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Formulation and Evaluation of Sustained Release Matrick Tablet of Diltiazem Hydrochloride

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ABSTRACT

The main objective of the present work was to develop sustained release matrix tablets of Diltiazem Hydrochloride. To reduce the frequency of administration and to improve the patient compliance, a twice daily sustained release formulation of Diltiazem Hydrochloride is desirable. So sustained release Matrix Tablet of Diltiazem Hydrochloride was designed by using different polymers viz. Hydroxyl Propyl Methyl Cellulose (HPMC) Ethyl Cellulose (EC) Varying ratios of polymer were selected for the study. After fixing the ratio of drug and polymer for control the release of drug up to desired time, the release rates was modulated by single polymer. The IR study revealed that there was no chemical interaction between drug and excipients. The granules were prepared by direct compression method. Precompression parameters results indicate that granules are good flowing characteristics. After evaluation of physical properties like Weight variation, Hardness, Thickness, Friability of tablet, the different formulations checked for the Percentage Drug content which having good uniformity, The in vitro release study was performed in phosphate buffer pH 7.4 up to 11 hrs. The effects of polymer concentration were studied. Dissolution data was analyzed by Percentage cumulative drug release, the results of drug dissolution studies showed improved drug release, retardation effects of the polymers and could achieve better performance. It was observed that matrix tablets contained polymer of HPMC/ EC were successfully sustained the release of drug up to 11 hrs. Stability studies ($40\pm2°c/75\pm5\%\ RH$) for 3 months indicated that Diltiazem Hydrochloride was table in the matrix tablets.

Keywords: Diltiazem Hydrochloride, Hydroxyl Propyl Methyl Cellulose, Ethyl Cellulose.

INTRODUCTION:

The expression "Drug Delivery" covers an extremely broad scope of systems used to deliver therapeutic agents into the human body. Drugs are controlled with a fundamental point of relieving patient sicknesses. Drugs are never directed in their unadulterated structure yet are changed over in an appropriate formulation with the goal that its beginning and power of action just as absolute duration of action can be checked .

Drugs are once in a while controlled as unadulterated chemical substances alone and are constantly given as detailed preparations or medicines (for example, drug delivery frameworks or measurement shapes). These can change from moderately basic answers for complex drug delivery frameworks using suitable additives or excipient in the formulations. It is the formulation excipient, solubility, suspend, additives that modify solvency, suspend, thicken, preserve, emulsify, modify dissolution, improve the compressibility, and flavor drug substances to frame different preparations. Before a drug substance can be effectively figured into the structure of the measurement, numerous variables must be considered. These can be extensively gathered into the accompanying three classifications

- Biopharmaceutical considerations, including variables influencing the absorption of the drug substance from various administration courses.
- Drug factors, for example, the physical and chemical properties of the drug substance.
- Therapeutic considerations, including thought of the clinical sign to be dealt with and patient elements.

In traditional drug treatment, it tends to be seen that the administration of a drug by either intravenous infusion or an extra-vascular route, for example, orally, intramuscularly, or rectally does not keep up drug blood level inside the therapeutic range for an all-encompassing period of time. The short action is because of the powerlessness of conventional dosage forms to control temporal delivery.

Oral drug delivery is the most favored course of the different drug molecules among every single other course of drug delivery due to the simplicity of administration, patient compliance, and flexible structure of dose structure. Drug discharge is the procedure by which a drug leaves a drug item and is exposed to absorption, distribution, metabolism, and excretion, in the long run, to getting to be accessible for pharmacological action. Presently multi-day customary measurement types of drugs are quickly being supplanted by the new and the novel drug delivery frameworks. Among, these the controlled discharge/sustained release drug delivery systems have turned out to be incredibly famous in present-day therapeutics.

