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FORMULATION AND *IN VITRO* EVALUATION OF CONTROLLED RELEASE MATRIX TABLETS OF DILTIAZEM HCL

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Abstract:

The present study involves in the formulation and evaluation of Controlled release tablets of Diltiazem HCl (100mg). The objective of the present study was to formulate Diltiazem hcl Controlled release tablets by Direct compression method by using HPMC K 15M, HPC 2M and HEC 2M. Lactose was used as diluting agent, Magnesium stearate was used as a lubricant and Aerosil was used as a glident. This Controlled release the drug up to 12 hours in predetermined rate. The formulated powder blend was evaluated for bulk density, tapped density, compressibility index and angle of repose. The formulated tablets were evaluated for physical characteristics of Controlled release tablets such as thickness, hardness, friability, weight variation and drug content. The results of the formulations found to be within the limits specified in official books. The tablets were evaluated for In-vitro drug release studies by using USP type II dissolution test apparatus. The dissolution test was performed in 0.1 N HCL for 2 hr and phosphate buffer pH 6.8 for 12hrs. The in-vitro cumulative drug release profile of all formulations F1-F12 hours showed good drug release. Hence, Formulation F7 was the most promising formulation as it gives satisfactory release (98.29 %) for 12 hours and F7 found to be the best formulation.

Keywords: *Diltiazem HCl, HPMC K 15M, HPC 2M and HEC 2M, Controlled release tablets.*

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INTRODUCTION:

The pharmaceutical industry today is caught between the downward pressure on prices and the increasing cost of successful drug discovery and development. The average cost and time for the development of a new chemical entity is approximately US $500 million and requires 10–12 years. It often, however, costs substantially less cost and time to develop new methods of administration for an existing drug (US $20–50 million and 3–4 years), which results in a product with improved efficacy and bioavailability together with reduced dosing frequency and minimum side effects. Pharmaceutical companies today are, therefore, under constant pressure to maximize the full potential of drug candidates at early stages of their life cycle. This objective can be accomplished by incorporating the drug into various drug delivery systems. Leading to extended patent life and convenient dosage forms that overcome previously presented administration problems. In the form of a newer delivery system, an existing drug molecule can get a new life, thereby increasing its market value and competitiveness and extending patent life. Limited formularies, patent expiry with subsequent entry of generic competition, and vertical integration have the entire pharmaceutical industry today focusing on designing and developing new and better methods of drug delivery. For the last two decades, there has been an enhanced demand for more patient-compliant dosage forms. A significant increase has been noted in approvals of newer drug delivery systems in the past couple of years and this is expected to continue at an impressive rate in the near future. The sale of drug delivery products is valued at more than US $22 billion worldwide, and this growth is expected to continue into the present century. It was estimated that the drug delivery market was at US $120 billion in 2007 [1,2]

Pharmaceutical dosage forms contain both drug substance commonly referred as active pharmaceutical ingredient (API) and excipients[3]. Excipients are not expected to show pharmacological actions themselves but they may play a major role on the delivery of API. As they bring the desired functionality to the formulations and therefore can have a major impact on the safety and efficacy of pharmaceutical dosage forms [4].

Reasons for including excipients in dosage forms are:

- ease of administration to the target patient populations by the intended route
- improved dosing compliance
- Consistency and control of drug bioavailability
- To enable bioavailability
- improved API stability including protection from degradation
- To ensure a robust and reproducible physical product [5]

