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FORMULATION AND EVALUATION OF DILTIAZEM HCL SUSTAINED RELEASE TABLETS BY USING DIRECT COMPRESSION METHOD.

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Abstract: Diltiazem is a calcium channel blocker is used to treat high blood pressure and to control angina (chest pain). Its main use is to relaxing the muscles of heart and tissues. The development of Diltiazem tablets of matrix by applying various polymers in various formulations in different compositions. First undergo to check the drug characteristic that is the bioavailability of drug is 50%. The selected polymers incorporating into the sustained preparation of tablets of Diltiazem. The HPMC100M, ethyl cellulose is used for development by using direct compression method. The talc is used as glident and Mg.stearate used as lubricant. After formulation development undergo for evaluation parameters such as weight variation, thickness, hardness, drug content, disintegration, drug release studies. The optimised formulation under go for mathematical modelling .It fallows the Zero order and Higuchi equation. The optimised formulation undergo for stability studies for longer period of time for 3months .In stability studies performs the drug release studies and drug content studies. There no degradation between in formulation after 3months.

Keywords: Diltiazem, Calcium channel blocker, direct compression method, Tablets.

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INTRODUCTION

To cure the disease we want medicine. Medicine will be different dosage form. The best suitable dosage form for a patient is the oral solid dosage form, which will give more patient compliance. In conventional dosage form having many disadvantages for better therapeutic activities. To overcome the demerits of conventional dosage form a new drug delivery system called modified dosage form arises from past two decades. One of the modified dosage form is sustained release dosage form for increase the duration of action, minimising dose dumping, and frequency of dosage form with least toxicity and adverse effect of drug. The dosage form should be modified rate, period of time and targeting of drug.

MATERIALS & METHODS

MATERIALS

Diltiazem is obtained from Micro lab, Hosur . HPMC K 100M and Ethyl Cellulose N45 were obtained from Colorcon Asia Pvt. Ltd., Goa. Micro Crystalline Cellulose, Talc and Magnessium Sterate were collected from Loba Chem, Mumbai.

METHODS

1) Physical properties:

It includes mainly solubility, organoleptic characters.

2) **Solubility:**

The solubility studies carried out by water, methanol, ethanol, DMSO and acetone.

3) Organoleptic characters:

An organoleptic character mainly involves color, odour, and taste.

4) Analytical development of drug:

A) Calibration curve:

I) Preparation of standard curve for Diltiazem in pH 6.8 buffer:

To take first 10 mg of drug taken in a10 ml volumetric flask and dissolved in a 6.8 phosphate buffer it is 1000 PPM. Again take 1 ml from 1000 PPM make up to 10 ml in volumetric flask it is to 100 PPM. After that take 1 ml from 100 PPM it is to 10 PPM. Aliquotes of 1, 2, 3, 4 and 5 ml of was taken as serial dilutions and kept under for absorbance under an u.v visible spectroscopy at the 237nm.

II) Preparation of standard curve for Diltiazem in Methanol:

To take first 10mg of drug taken in a volumetric flask and dissolved in a methanol, it is 1000 ppm. Again take 1 ml from 1000 ppm make up to 10 ml in volumetric flask; it is to 100 ppm. After that take 1 ml from 100 ppm it is to 10 ppm. Aliquotes of 1, 2, 3, 4 and 5 ml of was taken as serial dilutions and kept under for absorbance under an u.v visible spectroscopy at the 237nm.

5) Drug – Excipient Compatibility study:

FTIR is a technique measures the absorption of infrared radiation by the sample material versus wavelength. The infrared absorption bands identify molecular components and structure.

6) Formulation of different batches:

Table No. 1: Formulation of batch F1 to F9

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Diltiazem	100	100	100	100	100	100	100	100	100
HPMC K100M	100	-	150	-	200	-	250	100	150
MCC	296	296	246	246	196	196	146	196	96
Ethyl celluloseN45	-	100	-	150	-	200	-	100	150
Magnesium stearate	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2
Total wt	500	500	500	500	500	500	500	500	500

7) Pre compression parameters:

The all the formulations pre compression parameters such as the angle of repose, bulk density, tap density, hausner's ratio, compressibility calculated by proper method.

8) Preparation of tablet (Direct Compression Method**):**

The dispensing of active pharmaceutical ingredient and excipients is carried out as per the manufacturing formula. Accurately weigh required quantity of dry mix materials and sieve

through 30 sieve. Dry mix the materials geometrically in a polybag for 5 minutes. Dry the granulated mass at inlet temperature of 45°c ±5°c in tray drier to get LOD in the range of 0.5 – 1.0%w/w at 50°c using moisture analyzer. Sieve the dried granules through 24 sieves. Lubricate the blended mass with magnesium stearate for 5 minutes. The feeded matter will be compressed by following specifications.

