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Preparation and Characterization of Diltiazem Hydrochloride Matrix Tablets

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ABSTRACT

Developing oral controlled release tablets for highly water-soluble drugs with constant release rate has always been a challenge to the pharmaceutical technologist. The present work is focused on the effect of ethyl cellulose (EC), eudragit RS 100 and Eudragit RL 100 in controlling the release of highly water-soluble drug Diltiazem Hydrochloride from hydrophilic matrices prepared using Hydroxypropyl methylcellulose (HPMC) in various grades. Tablets were prepared by wet granulation method and all the batches of tablets were evaluated for thickness, hardness, and friability. *In vitro* dissolution in 900 ml of distilled water for a period of 12 hours using USP type II dissolution apparatus. The mechanism of drug release was analyzed using various kinetics models like zero order, first order, Higuchi and Korsmeyer-Peppas equations. Release profiles indicated that polymer type, increasing the polymer concentration has drastically retarded the release of diltiazem hydrochloride. Matrix tablets prepared with combination of hydrophilic and hydrophobic polymers namely HPMC K100M and Ethyl cellulose gave controlled release of drug over a period of 12h. The mechanism of drug release from all the matrix tablets followed Non-Fickian diffusion as n values lies between of 0.896 to 0.995 indicating that polymer swelling and relaxation were both involved in the release process. The results of the study revealed that, matrix tablets prepared using HPMC alone could not efficiently control the release of highly water-soluble drug diltiazem Hcl. The combination of hydrophobic polymers in hydrophilic matrices gave a controlled release over a period of 12hrs.

Keywords: Diltiazem Hydrochloride, Matrix tablets, Wet granulation, Controlled release, Non-Fickian diffusion.

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INTRODUCTION

The designing of sustained or controlled delivery systems 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 provide uniform drug delivery. So, controlled release dosage form is that which releases one or more drugs continuously in a predetermined pattern for a fixed period of time, either systemically or to a specified target organ. Controlled release dosage forms provide a better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery. In Pharmaceutical practice several approaches exist for administration of drugs to the patients. If the drug is given in conventional dosage form, it has to be administered several times a day, to produce the desired therapeutic effect. Because of frequent dosing, fluctuations in plasma drug level occur. The pronounced fluctuations resulting from the conventional drug administration are likely to yield period of therapeutic effects, when the drug concentration falls below the minimum therapeutic level. [1]

Matrix Tablets are the type of controlled drug delivery systems, which release the drug in continuous manner by both dissolution controlled as well as diffusion controlled mechanisms. To control the release of the drugs, which are having different solubility properties, the drug is dispersed in swellable hydrophilic substances, an insoluble matrix of rigid non swellable hydrophobic materials or plastic materials. [2,3]

Introduction of matrix tablet as sustained release (SR) has given a new breakthrough for novel drug delivery system (NDDS) in the field of Pharmaceutical technology. It excludes complex production procedures such as coating and pelletization during manufacturing and drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the preparations. Hydrophilic polymer matrix is widely used for formulating an SR dosage form [4-5]. Because of increased complication and expense involved in marketing of new drug entities, has focused greater attention on development of sustained release or controlled release drug delivery systems. [6]

Matrix systems are widely used for the purpose of sustained release. It is the release system which prolongs and controls the release of the drug that is dissolved or dispersed. In fact, a matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers. [7]

Diltiazem hydrochloride (diltiazem HCl), a calcium channel blocker, is widely used in the management of angina pectoris and hypertension. Because of its short biological half-life (3.5 hr) and low oral bioavailability (40%) due to hepatic metabolism leading to high frequency drug dosing, the continuous delivery of diltiazem HCl is required. [8]