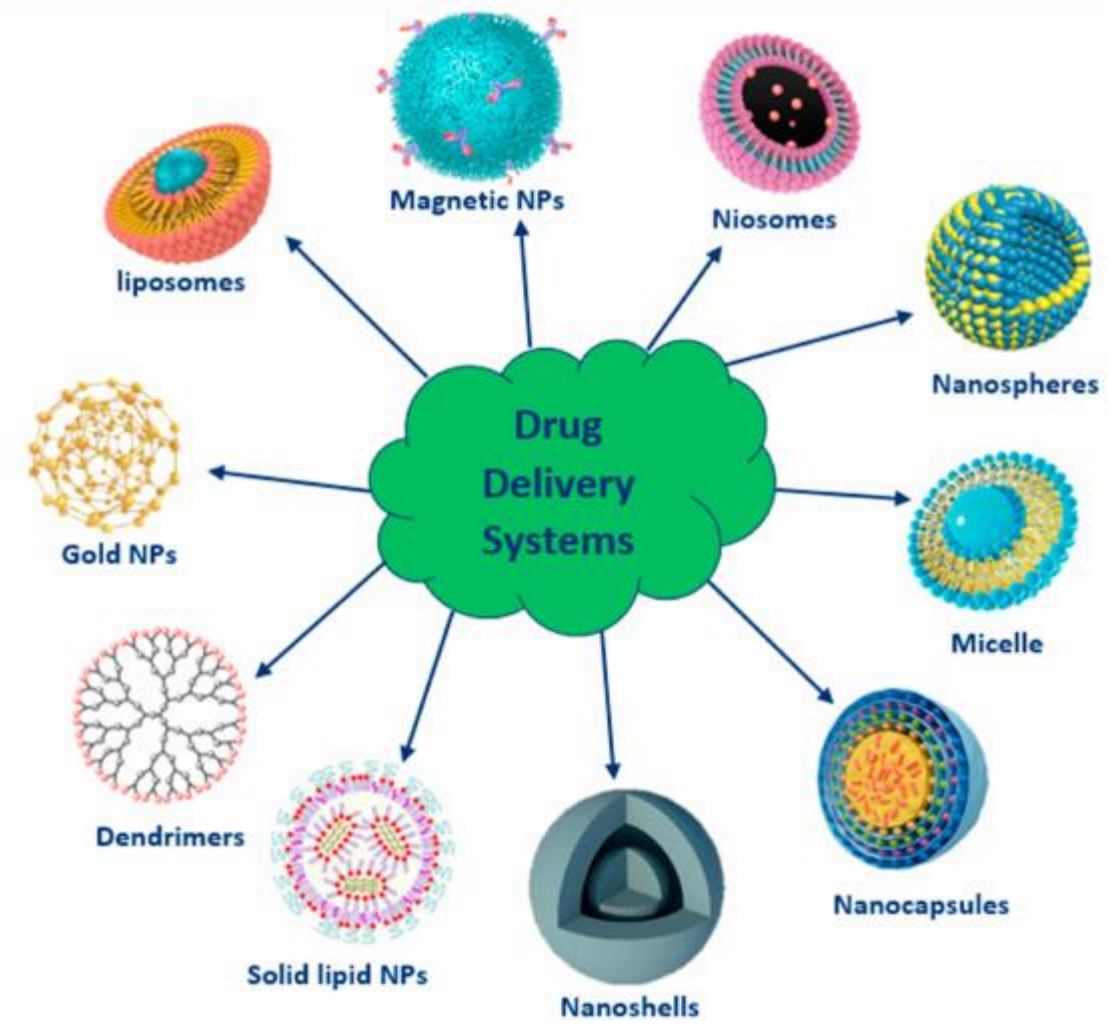


FIG 1.1: Drug delivery system

Drawback of conventional dosage form:

1) Poor patient compliance: Chances of missing of the dose of a drug.

2) The unavoidable fluctuations of drug concentration may lead to under medication or over medication.

3) A typical peak-valley plasma concentration-time profile is obtained which makes attainment of Drawback of conventional dosage form.

4) The fluctuations in drug levels which causes precipitation of adverse effects mainly the drug which having the small Therapeutic Index whenever over medication occur. [6,7,8]

Advantages of oral controlled release formulations

This type of drug delivery has been at the centre of research due to its many benefits over conventional dosage forms, some of which are as follows:

- The frequency of dosing is reduced due to drug being released over a longer period of time unlike conventional tablets (Kojima et al. 2008). This is extremely valuable for patients with chronic illnesses which require the plasma concentrations of a drug to be within its therapeutic range to avoid breakthrough symptoms, for example, overnight management of pain in terminally ill patients (Aulton 2008).
- The reduction or avoidance of side effects due to high plasma drug concentrations or 'dose dumping' (Maderuelo et al. 2011).
- Improvement in patient compliance due to reduced dosing (Maderuelo et al. 2011).
- Better control of therapeutic drug concentration;
- Cost effective manufacturing (Maderuelo et al. 2011) as the amount of tablets needed per patient would be reduced compared to its conventional form.

Disadvantages of oral controlled release formulations

- Oral controlled release formulations like other formulations have several disadvantages. These

include (DiMatteo and DiNicola 1982, Jayanthi et al. 2011, Kayser et al. 2005, Sansom 1999):

- Development costs: Expensive specialised equipment and inert ingredients may be required for some controlled release formulations.
- Release rate: The drug release rate can be altered by food and gastric transit time; as a result differences may arise in the release rate between doses.
- Can not crush or chew products: Controlled release products should not be crushed or chewed as it can lead to loss of the 'slow release' characteristics as well as toxicity.

The effect of drug properties in developing oral controlled release:

Along side the benefits and disadvantaged, sustained release dosage forms have also posed many challenges for pharmaceutical technologists (Khan 1996). In order for drug release to be manipulated and for the resulting product to possess the above mentioned characteristics there are many factors that need to be taken into consideration when designing such formulations. Some of these are as follows:

- Different drug solubility's need to be considered (Sudha et al. 2010) as highly soluble drugs will dissolve immediately after administration (Siahi et al. 2005). Reduced drug solubility increases the tendency of the tablet to erode due to particle displacement (Bettini et al. 2001).
- The drug should have a short half-life (Aulton 2008). If a drug has a long half-life then there is a risk of accumulation as it will be eliminated at a slower rate compared to its absorption (Kim 2000).
- A drug that is tested in-vitro needs to be able to provide similar release characteristics once administered and is under pathophysiological or in-vivo conditions (Khan 1996, Diakidoua et al. 2009). A direct correlation of in-vitro data with in-vivo release is not possible without thorough and careful analysis (Khan 1996). For example, there is a difference in the availability of water in different parts of the gastrointestinal tract and such factors need to be considered when designing tablets for extended release (Khan 1996, Kojima et al. 2008).
- The dissolution characteristics should allow for drug to be released in a controlled manner, highlighting the importance for the correct selection of polymers according to their physical, mechanical and pharmacokinetic properties (Kim 2000). [15]

Clinical pharmacology studies [16,17,18]:

Participants:

All participants were healthy, as determined from a detailed medical history and complete physical examination including vital signs, complete blood count, blood chemistries, urinalysis, urine drug screen, and electrocardiogram. Written informed consent was obtained from each participant prior to enrolment, and the studies were conducted with appropriate ethical guidelines.

Study designs:

Two single-dose studies and two multiple-dose studies were conducted to characterize the pharmacokinetic profile of doxazosin GITS in healthy volunteers. Two studies included comparisons with doxazosin standard. All studies were conducted in compliance with the Declaration of Helsinki (1964) and the Hong Kong (1989) Revision.

Single-dose/food-effect study:

This open-label, randomized, three-way crossover study in 24 young, healthy male volunteers (aged 18–40 years) assessed the comparative bioavailability of single 8 mg doses of doxazosin GITS under fasting and fed conditions and a single doxazosin standard 2 mg dose under fasting condition. Each subject was randomly assigned to one of three treatment sequences, with a 7 day washout period between treatments. Under fasting condition, each dose was given after an overnight 10 h fast; subjects continued to fast for 4 more hours postdose. Under fed condition, each dose was given within 15 min of finishing a high-fat breakfast consisting of two slices of buttered toast, two eggs fried in butter, two slices of bacon, 4 oz hash-brown potatoes, and 8 oz whole milk. Blood samples were drawn immediately before dosing; hourly up to 4 h postdose; every 2 h thereafter up to 16 h postdose; and at 24 h postdose, then once daily up to 96 h postdose. Plasma was immediately separated from the blood samples and frozen until assayed.

