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DESIGN AND DEVOLOPMENT OF DILTIAZEM HYDROCHLORIDE SUSTAINED RELEASE DRUG DELIVERY SYSTEM

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ABSTRACT

The present study was to design and development of sustained and controlled release drug delivery system with using drug Diltiazem Hydrochloride. Prepare the matrix tablets with using of different polymers with different grades. The polymers used hydrophilic HPMC K100, HPMC K4M. The hydrophobic polymers used Eudragit L100. The natural polymer Xanthan gum also used prepare formulations. First to develop the new formulation with drug and polymer. The tablets were prepared with using single polymer with different grade and using combination of polymers with different proportions. The matrix tablets were prepared by using direct compression method. Then those tablets subjected to pre-compression and post compression evaluation studies and *in-vitro* drug release studies. And also compare with marketed product of Diltiazem with prepared formulation and observe the evaluation studies. The above study was clearly indicated Diltiazem Hydrochloride formulated as sustained release tablet with using different polymers tablets shows achieve slow release of drug over an extended period of time after administration of dose. Drug releases at predetermined rate, for locally or systemically, for a specified period of time.

KEYWORDS: Sustained release, Matrix tablets, Controlled release, Diltiazem Hydrochloride, Polymers, *in-vitro* studies.

INTRODUCTION

In recent years, considerable attention has been focused on the development of new drug delivery systems. There are number of reasons for intense interest in new systems. First,

recognition of the possibility of reparenting successful drugs by applying the concepts and techniques of controlled release drug delivery systems, coupled with increasing expense in bringing new drug entities to market, has encouraged the development of new drug delivery systems. Second, new systems need to deliver the novel, genetically engineered pharmaceuticals that is peptides and proteins, to their site of action without incurring significant immunogenicity or biological inactivation. Third, treating enzyme deficient diseases and cancer therapies can be improved targeting. Finally, therapeutic efficacy and safety of drugs, administered by conventional methods can be improved by more precise spatial and temporal placement with in the body, thereby reducing both size and number of doses.

The general consensus is that controlled release denote system which can provide some control, whether this be of a temporal or spatial nature or both of drug release in the body. This system attempts to control drug concentrations in the target tissue or cells. For the sustained release systems prolongs the release, which only prolong therapeutic blood or tissue levels of the drug for an extended period of time. It cannot be considered as controlled release as per definition. They are distinguished from rate-controlled drug delivery systems, which are able to specify the release rate and duration in-vivo precisely, on the basis of simple in-vitro tests. Drug targeting on other hand can be considered as a form of controlled release in that exercises spatial control of drug release with in the body.

Controlled drug delivery: "Controlled drug delivery is which delivers the drug at a predetermined rate, for locally or systemically, for a specified period of time".

Sustained drug delivery: "Sustained release drug delivery system that achieve slow release of drug over an extended period of time after administration of single dose".

Rationale of sustained/controlled drug delivery

The basic rationale for controlled drug delivery is alter the pharmacokinetic and pharmacodynamics of pharmacologically active moieties by using novel drug delivery systems. By modifying the molecular structure and physiological parameters inherent in selected route of administration. It is desirable that the duration of drug action becomes more a design property od rate-controlled dosage form, and less or not at all, a property of the drug molecule's inherent kinetic properties. The optimal design of controlled release systems

necessities a thorough understanding of the pharmacokinetic and pharmacodynamics of the drug.

$K < t_{1/2}$ (in TI)/In 2

Where,

K = relationship between dosing intervals and therapeutic index

$T_{1/2}$ = half life

TI = therapeutic index

MATERIALS

Sustained - release matrix tablets of Diltiazem Hydrochloride using different polymers with different proportions.

Drug - Diltiazem Hydrochloride

Polymers - HPMC K100

HPMC K4M

Eudragit L100

Xanthan gum

Other Excipients - MCC

Lactose

Mg Stearate

METHODOLOGY

Direct Compression

- ✓ Drug and the other excipients weigh and passed through sieve no10.
- ✓ Add Magnesium stearate to the above mixture and blended uniformly in motor and pestle for 2-3 min.
- ✓ The tablet was compressed by using 10 mm punches.

Analytical Method

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 taken for above stock solution between the wavelength of 200-400nm. The absorption maximum was found to be 237nm and this wavelength was selected and utilized for further studies.

FTIR: Fourier Transforms Infra-Red Spectroscopy (FT-IR) Fourier-transform infrared (FTIR) spectroscopy was performed on each of the samples to determine the structure of the organic compounds and to identify the presence of specific functional groups within a sample. Furthermore, drug-polymer interactions were examined using the resulting spectra. Spectra are obtained by passing infrared radiation through a sample and determining what fraction of incident radiation is absorbed at a particular energy. The energy of a peak in the spectrum corresponds to the frequency of vibration of part of the sample compound.

FORMULATION DESIGN (with synthetic polymers).

