CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
SJIF Impact Factor: 7.187

Available online at: http://www.iajps.com *Research Article*

FORMULATION AND EVALUATION OF CONTROLLED RELEASE TABLETS OF FELODIPINE

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Article Received: August 2023 Accepted: September 2023 Published: October 2023

Abstract:

In the present work, an attempt has been made to developed Controlled release tablets of Felodipine by selecting different types of Na CMC, HPMC K 100 and Sodium alginate as retarding polymers. All the formulations were prepared by direct compression method. The blend of all the formulations showed good flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Among the entire formulations 9 formulations showed maximum % drug release i.e., 98.68 % in 12 hours. Hence it is considered as optimized formulation F5 which contains HPMC K 100 (30mg). The optimized formulation dissolution data was subjected to release kinetics; from the release kinetics data it was evident that the formulation followed Peppas release kinetics mechanism of drug release.

Keywords: *Felodipine, Na CMC, HPMC K 100, Sodium alginate and Controlled release tablets.*

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Please cite this article in press ***Takur Nagamalleshwari Bai*** *et al,* ***Formulation And Evaluation Of Controlled Release Tablets Of Felodipine,*** *Indo Am. J. P. Sci, 2023; 10 (10).*

INTRODUCTION:

Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage form. Oral route is considered most natural, convenient and safe due to its ease of administration, patient acceptance, and cost effective manufacturing process. Pharmaceutical products designed for oral delivery are mainly immediate release type or conventional drug delivery systems, which are designed for immediate release of drug for rapid absorption [1]

Controlled drug delivery systems can include the maintenance of drug levels within a desired range, the need for fewer administrations, optimal use of the drug in question, and increased patient compliance. While these advantages can be significant, the potential disadvantages cannot be ignored like the possible toxicity or non-biocompatibility of the materials used, undesirable by-products of degradation, any surgery required to implant or remove the system, the chance of patient discomfort from the delivery device, and the higher cost of controlled-release systems compared with traditional pharmaceutical formulations. [2,3] The ideal drug delivery system should be inert, biocompatible, mechanically strong, comfortable for the patient, capable of achieving high drug loading, safe from accidental release, simple to administer and remove, and easy to fabricate and sterilize. The goal of many of the original controlled-release systems was to achieve a delivery profile that would yield a high blood level of the drug over a long period of time. [4] With traditional drug delivery systems, the drug level in the blood follows the in which the level rises after each administration of the drug and then decreases until the next administration. The key point with traditional drug administration is that the blood level of the agent should remain between a maximum value, which may represent a toxic level, and a minimum value, below which the drug is no longer effective.

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

ADVANTAGES:

1] Therapeutic advantage:
Reduction in drug plasma level fluctuation, maintenance of a steady plasma level of the drug over a prolonged time period, ideally simulating an intravenous infusion of a drug.

2] Reduction in adverse side effects and improvement in tolerability:
Drug plasma levels are maintained within a narrow window with no sharp peaks and with AUC of plasma concentration Vs time curve comparable with total AUC from multiple dosing with immediate release dosage form.

3] Patient comfort and compliance:
Oral drug delivery is the most common and convenient for patient and a reduction in dosing frequency enhances compliance.

4] Reduction in Health care cost:
The total cost of therapy of the controlled release product could be comparable or lower than the immediate release product with reduction in side effects. The overall expense in disease management also would be reduced. This greatly reduces the possibility of side effects, as the scale of side effects increases as we approach the maximum safe concentration.
Avoid night time dosing: It also good for patients to avoid the at night time.

5] Economy: The initial unit cost of sustained release products is usually greater than that of conventional dosage form because of the special nature of these compounds but importantly average cost of treatment over an prolong period of time may be less

Disadvantages of sustained release dosage form:

1] Dose dumping:
Dose dumping is a phenomenon whereby relatively large quantity of drug in a controlled release formulation is rapidly released, introducing potentially toxic quantity of the drug into systemic circulation. Dose dumping can lead to fatalities in case of potent drugs, which have a narrow therapeutic index.

2] Less flexibility in accurate dose adjustment:
In conventional dosage forms, dose adjustments are much simpler e.g. tablet can be divided into two fractions. In case of controlled release dosage forms, this appears to be much more complicated. Controlled release property may get lost, if dosage form is fractured.

3] Poor In-vitro In-vivo correlation:
In controlled release dosage form, the rate of drug release is deliberately reduced to achieve drug release possibly over a large region of gastrointestinal tract. Here the so- called ‘absorption window’ becomes important and may give rise to unsatisfactory drug

absorption in-vivo despite excellent in-vitro release characteristics.