Multiple-dose crossover study:

This open, randomized, multiple-dose, two-way crossover study assessed the pharmacokinetic characteristics of multiple doses of doxazosin GITS 4 mg and 8 mg and doxazosin standard 4 mg and 8 mg in 35 healthy male subjects (aged 18–60 years). Each subject was randomized to one of the following initial treatment arms: placebo for 7 days, doxazosin GITS 4 mg for 7 days, then 8 mg for 7 days; or doxazosin standard 1 mg for 2 days, 2 mg for 5 days, 4 mg for 7 days, and 8 mg for 7 days. After a 7 day washout period, subjects crossed over to the alternate regimen. Blood samples were drawn for each treatment arm predose on days 1, 13, 14, 20, and

21; as well as 1, 2, 3, 4, 6, 8, 10, 12, 18, and 24 h postdose on days 14 and 21, and 48, 72, and 96 h after the last dose on day 21. Plasma was immediately separated from the blood samples and frozen until assayed.

Dose strength bioequivalence study:
An open, randomized, single-dose, two-way crossover study was performed in 24 healthy male subjects (aged 18–40 years) to determine the relative bioavailability and pharmacokinetics of two 4 mg doxazosin GITS tablets vs one 8 mg doxazosin GITS tablet. There was a 7 day washout period between treatments. Blood samples were obtained predose, and 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 24, 48, 72, and 96 h postdose.

Age and gender study:
An open, multiple-dose parallel-group study was conducted to determine the steady-state relative bioavailability and pharmacokinetics of doxazosin GITS 4 mg in 41 healthy young (18–40 years of age) and elderly (≥65 years of age) males and females. Each subject received one 4-mg doxazosin GITS tablet for 7 consecutive days. Blood samples were collected predose and 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, and 24 h postdose on days 1 and 7; predose on days 5 and 6; and 48, 72, and 96 h after the last dose on day 7.

Analytical methods:
Plasma samples were analysed using a validated high-performance liquid chromatography (h.p.l.c.) assay with fluorescence detection . Doxazosin was extracted from plasma sample after addition of internal standard prazosin and 50% ammonium hydroxide into ethyl acetate. Separation, subsequent detection, and quantification of doxazosin were achieved on a C8 column of an isocratic, reverse-phase h.p.l.c. assay system coupled to a fluorescence detector set at an excitation wavelength of 248 nm and an emission filter at 370 nm. Peak height ratios of doxazosin to the internal standard were computed for all study samples, calibration standards, and quality-control samples. Quality-control samples of 0.8, 4, and 16 ng ml−1 were prepared, stored, and analysed along with the study samples to verify analyte stability, assay accuracy, and precision.

The assay was linear over the calibration standard concentration range for doxazosin of 0.2–20 ng ml−1. The limit of quantification was determined to be 0.2 ng ml−1. The slopes of the standard curves were consistent among all runs with correlation coefficients >0.994. The variability of the calibration standards from 0.2 to 20 ng ml−1 ranged from 1.9% to 7.5%. The interday and within-day precision for the quality-control samples was >93%. The mean quality-control samples deviated <4% from the nominal concentrations. Thus, the assay was linear, reproducible, precise, and specific; and demonstrated that doxazosin was stable in human plasma during 2 months of storage at −20° C.

MATERIALS:
Diltiazem hcl Provided by SURA LABS, Dilsukhnagar, Hyderabad.,HPMC K-15M Merck Specialities Pvt Ltd.HEC 2M-Merck Specialities Pvt Ltd,HPC 2M[-Merck Specialities Pvt Ltd,MCC-Merck Specialities Pvt Ltd.AC,Aerosil-Merck Specialities Pvt Ltd,Magnesium Stearate-Merck Specialities Pvt Ltd

METHODOLOGY:
a) Determination of absorption maxima:
100mg of Diltiazem HCl pure drug was dissolved in 100ml of Methanol (stock solution)10ml of above solution was taken and make up with100ml by using 0.1 N HCl (100µg/ml).From this 10ml was taken and make up with 100 ml of 0.1 N HCl (10µg/ml). And pH 6.8 Phosphate buffer UV spectrums were taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400 nm.

Preparation calibration curve:
100mg of Diltiazem HCl pure drug was dissolved in 100ml of Methanol (stock solution)10ml of above solution was taken and make up with100ml by using 0.1 N HCl (100µg/ml).From this 10ml was taken and make up with 100 ml of 0.1 N HCl (10µg/ml). The above solution was subsequently diluted with 0.1N HCl to obtain series of dilutions Containing 2,4,6,8 and 10 µg/ml of Diltiazem HCl per ml of solution. The absorbance of the above dilutions was measured at 237 nm by using UV-Spectrophotometer taking 0.1N HCl as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R2) which determined by least-square linear regression analysis. The above procedure was repeated by using pH 6.8 phosphate buffer solutions.

9.2. Preformulation parameters:
The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per

Pharmacopoeia.