9) Evaluation parameters:

A) Weight variation test:

To perform the weight variation test the 20 tablets are taken. The individual weights of tablets are dispensed. The weights of the group of tablets are taken Essae electronic balance and the test was performed according to the official method. The calculation is done by the using fallowing formula, none of the individual Tablet weight should be less than 90% and more than 110% of the average weight.

Calculated by using the following formula;

$$\text{Weight variation} = \frac{\text{(Weight of tablet-Average weight)}}{\text{Average weight of tablet}} \times 100$$

B) Hardness:

The formulated tablets are under kept for the hardness studies. The hardness studies are performed by using hardness apparatus Pfizer. The hardness will do because knowing of the ability of a tablet to withstand mechanical shocks while handling. It is expressed in kg/cm2. Three tablets were randomly picked and hardness of the tablets was determined.

C) Thickness:

The thickness can be determined by the using thickness apparetus. The thickness can be estimated by the using Digital vernier calipers. Five tablets were used, and average values were calculated.

D) Appearances and Colour:

The shape, appearance and colour were determined by seeing visually in light.

E) Friability Test:

The formulated tablets are done by using the Roche friabilator (USP EF-2 Electrolab.). The 10 tablets initial weight is taken after tablets are poured in the fraiabilator. It is expressed in percentage (%).The friabilator was operated at 25rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W). The % friability was then calculated by

%F = 100 (1-W0/W) %. Friability of tablets less than 1% are considered acceptable.

F) Drug content test:

The drug content is estimated by the taking 20 tablets randomly and taken mortar and pestle crush it properly and take powder that is equivalent to the 100 mg of the diltiazem drug. The taken powder is dissolved in the ph 6.8 buffer solution and that is under kept for the sonication for freely dissolving the dissolved solution take and prepares dilutions and analysing by U.V to know the absorbance at 237 nm.

G) In-vitro dissolution studies:

The In-vitro dissolution studies done by the using USP-II apparatus. The paddle type apparatus is used. The pH 6.8 buffer is used as the dissolution medium for drug release studies. The each tablet is taken in the each basket with 900 ml of the dissolution medium. The room temperature is maintained 37.5^0c.The applied RPM is 100.The 5 ml of sample is withdrawn the same amount of sample is replaced by using 6.8 buffer solution to maintain the sink conditions. The dilutions are made and analysing of the absorbance in U.V apparatus at 237nm.

10) Mathematical Modelling of Drug Release Profile:

A) Zero Order Kinetic:

It describes the system in which the drug release rate is independent of its concentration.

Qt = Qo + Ko t , Where

Qt= Cumulative amount of drug dissolved in time t.

Qo = Initial amount of drug in the solution.

Ko = zero order release constant.

t = is the time at which the drug release is calculated or measured.

If the zero order drug release kinetic is obeyed, then a plot of Qt versus t will give a straight line with a slope of Ko and an intercept at zero.

B) First Order Kinetic:

It describes the drug release from the systems in which the release rate is concentration depended.

$\log Qt = \log Qo + kt/ 2.303$

Where

Qt = amount of drug released in time t.

Qo = initial amount of drug in the solution

k = first order release constant

C) Higuchi Model:

It describes the fraction of drug release from a matrix is proportional to square root of time.

$Mt / M\infty = kHt^{1/2}$

Where

Mt and M∞ are cumulative amounts of drug release at time t and infinite time,

kH = Higuchi dissolution constant .

D) Korsmeyer-Peppas model (Power Law):

The power law describes the drug release from the polymeric system in which release deviates from Fickian diffusion, as expressed in following equation.

$Mt / M\infty = ktn$

$\text{Log } [Mt / M\infty] = \log k + n \log t$

Where, Mt and M∞ are cumulative amounts of drug release

k = constant incorporating structural and geometrical characteristics of CR device,

n = Diffusional release exponent

11) Stability studies of optimised formulation:

The formula of F9 was optimized and selected for evaluation studies. Further stability study was done for F9

The selected formulations were packed in bottles, which are tightly plugged with cotton and capped. They were then stored at and 40^0C / 75% RH for 3 months and evaluated for Assay and *In vitro* drug release. Storage Conditions for accelerated is 40 ± 2^0C/75±5% RH for intermediate is 30 ± 2^0C/65±5% RH for long term is 25 ± 2^0C/60±5% RH. Testing Intervals for accelerated is initial, 1, 2, 3 & 6 months for long term is initial, 3, 6, 9, 12, 18, 24 & 36 months for intermediate is initial, 3, 6, 9 & 12 months.