The regular measurement structures are quickly supplanted by this novel's sustained discharge procedures. The terms Sustained Release, Delayed Release or Prolong Release formulations are utilized to recognize drug delivery systems that are intended to accomplish or expand therapeutic impact by ceaselessly discharging medicine over an all-encompassing period of time after administration of a unit dose . Any drug or measurement structure adjustment that draws out the therapeutic action of the drug. The arrival of the drug is hindered for a postponed and delayed period of time in the fundamental circulation. Sustained Release formulation keeps up a uniform drug level in blood with better patient compliance.

just as expanded adequacy of drug . Sustained discharge tablets are commonly taken more than once per day during a course of treatment, though in conventional drug delivery systems, there is have to take 3-4 times dose in multi-day to accomplish a similar therapeutic action. Diltiazem hydrochloride is a Calcium channel foe and broadly utilized in the treatment of specific kinds of cardiovascular issues. The therapeutic impacts of Diltiazem hydrochloride are identified with its capacity to hinder the flood of calcium particles in cardiovascular and vascular smooth muscle during membrane depolarization. A basic dosing plan with more than once every day administration of the antihypertensive agent is known to expand patient compliance .

Here in this investigation, the all-inclusive discharge tablets were set up by a direct compression strategy. Direct compression is a favored strategy for the readiness of tablets as it offers a few points of interest like:

i. It is prudent contrasted with wet granulation since it requires less unit activity.

ii. Progressively appropriate for dampness and warmth delicate APIs.

iii. Changes in the dissolution profile do not happen on long haul storage ..

Direct compression excipients, for the most part, incorporate diluents, fasteners, and break down. The all-inclusive formulation Diltiazem hydrochloride were planned by utilizing Hydroxypropyl methylcellulose (HPMC) and povidone in various proportions, the all-encompassing discharge conduct of fabricated tablets were then explored. The present research try was coordinated towards the improvement of an all-inclusive discharge tablet formulation containing diltiazem HCl to be taken once instead of numerous times a day .

MATERIALS AND METHODS:

Material: Diltiazem hydrochloride API and HPMC was received as a gift sample from Torrent Pharmaccutical, Gujurat. All other ingredients used were of Pharmaceutical grade.

The batch size prepared for each formulation was of 20 tablets.

The sustained release tablet of diltiazem hydrochloride with HPMC K100M grade/EC were prepared by direct compression method.

Procedure : all the ingredients weighed accurately were passed through sieve mesh 60 and drug polymers were blended geometrically in mortar for 15 minutes to blend content uniformly then add microcrystalline cellulose, magnesium stearate and talc. After blending these ingredients, machine using single 8mm flat punches. The composition of batches shown in table no. 3

Formulation code :

- Tablets containing HPMC- DH
- Tablets containing EC – DE

Table No 1 : Formulation design of Sustained Release Matrix tablets by Direct Compression nod using Single Polymer.

Ingredient	**DH1**	**DH2**	**DH3**	**DH4**	**DC1**	**DC2**	**DC3**	**DC4**
Diltiazem Hydrochloride	120	120	120	120	120	120	120	120
HPMC K100M	80	100	120	140	-	-	-	-

EC	-	-	-	-	80	100	120	140
Microcrystalline cellulose	94	74	54	34	94	74	54	34
Mg Stearate	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3
Total	300	300	300	300	300	300	300	300

EVALUATION OF TABLETS

Evaluation of Tablets: Prepared tablets were evaluated for certain properties like tablet weight variation, assay, hardness, friability, dissolution study, *etc.*

Pre-compression Parameters: Pre-compression parameters of tablet powder blends such as bulk density, tapped density, carr's index, compressibility index, and Hausner ratio were calculated

Post-compression Parameters: The post-compression parameters for various batches were evaluated accordingly, such as tablet weight variation, hardness, friability, disintegration, *in-vitro* dissolution study.

1. Thickness

Thickness of tablets was determined using Vernier caliper. Five tablets form each batch were used, and average values were calculated.

2. **Weight variation Test**

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance (A W – 220 , Shimadzu) and the test was performed according to the official method.