Recently, controlled release drug delivery has become the standards in the modern pharmaceutical design and intensive research has been undertaken in achieving much better drug product effectiveness, reliability and safety. Oral sustain release drug delivery medication

will continue to account for the largest share of drug delivery systems. Hence in this work to formulate tablets in order to avoid the first pass metabolism and increase the bioavailability. Hence in this work an attempt was made to formulate sustain/controlled release system for in order to achieve even plasma concentration profile up to 12 hrs. [9]

MATERIALS AND METHODS

Diltiazem HCl as a gift sample from Dr. Reddy's lab (Hyderabad, India). HPMC (K4M, K15M, and K100M) procured from Colorcon, Goa. Eudragit (RS100 and RL100) gifted by Evonik Degussa India Pvt Ltd, Mumbai. All other chemicals used were of analytical grade.

Preparation of matrix tablets

Tablet containing 90 mg diltiazem hydrochloride were prepared by wet granulation technique with composition detailed in table 1. All the powders were passed through mesh 80# sieve. Drug and polymer were mixed thoroughly and added sufficient volume of granulating agent, prepared wet mass sieved through 22/44# mesh. The granules were dried at 40^{o} C for 12 h. Magnesium stearate was used as lubricant. The final granules were compressed using a tablet compression machine (Rimek tablet machine, minipress) equipped with 8.4 mm tooling.

Evaluation of granules [10]

Granules were evaluated for bulk density, tapped density, Carr's index, angle of repose

Bulk density:

Density was term determined by dividing weight of powder by volume of powder. It is given as g/cm^3. Bulk density ($D_{B)}$ determined by the bulk volume and the weight of dry powder in graduated cylinder. Bulk volume of powder is sum of tapped volume plus void volume.

$$D_B = W/V\ B$$

Where, "W" weight of granules
"V B" bulk volume or untapped volume.

Tapped density:

Tapped density was determined by weight of powder by tapped volume of powder. The tapped volume is measured by tapping powder for 100 taps by using densiometer. It is measured by $g/cm^{3.}$

$$D_T = W/V\ T$$

Where, "W" weight of granules.
"V T" tapped volume

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Table 1: Composition of matrix tablets of Diltiazem HCl in various ratios

CODE	HPMC K4M	HPMC K15M	HPMC K100M	EC	EGT RS 100	EGT RL 100	Lactose	MCC	IPA	Mg St
Drug:Polymers ratio(1:1)										
S1A	45			45			110	5	Q.S	5
S2A	45				45		110	5	Q.S	5
S3A	45					45	110	5	Q.S	5
M1A		45		45			110	5	Q.S	5
M2A		45			45		110	5	Q.S	5
M3A		45				45	110	5	Q.S	5
D1A			45	45			110	5	Q.S	5
D2A			45		45		110	5	Q.S	5
D3A			45			45	110	5	Q.S	5
Drug:Polymers ratio(1:1.5)										
S1B	67.5			67.5			110	5	Q.S	5
S2B	67.5				67.5		110	5	Q.S	5
S3B	67.5					67.5	110	5	Q.S	5
M1B		67.5		67.5			110	5	Q.S	5
M2B		67.5			67.5		110	5	Q.S	5
M3B		67.5				67.5	110	5	Q.S	5
D1B			67.5	67.5			110	5	Q.S	5
D2B			67.5		67.5		110	5	Q.S	5
D3B			67.5			67.5	110	5	Q.S	5
Drug:Polymers ratio(1:2)										
S1C	90			90			110	5	Q.S	5
S2C	90				90		110	5	Q.S	5
S3C	90					90	110	5	Q.S	5
M1C		90		90			110	5	Q.S	5
M2C		90			90		110	5	Q.S	5
M3C		90				90	110	5	Q.S	5
D1C			90	90			110	5	Q.S	5
D2C			90		90		110	5	Q.S	5
D3C			90			90	110	5	Q.S	5

Bulkiness: Bulkiness is the reciprocal of Bulk density.