Angle of repose:

The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose was calculated using the following formula:

$\tan \theta = h / r$ $\tan \theta$ = Angle of repose

h = Height of the cone , r = Radius of the cone base

Formulation composition for tablets:

INGREDIENTS (mg)	FORMULATION CHART								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Diltiazem HCl	60	60	60	60	60	60	60	60	60
HPMC K 15M	5	10	15	20	-	-	-	-	-
HPC 2M	-	-	-	-	5	10	15	20	-
HEC 2M	-	-	-	-	-	-	-	-	5
Lactose	26	21	16	11	26	21	16	11	26
Aerosil	5	5	5	5	5	5	5	5	5
Magnesium Stearate	4	4	4	4	4	4	4	4	4
Diltiazem HCl	60	60	60	60	60	60	60	60	60
HPMC K 15M	5	10	15	20	-	-	-	-	-

All the quantities were in mg

RESULTS AND DISCUSSION:

Standard Calibration curve of Diltiazem HCl:

Table 8.1: Concentration and absorbance obtained for calibration curve of Diltiazem HCl in 0.1 N hydrochloric acid buffer (pH 1.2**)**

S. No.	Concentration (µg/ml)
1	0
2	5
3	10
4	15
5	20
6	25

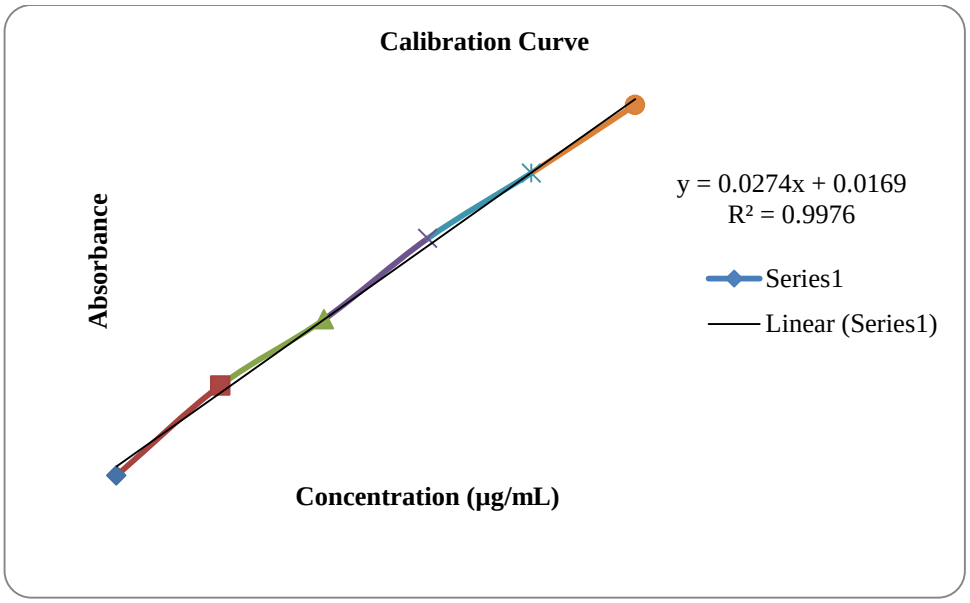
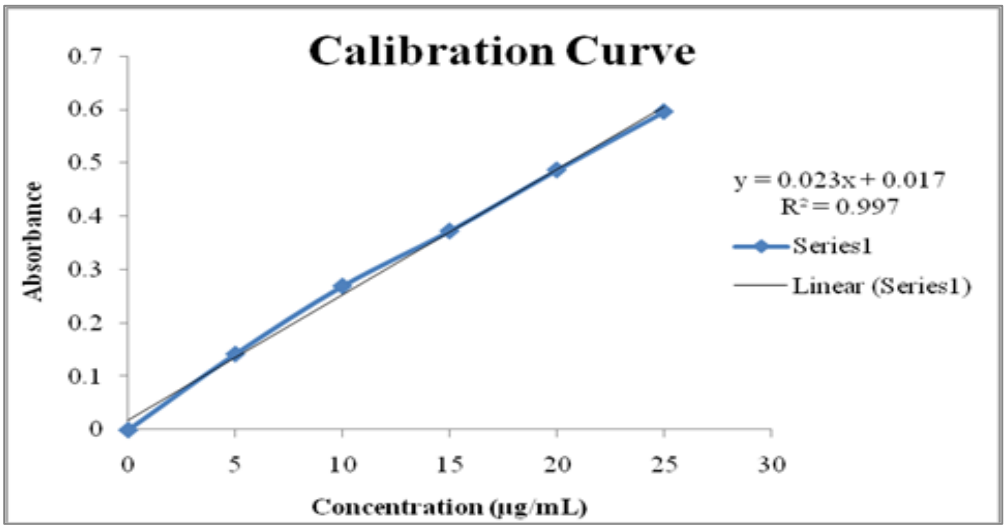


Fig 8.1 : Standard graph of Diltiazem HCl in 0.1 N HCl

Table : Observations for graph of Deflazacort in p H 6.8 phosphate buffer

Conc [µg/ml]	Abs
0	0
5	0.142
10	0.269
15	0.372
20	0.486
25	0.595

Figure: Standard graph of Deflazacort pH 6.8 phosphate buffer (244 nm)



Preformulation parameters of powder blend

Table : Pre-formulation parameters of Core blend

Table : Pre-compression parameters					
Formulations	**Bulk Density(gm/cm^2)**	**Tap Density (gm/cm^2)**	**Carr's Index (%)**	**Hausner ratio**	**Angle Of Repose(Ɵ)**
F_1	0.307±0.07	0.353±0.05	14.3±0.06	1.11±0.05	23.7±0.11
F_2	0.304±0.09	0.345±0.09	11.5±0.05	1.14±0.07	23.4±0.08
F_3	0.301±0.09	0.367±0.11	15.8±0.09	1.17±0.05	24.1±0.16
F_4	0.314±0.12	0.351±0.08	10.7±0.06	1.12±0.09	24.8±0.12
F_5	0.308±0.14	0.355±0.09	12.4±0.13	1.15±0.06	24.5±0.09
F_6	0.305±0.08	0.359±0.08	13.1±0.08	1.18±0.09	25.2±0.11
F_7	0.319±0.09	0.364±0.13	11.9±0.11	1.13±0.07	24.9±0.12
F_8	0.306±0.12	0.348±0.09	11.6±0.05	1.16±0.05	23.6±0.09

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.41±0.004 to 0.58±0.004 (gm/cm3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.51±0.003 to 0.66±0.003 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging between 8.27±0.28 to 30.45±0.07 which shows that the powder has good flow properties. All the formulations has shown the hausner ratio ranging between 1.01±0.010 to 1.55±0.007 indicating the powder has good flow properties.