RESULTS & DISCUSSIONS:

1) Organoleptic characters:

Table No.2: Organoleptic properties of API.

Properties	Results
Description	White powder
Taste	Tasteless
Odour	Odourless
Colour	Colourless

2) Solubility studies:

Table No. 3: Solubility of the Diltiazem in various solvents.

Solvent	Solubility properties of drug (1gm)
Water	Slightly Soluble
Ethanol	Freely Soluble
Methanol	Freely Soluble
Ether	Insoluble

3) Calibration curve of the Diltiazem at 6.8 buffers:

Table No. 4: Absorbance of the Diltiazem at 6.8 buffers:

Concentration(µg/ml)	Absorbance in p^H 6.8 Buffer
0	0
1	0.166
2	0.330
3	0.492
4	0.639
5	0.811

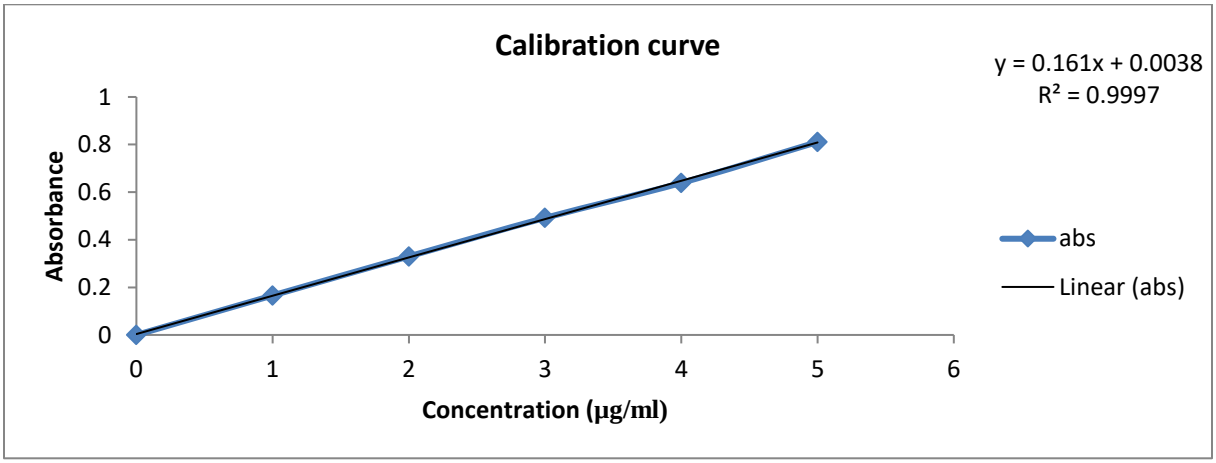

Fig. No. 1: Calibration curve of the Diltiazem at 6.8 buffers.

Table No. 5: Absorbance of diltiazem in methanol

Concentration(µg/ml)	Absorbance in methanol
0	0
10	0.18
20	0.34

30	0.48
40	0.62
50	0.78

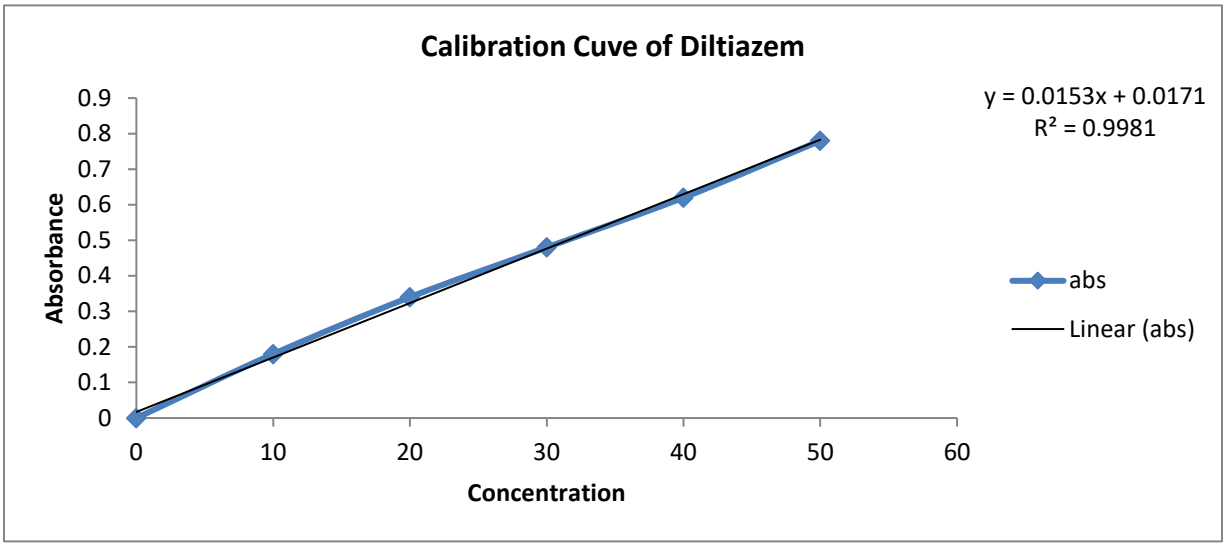

Fig. No-2: Calibration curve of Diltiazem in Methanol.