Ingredients	F1	F2	F3	F4	F5	F6
Diltiazem Hydrochloride	90	90	90	90	90	90
HPMC K100	90	-	-	90	90	-
HPMC K4M	-	90	-	90	-	90
Eudragit L100	-	-	90	-	90	90
MCC	132.75	132.75	132.75	87.75	87.75	87.75
Lactose	132.75	132.75	132.75	87.75	87.75	87.75
Mg stearate	4.5	4.5	4.5	4.5	4.5	4.5

FORMUATION DESIGN (with natural and synthetic polymers)

Ingredients	F7	F8	F9	F10	F11	F12
Diltiazem Hydrochloride	90	90	90	90	90	90
Xanthan Gum	30	60	90	60	60	60
HPMC K100	-	-	-	60	-	-
HPMC K4M	-	-	-	-	60	-
Eudragit L100	-	-	-	-	-	60
MCC	162.75	147.75	87.75	147.75	147.75	147.75
Lactose	162.75	147.75	87.75	147.75	147.75	147.75
Mg stearate	4.5	4.5	4.5	4.5	4.5	4.5

✓ F13 – Is a marketed product (DILZEM – SR) of Diltiazem Hydrochloride IP.

PREFORMULATION STUDIES

Preformulation study is the first step in the development of dosage form of a drug substance and is the process of optimizing the delivery of drug through determination of physicochemical properties of the new compound that could affect drug performance and development of an efficacious, stable and safe dosage form. Hence, Preformulation studies of obtained sample of drug were performed for identification and compatibility studies.

OBJECTIVES

- ✓ To establish the physicochemical parameters of new drug.
- ✓ To determine the kinetics and stability.
- ✓ To establish the compatibility with common excipients.
- ✓ It provides insights into how drug products should be processed and stored to ensure their quality.

a) Angle of repose

The angle of repose is maximum angles that the plane of powder makes with the horizontal surface on rotation. Angle of repose is helpful is assessment of flow properties of particles which could be further related to packing densities and mechanical arrangements of particles.

The granules were determined by funnel-method. The accurately weighed were taken in a funnel. The height of funnel was adjusted in such a manner that tip of the funnel just touched the apex of heap of the granules. The granules could flow through the funnel freely on to the surface. The diameter of the powder cone measured, and angle of repose was calculated using the following equation.

Tan θ = h/r

Where h = height of the powder

r = radius of the powder heap

θ = angle of repose

b) Bulk density and Tapped density

An accurately weighed quantity of granules or powder (W) was carefully poured in to the graduated cylinder and volume (V_0) measured. The graduated cylinder was closed with lid set into the tap density tester. The apparatus of density was set for 50 to 100 tabs and after that volume (V_f) was measured and continued operation till the two consecutive readings was equal.

Bulk density = W/V_0

Tapped density = W/V_f

c) Carr's compressibility index

It is a simple index that can be determined on small quantities of powder or granules, in less compressible a material than more flowable it is.

Carr's compressibility index (%) = [(TBD-LBD)/TBD] × 100

d) Hausner's ratio

Hausner,s ratio is the ratio between tapped density and bulk density. Hausner's ratio less than 1.25 is good flow properties while Hausner's ratio greater than 1.25 shows poor flow of granules.

Standard values for carr's index and hausner's ratio

Flow Character	Carr's index	Hausner's ratio
Excellent	≤10	1-1.1
Good	11-15	1.12-1.18
Fair	16-20	1.19-1.25
Passable	21-25	1.26-1.34
Poor	26-31	1.35-1.45
Very poor	32-27	1.46-1.59
Very, Very poor	>38	>1.6

EVALUATION OF TABLETS

a) Appearance

The tablets were visually observed for capping, chipping and lamination.

b) Thickness

The thickness and diameter of tablets were important for uniformity of the tablet size. The thickness and diameter of tablets were determined by Vernier caliper. Few tablets from each formulation were used and average values was calculated.

c) Weight variation test

For the weight variation take 20 tablets and weigh each formulation individually on electronic weighing balance. The average weight was calculated, and individual weight was then compared with the average value to find out the deviation in weight. (IP).

d) Hardness

Hardness of core tablets determined by using Monsanto hardness tester. 2 to 5 tablets were used for determined hardness. Record the optimized value. It is expressed in kg/cm^2.

e) Friability test

Friability is measured for tablet strength. This test subject 10 - 20 tablets are subject to Roches Friabilator. The combined effect of shock abrasion by utilizing chamber which resolves at a speed of 25 rpm, dropping the tablets to a distance 6 inches in each revolution. All the tablets were dedusted and reweighed. A loss of less than 1% in weight is acceptable.

$$\text{Percentage of friability} = \frac{\text{initial weight} - \text{final weight}}{\text{initial weight}} \times 100$$

f) Drug Content

The amount of the achieve ingredients in each of the 10 tested tablets within the range of 90% to 110% of the standard amount. The tablets were weighed and take in to mortar and pestle crushed into fine powder. An accurately weighed portion of the powder is equivalent to about 100mg of drug was transferred into 100 mL of volumetric flask containing 70mL of 0.1N HCL and shake it for 1hr on magnetic stirrer. And the 100mL 0.1n HCL solution was filtered through Whatman filter paper. Resulted solution 1mL was taken and diluted to 50mL with 0.1n HCL and observe the absorbance and record it.

g) *In-Vitro* drug release characteristics

The drug release was assessed by dissolution test and with using of Dissolution apparatus USP type Ⅱ paddle method at 50rpm in 900mL of 0.1N HCL for the first 2 hours and replace the phosphate buffer 6.8pH from 3 to 12 or round the clock. The temperature-maintained 37±0.5^{o} C, n = 3. An aliquot 5mL was withdrawn at specific time intervals and replaced with same volume of fresh dissolution medium (buffer). Collected Samples were filtered through Whatman filter paper and drug content in each sample was analyzed by UV-visible spectrophotometer at drug's wavelength (237nm).