***In-Vitro* Dissolution studies:** *In-Vitro* dissolution studies were carried out by using 900ml of 0.1 N HCl in USP dissolution apparatus by using paddle method for about 2 hours. After 2 hours the dissolution medium was withdrawn keeping the tablet in the dissolution basket. Then pH 6.8 phosphate buffer was added to the dissolution medium (900ml) and the dissolution was carried out for about 12 hours. The samples were withdrawn at regular time intervals of 30 min,1 hour,2 ,3,4,5,6,7,8,9, 10,11 and 12 hours respectively. The results were displayed in table 8.5.

Table:. *In -vitro* dissolution data

Time(Hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
1	21.52	22.60	20.32	41.53	13.75	11.61	19.62	9.25	33.3	7.16	11.08	21.91
2	34.11	35.82	41.67	44.39	26.98	24.18	20.17	11.71	56.0	11.36	15.31	25.56
3	47.75	48.91	54.23	57.48	39.57	27.27	21.34	24.59	59.1	24.84	29.64	33.15
4	52.24	49.76	57.47	62.32	42.92	32.69	34.23	27.31	62.5	37.33	30.72	36.28
5	55.96	53.95	58.62	65.67	55.11	45.41	47.60	32.29	65.1	42.94	33.09	40.87
6	63.21	66.72	59.83	78.52	58.35	58.61	49.57	35.40	78.2	52.41	45.15	51.19
7	86.79	79.95	63.76	79.28	61.42	63.83	52.82	48.01	81.4	55.66	57.46	54.69
8	99.63	81.10	66.91	80.32	64.57	66.71	65.71	53.32	94.5	68.07	58.85	67.38
9		94.86	69.54	81.94	77.20	70.82	68.22	56.75		73.14	61.41	69.79
10		97.25	72.43	84.71	79.39	71.29	73.99	60.21		86.37	74.03	72.33
11			75.27	87.15	82.48	84.32	86.18	61.98		90.05	77.81	75.94
12			78.56	88.40	85.21	93.53	98.29	77.25		91.92	82.32	83.68

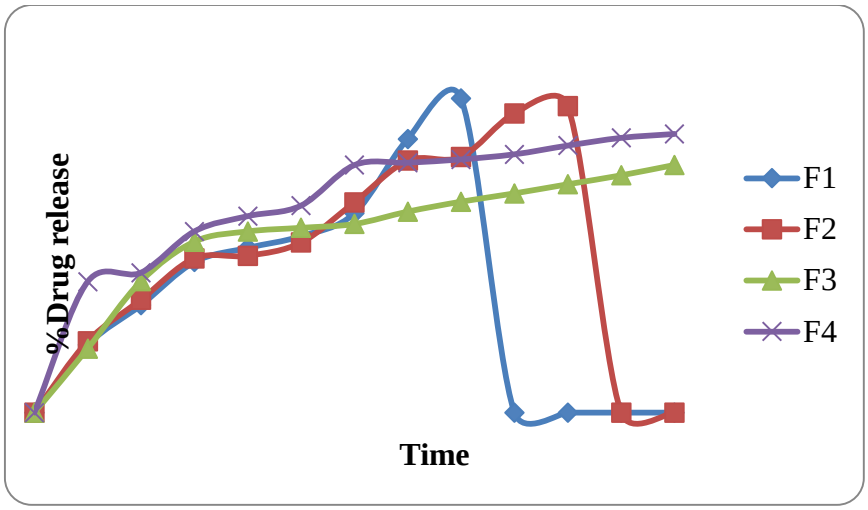


Fig : Dissolution profile of formulations prepared with HPMC K 15M polymer

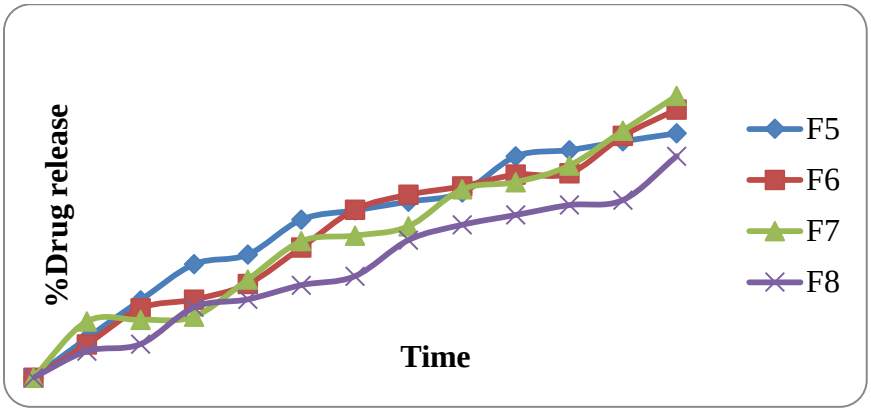


Fig : Dissolution profile of formulations prepared with HPC 2M polymer

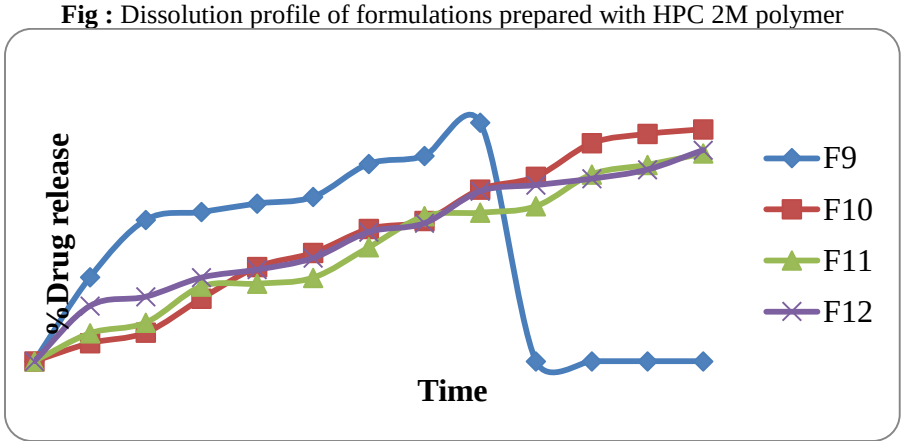


Fig : Dissolution profile of formulations prepared with HEC 2M as polymer

From the tabular column 8.5 it was evident that the formulations prepared with HPMC K 15M as retarding polymer in low concentrations the polymer was unable to produce the required retarding action to the tablets. As the concentration of polymer increases the retarding nature was also increased. HPMC K 15M in the concentration of 20 mg showed good % drug release i.e., 88.40 in 12 hours.

