro release data thus obtained was subjected to different kinetic treatments (Zero order, First order, Higuchi and peppas model). The results are shown in Tables respectively. The coefficient of determination (R2) was considered as main parameter for interpreting the release kinetics. For Zero order treatment the R2 values ranged from 0.892 to 0.994 which indicates that, the formulations follow zero order kinetics. The R2 values of first order treatment ranges from 0.659 to 0.890, so no formulations is showing fair linearity in release of drug from the matrices as the R2 values are not satisfactory When the data was subjected to Higuchi treatment the R2 values ranged from 0.795 to 0.985The formulations containing EGT RL100 and HPMC K4M produce fair linearity, R2 values ranging from 0.0.950 to 0.985 further strengthen the statement . When the in- vitro dissolution data was fitted to exponential model, the 'R2' values were found to be in the range of 0.896 to 0.995 , indicating the data fits the exponential model well. The slope (n) values of exponential equation were found to be >0.45 and <1 indicating drug release is governed by non-Fickian diffusion mechanism. stability studies were carried out for formulations like D1A, D1B and D1C,at 250c/60% RH and 400c/75% RH for 30 days. The results of stability studies revealed no change in physical appearance, hardnes ,and drug content, indicating the formulations are stable.

SUMMAY AND CONCLUSION:

Diltiazem hydrochloride is a calcium channel blocking agent used in the treatment of hypertension, which has a short biological half-life of 4.5 hours. Its dose is 30 to 120 mg daily in divided doses. Because of frequent administration and short biological half-life diltiazem hydrochloride is considered as an ideal drug for designing a controlled release formulation. In the present study, an attempt was made to prepare matrix tablets of diltiazem hydrochloride by wet granulation method using HPMC K4M, HPMC K15M, HPMC K100M, EC, EGT RS100 and EGT RL 100 as matrix material with lactose, microcrystalline cellulose and as co-excipients. The matrix tablets of diltiazem hydrochloride by wet granulation method. It is suitable for high dose drugs which have poor flowability, binder which enhance the compressibility, cohesive property of the powder, and the dissolution rate of insoluble drug can be enhanced, it is also suitable for bulky and dust producing powders. The Prepared matrix tablets were evaluated for hardness, friability, weight variation, drug content , in- vitro drug release , drug polymer interactions and short-term stability studies. Increasing the amount of EC in the tablets resulted in the reduction in the drug release rate and linearization of the drug release curve and the release of drug from the formulations was governed by non-Fickian diffusion mechanism. In IR spectrum of diltiazem hydrochloride pure and physical mixture of drug and the polymers indicates good compatability between drug and polymer.During dissolution process, it was observed that increase in the amount of polymer in the tablets resulted in a reduction in the drug release rate up to 1:2 ratios. Drug release from HPMC matrices showed that viscosity of polymer plays Important role. Retardation of drug release was in following order. HPMCK100M> HPMCK15M> HPMCK4M.Drug release from hydrophobic matrices showed that type of polymers plays important role . Retardation of drug release was in the following order. EC> EGT RS 100> EGT RL 100. Overall the curves fitting into various kinetic models confirmed that in-vitro release kinetics of all formulations was best fitted into zero order model and Higuchi model. The n values more than 0.5 indicates that the mechanism in which the drug release from matrices follow non-fickian diffusion mechanism.

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