0.1N HCL Solution - Take 8.4mL of concentrated HCL in 1000mL of Distilled water.

6.8 pH Phosphate buffer - Stock 1: Take 8gm of NaOH in 1000mL and 27.5gm of KH_2PO_4 in 1000mL Stock 2: Take 112mL of NaOH and 250mL of KH_2PO_4 both make up for 1000mL with distilled water.

Parameter	Details
Dissolution test apparatus	USP Ⅱ
Speed	100±0.1 rpm
Stirrer type	Paddle
Volume of medium	900 mL
Time intervals	1, 2, 3. 4, 5, 6, 7, 8, 12, 24
Dissolution Medium	0.1N HCL in 2 hours after 6.8pH phosphate buffer
Temperature	37 ± 0.5^{o} C

Dissolution parameters

Kinetic study analysis of Dissolution data

To analysis of the *in-vitro* release of data various kinetic models were used to describe the release kinetics. The Zero Order rate equation 1 describes the systems where the drug rate is independent of its concentration.

The First Order equation describes the release from system where release rate is concentration dependent. Equation 3 Higuchi (1963) described the release of the drug from insoluble matrix as a square root of time dependent process based on fickian diffusion. Equation 4 Hixson-crowell (1931) cube law describes the release from systems where there is a change in surface area and diameter of tablets or particles.

$C = K_0 t$ (1)

In this equation K_0 is zero order rate constant expressed in units of concentration/time and t is time.

$LogC = LogC_0 – K_1 t/2.303$ (2)

In this equation C_0 is initial concentration of drug and K_1 is first order constant.

$Q = K_{Ht}^{1/2}$ (3)

In this equation K_H is constant reflecting the design variable of the system.

$Q_0^{1/3} – Q_t^{1/3} = K_{HC} t$ (4)

In this equation Q_t is the amount of drug remained in time t,

Q_0 is the initial amount of drug in tablet

K_{HC} is Hixson-crowell rate constant

Drug release mechanism

The mechanism of drug release was derived by Korsmeyer et al., in 1983. A simple relationship described drug release from a polymeric system in equation 5. To find out the mechanism of drug release, first 60% of drug release data was fitted in Korsmeyer-Peppas model.

$M_t/M_\infty = K_t^n$ (5)

In the equation 5 M_t/M_∞ is fraction of drug released time t, K is the release rate constant incorporating structural and geometric characteristics of the tablet, and n is the release of exponent. The n value is used to characterize different release mechanisms. The plot of Log cumulative % drug release vs Log time. Slope of the line was n. The n value is used to characterize different release mechanisms as given in lower table. Case Ⅱ is generally refers

to erosion of polymeric chain and anomalous transport (also called as Non-Fickian) refers to a combination of both diffusion and controlled release drug delivery system.