Bulkiness = 1/Bulk density

Carr's index:

It gives the property of granules. It denoted as I, unit is (%) and calculated by the following equation:

I = (Tapped density – Bulk density/Tapped density) *100

Angle of repose:

The angle of repose of the granules was determined by using funnel method. Granules were poured through the funnel fixed over a graph paper. The height of heap was measured with the help of scale. The circumference occupied by the pile of powder was marked and the area was measured, from which the value of radius was found. The angle of repose was calculated by using the equation.

$$\theta = \tan^{-1} h/r$$

Where, "h" and "r" are the height and radius of the powder cone.

Evaluation of tablets

The prepared matrix tablets were evaluated for hardness, weight variation, thickness, friability and drug content. Hardness of the tablets were tested using a Monsanto hardness tester (Dolphin)**,** Friability of the tablets was determined in a Roche friabilator (VEEGO Scientific Devices, Bombay). The thickness of the tablet was measured by Vernier calipers.

***In vitro* drug release studies**

In vitro drug release studies were performed according to USP XXIII type II apparatus in distilled water. The temperature was maintained at 37 ± 0.5° C and the rotation speed was 100 rpm. The samples were withdrawn at various time intervals and analyzed spectrophotometrically at 236 nm. [11]

Stability studies

In the present study, stability studies were carried out for a specific time period up to 30 days for selected formulations. The selected formulations were analyzed for the following parameters. Physical evaluation like appearance, hardness and chemical evaluation drug content.

RESULTS AND DISCUSSION

The use of hydrophilic polymer alone for controlling the drug release of highly water soluble drugs is restricted due to rapid diffusion of the dissolved drug through the hydrophilic gel layer. Hence, the present study was aimed to investigate the effect of hydrophobic polymers like ethyl cellulose and Eudragit RS & RL100 on matrices for controlling the release of highly water soluble drug diltiazem HCl.

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Pre-compressional evaluation of granules:

The granules of different formulations were evaluated for angle of bulk density, tapped density, bulkiness untapped, bulkiness tapped, Carr's index, and angle of repose. The results of angle of repose and Carr's index (%) ranged from 24.62 to 37.69, and 1.98 to 18.75, respectively. The results of BD and TD ranged from 0.3237 to 0.5403 and 0.3391 to 0.6385 respectively. The results of all these studies are given in the table no: 2.

Table 2: Evaluation of granules in various ratios

Code	Bulk density (g/ml)	Tapped density (g/ml)	Bulkiness untapped (ml/g)	Bulkiness tapped (ml/g)	Carr's index (%)	Angle of repose (θ)
Drug:Polymers ratio(1:1)						
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
Drug:Polymers ratio(1:1.5)						
S1B	0.3529	0.3921	2.8330	2.5500	9.99	32.61
S2B	0.3661	0.3864	2.7314	2.5879	5.25	30.96
S3B	0.3881	0.4109	2.5765	2.4334	5.54	31.60
M1B	0.3962	0.4490	2.5239	2.2710	11.75	31.32
M2B	0.4717	0.5032	2.1190	1.9870	6.25	33.11
M3B	0.3860	0.4100	2.5900	2.4380	5.85	30.65
D1B	0.4184	0.4742	2.3896	2.1088	11.76	29.24
D2B	0.4077	0.4317	2.4520	2.3160	5.55	33.69
D3B	0.4673	0.5341	2.1390	1.8723	12.50	32.00
Drug:Polymers ratio(1:2)						
S1C	0.3237	0.3391	3.0890	2.9489	4.54	31.26
S2C	0.3614	0.4015	2.7670	2.4906	9.98	37.69
S3C	0.3827	0.4306	2.6130	2.3223	11.12	32.31
M1C	0.4141	0.4969	2.4140	2.0120	16.16	27.47
M2C	0.4570	0.4874	2.1881	2.0517	6.23	32.00
M3C	0.4212	0.4476	2.3736	2.2340	5.89	34.21
D1C	0.3700	0.3775	2.7027	2.6490	1.98	31.26
D2C	0.4183	0.4429	2.3906	2.2578	5.55	30.96
D3C	0.4190	0.4713	2.3806	2.1217	11.09	29.98