4) FTIR studies:

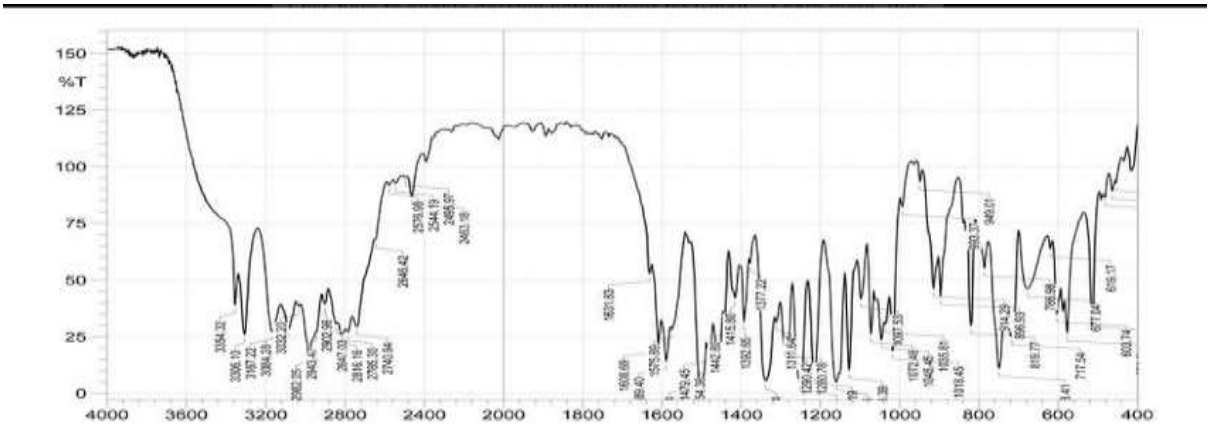

Fig.No.3: The pure drug of Diltiazem

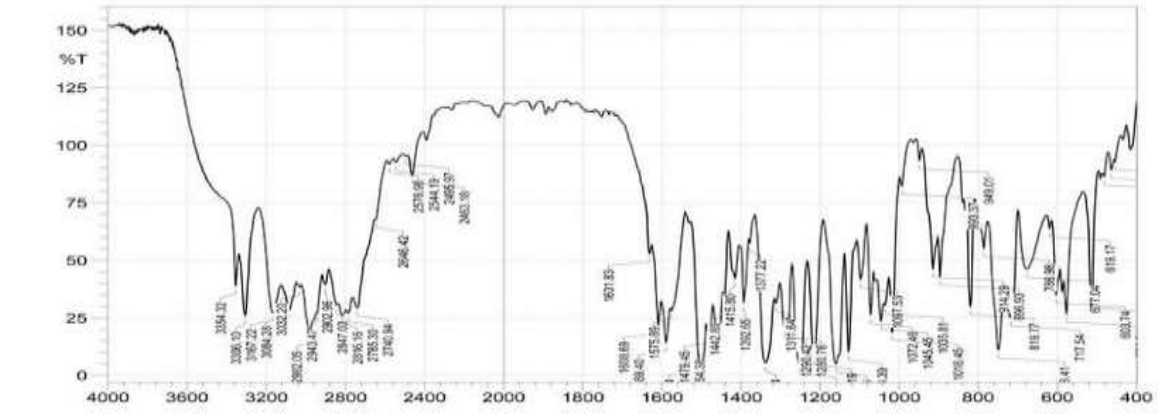

Fig.No.4: It showing the results of the pure spectra of Diltiazem and HPMC100M

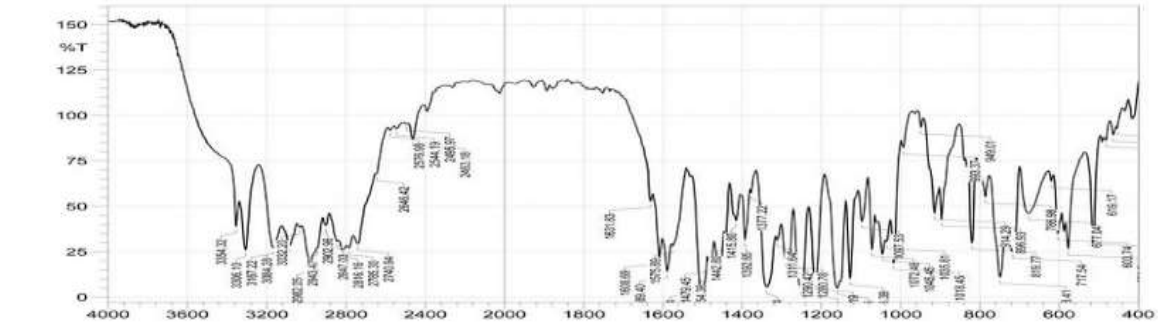

Fig.No.5: Results of the pure spectra of the Diltiazem and Ethyl CelluloseN45.

Table.No.6: FTIR spectra data for Diltiazem.

S.No	FUNCTIONAL GROUPS	IR ABSORPTION BAND OF PURE DILTIAZEM
1	C-N	1215
2	C-H(Alkane)	2847
3	N-H(Bending)	1630
4	OCH_3	1159
5	C=C	3306

Table No.7: FTIR spectra data for Diltiazem and HPMC100M

S.No	FUNCTIONAL GROUPS	IR ABSORPTION BAND OF PURE DILTIAZEM + HPMC 100M
1	C-N	1219
2	C-H(Alkane)	2850
3	N-H(Bending)	1639
4	OCH_3	1212
5	C=C	3312

Table No.8: FTIR spectra data for Diltiazem and Ethyl cellulose N45.

S.No	FUNCTIONAL GROUPS	IR ABSORPTION BAND OF PURE DILTIAZEM + ETHYL CELLULOSE N45
1	C-N	1217
2	C-H(Alkane)	2855
3	N-H(Bending)	1649
4	OCH_3	1219
5	C=C	3318

IR Spectral analysis Diltiazem (drug) showed the peaks at wave numbers of 1215(C-N) 2847 (C-H Alkane) 1630 (N-H Bending) 1159 (OCH_3- stretching) 3306(C=C) confirming the purity of the drug with the standard respectively.

In physical mixture of Diltiazem with HPMC 100 m major peaks of Diltiazem were 1219(C-N) 2850(C-H Alkane) 1639 (N-H Bending) 1212 (OCH3- stretching) 3312(C=C) wave numbers. However the additional peaks were observed in physical mixtures which could be due to the presence of excipients and it can be said that there was no chemical interaction between the drug and excipients from the spectra.