Table No. 2 Specifications for tablets as per Pharmacopoeia on India

Average Weight of Tablet	**% Deviation**
80 mg or less	10
More than 80mg but less than 250 mg	7.5
250 mg or more	5

2. Drug Content

Five tables were randomly chose and finely powdered; quantity equivalent to 50 mg of Diltiazem Hydrochloride was accurately weighed and transferred to 100 ml volumetric flask containing 50 ml of phosphate buffer pH (7.4) This transferred to 100 ml volumetric flask containing 50 ml of phosphate buffer pH(7.4) This was allowed to stand for 6 h to ensure complete solubility of the drug. Solutions were made up to volume, filtered, suitably diluted

And estimated for diltiazem Hydrochloride contents at 237 nm, using a UV-visible spectrophotometer using phosphate duffer as blank The average result taken.

3. Hardness

For each formulation, the hardness of 6 tablets were determined using the Monsanto hardness tester (Candmach). The tablet was held along its oblong axis in between the tow jaws of the tester. At this point, reading should be zero kg/cm^2 Then constant force was applied by rotating the knob until the tablet fractured.

4. Friabilty

It is measure of tablet strength. It is related to tablet ability to withstan shock and abrasion without crumbling during the handling of manufacture, packing, shipment and consumer sue.

Method : 6 matrix tablets were weighed and placed Roche's Friabilator where the tablets were exposed to rolling and repeated shock resulting from free within the apparatus. After 25 revolutions the tablets were de-dusted and weighed again. The friability was determined as the percentage loss in the weight of the tablets. A loss of less than 1 % in weight is generally considered acceptable.

1. In Vitro Release Studies

In vitro drug release study for the prepared matrix tablets conducted for period of 10-12 hours using a six station USP XXVI type II (paddle) apparatus at 37^0 C $\pm 0.5^0$C and 50 rpm speed. The dissolution studies were carried out in triplicate for 12 hours in phosphate buffer of pH 7.4 under sink condition. At first half an hour and then every 1- hour interval samples of 5ml were withdrawn form dissolution medium and replaced with fresh medium to maintain the volume contestant. After filtration and appropriate dilution, the sample solution was analyzed at 237 nm for Diltiazem Hydrochloride by a UV- spectrophotometer for determining its cumulative % drug release or amount present in the sample.

STABILITY STUDIES

The selected formulation (DH3 & DE1) was tested for 3 Months at the storage conditions at room temperature and 40^0 C at 75 % RH, were analyzed for their drug content. The residual drug contents of formulations were found to be within the permissible limits as shown in the tbale. The tablets showed satisfactory physical stability at room temperature and 40^0C at 75 % RH. No appreciable changes were found in any of the formulations.

RESULTS AND DISCUSSION:

DILTIAZEM HYDROCHLORIDE CHARACTERIZATION

The characterization of drug was carried out by conducting various Physicochemical tests including melting point determination, spectral analysis such as UV spectrum and IR Spectrum for pure Diltiazem Hydrochloride.

Spectroscopic Studies :

1. UV Spectroscopy (Determination of) :

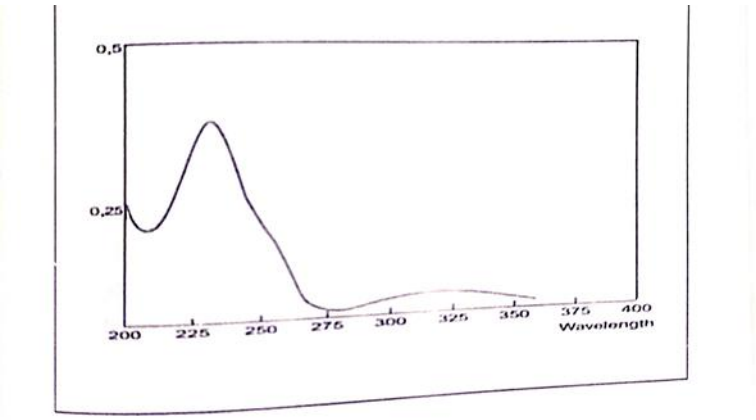

Fig No. 1 UV Spectrum of Diltiazem Hydrochioride.

The wavelength of maximum absorption (max) value of Dilitazem Hydrochloide is found to be 237 nm.