4] Increased potential for first pass clearance:

Hepatic clearance is a saturable process. After oral dosing, the drug reaches the liver via portal vein. The concentration of drug reaching the liver dictates the amount metabolized. Higher the drug concentration, greater is the amount required for saturating an enzyme surface in the liver. Conversely, smaller the concentration found with the controlled release and a sustained release dosage form, lesser is the possibility of saturating the enzyme surface. The possibility of reduced drug availability due to the first pass metabolism is therefore greater with controlled release and sustained released formulation than with conventional dosage form.

MATERIALS AND METHODS:

FelodipineProcured From Plendil Pharmaceuticals Pvt. Ltd, India. Provided by SURA LABS, Dilsukhnagar, Hyderabad, Na CMC Loba Chemie Pvt.Ltd Mumbai, India, HPMC K 100 Merck Specialities Pvt Ltd, Mumbai, India Sodium alginate Aravind Remedies (AR), Chennai, India PVP K30 Unify chemicals, Jothi Aromas and DK Enterprises, India MCC PH 101 S.D. Fine Chemicals. India Magnesium stearate Merck Specialities Pvt Ltd, Mumbai, India, Talc Merck Specialities Pvt Ltd, Mumbai, India.

Analytical method development:

a) Determination of absorption maxima:

100mg of Felodipine 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 was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400 nm.

b) Preparation calibration curve:

100mg of Felodipine 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 Felodipine per ml of solution. The absorbance of the above dilutions was measured at 363nm 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 (R^2) which determined by least-square linear regression analysis. The above procedure was repeated by using pH 6.8 phosphate buffer solutions.

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

Table : Angle of Repose values (as per USP)

Angle of Repose	Nature of Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Bulk density:
Density is defined as weight per unit volume. Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment. 10 gm powder blend was sieved and introduced into a dry 20 ml cylinder, without compacting. The powder was carefully leveled without compacting and the unsettled apparent volume, Vo, was read.
The bulk density was calculated using the formula:

$$\text{Bulk Density} = M / V_o$$

Where, M = weight of sample
V_o = apparent volume of powder

Tapped density:
After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this was repeated until difference between succeeding measurement is less than 2 % and then tapped volume, V measured, to the nearest graduated unit. The tapped density was calculated, in gm per L, using the formula:

$$\text{Tap} = M / V$$

Where, Tap= Tapped Density
M = Weight of sample
V= Tapped volume of powder

Measures of powder compressibility:
The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it is measures of the relative importance of interparticulate interactions. In a free-flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value.

For poorer flowing materials, there are frequently greater interparticle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index which is calculated using the following formulas:

$$\text{Carr's Index} = [(\text{tap} - b) / \text{tap}] \times 100$$

Where, b = Bulk Density
Tap = Tapped Density

Table : Carr's index value (as per USP)

Carr's index	Properties
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair to Passable
21 – 35	Poor
33 – 38	Very Poor
>40	Very Very Poor

Formulation development of Tablets:
All the formulations were prepared by direct compression. The compositions of different formulations are given in Table 7.3.The tablets were prepared as per the procedure given below and aim is to prolong the release of Felodipine Total weight of the tablet was considered as 100mg.

Procedure:

1) Felodipine and all other ingredients were individually passed through sieve no ≠ 60.
2) All the ingredients were mixed thoroughly by triturating up to 15 min.
3) The powder mixture was lubricated with talc.
4) The tablets were prepared by using direct compression method.

Table : Formulation composition for tablets

INGREDIENTS (MG)	FORMULATION CODE								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Felodipine	10	10	10	10	10	10	10	10	10
Na CMC	10	20	30	-	-	-	-	-	-
HPMC K 100	-	-	-	15	30	45	-	-	-
Sodium alginate	-	-	-	-	-	-	20	40	60
PVP K30	5	5	5	5	5	5	5	5	5
MCC PH 101	65	55	45	60	45	30	55	35	15
Magnesium stearate	6	6	6	6	6	6	6	6	6
Talc	4	4	4	4	4	4	4	4	4
Total tablet weight	100	100	100	100	100	100	100	100	100

All the quantities were in mg

RESULT AND DISCUSSION:

Standard Calibration curve of Felodipine:

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

S. No.	Concentration (µg/ml)	Absorbance* (at 363 nm)
1	0	0
2	2	0.145
3	4	0.281
4	6	0.423
5	8	0.547
6	10	0.666

It was found that the estimation of Felodipine by UV spectrophotometric method at λ_{max} 363 nm in 0.1N Hydrochloric acid had good reproducibility and this method was used in the study. The correlation coefficient for the standard curve was found to be closer to 1, at the concentration range, 2-10µg/ml.