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Post-compressional evaluation of Tablets:

The prepared tablets were tested for physical parameters like, hardness, weight variation, thickness, friability, drug content, and *in-vitro* drug release. The results of all these studies are given in the table no: 3. Hardness of the tablets was found to be in the range of 8.0 to 9.5 kg/cm$^{2.}$ The friability of all the formulations was found to be 0.05% (not more than 1%), the thickness of the tablets ranged from 4.0 ± 0.2357 to 5.0 ± 0.0785. Drug content was found to be uniform among different batches of the tablets and ranged from 97.17 ± 0.4270 to 99.18 ± 0.2749 respectively.

Table 3: Evaluation of matrix tablets in various ratios

Code	Thickness (mm)	Hardness (kg/c^2)	Weight variation (mg)	Friability (%)	Drug content (%)
Drug:Polymers ratio(1:1)					
S1A	4.0 ±0.2749	8.0 ±0.2553	0.300 ±0.0008	0.0555 ±0.000	99.27 ±0.3154
S2A	5.0 ±0.0785	9.5 ±0.2749	0.302 ±0.0001	0.0552 ±0.000	97.70 ±0.2396
S3A	5.0 ±0.0785	9.0 ±0.0982	0.299 ±0.0012	0.0559 ±0.000	97.53 ±0.2997
M1A	5.0 ±0.0785	9.5 ±0.2749	0.306 ±0.0012	0.0545 ±0.000	98.23 ±0.0522
M2A	5.0 ±0.0785	8.0 ±0.2553	0.306 ±0.0012	0.0543 ±0.000	98.26 ±0.0416
M3A	5.0 ±0.0785	9.0 ± 0.0982	0.303 ±0.0001	0.0550 ±0.000	99.18 ±0.2836
D1A	4.0 ±0.2749	9.0 ±0.0982	0.302 ±0.0001	0.0549± 0.000	99.32 ±0.331
D2A	5.0 ±0.0785	8.5 ±0.0785	0.308 ±0.0019	0.0541 ±0.000	97.17 ±0.4270
D3A	5.0 ±0.0785	8.0 ±0.2553	0.296 ±0.0022	0.0560 ±0.000	98.74 ±0.1280
Drug:Polymers ratio(1:1.5)					
S1B	4.0 ±0.2357	9.0 ±0.0392	0.304 ±0.0013	0.0547 ±0.000	97.58 ±0.2906
S2B	5.0 ±0.1178	9.0 ±0.0392	0.295 ±0.0018	0.0564 ±0.000	99.38 ±0.3456
S3B	5.0 ±0.1178	9.0 ±0.0392	0.297 ±0.0011	0.0559 ±0.000	98.28 ±0.0432
M1B	5.0 ± 0.1178	9.0 ±0.0392	0.294 ±0.0022	0.0594 ±0.001	98.84 ±0.1547
M2B	4.0 ±0.2357	9.0 ±0.0392	0.305 ±0.0016	0.0518 ±0.001	97.78 ±0.2199
M3B	5.0 ±0.1178	9.0 ±0.0392	0.301 ±0.0002	0.0548 ±0.000	99.18 ±0.2749
D1B	4.0 ±0.2357	9.0 ±0.0392	0.303 ±0.0009	0.0543 ±0.000	99.10 ±0.2467
D2B	5.0 ±0.1178	8.0 ±0.3142	0.299 ±0.0004	0.0545 ±0.000	97.37 ±0.3649
D3B	5.0 ±0.1178	9.0 ±0.0392	0.304 ±0.0013	0.0546 ±0.000	98.11 ±0.1033
Drug:Polymers ratio(1:2)					
S1C	4.0 ±0.2749	9.0 ±0.0589	0.296 ±0.0004	0.0564 ±0.001	99.28 ±0.3280
S2C	5.0 ±0.0785	9.5 ±0.2357	0.300 ±0.0009	0.0558 ±0.001	97.47 ±0.3119
S3C	5.0 ±0.0785	8.5 ±0.1178	0.296 ±0.0004	0.0557 ±0.001	97.77 ±0.2058
M1C	4.0 ±0.2749	8.5 ±0.1178	0.298 ±0.0002	0.0586 ±0.002	97.13 ±0.4321
M2C	5.0 ±0.0785	9.5 ±0.2357	0.295 ±0.0008	0.0564 ±0.001	99.18 ±0.2926
M3C	5.0 ±0.0785	8.5 ±0.1178	0.296 ±0.0004	0.0575 ±0.002	98.57 ±0.0769
D1C	5.0 ±0.0785	8.0 ±0.2946	0.300 ±0.0009	0.0554 ±0.001	97.76 ±0.2093
D2C	5.0 ±0.0785	9.0 ±0.0589	0.300 ±0.0009	0.0557 ±0.001	99.24 ±0.3138
D3C	5.0 ±0.0785	9.0 ±0.0589	0.295 ±0.0008	0.0565 ±0.001	98.77 ±0.1477