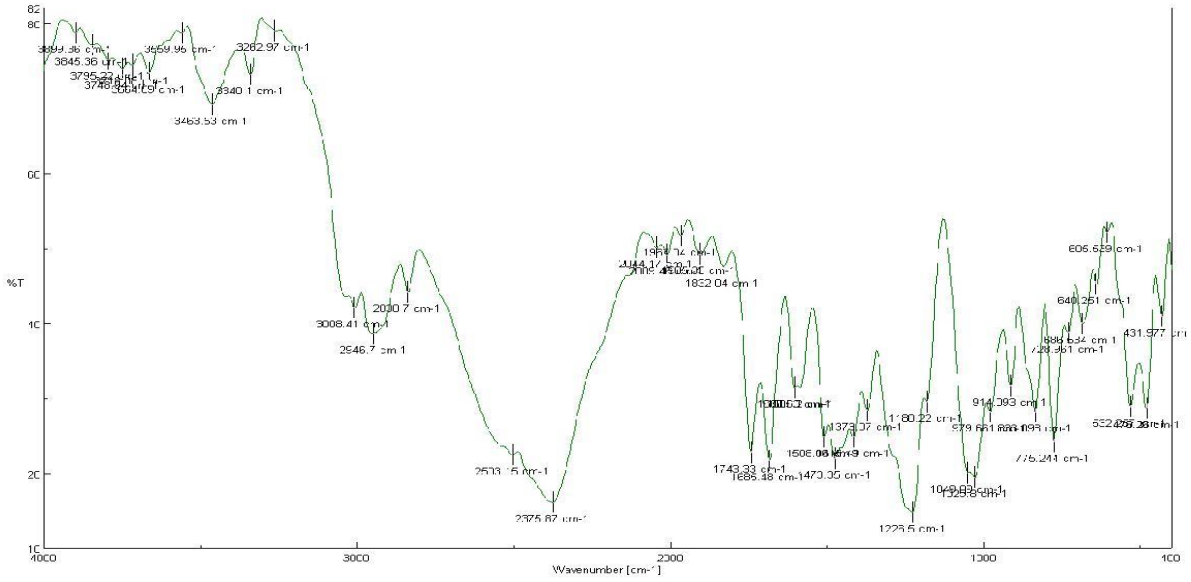
FTIR Studies

Fourier Transforms Infra-Red Spectroscopy (FT-IR) Fourier-transform infrared (FTIR) spectroscopy was performed on each of the samples to determine the structure of the organic compounds and to identify the presence of specific functional groups within a sample. Furthermore, drug-polymer interactions were examined using the resulting spectra. Spectra are obtained by passing infrared radiation through a sample and determining what fraction of incident radiation is absorbed at a particular energy. The energy of a peak in the spectrum corresponds to the frequency of vibration of part of the sample compound. 3-5 mg of composite sample was added to approximately 100 mg of KBr (s). The mixture was then ground to a fine powder using a mortar and pestle and transparent discs were formed using a pellet press. The discs were then placed in the FTIR spectroscopy apparatus, and spectra were collected. The range of the collected spectra was 4000-400cm-1.

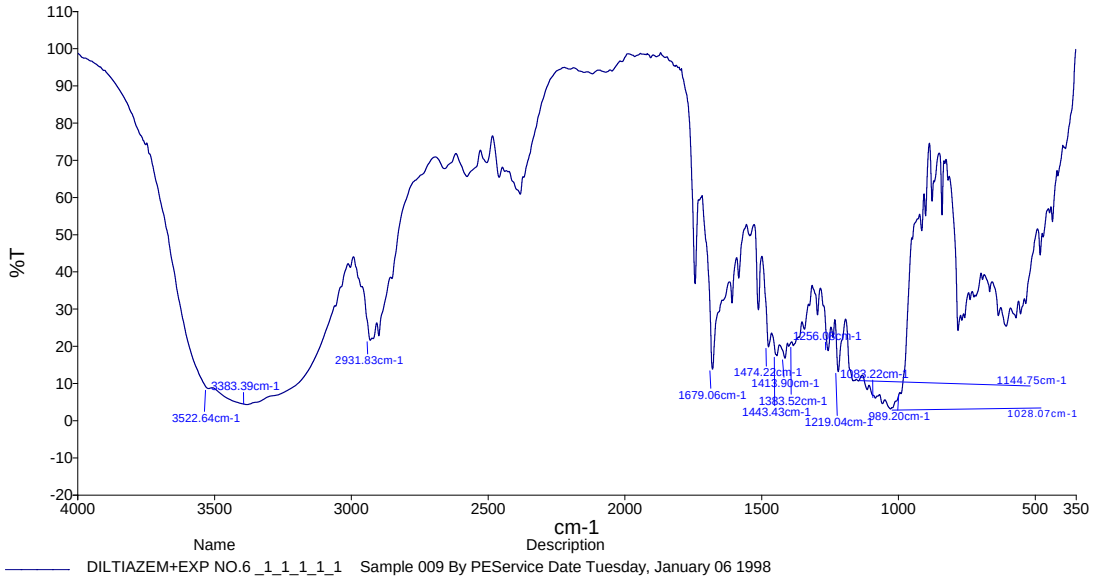
RESULTS AND DISCUSSION

FTIR SPECTROSCOPIC ANALYSIS

Fourier Transformed Infrared (FT-IR) Spectroscopic Analysis



Compatibility Study of Optimized formulation (F8)



Preformulation parameters

Parameters like angle of repose, bulk density, tapped density, carr's index and hausner's ratio were evaluated in order to determine the flow properties of the prepared powder mixture. Angle of repose and compressibility index for all the formulations were found to be in the range that indicated good flow properties and hence were suitable for compression into floating tablets.

Pre-compression parameters

Formulations	Angle of repose (^{0})	Bulk density (g/mL)	Tapped density (g/mL)	Carr's index (%)	Hausner's ratio
F1	23.89	0.510	0.555	8.10	1.08
F2	24.12	0.532	0.535	0.56	1.00
F3	22.46	0.526	0.555	5.22	1.05
F4	26.48	0.515	0.566	9.01	1.09
F5	22.15	0.511	0.573	10.8	1.11
F6	23.65	0.552	0.565	2.33	1.02
F7	25.23	0.572	0.635	9.92	1.11
F8	26.25	0.582	0.631	7.76	1.08
F9	28.30	0.562	0.585	3.93	1.04
F10	26.26	0.523	0.551	5.08	1.05
F11	27.35	0.526	0.532	1.12	1.01
F12	28.45	0.555	0.578	3.97	1.04