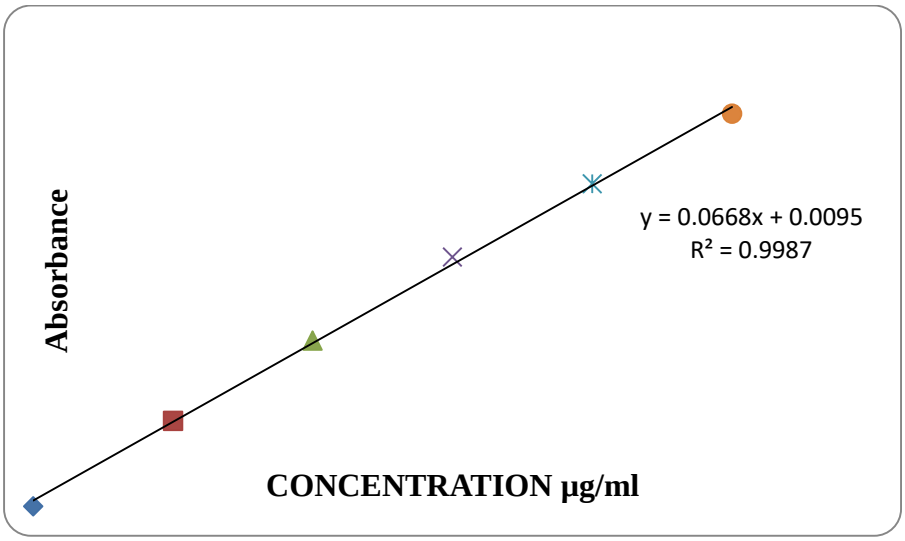

Fig : Standard graph of Felodipine in 0.1 N HCl

Table : Concentration and absorbance obtained for calibration curve of Felodipine in pH 6.8 Phosphate buffer.

S. No.	Concentration (µg/ml)	Absorbance* (at 365 nm)
1	0	0
2	2	0.136
3	4	0.245
4	6	0.358
5	8	0.491
6	10	0.599

It was found that the estimation of Felodipine by UV spectrophotometric method at λ_{max} 365 nm in pH 6.8 Phosphate buffer. It had good reproducibility and this method was used in the study. The correlation coefficient for the standard curve was found to be closer to 1, at the concentration range, 2-10µg/ml.

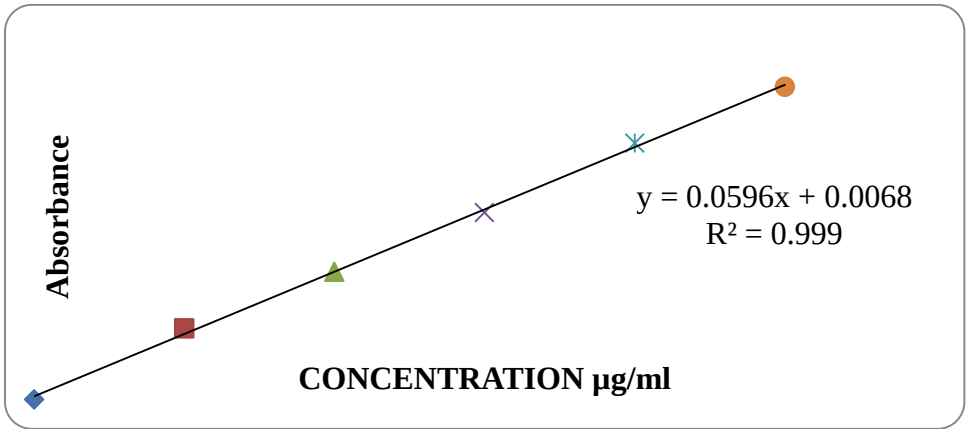

Fig : Standard graph of Felodipine in pH 6.8 Phosphate buffer

Evaluation Parameters for sustained release tablets of Felodipine:

Pre-compression parameters:

The data's were shown in Table 8.3.The values for angle of repose were found in the range of 25.43±0.48-28.52±0.35. Bulk densities and tapped densities of various formulations were found to be in the range 0.44±0.09 to 0.58±0.05 (gm/cc) and 0.54±0.05 to 0.69±0.04 (gm/cc) respectively. Carr's index of the prepared blends fall in the range of 14.93±0.01% to 18.56±0.09 %. The Hausner ration fall in range of 1.15±0.07 to 1.21±0.06 . From the result it was concluded that the powder blends had good flow properties and these can be used for tablet manufacture.

Table : Pre-compression parameters

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	25.43±0.48	0.57±0.01	0.65±0.05	15.74±0.01	1.17±0.04
F2	25.64±0.52	0.44±0.09	0.54±0.05	15.48±0.05	1.18±0.06
F3	28.52±0.35	0.51±0.02	0.62±0.04	16.12±0.04	1.15±0.07
F4	27.38±0.47	0.58±0.05	0.69±0.04	15.82±0.05	1.18±0.08
F5	25.72±0.51	0.55±0.02	0.66±0.05	18.56±0.09	1.20±0.07
F6	26.45±0.65	0.52±0.03	0.63±0.02	15.25±0.02	1.16±0.05
F7	25.61±0.21	0.49±0.05	0.59±0.06	14.93±0.01	1.19±0.02
F8	26.31±0.35	0.56±0.04	0.65±0.08	16.61±0.00	1.18±0.05
F9	27.74±0.42	0.53±0.09	0.67±0.02	18.35±0.09	1.21±0.06

Post compression Parameters:

Weight variation:

Tablets of each batch were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet and was shown in the Table 8.4. The average weight of the tablet is approximately in range of 95.73 to 102.14 mg, so the permissible limit is ±5% (100 mg). The results of the test showed that, the tablet weights were within the pharmacopoeia limit.