Table No 3 : Standard Calibration curve of Diltiazem Hydrochloide in Distilled water

Sr. No	Concentration (pg/ml)	Absorbance
1	0	0.00
2	2	0.091
3	4	0.180
4	6	0.260
5	8	0.356
6	10	0.430
7	12	0.520

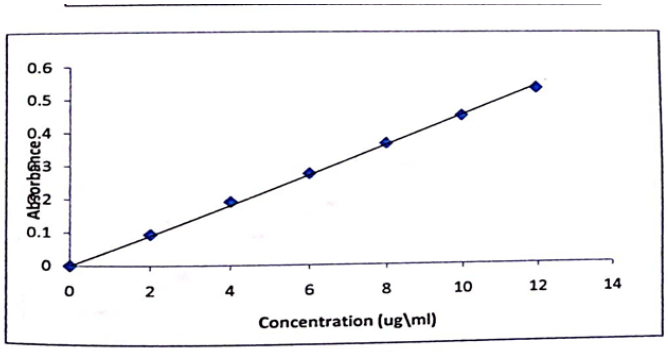

Fig No 2 : standard Curve of Diltiazem Hydrochloride in Distilled Water.

Table No. 4 : Standard Calibration curve of Diltiazem Hydrochloride in Phosphate Buffer.
(pH 7.4)

Sr. No	Concentration (pg/ml)	Absorbance
1	0	0.00
2	2	0.091
3	4	0.180
4	6	0.260
5	8	0.356
6	10	0.430
7	12	0.520

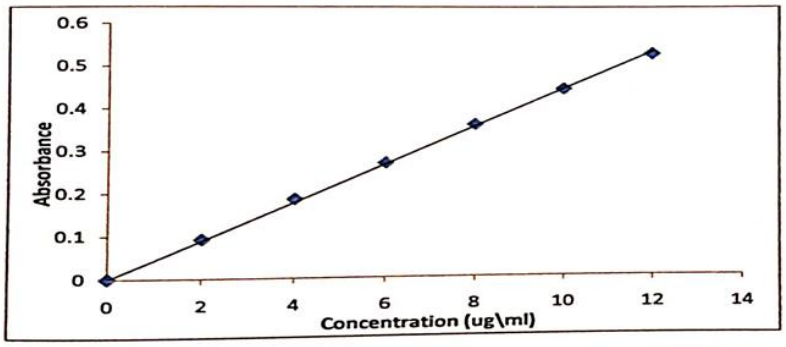

Fig No 3 : Standard Curve of Diltiazem Hydrochloride in Phosphate Buffer (pH 7.4)

DETERMINATION OF INFRARED ABSORPTION SPECTRUM :

The infrared absorption spectrum of Diltiazem Hydrochloride obtained on Ir is presented in Figure No. 6 Spectral assignments for major absorption bands are given below absorption bands are consistent with the reported spectrum of Dilitiazem Hydrochloride.

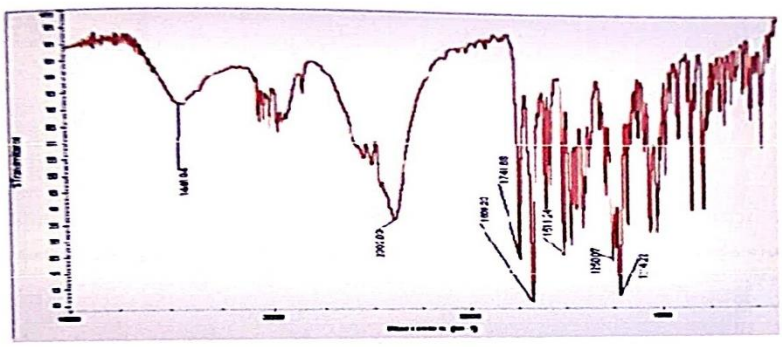

Figure No. 4 : infrared Spectrum of Diltiazem Hydrochloride.