Pre-compression parameters

Post compression parameters

Formulations	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)
F1	440 ± 4.50	5.1 ± 0.07	5.0 ± 0.03	1.8 ± 0.05
F2	444 ± 2.28	5.0 ± 0.05	5.1 ± 0.04	1.1 ± 0.03
F3	443 ± 2.30	5.1 ± 0.09	5.0 ± 0.05	2.0 ± 0.04
F4	438 ± 2.30	5.2 ± 0.05	5.1 ± 0.01	1.9 ± 0.02
F5	447 ± 2.47	5.2 ± 0.07	5.0 ± 0.02	0.9 ± 0.01
F6	449 ± 2.50	5.0 ± 0.06	5.1 ± 0.01	0.7 ± 0.05
F7	448 ± 3.39	5.1 ± 0.02	4.5 ± 0.01	0.5 ± 0.01
F8	447 ± 3.90	5.0 ± 0.05	5.0 ± .0.03	0.2 ± 0.01
F9	449 ± 2.25	5.2 ± 0.01	4.5 ± 0.05	1.6 ± 0.06
F10	446 ± 4.10	5.1 ± 0.05	4.9 ± 0.06	0.8 ± 0.01
F11	449 ± 1.10	5.0 ± 0.02	5.1 ± 0.01	1.2 ± 0.05
F12	450 ± 0.05	5.0 ± 0.09	4.9 ± 0.06	0.8 ± 0.07
F13 (M)	118 ± 2.20	5.0 ± 0.08	3.9 ± 0.09	0.9 ± 0.04

Post compression parameters

Hardness of the tablets were in the range of 4.9 ± 0.09 to 5.2 ± 0.05, the combination HPMC and Eudragit was showed good hardness value. The Xanthan gum contained polymer tablets were shows hardness in between 5.0 ± 0.02 to 5.2 ± 0.01. Matrix tablets of Diltiazem all formulations thickness will be range in 4.5 ± 0.01 to 5.1 ± 0.01. for all the prepared formulations friability percentage was less than 2% these results were acceptable limit. For weight variation of tablets within range of 440 ± 4.50 to 450 ± 0.05 with 5% deviation from mean weight is acceptable limit. Marketed product also shows good results as in between range as per IP. Matrix tablets of Diltiazem Hydrochloride were prepared by direct compression method and subjected in to evaluation tests. As per IP drug content of each tablet should be range of 80 to 110% of theoretical label claim. All formulations showed good uniformity in drug content and the percentage of drug content 88% to 96.7%. All the formulations take more than 4 hours' time taken for Disintegration of tablet.

***IN-VITRO* DRUG RELEASE**

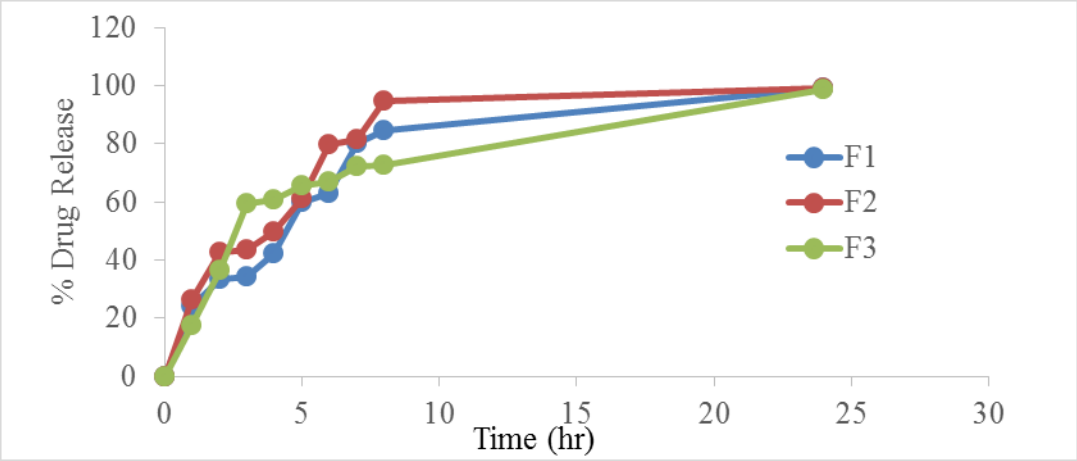
Effect of Synthetic polymers HPMCK100, HPMCK4M, EudragitL100 on Diltiazem Hydrochloride release from Sustained Release Matrix tablets.

Time (hours)	F1	F2	F3	F4	F5	F6
0.5	16.5±0.30	14.6±0.25	9.5±0.15	15.2±0.40	10.6±0.30	9.8±0.11
1	24.2±0.24	26.1±0.50	17.3±0.32	25.6±0.65	16.6±0.25	17.6±0.35
2	33.2±0.14	42.8±0.30	36.5±0.66	33.3±0.12	31.3±0.35	39.6±0.65
3	34.2±0.25	43.4±0.34	59.5±0.12	40.2±0.45	45.2±0.80	47.5±0.25
4	42.1±0.44	49.7±0.22	60.6±0.33	52.6±0.40	50.3±0.46	51.5±0.56
5	59.8±0.35	61.1±0.36	65.7±0.50	55.9±0.35	62.6±0.54	56.1±0.44
6	62.8±0.65	79.7±0.44	66.9±0.35	70.3±0.80	70.5±0.55	62.3±0.22
7	80.1±0.32	81.6±0.45	72.3±0.60	79.2±0.60	80.4±0.80	69.4±0.36
8	84.4±0.85	94.7±0.66	72.8±0.40	83.2±0.10	87.9±0.75	76.9±0.88
24	99.2±0.20	99.2±0.80	98.8±0.20	94.1±0.25	94.9±0.55	93.5±0.50