Hardness test:

Hardness of the three tablets of each batch was checked by using Pfizer hardness tester and the data's were shown in Table 8.4. The results showed that the hardness of the tablets is in range of 4.2 to 5.5 kg/cm^2, which was within IP limits.

Thickness:

Thickness of three tablets of each batch was checked by using Vernier Caliper and data shown in Table-8.4. The result showed that thickness of the tablet is raging from 4.14 to 4.95 mm.

Friability:

Tablets of each batch were evaluated for percentage friability and the data's were shown in the Table 8.4. The average friability of all the formulations lies in the range of 0.16 to 0.91 % which was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets.

Assay: Assay studies were performed for the prepared formulations. From the assay studies it was concluded that all the formulations were showing the % drug content values within 96.14 -99.71 %.

Table : post compression parameter

Formulations	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Assay (%)
F1	96.36	4.7	4.79	0.63	99.71
F2	97.12	4.4	4.41	0.78	98.40
F3	98.05	5.1	4.14	0.48	96.14
F4	96.38	4.8	4.82	0.16	98.89
F5	101.50	5.5	4.58	0.82	99.55
F6	102.14	4.2	4.25	0.50	97.29
F7	95.73	4.9	4.95	0.91	98.96
F8	97.12	4.6	4.60	0.65	99.62
F9	100.36	4.3	4.39	0.36	98.31

***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 hr,3,5,5,6,7,8,9, 10,11 and 12 hours respectively.

Table : *In -vitro* dissolution data

Time (H)	% Of Drug release								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0	0	0	0	0	0
1	19.54	20.43	18.36	14.95	14.81	19.59	26.91	16.12	11.28
2	21.71	23.86	25.15	18.76	21.99	23.12	33.75	21.87	15.17
3	34.82	38.91	29.82	23.31	36.76	24.71	37.38	25.40	20.83
4	35.90	45.85	33.67	28.50	43.52	37.68	40.59	33.56	24.50
5	42.73	48.21	42.24	36.93	59.19	39.15	45.16	39.11	33.19
6	49.24	57.53	44.17	44.15	62.74	41.99	53.72	41.08	39.77
7	56.19	60.99	57.78	46.89	65.60	48.17	60.80	45.41	44.99
8	63.98	61.20	58.99	51.73	74.25	53.25	68.98	56.32	45.02
9	70.21	70.85	61.52	57.81	77.15	60.79	71.64	59.49	59.14
10	87.75	78.17	66.63	60.13	83.70	77.38	78.48	66.70	65.30
11	84.63	85.90	73.38	76.96	85.31	85.42	83.15	79.16	79.11
12	91.55	88.13	84.11	83.73	98.68	93.05	90.34	81.21	83.23