Drug polymer interaction was checked by comparing the IR spectra of the physical mixture of drug with the excipients used with the IR spectrum of pure drug. IR spectral assignments for Diltiazem Hydrochloride revels that it gives characteristic peaks at 3056 cm-1, 3035 cm-1 , 2966 cm-1 , 2837 cm – 1 , 1740 cm- 1 , 1679 cm -1 , 839 cm – 1 and 781 cm- 1 frequencies in the region 400 cm-1 to 4000 cm- 1 Frequencies functional groups of pure drug remained intact in physical mixture containing different polymers. So it was concluded that there was no major interaction occurred between the drug and excipients used in the study. This established the stability of the drug in the formulation shown in figure no 7 and 8

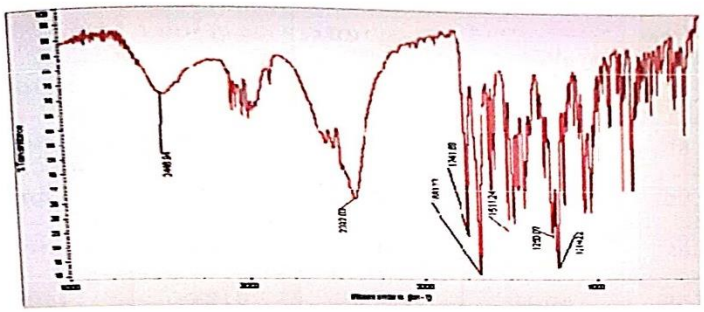

Figure No.7: Infrared spectrum of Combination of Diltiazem Hydrochloride and HPMC

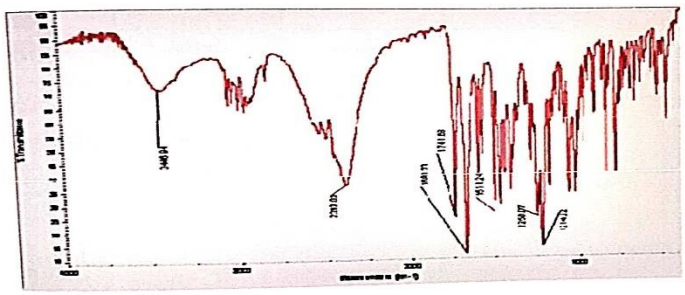

Figure No. 5 Infrared spectrum of combination of diltizem Hydrochloride Ethyl Cellulose.

Table No. 5 : Evaluation of Granules properties of single polymer

Formulation Code	**LBD* (g/ml)**	**TBD*(g/ml)**	**Carr's Index* (%)**	**Angle of repose* (0)**
DH_1	0.310	0.360	13.88	27.71
DH_2	0.315	0.354	11.01	28.10
DH_3	0.318	0.348	8.62	27.78

DH_4	0.320	0.343	6.70	26.52
DE_1	0.315	0.358	10.33	28.81
DE_2	0.321	0.358	9.72	27.11
DE_3	0.325	0.360	9.72	27.11
DE_1	0.327	0.363	9.91	26.14

Average of three determinations n =

EVALUTION OF TABLETS

Table No. 6 Evaluation of tablets of Single Polymer

Formuation Code	**Hardness* (Kg/cm2)**	**Thickness* (mm)**	**% Friability**	**Weight Variation (mg)**	**Drug content (%)**
DH_1	3.21± 0.13	3.1	0.45	298.23±2.41	99.20
DH_2	3.13±0.22	3.1	0.48	299.22±2.21	99.51
DH_3	3.14±0.15	3.1	0.51	299.27±1.34	99.55
DH_4	3.11±0.10	3.1	0.58	300.44±2.25	99.89
DE_1	3.01±0.12	3.1	0.49	301.83±1.40	99.11
DE_2	3.2±0.11	3.1	0.60	302.83±1.10	99.23
DE_3	3.2±0.18	3.1	0.59	299.57±1.56	98.58
DE_4	3.18±0.15	3.1	0.65	298.29±2.23	98.84