Cumulative % dug release F1 – F6

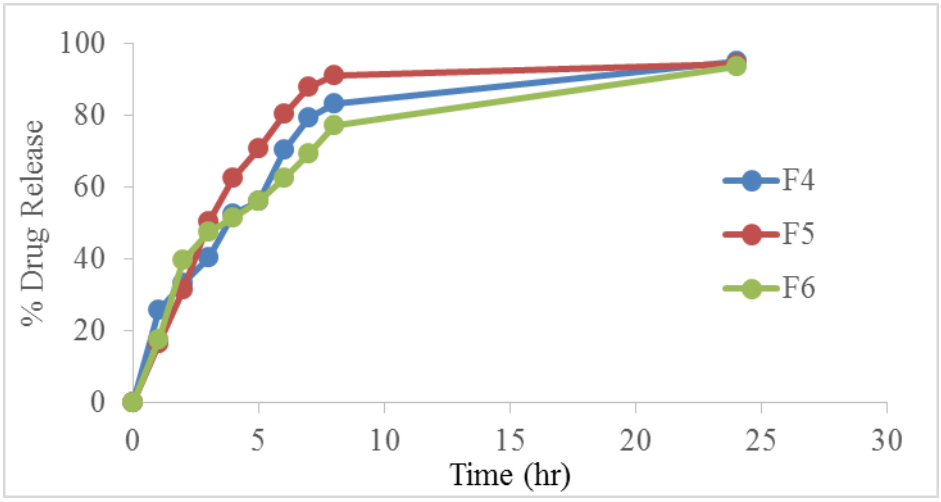
The tablets were prepared with one master formula (1:1 ratio) with different polymers and different combination of polymers. The polymers used HPMC K100, HPMC K4M, Eudragit L100. Prepared tablets subjected to *in-vitro* studies. The drug release was controlled by the polymer. HPMC K100 is somewhat less viscosity polymer, therefore 10% to 20% of polymer level showed a fast drug release from the matrix HPMC K4M drug release. Eudragit L100 is polymer which releases drug at intestine with controlled release. The prepare matrix tablets and in 0.1N HCL solution in hour and then changed in to 6.8 pH phosphate buffer solution. The collect samples (1,2,3,4,5,6,7,8 and 24) as per releasing of drug.

An increase in polymer amount causes an increase in the viscosity of the gel and gel layer with a longer diffusional path. The ultimate effect was a decrease in the effective diffusion coefficient of the drug with a reduction in the drug release rate. In all synthetic formulations after changing of 0.1N HCL solution to 6.8pH phosphate buffer the drug release was increased and controlled.



Drug release pattern of F1 – F3

The formulations (F1-F3) was prepared with HPMC K100, HPMC K4M and Eudragit L100. In 0.1N HCL the drug F1 (HPMC K100) is 24.2%, F2 (HPMC K4M) is 26.1%, F3 is (Eudragit L100) 17.3%. The drug release after 24 hours HPMC K100 was found to be 99.2%, HPMC K4M was found to be 92.2% and Eudragit L100 was found to be 98.8%. In these formulations Eudragit L100 shows high amount of drug released around 24 hours. All formulations after changing of 0.1N HCL solution to 6.8pH phosphate buffer the drug release was increased.



Drug release pattern of F4 – F6

the drug release of the formulations F4, F5 and F6. These are prepared with the combination of the polymers. Synthetic polymers are used. Formulation 4 was combination of HPMC K100 and HPMC K4M, this was hydrophilic combinate formulation. It was showed 52.6% of the drug release after 4 hours. This formulation shows 94.9% drug release in 24 hours. Formulation 5 was prepared with combination of hydrophilic and hydrophobic polymers they

are HPMC K100 and Eudragit L100. This F5 was 16.6% of drug was released in 0.1N HCL. After 4 hours of half-life 50.3% of drug was released form tablet. Finally, the *in-vitro* release 94.1% of drug in 24 hours. Formulation 6 was prepared with combination of HPMC K4M and Eudragit L100. F6 was release 51% of drug in 4 hours and 93.5% *in-vitro* drug release in 24 hours. These all synthetic polymers make sustained the drug release and take more time in our body show controlled release of the drug around clock. F5 was showed better release than other combinations.