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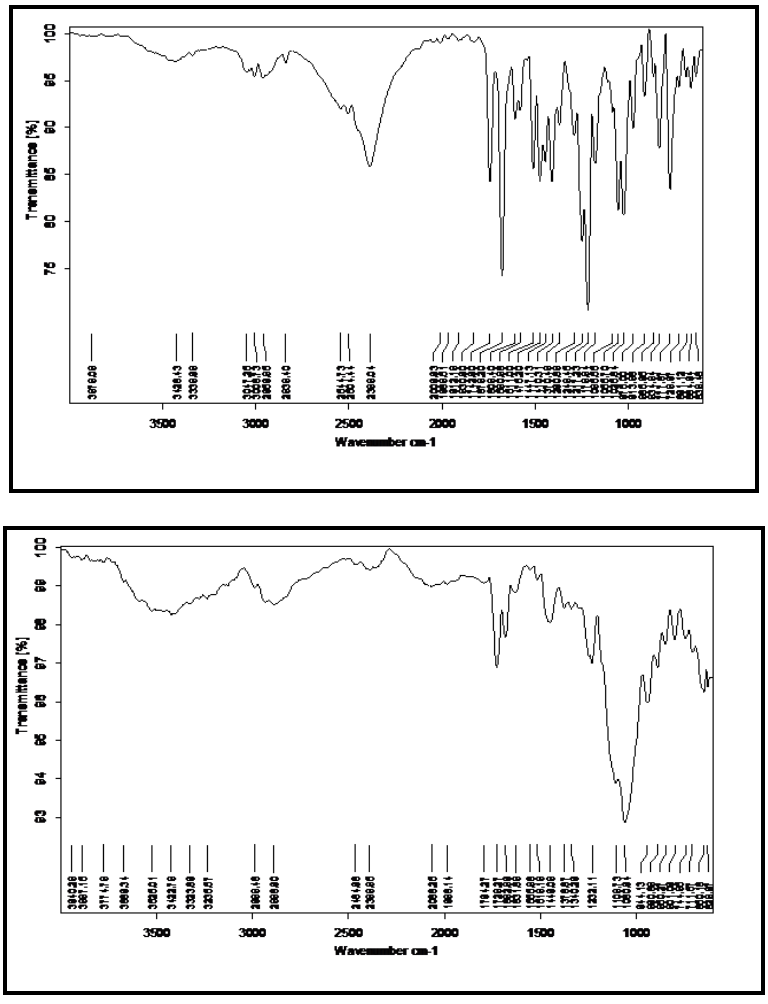
Pre-compressional and post-compressional evaluation of various matrix formulations:

Drug excipients interactions were characterized by IR spectroscopy studies, the IR spectrum of diltiazem HCl and drug with polymers mixture (Fig: 1). The IR spectrum of diltiazem HCl 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 spectrum of diltiazem HCl pure, physical mixture of polymers were taken All the major bands present in the spectrum of the pure drug are clearly observed in the IR spectra of formulations with negligible change in their positions (Fig.1). This study clearly suggests that the drug remains in its normal form even in its formulations without undergoing any type of interaction with the polymer or other excipients present in the formulations.