In physical mixture of Diltiazem with ethyl cellulose major peaks of Diltiazem were 1217(C-N) 2850(C-H Alkane) 1646(N-H Bending) 1219(OCH3- stretching) 3318(C=C) wave numbers. However the additional peaks were observed in physical mixtures which could be due to the presence of excipients and it can be said that there was no chemical interaction between the drug and excipients from the spectra.

Table No. 9: Pre-compression parameters for F1-F9 Formulation:

Formulation	Angle of Repose(Ø)	Bulk density (gm/ml)	Tapped density(gm/ml)	Carr's index (%)	Hausner's ratio
F1	22.58±0.13	0.44±0.02	0.58±0.02	16.28±0.13	1.28±0.01
F2	21.82±0.28	0.43±0.02	0.57±0.04	17.18±0.041	1.24±0.01
F3	23.29±0.19	0.42±0.00	0.55±0.01	16.11±0.11	1.21±0.02
F4	22.41±0.16	0.43±0.01	0.56±0.01	15.13±0.15	1.20±0.01
F5	21.21	0.44±0.01	0.53±0.00	15.15±0.05	1.25±0.02
F6	23.38±0.13	0.40±0.02	0.51±0.02	13.48±0.13	1.22±0.01
F7	21.52±0.28	0.44±0.02	0.52±0.04	13.28±0.041	1.21±0.01
F8	21.39±0.19	0.42±0.00	0.53±0.01	14.11±0.11	1.26±0.02
F9	21.16±0.16	0.42±0.01	0.54±0.01	14.33±0.15	1.22±0.01

Discussion: The all the F1-F9 formulations pre compression parameters such as the angle of repose, bulk density, tap density, hausners ratio, compressibility index all comes under the within range of limits. All the formulations fallow the good flow.