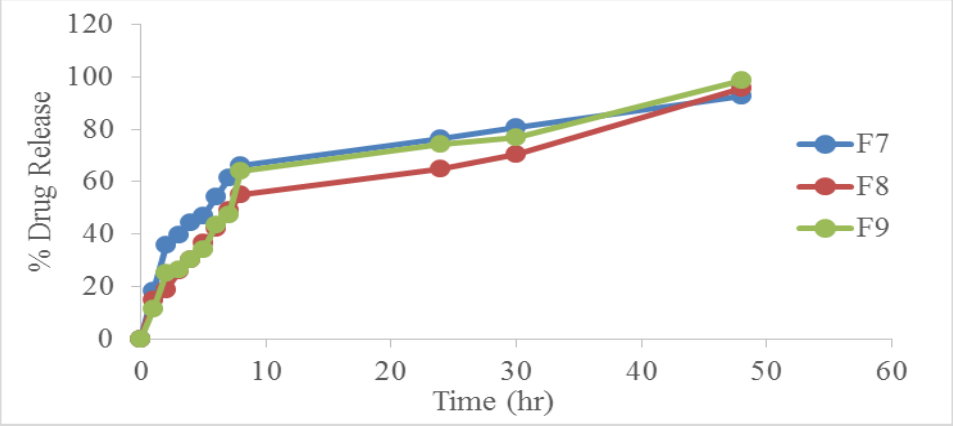
Effect of Natural polymer Xanthan gum on Diltiazem Hydrochloride release from Sustained Release Matrix tablets.

Time (hours)	F7	F8	F9	F10	F11	F12
0.5	10.5±0.15	8.9±0.23	6.3±0.20	9.9±0.55	11.3±0.26	8.6±0.35
1	18.4±0.40	14.8±0.33	11.4±0.14	21.1±0.46	21.5±0.84	16.5±0.22
2	36±0.65	18.6±0.12	25.3±0.32	36.1±0.54	33.7±0.54	29.5±0.57
3	39.5±0.33	25.9±0.50	26.2±0.65	43.7±0.55	39.5±0.64	33.2±0.63
4	44.3±0.72	30.1±0.36	30.4±0.44	46.7±0.30	41.5±0.71	47.1±0.80
5	47.1±0.55	36.6±0.44	33.9±0.35	47.6±0.12	46.1±0.50	59.4±0.72
6	54.1±0.20	42.2±0.71	43.4±0.66	50±0.25	48.3±0.44	61.5±0.63
7	61.6±0.63	49.1±0.54	47.5±0.45	53.2±0.42	59±0.36	69.6±0.75
8	66.3±0.80	55.1±0.22	64.2±0.25	61.6±0.25	64.2±0.12	79.8±0.33
24	76.3±0.57	65±0.64	74.2±0.70	79.4±0.80	87±0.66	88.5±0.40
30	80.7±0.22	70.3±0.26	76.8±0.76	93.2±0.45	95.8±0.80	90.8±0.75
48	92.7±0.35	95.8±0.84	98.5±0.55	-	-	-

Cumulative % drug release F7 – F12

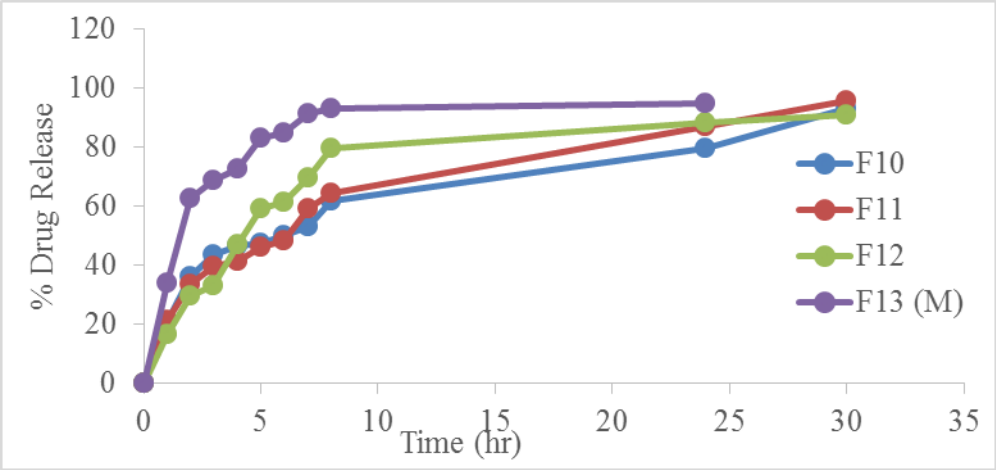
Time	0.5	1	2	3	4	5	6	7	8
F13 (M)	16.6± 0.55	34.2± 0.25	62.7± 0.32	68.8± 0.44	72.8± 0.72	83.3± 0.65	84.7± 0.45	91.2± 0.76	95± 0.40

Cumulative % drug release F13 Marketed product



Drug release pattern of F7 – F9

Formulation 7 was prepared with Xanthan gum with 1:3 ratio. It was releasing the 18.4% the drug in 0.1N HCL. In these times the tablet swelled. The drug release increased after changing in buffer 6.8pH. 44.3% of the drug is release after 4 hours. 92.7% of drug was released *in-vitro* after 48 hours. Formulation 8 was prepared with Xanthan gum with 1:2 ratio. It was releasing the 14.8% the drug in 0.1N HCL. In these times the tablet swelled. The drug release increased after changing in buffer 6.8pH. 30.1% of the drug is release after 4 hours and 95.8% of drug was released *in-vitro* after 48 hours. Formulation 9 was prepared with Xanthan gum with 1:1 ratio. It was releasing the 11.4% the drug in 0.1N HCL. In these times the tablet swelled. The drug release increased after changing in buffer 6.8pH. 30.4% of the drug is release after 4 hours and 98.5% of drug was released *in-vitro* after 48 hours.