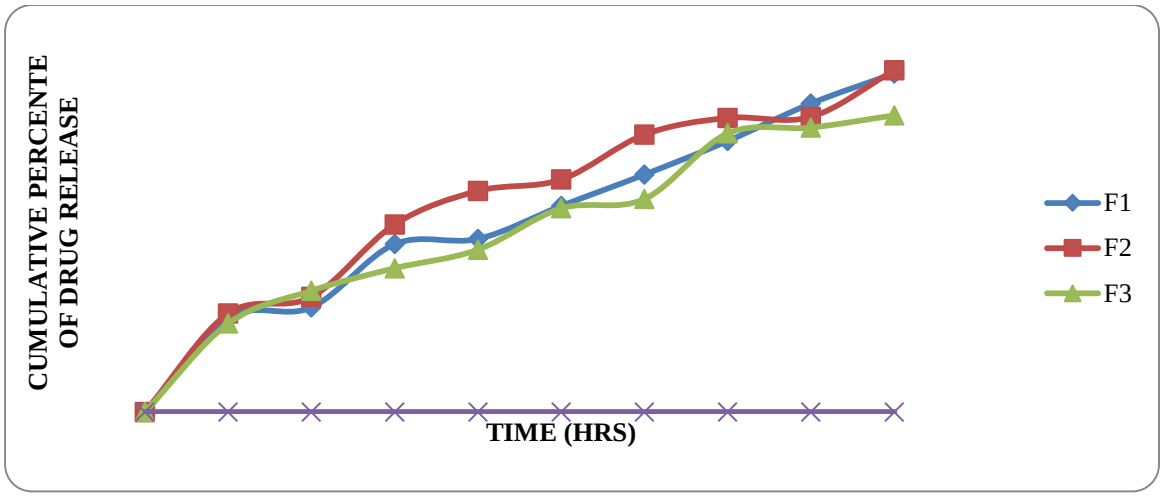

Fig : Dissolution profile of formulations prepared with Na CMC polymer

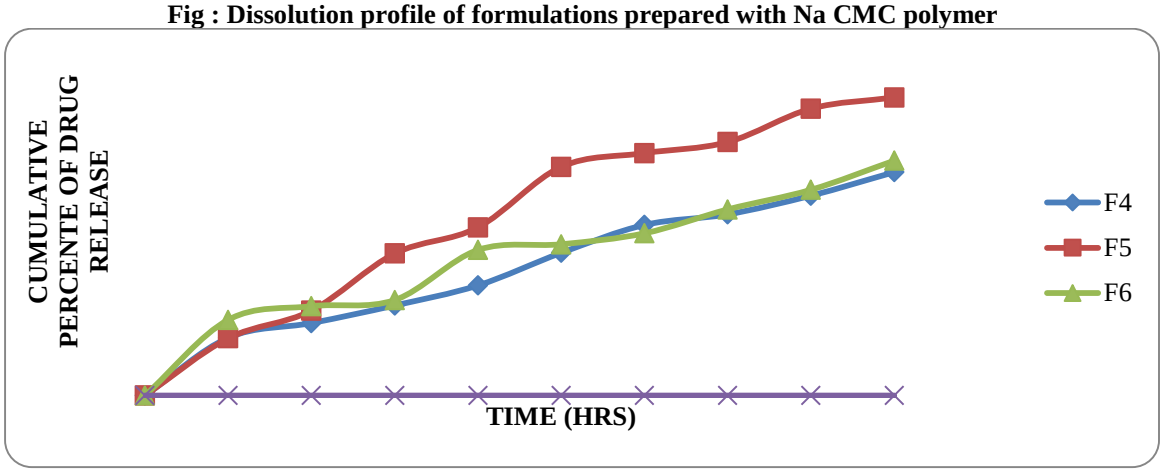

Fig: Dissolution profile of formulations prepared with HPMC K 100 polymer

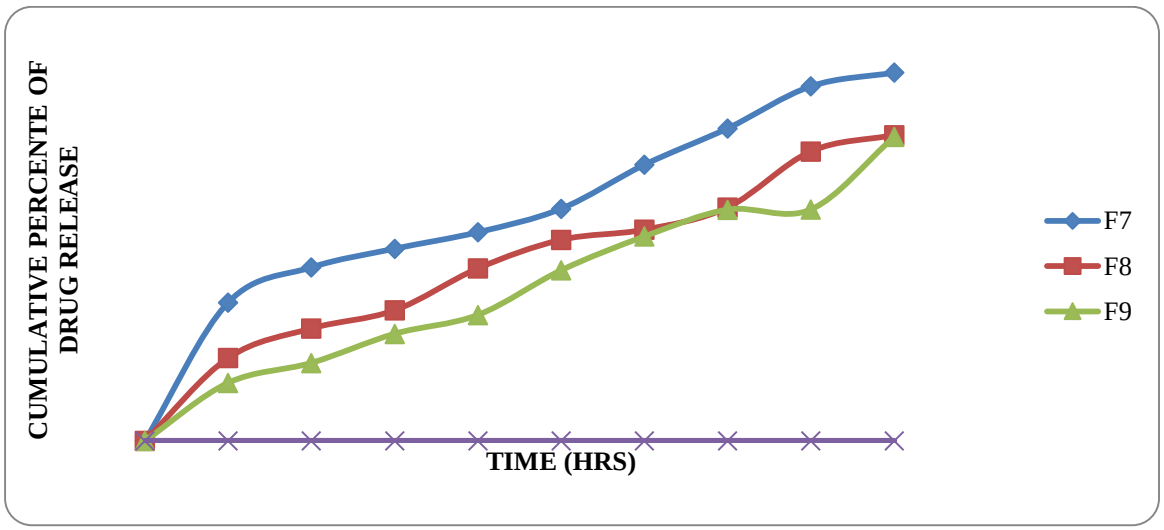

Fig: Dissolution profile of formulations prepared with Sodium alginate as polymer

From the tabular column 8.5 it was evident that the formulations prepared with Na CMC as retarding polymer in higher concentrations the polymer was unable to produce the required retarding action to the tablets. As the concentration of polymer increases the retarding nature was decreased. Na CMC in the

concentration of 10 mg showed good % drug release i.e., 91.55 in 12 hours.