Table No: 10 Post compression parameters for F1-F9 Formulations:

Formulation	Weight Variation	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Drug content(%)	Disintegration (Min)
F1	499±1.02	3.50±0.01	4.5±0.06	0.622	95.24±0.22	26
F2	500±0.08	3.65±0.00	4.6±0.06	0.656	95.57±0.42	25

F3	500±0..02	3.7±0.01	4.5±0.00	0.696	96.43±0.13	25
F4	500±0.003	3.58±0.01	4.85±0.06	0.536	96.83±0.42	24
F5	500±0.08	3.42±0.01	4.7±0.010	0.556	97.86±0.32	23
F6	500±1.02	3.50±0.01	4.5±0.06	0.622	95.24±0.22	26
F7	500±0.08	3.65±0.00	4.6±0.06	0.656	99.57±0.42	25
F8	500±0..02	3.7±0.01	4.5±0.00	0.696	96.43±0.13	27
F9	500±0.003	3.58±0.01	4.85±0.06	0.536	96.83±0.42	24

Table No. 11: In–vitro drug release studies for all Formulations.

Time(Hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	26.32	16.52	18.32	19.15	18.32	22.52	24.65	25.15	25.21
2	14.62	23.52	23.52	26.15	25.53	33.53	38.62	31.15	33.65
3	23.31	29.12	29.13	32.45	35.65	49.72	56.46	41.12	44.52
4	28.61	35.46	37.25	43.13	42.55	54.62	60.62	55.32	58.22
5	34.21	41.15	49.12	51.18	57.18	69.43	68.65	61.63	65.23
6	51.53	52.32	54.12	65.25	69.83	76.53	75.65	73.65	72.23
7	74.65	51.65	62.56	74.45	74.13	79.15	89.65	82.65	82.23
8	92.52	62.32	75.32	80.25	82.12	84.35	96.23	94.56	92.56
9	94.32	71.16	79.41	83.13	93.12	92.56	96.55	94.65	99.86

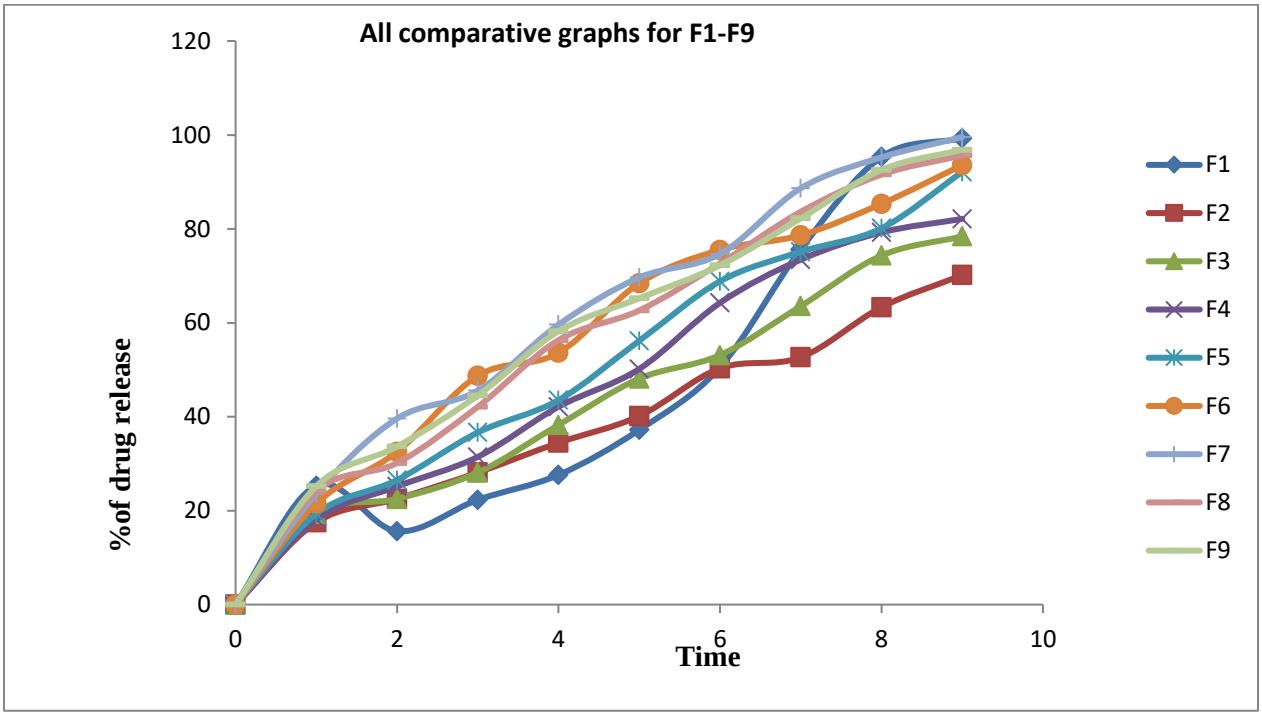

Fig.No.6: All comparative graphs for the F1-F9 Formulations

Table No.12: Kinetic studies for optimised Formulation (F9).