*Average of three determinations n=3

ZERO ORDER

1. In = vitro dissolution studies for sustained release matrix tablet of Diltiazem

Hydrochlorilde using $HPMC_1$

Table No 7 Dissolution data of formulation containing JIPMC

Time (hrs)	**DH1**	**DH2**	**DH3**	**DH4**
0	0	0	0	0
0.5	25.14	27.31	27.01	26.13
1	27.91	29.87	29.13	27.13
1.5	36.15	37.25	40.16	32.13
2	49.29	52.86	56.02	50.16
2.5	54.08	58.61	61.42	53.15
3	62.58	64.59	66.81	60.02
4	67.11	68.80	69.48	63.23
5	72.38	73.17	75.38	70.76
6	75.16	76.12	78.61	74.32
7	80.29	82.88	84.94	78.14
8	86.71	85.22	88.14	82.15
9	90.87	91.49	92.32	86.54

10	92.85	93.43	95.24	89.76
11	93.15	95.00	98.38	91.34

2. In –vitro dissolution studies for sustained release Matrix table of Diltiazem Hydrochloride using Ethyl cellulose:

Table No .8.Dissolution data of formulation containing Ethyl cellulose.

Time (hrs)	**DE1**	**DE2**	**DE3**	**DE4**
0	0	0	0	0
0.5	19.01	17.68	15.16	14.47
1	22.17	21.95	19.18	18.30
1.5	23.62	22.24	21.62	20.14
2	25.17	23.19	22.18	21.23
2.5	28.92	25.36	24.39	23.01
3	31.11	29.80	27.11	24.87
4	36.24	34.85	31.47	29.53
5	39.35	39.42	37.14	34.32
6	43.26	42.69	40.58	30.09
7	49.48	45.58	43.32	40.34
8	56.37	50.89	46.28	44.87
9	67.12	53.12	49.23	47.67
10	70.15	57.19	52.54	51.23
11	71.65	61.16	57.40	53.46

FIRST ORDER

Table No.9:Log cumulative percent of drug release vs time of formulation

DH to DH and DE1 to DE4.

Time in hours	**Log cumulative percent drug remained from the formulation prepared with HPMC by direct compression method**				**Log cumulative percent drug remained from the formulation prepared with EC by direct compression method**			
	DH1	**DH2**	**DH3**	**DH4**	**DE1**	**DE2**	**DE3**	**DE4**
0	2	2	2	2	2	2	2	2
0.5	1.87	1.86	1.86	1.87	1.90	1.91	1.92	1.93
1	1.85	1.84	1.85	1.86	1.89	1.90	1.90	1.91
1.5	1.80	1.79	1.77	1.83	1.88	1.89	1.89	1.90
2	1.70	1.67	1.64	1.69	1.87	1.88	1.89	1.89
2.5	1.66	1.61	1.58	1.67	1.85	1.87	1.87	1.88
3	1.57	1.50	1.52	1.60	1.83	1.84	1.86	1.87
4	1.51	1.49	1.48	1.56	1.80	1.81	1.83	1.84
5	1.44	1.42	1.39	1.46	1.78	1.78	1.79	1.81
6	1.39	1.37	1.33	1.40	1.75	1.75	1.77	1.78
7	1.29	1.23	1.17	1.33	1.70	1.73	1.75	1.77
8	1.12	1.16	1.07	1.25	1.63	1.69	1.73	1.74
9	0.96	0.92	0.88	1.12	1051	1.67	1.70	1.71
10	0.85	0.81	0.67	1.01	1.47	1.63	1.67	1.68
11	0.83	0.69	0.21	0.93	1.45	1.58	1.62	1.66

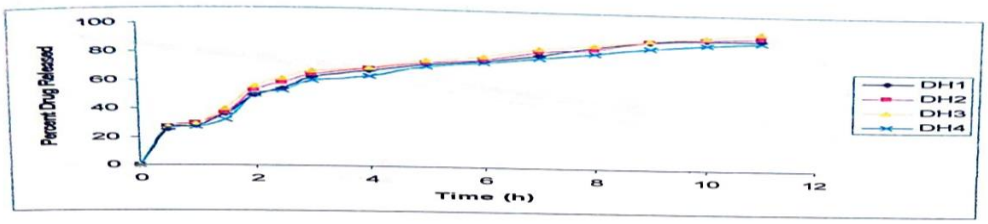

Fig. No. 9: Dissolution profile of formulations DH1-DH4.