Where as in case of formulations prepared with HPMC K 100 as retarding polymer, the formulations with 30 mg concentration of polymer showed complete drug release in 12 hours only, whereas the concentration of polymer increases the retarding nature Decreased. The Formulation Containing HPMC K 100 in 30 mg Concentration Showed good retarding nature with required drug release in 12 hours i.e., 98.68 %

Where as in case formulations prepared with Sodium alginate as retarding polymer, as the concentration of polymer increases the retarding nature was also decreased.

From the above results it was evident that the formulation F5 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
14.81	1	1.000	1.171	0.000	1.930	14.810	0.0675	-0.829	85.19	4.642	4.400	0.241
21.99	2	1.414	1.342	0.301	1.892	10.995	0.0455	-0.658	78.01	4.642	4.273	0.369
36.76	3	1.732	1.565	0.477	1.801	12.253	0.0272	-0.435	63.24	4.642	3.984	0.657
43.52	4	2.000	1.639	0.602	1.752	10.880	0.0230	-0.361	56.48	4.642	3.837	0.805
59.19	5	2.236	1.772	0.699	1.611	11.838	0.0169	-0.228	40.81	4.642	3.443	1.199
62.74	6	2.449	1.798	0.778	1.571	10.457	0.0159	-0.202	37.26	4.642	3.340	1.302
65.6	7	2.646	1.817	0.845	1.537	9.371	0.0152	-0.183	34.4	4.642	3.252	1.389
74.25	8	2.828	1.871	0.903	1.411	9.281	0.0135	-0.129	25.75	4.642	2.953	1.689
77.15	9	3.000	1.887	0.954	1.359	8.572	0.0130	-0.113	22.85	4.642	2.838	1.804
83.7	10	3.162	1.923	1.000	1.212	8.370	0.0119	-0.077	16.3	4.642	2.535	2.106
85.31	11	3.317	1.931	1.041	1.167	7.755	0.0117	-0.069	14.69	4.642	2.449	2.192
98.68	12	3.464	1.994	1.079	0.121	8.223	0.0101	-0.006	1.32	4.642	1.097	3.545