Time	%CDR	logT	√T	Log%CDR	ARA	Log%ARA
0	0	1	0	1	100	2
1	25.21	0	1	1.373	74.79	1.882
2	33.65	0.30103	1.414	1.597	66.35	1.7808
3	44.52	0.47712	1.732	1.658	55.48	1.7359
4	58.22	0.60206	2	1.775	41.78	1.6061
5	65.23	0.69897	2.236	1.842	34.77	1.4821
6	72.23	0.778151	2.449	1.873	27.77	1.4039
7	82.23	0.845098	2.645	1.947	17.77	1.0549
8	92.56	0.90309	2.828	1.978	7.44	0.678
9	99.86	0.954243	3	1.998	0.14	0.346

Zero order plot:

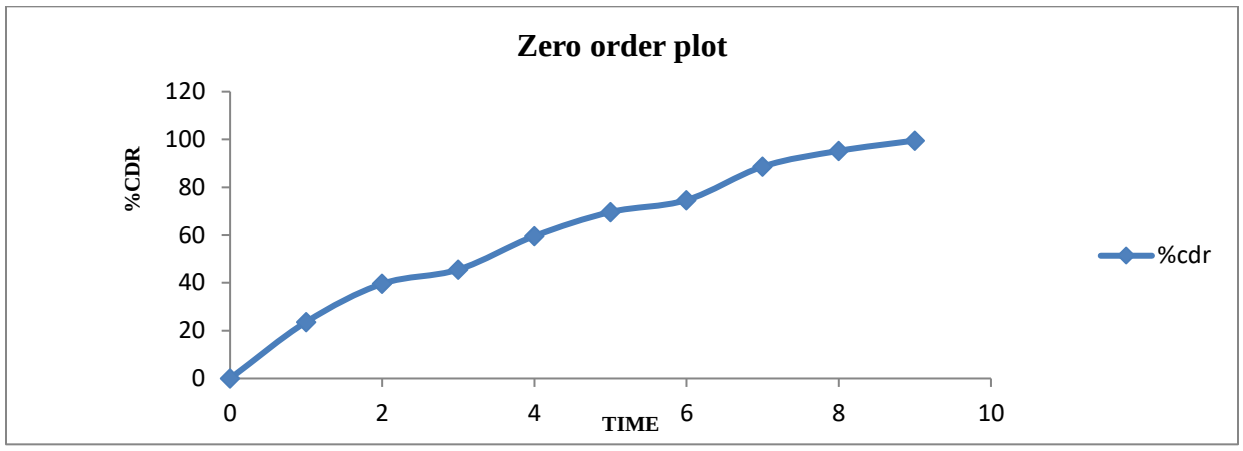

Fig No. 7: Zero order plot of optimized Formulation.

First order plot:

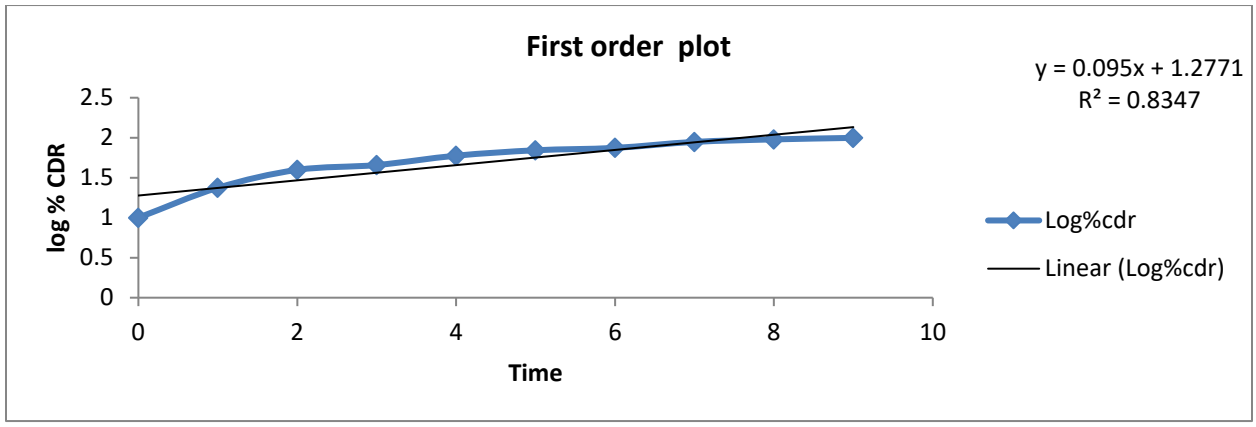

Fig No. 8: First order plot of optimized Formulation.