Where as in case of formulations prepared with HPC 2M as retarding polymer, the formulations with 15 mg concentration of polymer showed complete drug release in 12 hours only, whereas the concentration of polymer increases the retarding nature also increased. The Formulation Containing HPC 2M in 15 Mg

Concentration Showed good retarding nature with required drug release in 12 hours i.e., 98.29 %.

Where as in case of formulations prepared with HEC 2M as retarding polymer, the formulations with 10 mg concentration of polymer showed complete drug release in 12 hours only, The Formulation Containing HEC 2M in 10 Mg Concentration Showed good retarding nature with required drug release in 12 hours i.e., 91.92 %.

From the above results it was evident that the formulation F7 is best formulation with desired drug release pattern extended up to 12 hours.

Application of Release Rate Kinetics to Dissolution Data:

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release mode

Table : Release kinetics data for optimised formulation

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
19.62	1	1.000	1.293	0.000	1.905	19.620	0.0510	-0.707	80.38	4.642	4.316	0.326
20.17	2	1.414	1.305	0.301	1.902	10.085	0.0496	-0.695	79.83	4.642	4.306	0.336
21.34	3	1.732	1.329	0.477	1.896	7.113	0.0469	-0.671	78.66	4.642	4.285	0.357
34.23	4	2.000	1.534	0.602	1.818	8.558	0.0292	-0.466	65.77	4.642	4.037	0.605
47.6	5	2.236	1.678	0.699	1.719	9.520	0.0210	-0.322	52.4	4.642	3.742	0.900
49.57	6	2.449	1.695	0.778	1.703	8.262	0.0202	-0.305	50.43	4.642	3.695	0.947
52.82	7	2.646	1.723	0.845	1.674	7.546	0.0189	-0.277	47.18	4.642	3.613	1.028
65.71	8	2.828	1.818	0.903	1.535	8.214	0.0152	-0.182	34.29	4.642	3.249	1.393
68.22	9	3.000	1.834	0.954	1.502	7.580	0.0147	-0.166	31.78	4.642	3.168	1.474
73.99	10	3.162	1.869	1.000	1.415	7.399	0.0135	-0.131	26.01	4.642	2.963	1.679
86.18	11	3.317	1.935	1.041	1.141	7.835	0.0116	-0.065	13.82	4.642	2.400	2.242
98.29	12	3.464	1.993	1.079	0.233	8.191	0.0102	-0.007	1.71	4.642	1.196	3.446