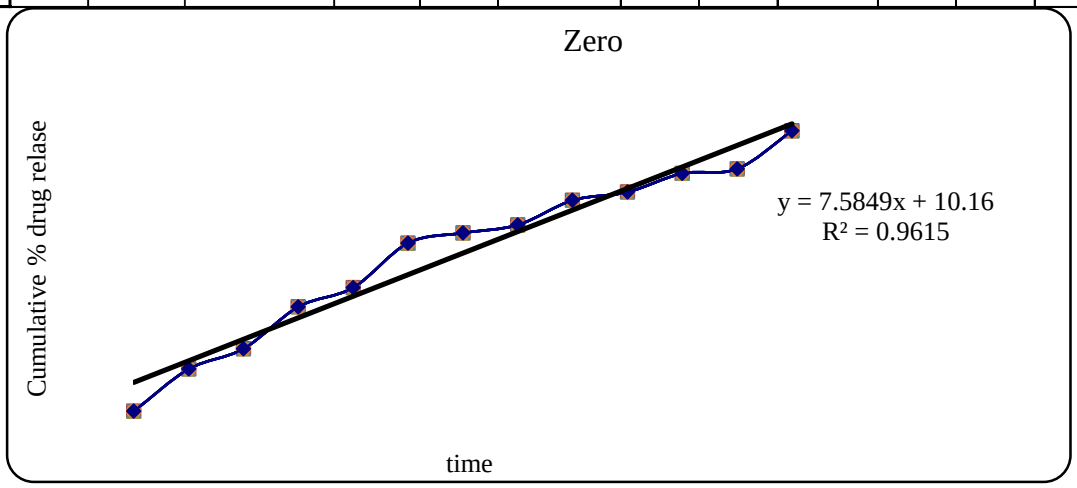

Fig : Zero order release kinetics graph

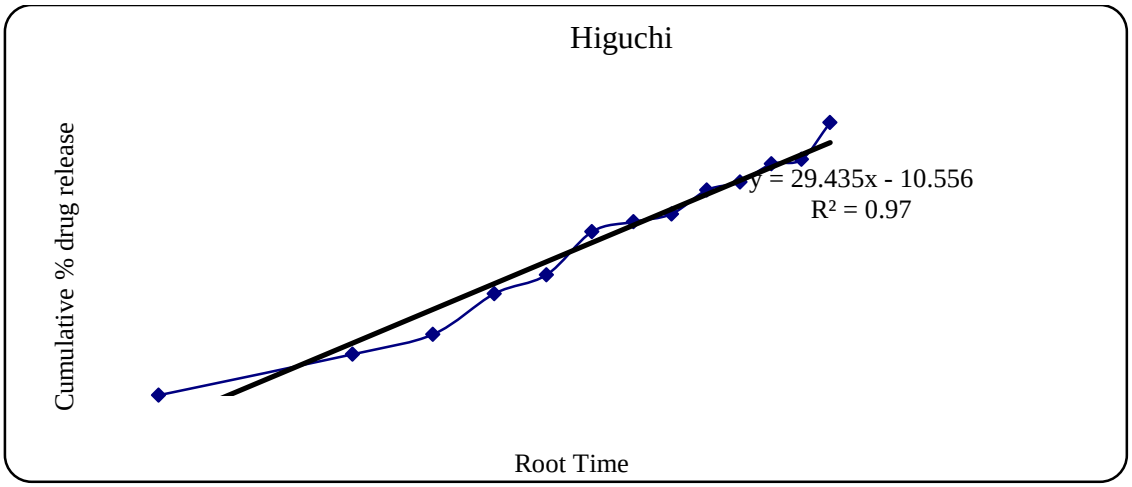

Fig : Higuchi release kinetics graph

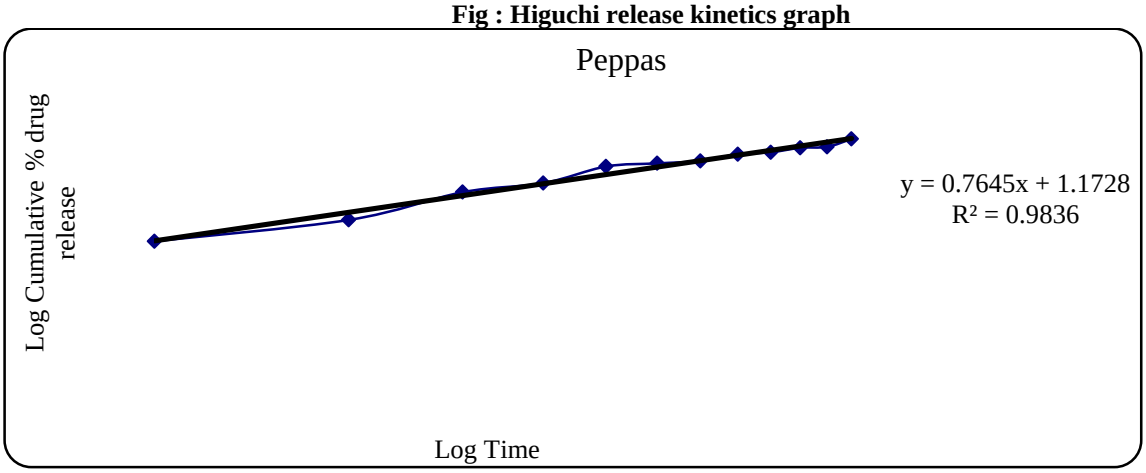

Fig: Kars mayer peppas graph

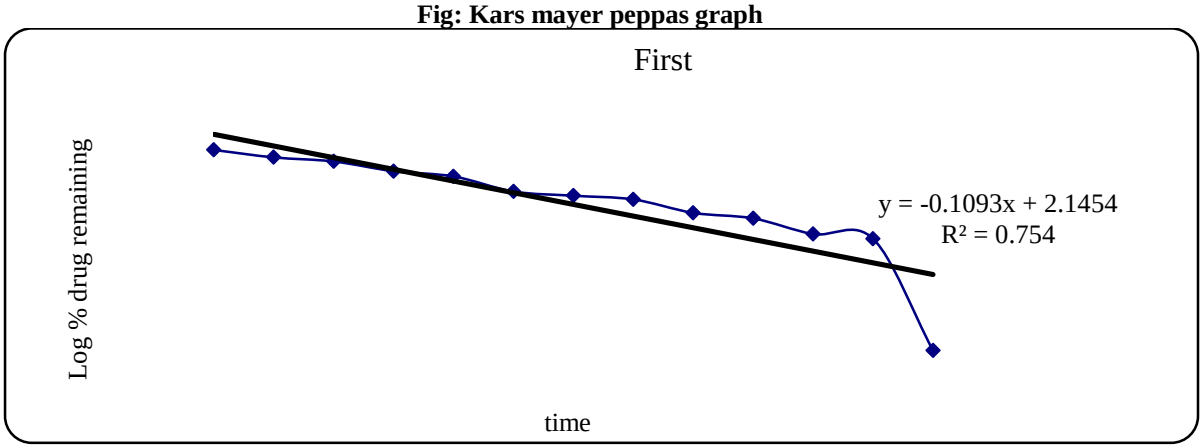

Fig : First order release kinetics graph

From the above graphs it was evident that the formulation F5 was followed peppas release kinetics mechanism.