Higuchi plot:

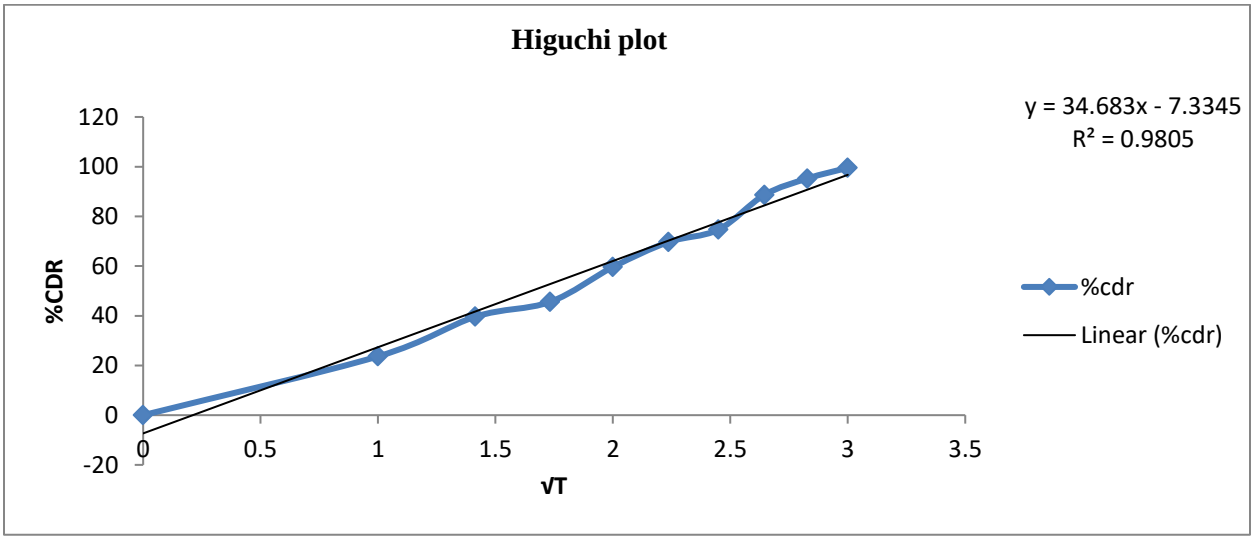

Fig No. 9: Higuchi plot of optimized Formulation.

Table No. 13: kinetic profile values

Sl. No.	Zero order	First order	Higuchi
Code	R^2	R^2	R^2
F9	0.989	0.834	0.980

Discussion: It was concluded that the optimized formulation F9 followed zero order release where the regression value was found to be 0.989. It was also found that the drug was released by diffusion as the regression in Higuchi's plot was 0.980.

Stability Results:

Table no. 14: Results of stability studies of optimized formulation F-9

Formulation Code	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per specifications
F9	25°C/60%RH % Release	99.86	99.99	99.86	99.53	Not less than 85%
F9	30°C/75%RH	99.86	99.68	99.92	99.89	Not less than 85%

	% Release					
F9	40°C/75%RH % Release	99.86	99.85	99.85	99.56	Not less than 85%

DISCUSSION:

It was concluded that stability studies of the optimized F9 was carried out using the samples at temperatures $40^0C \pm 2^0C$/ 75% ± 5%RH for a period 3 months, the Diltiazem matrix tablets are observed and there is no significant change in the release characteristics and physicochemical properties.

CONCLUSSION

The sustained release Diltiazem Hcl tablets prepared by using different excipients .The before going to formulate the tablets the pre-formulation studies are carried out such as FTIR, calibration, organoleptic characters. The formulation is developed by using polymers such as HPMC 100M and ethyl cellulose used in different trails. The pre compression parameters such as angle of repose, bulk density, true density, compressibility index, these are found to be within the limits. The tablets of Diltiazem Hcl sustained release prepared by direct compression method. The talc used as glident and magnesium sterate used as lubricant. The after development of sustained release tablets of Diltiazem Hcl they undergo for evaluation parameters. Such as weight variation, thickness, friability, drug content, disintegration, and in vitro dissolution studies. They all are found in within range of limits. The in vitro drug release studies carried out by USP-II apparatus. The buffer medium is P^H 6.8 .The optimised formulation F9 undergo for mathematical modelling to know about the diffusion mechanism .It fallows the zero order and Higuchi equation .The optimised formulation undergo for stability studies for 90 days. In stability studies the drug content and drug release studies carried out. These no degradation takes place in the drug content and drug release studies.

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