Drug release pattern of F10 – F13

Formulation 10 was prepared with Natural and hydrophilic polymers Xanthan gum and HPMC K100. It was releasing the 9.9% the drug in 0.1N HCL. The drug release increased after changing in buffer 6.8pH. 47.6% of the drug is release in 5 hours and 93.2% of drug was released *in-vitro* after 30 hours. Formulation 11 was prepared with Natural and hydrophilic polymers Xanthan gum and HPMC K4M. It was releasing the 11.9% the drug in 0.1N HCL. The drug release increased after changing in buffer 6.8pH. 46.1% of the drug is release in 5 hours and 95.8% of drug was released *in-vitro* after 30 hours. Formulation 12 was prepared with Natural and hydrophobic polymers Xanthan gum and Eudragit L100. It was releasing the 8.6% the drug in 0.1N HCL. The drug release increased after changing in buffer 6.8pH. 47.1% of the drug is release in 5 hours. 90.8% of drug was released *in-vitro* after 30 hours.

KINETICE STUDIES

RELEASE KINETIC DATA OF ALL FORMULATIONS (R^2)

Formulations	Zero order	First order	Higuchi	Hixson - crowell	Korse meyer-peppass	"n"
F1	0.7738	0.9958	0.9775	0.0887	0.9149	0.3300
F2	0.6180	0.9145	0.9312	0.0887	0.9041	0.2032
F3	0.8077	0.9878	0.9404	0.0887	0.9290	0.7067
F4	0.7332	0.9969	0.9697	0.0887	0.9224	0.2669
F5	0.5472	0.8685	0.9138	0.0887	0.7214	0.4525
F6	0.7287	0.9889	0.9658	0.0887	0.9557	0.2896
F7	0.7023	0.9807	0.9318	0.0938	0.9150	0.6338
F8	**0.8994**	**0.9834**	**0.9775**	**0.0938**	**0.9997**	**0.6755**
F9	0.7617	0.9921	0.9585	0.5326	0.9002	0.5737
F10	0.8123	0.9452	0.9580	0.3009	0.9862	0.6748
F11	0.8464	0.9730	0.9757	0.3009	0.9859	0.5639
F12	0.5928	0.8870	0.8879	0.3009	0.9595	0.6940
F13 (M)	0.5363	0.9544	0.9942	0.0887	0.9999	0.2765

Release kinetic data F1 – F13

The in-vitro release data was treated according to zero order, first order, Higuchi's, Hixson-Crowell cube root law and Korse meyer-peppass. The release rate kinetic data for all the models can be seen in Table 8.9. In the present study, the in vitro release profiles of drug from F8 shows best kinetics. In F8 zero order 0.8994 and first order 0.9834 these are found to be better and optimized kinetic release. Higuchi's equation and Korse meyer-peppass. Correlation coefficient value (r^2): 09775. and 0.9997 shows high linearity respectively. The high correlation coefficient (above 0.99) obtained indicates a square root of time dependent release kinetics. Thus, as the data fitted the Higuchi model, it conforms diffusion drug release mechanism.

F13 Marketed formulation zero order 0.5363 and first order 0.9544. Higuchi's equation and Korse meyer-peppass. Correlation coefficient value (r^2): 0.9999 and 0.9942 shows high linearity respectively. The high correlation coefficient (above 0.99) obtained indicates a square root of time dependent release kinetics. Thus, as the data fitted the Higuchi model, it conforms diffusion drug release mechanism. To confirm the diffusion mechanism, data were fit into Korsemeyer equation. The zero order and first order values in F8 found to be better than marketed product.

The n value of 0.6755 for F8 and n value of 0.2765 for marketed formulation shows a coupling of diffusion and erosion mechanisms so-called anomalous (non-fickian) diffusion. It

is suggested that the main driving force for the drug release in case of water-soluble drug like diltiazem hydrochloride. Also, as observed in, as the polymer level in the formulation is increased, that makes drug release was slow and sustained it reaches controlled release drug delivery.

CONCLUSION

The above study was clearly indicated Diltiazem Hydrochloride formulated as sustained release tablet with using different polymers tablets show achieve slow release of drug over an extended period of time after administration of dose. Drug releases at predetermined rate, for locally or systemically, for a specified period of time.

Optimized sustained release Diltiazem hydrochloride matrix tablets, showed square root of time dependent kinetics of drug release indicating a dissolution and diffusion-controlled release mechanism. Selected polymers and their concentrations are also capable of sustaining the release of drug Diltiazem hydrochloride beside drug concentration.

Based on the above, it is concluded that sustained release Diltiazem hydrochloride matrix tablets was developed using HPMC, Eudragit and Xanthan gum (single and combinations) as the release sustaining excipients. *In-vitro* testing indicated that sustained release Diltiazem hydrochloride matrix tablets had similar dissolution behavior to the marketed product according to the model independent FDA guideline. As per results optimized formulation was shows best kinetic profile than marketed product. And the other synthetic and natural polymer formulations was shows good percentage of drug release and showed better kinetic profiles.

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