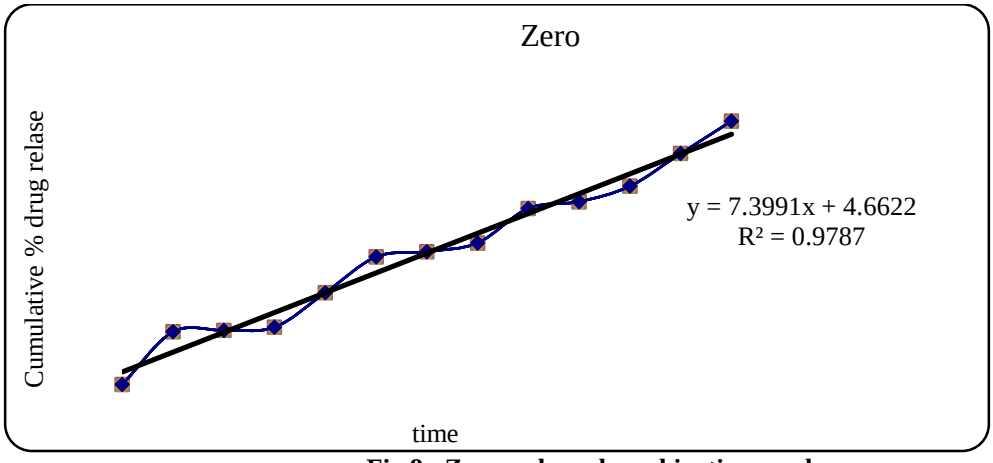


Fig 8 : Zero order release kinetics graph

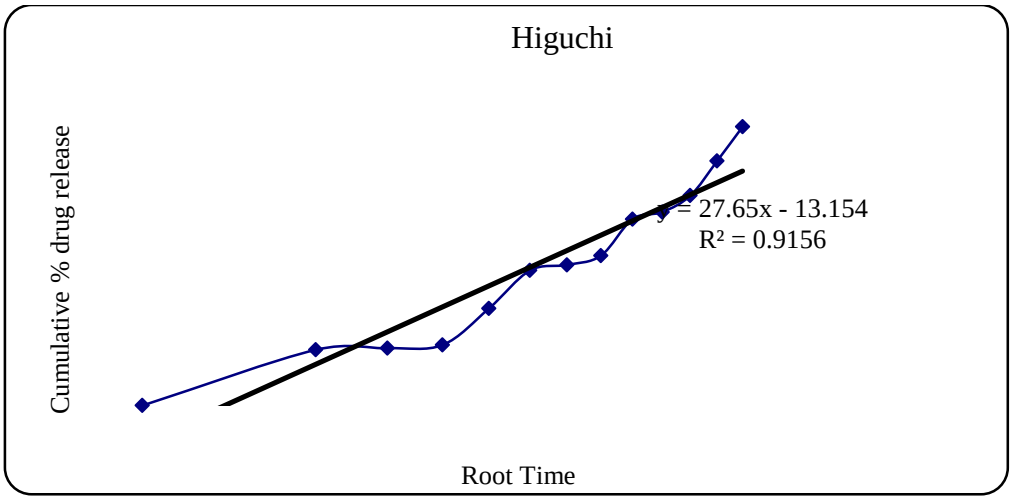


Fig : Higuchi release kinetics graph

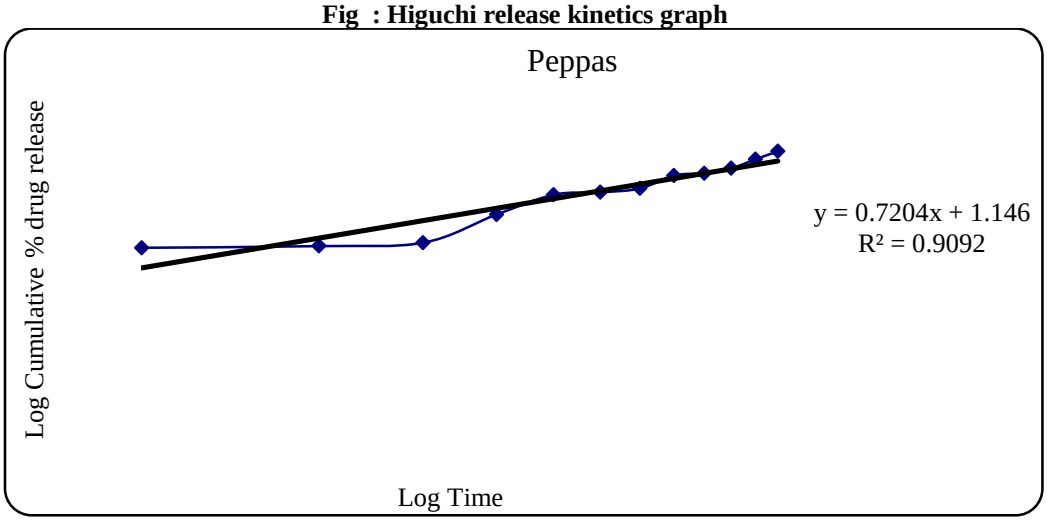


Fig : Kars mayer peppas graph

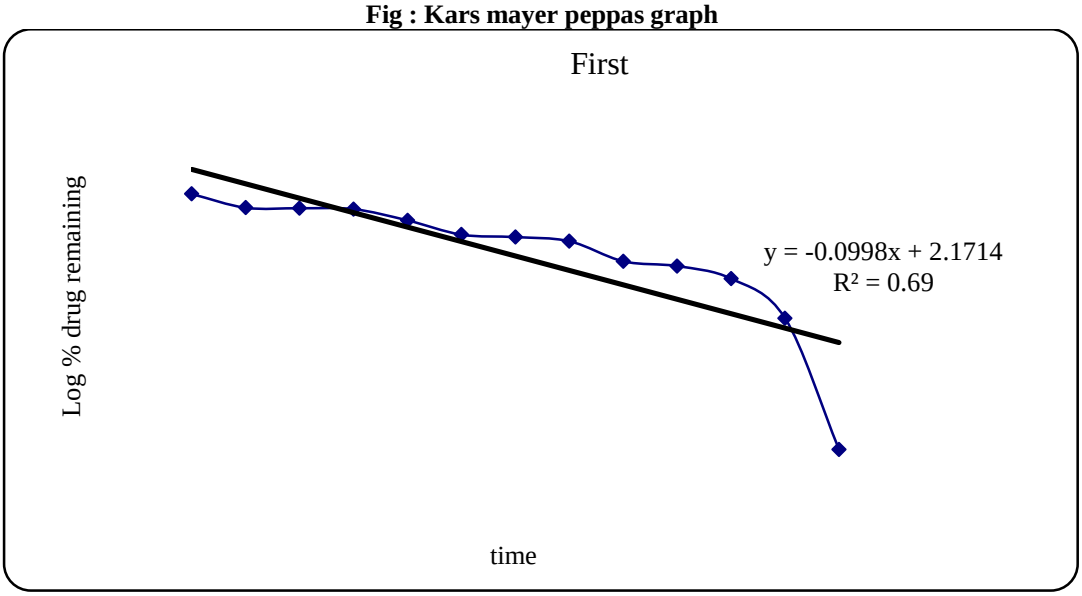


Fig : First order release kinetics graph

From the above graphs it was evident that the formulation F7 was followed Zero order release mechanism.