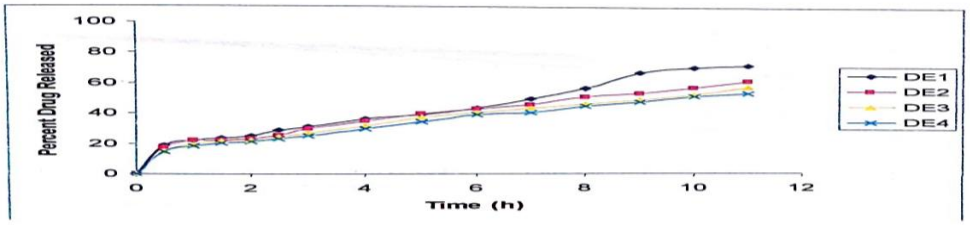

Fig No.10: Dissolution profile of formulations DE1-DE4.

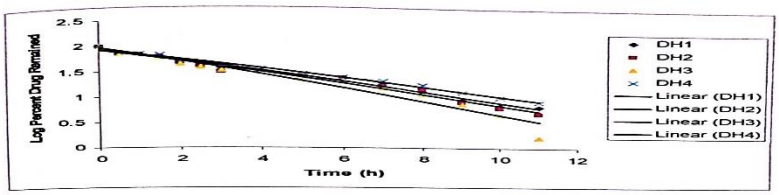

Fig. No.11:- Log Cumulative percent of Drug release vs Time of formulations DH1 – DH4

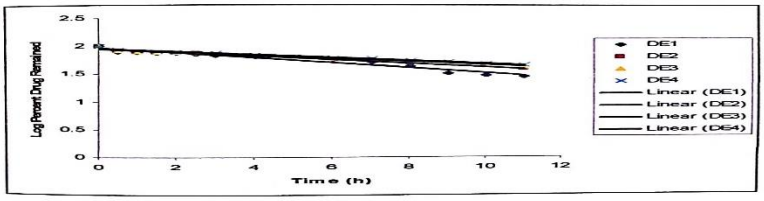

Fig. No.12: Log Cumulative percent of Drug release vs Time of formulations DE1-DE4

HIGUCHI

Table No.10: Cumulative percent of drug release vs square root of time of formulations DH1-DH4 and DE1-DE4

Square root of time	**DH1**	**DH2**	**DH3**	**DH4**	**DE1**	**DE2**	**DE3**	**DE4**
5047722	25.14	27.31	27.01	26.13	19.01	17.68	15.16	14.47
7.74596	27.91	29.87	29.13	27.13	22.17	21.95	19.18	18.30
9.48683	36.15	37.25	40.16	32.13	23.62	22.24	21.62	20.14
10.95445	49.29	52.86	56.02	50.16	25.17	23.19	22.18	21.23
12.24744	54.08	58.61	61.42	53.15	28.92	25.36	24.39	23.01
13.41640	62.58	64.59	66.81	60.02	31.11	29.80	27.11	24.87
15.49193	67.11	68.80	69.48	63.23	36.24	34.85	31.47	29.53
17.32050	72.38	73.17	75.38	70.76	39.35	39.42	37.14	34.32

18.97366	75.16	76.12	78.61	74.32	43.26	42.69	40.58	39.09
20.49390	80.29	82.88	84.94	78.14	49.48	45.58	43.32	40.34
21.90890	86.71	85.22	88.14	82.15	56.37	50.89	46.28	44.87
23.23790	90.87	91.49	92.32	86.54	67.12	53.12	49.23	47.67
24.49489	92.85	93.43	95.24	89.76	70.15	57.19	52.54	51.23
25.69046	93.15	95.00	98.38	91.34	17.65	61.16	57.40	53.46