FTIR

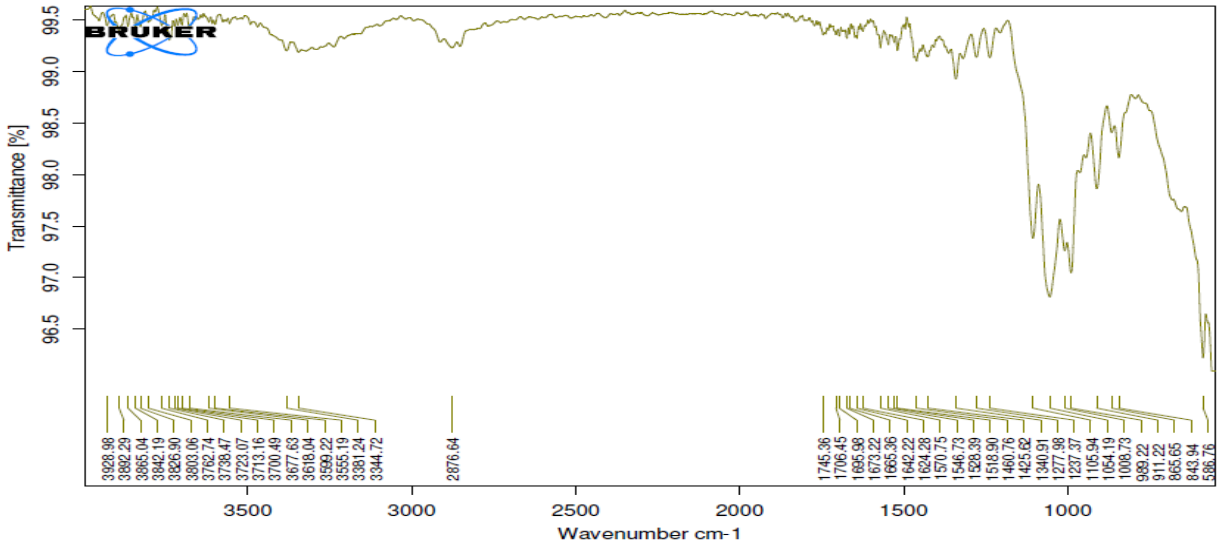

Fig no: FT-TR Spectrum of Felodipine pure drug

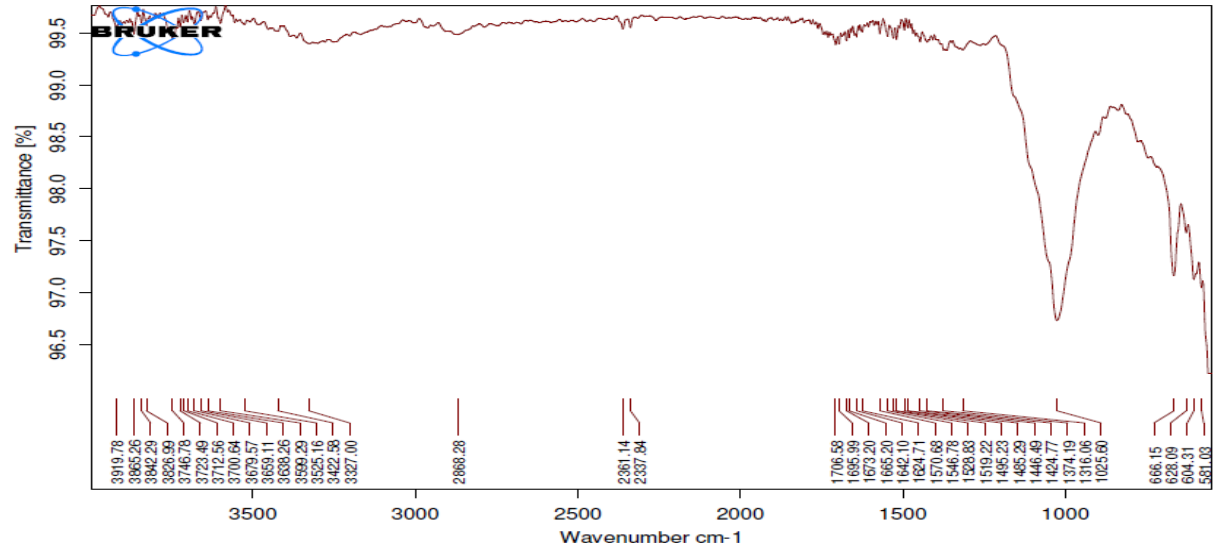

Fig No :FT-IR Spectrum of Optimised Formulation

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

CONCLUSION:

In the present work, an attempt has been made to develop Controlled release tablets of Felodipine by selecting different types of polymers Na CMC, HPMC K 100 and Sodium alginate as retarding polymers. All the formulations were prepared by direct compression method. The blend of all the formulations showed good flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations F5 formulation showed maximum % drug release i.e., 98.68 % in 12 hours hence it is considered as optimized formulation F5 which contains HPMC K 100 (30mg). Finally concluded release kinetics to optimized formulation (F5) has followed peppas release kinetics mechanism.

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