Fig 1: IR specta of pure drug and mixture of diltiazem HCL and polymers



Effect of HPMC on release rate of drug:

HPMC, which is commonly used in hydrophilic matrix drug delivery systems, is mixed with alkyl hydroxyl alkyl cellulose either containing methoxyl and hydroxyl propyl groups. The hydration rate of HPMC depends on the nature of the 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 HCl 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% and 30%). Formulations containing HPMC K100M showed delayed release as compared to others. This revealed that as viscosity of HPMC increased release rate of drug was decreased. HPMC K100M tablets exhibited significant effect on drug release, his is due to more viscosity and high molecular weight of HPMC K100M in addition to its slower rate of erosion and more swelling. Different ratios 1:1, 1:1.5, and 1:2 of HPMC (K4M, K15M, and K100M) with hydrophobic polymers like EC, EGT RS100 and EGT RL100, with respect to the drug release was retarded with HPMC K100M in concentration of 1:2 up to 80% 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 coefficient 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 role in the retardation of drug release as HPMC (K100M>K15M> K4M)

Effect of ethyl cellulose, EGT RS100 and EGT RL100 with HPMC on release rate of drug:

Drug release studies were observed in case of Ethyl cellulose 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 matrix 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 12 hrs 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 and 1:2.

Combination of drug: EC + HPMC K4M kept in the ratio of 1:1, 1:1.5, and 1:2. The drug release was found in the formulations of S1A, S1B, and S1C. It was found to be 97.33%, 95.03%, and 92.40% of diltiazem hydrochloride in 12 hrs.

Combination of drug: EC + HPMC K15M kept in the ratio of 1:1, 1:1.5, and 1:2. The drug release was found in the formulations of M1A, M1B, and M1C. It was found to be 95.93%, 91.61%, and 90.09% of diltiazem HCl in 12 hrs.

Combination of drug: EC + HPMC K100M kept in the ratio of 1:1, 1:1.5, and 1:2. The drug release was found in the formulations of D1A, D1B, and D1C. It was found to be 93.93, 89.61, and 80.99% of diltiazem hydrochloride in 12 hrs.

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 was slow down in EGT RS100 than in EGT RL100 due to 5% of functional quaternary ammonium groups present in EGT RS 100 and it was 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 to 1:1, 1:1.5, and 1:2.

Combination of drug: EGT RS100 + HPMC K4M in the ratios of 1:1, 1:1.5, and 1:2. The drug release was found in the formulations of S2A, S2B, and S2C was 98.21%, 97.65%, and 95.32% of diltiazem hydrochloride in 12 hrs.

Combination of drug: EGT RS100 + HPMC K15M in the ratios of 1:1, 1:1.5, and 1:2. The drug release was found in the formulations of M2A, M2B, and M2C was 96.73%, 94.71%, and 92.87% of diltiazem hydrochloride in 12 hrs.

Combination of drug: EGT RS100 + HPMC K100M in the ratios of 1:1, 1:1.5, and 1:2. The drug release was found in the formulations of D2A, D2B, and D2C was 95.98%, 92.91%, and 91.74% of diltiazem hydrochloride in 12 hrs.

Combination of drug: EGT RL100 + HPMC K4M in the ratios of 1:1, 1:1.5, and 1:2. The drug release was found in the formulations of S3A, S3B, and S3C was 99.16%, 98.34%, and 96.75% of diltiazem hydrochloride in 12 hrs.