Drug and excipient compatibility studies

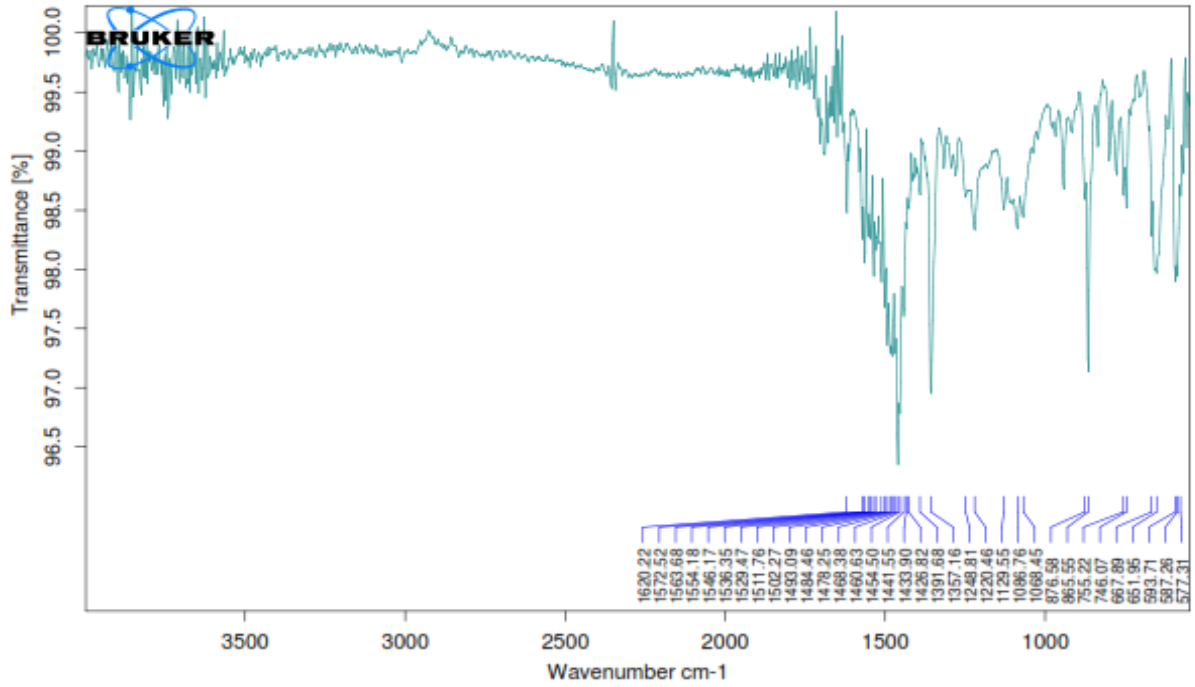


Figure 10.10: FT-IR Spectrum of Diltiazem hcl pure drug

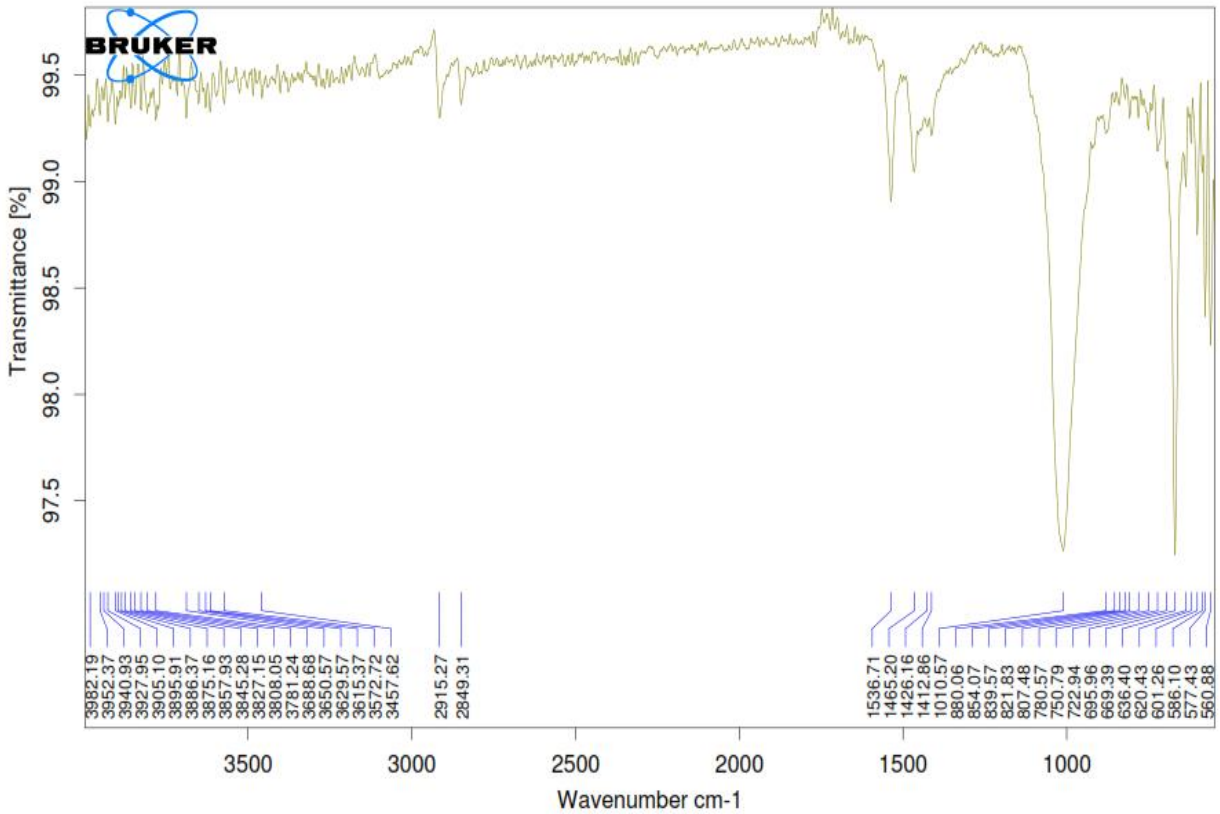


Figure 10.11: FT-IR Spectrum of Optimised Formulation

There is no incompatibility of pure drug and excipients. There is no disappearence of peaks of pure drug and in optimised formulation.

CONCLUSION:

Controlled release tablets Diltiazem HCl was formulated by Direct compression method using the semi synthetic polymers HPMC K 15M, HPC 2M and HEC 2M. Infrared spectra of the drug along with polymers reveal that there is no significant interaction between drug and polymers. Preformulation studies were done initially and the results were found within the limits. The evaluation tests results are found to be within Pharmacopeial specifications. From *in-vitro* dissolution study it was concluded that the formulation F7 containing HPC 2M in the ratio 1:3 was taken optimized formulation of sustained release tablet for 12 hours release as it fulfills all the requirement of Controlled release tablets. Kinetic studies were observed as Zero order release mechanism.

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