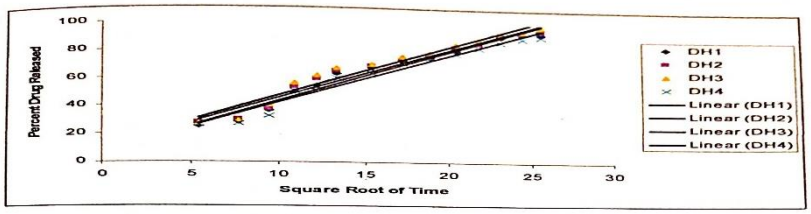

Figure No. 13: Cumulative percent of drug release vs square root of time of DH1 to DH4

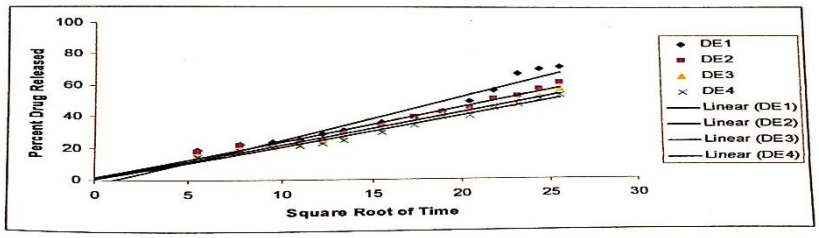

Figure No. 14 Cumulative percent of durg release vs square root of time of DE1 to DE4

PEPPAS

Table No 11. Log Time vs Log Cumulative percent of Drug Release of DH1 to DH4

Time	Log T	DH1	DH2	DH3	DH4
1	0.00	1.45	1.48	1.46	1.43
1.5	0.18	1.56	1.57	1.60	1.51
2	0.30	1.69	1.72	1.75	1.70
2.5	0.40	1.73	1.77	1.79	1.73
3	0.48	1.80	1.81	1.82	1.78
4	0.60	1.83	1.84	1.84	1.80
5	0.70	1.86	1.86	1.88	1.85
6	0.78	1.88	1.88	1.90	1.87
7	0.85	1.90	1.92	1.93	1.89
8	0.90	1.94	1.93	1.95	1.91
9	0.95	1.96	1.96	1.97	1.94
10	1.00	1.97	1.97	1.98	1.95
11	1.04	1.97	1.98	1.99	1.96

STABILITY STUDY :

Table No. 12 Drug content data for stability study of DH3 & formulations :

Formulation	Time	Percent drug content at Room Temperature		Percent drug content at 40^0C	
		Before storage	After storage	Before storage	After storage
	First day	98.38	98.37	98.38	98.19

DH3	1st month	98.38	98.36	98.38	98.13
	2nd month	98.38	98.36	98.38	97.94
	3rd month	98.38	98.35	98.38	97.86
DE1	First day	71.65	71.63	71.65	71.27
	1st month	71.65	71.50	71.65	71.04
	2nd month	71.65	71.34	71.65	70.83
	3rd month	71.65	71.20	71.65	70.81

CONCLUSION:-

The aim of the present study was to prepare sustained release matrix tablets of Diltiazem Hydrochloride for improved patient compliance, better therapeutic efficacy, less side effects and reduced dosage regimen with less toxicity for treatment of Angina Pectoris.

The Sustained released matrix tablet of Diltiazem Hydrochloride was designed by using hydrophilic polymers like Hydroxyl propyl methyl cellulose (HPMC K100M) HYDROPHOBIC polymer Ethyl Cellulose with suitable directly compressible agents. Different ratios of rug and polymer were selected for the study and drug release rates were studied. Following conclusions have been drawn form the present study.

- The analytical method used in the present study was found to be suitable for the estimation of Diltiazem Hydrochloride in different dissolution media. IR indicates that the drug is compatible with the polymers.
- The Lubricated blend was further confirmed with respect recompression parameters such as flow properties, bul density, compressibility index. Angle of repose. Post compressional parameter(hardness, friability, thickness and drug content.) was within the acceptable limit.
- Sustained release matrix Tablet of Diltiazem Hydrochloride containing blend of HPMC and EC successfully sustains the release of Diltiazem Hydrochloride for the period of 11 Hrs.
- Stability study indicates that there is insignificant change either in the physical appearance or in the drug content of the formulations.

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