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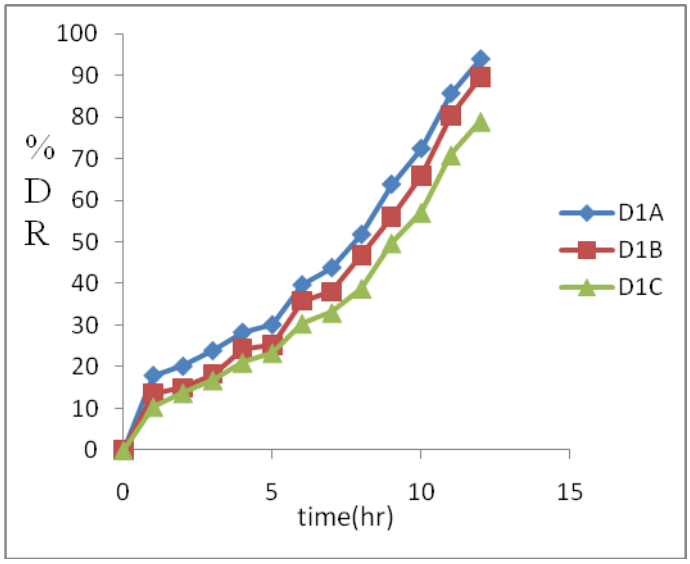
Combination of drug: EGT RL100 + HPMC K15M in the ratios of 1:1, 1:1.5, and 1:2. The drug release was found in the formulations of M3A, M3B, and M3C was 97.02%, 95.08%, and 93.75% of diltiazem hydrochloride in 12 hrs.

Figure2: Effect of polymer level on *in-vitro* release of Diltiazem HCL from HPMC K 100 M with EC matrix tablets in various ratios.



Combination of drug: EGT RL100 + HPMC K100M in the ratios of 1:1, 1:1.5, and 1:2. The drug release was found in the formulations of D3A, D3B, and D3C was 96.18%, 94.08%, and 92.63% of diltiazem hydrochloride in 12 hrs

During dissolution process: it was observed that the increase in 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 order of EC>EGT RS 100>EGT RL 100.

The stability studies were carried out for the selected formulations like D1A, D1B, and D1C, at 25^0 C/60% RH and 40^0 C/75% RH as per ICH guidelines for a period of 30 days, indicated the absence of any physical changes (hardness and friability) during the study period. The drug content was found above 98% at the end of 30 days. Thus the optimized formulations remained stable at the accelerated conditions of temperature and humidity.

Mechanism of drug release:

To investigate the mechanism of drug release from the matrix tablets, various kinetics models like zero order, first order, Higuchi's and Korsmeyer-Peppas equations were applied to the *in-vitro* release data obtained from different formulations.

The coefficient of determination (R^2) was considered as main parameter for interpreting the release kinetics. For Zero order treatment the R^2 values ranged from 0.892 to 0.994 which indicates that, the formulations follow zero order kinetics.

The R^2 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 R^2 values are not satisfactory.

When the data was subjected to Higuchi treatment, the R^2 values ranged from 0.795 to 0.985. The formulations containing EGT RL100 and HPMC K4M produce fair linearity; R^2 values ranging from 0.950 to 0.985 further strengthen the statement.

When the *in- vitro* dissolution data was fitted to exponential model, the R^2 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.

Matrix tablets serve the dual purpose of masking the bitter taste of the drug and controlling the release.

CONCLUSION

The result generated in this study showed that the release profile and kinetics of drug release were function of polymer type, polymer grade and polymer concentration. As the polymer level is increased, the drug release rates were found to be decreased the present study clearly manifests the necessity of combining different class of polymers to get an acceptable drug release profile. The mechanism of drug release from all the matrix tablets followed Non-Fickian diffusion indicating that polymer swelling and relaxation were both involved in the release process. In view of the above findings, it can be suggested that formulations containing combinations of HPMC K100M and EC can be employed successfully for the development of controlled release tablets of diltiazem HCl.

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