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Research Article

FORMULATION AND EVALUATION OF BILAYERED TABLET OF CANDISERTAN CILEXETIL

Raja Narender. B*, P. Pavan Kalyan
Sree Chaitanya Institute of Pharmaceutical sciences, Thimmapoor, Karimnagar, Telangana 505527.
Email: rajanarenderbongoni@gmail.com

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Abstract

The goal of the present investigation was to formulate and evaluate of bilayered tablets of Candisartan Cilexetil for extended period of time. The tablets were prepared by using different polymers (Sodium Alginate, Ethyl Cellulose, HPMC K100M) in various proportions by using (Direct compression method technique). The tablets were evaluated for Angle of Repose, Bulk Density, Taped Density, Weight Variation, Thickness, Hardness, Friability, Determination of drug content, Scanning Fourier transform- infrared spectroscopic analysis (FT- IR), *In vitro* Disintegration time Studies, *In-vitro* drug release studies, Stability studies of tablets and *ex-vivo* residence time. Nine formulations were developed by using different polymers in different proportion. The formulation F7 shows an in vitro drug release of 96.28% in 12 h along with satisfactory results. From the experimental results it was concluded that F7 as best formulation based on dissolution profile and physical characteristics. Formulation (F7) showed total drug release in 12hr and showed fair flow properties when compared to other formulations.

Key Words:

Candisartan Cilexetil, Direct compression method technique, Sodium Alginate, Ethyl Cellulose, HPMC K100M.

Introduction

Usually conventional dosage form produce wide ranging fluctuation in drug concentration in the blood stream and tissues with consequent undesirable toxicity and poor efficiency. This factor such as repetitive dosing and unpredictable absorption led to the concept of controlled drug delivery systems. The goal in designing sustained or controlled delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery.

The primary objective of sustained release drug delivery is to ensure safety and to improve efficacy of drugs as well as patient compliance.1)Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose.2) There is various application of the bi-layer tablet it consist of monolithic partially coated or multilayered matrices. In the case of bi-layered tablets drug release can be rendered almost unidirectional if the drug can be incorporated in the upper non-adhesive layer its delivery occurs into the whole oral cavity.

From various current methods for treating illness and diseases, chemotherapy (treatment with drugs) is the most frequently used technique. It has the broad range of applications over the greatest variety of disease states and is frequently the preferred treatment method[1]. For many decades, treatment of acute disease or chronic illness has been mostly accomplished by delivery of drugs to patients using various pharmaceutical dosage forms including tablets, capsules, pills, suppositories, creams, ointments, liquids, aerosols and injectable as drug carriers[2,3].

However, if it is a viable option, oral drug delivery will be chosen in all but the most exceptional circumstances. Moreover, if the oral route is not immediately viable, pharmaceutical companies will often invest resources in making it viable, rather than plumping for an alternative delivery system[4,5]. oral route of drug administration have wide acceptance up to 50-60% of total dosage forms and is the most convenient and preferred route for systemic effects due to its ease of dosing administration, pain avoidance, accurate dosage, patient compliance and flexibility in formulation[6,7].

Conventional dosage form are accused of repetitive dosing and unpredictable absorption window that cause wide range of fluctuation in drug concentration in the blood stream and tissues with subsequent undesirable toxicity and poor therapeutic efficiency[8]. This dynamic such as repetitive dosing and erratic absorption led to the concept of controlled drug delivery systems.

Formulation of layers from different polymers allows manipulation over more than one rate-controlling polymer, thus enabling different types of drug delivery of one or more drugs, i.e. where the drug may be released with a bolus and then at a controlled rate or by targeted drug delivery in the GI tract using pH dependent polymers[9]. The aim in designing sustained or controlled delivery systems is to decrease the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or provide uniform drug delivery. The main objective of sustained release drug delivery is to make sure safety and to improve effectiveness of drugs as well as patient compliance.

But often this controllers drug delivery system fails to achieve the stated advantages due to lack of releasing the initial bolus dose. Dose dumping and failure to achieve site specific drug delivery Immediate release drug delivery system is intended to disintegrate rapidly, and exhibit instant drug release. It is associated with fluctuations in drug plasma levels, which leads to reduction or loss in drug effectiveness or increase incidence of side effects. Administration of the DDS (drug delivery system) several times per day is therefore necessary to compensate the decrease in drug plasma concentration due to metabolism and excretion.

A relatively constant plasma level of a drug is often preferred to maintain the drug concentration within the therapeutic window. However, it is difficult to achieve, especially for once-daily dosage forms, partly because the environment for drug diffusion and/or absorption varies along the gastrointestinal (GI) tract. On the basis of these considerations, we have proposed a bilayer tablet[11,12].

Candesaratan Cilexetil is an Angiotensin Receptor Blocker having highest affinity for AT-1 blocker and produces largely un surmountable antagonism. The plasma half life is 8-12 hours. The aim of the present study was to design and evaluation of bilayered tablets Candesartan celexetil, an attempt was made to develop bi-layer tablet is suitable for delivering same drugs with different release pattern like one layer of drug as immediate release to get quick relief from hypertension and second drug as sustained release of drug which gives effect of drug for sufficient long time and reduce frequency of dose.

Materials and methods

1. Preformulation Study:

A. Colour, odor, taste and appearance:

The drug sample was evaluated for its colour and odor. The results are shown in Table 10.

B. Melting point determination:

Melting point of the drug sample was determined by capillary method by using melting point apparatus.

C. Determination of solubility:

The solubility of the Candesartan cilexetil was determined by adding excess amount of drug in the solvent and equilibrium solubility was determined by taking supernatant and analyzing it on Perkin Elmer Lambda35, double beam spectrophotometer.

D. Ultraviolet Visible (UV-visible) spectroscopy:

Construction of Calibration Curve:

Standard Stock solution:

Accurately weighed 100 mg of Candesartan cilexetil was dissolved in 100 ml of different buffers (1.2pH 0.1N HCl& 7.4pH phosphate). The resultant solutions were having concentration of 1000 µg/ml (1.1 mg/ml). 10 ml of this solution was further diluted up to 100.0 ml with buffer and to give a solution of Concentrations 100 µg/ml. This resultant solution is used as working stock solution for further study. Further dilutions were prepared from the same solution.

Preparation of calibration curve for Candesartan cilexetil:

Appropriate aliquots were pipette out from the standard stock solution in to a series of 10 ml volumetric flasks. The volume was made up to the mark with buffer to get a set of solutions having the concentration range of 2, 4, 6, 8 and 10 µg/ml for Candesartan cilexetil. Absorbance's of the above solutions were measured at 257 nm and a calibration curve of absorbance against concentration was plotted and the drug follows the Beer's & Lambert's law in the concentration range of 2-10 µg/ml. The regression equation and correlation coefficient was determined.

E. Bulk density, Tapped density, % Compressibility index & Hausner's ratio:

1) Apparent Bulk Density: The bulk density was determined by transferring the accurately weighed sample of powder to the graduated measuring cylinder. The initial volume and weight was noted. Ratio of weight of the sample was calculated by using the following formula.

Density = Mass/Volume

2) Tapped Density:

Weighed powder sample was transferred to a graduated cylinder and was placed on the tap density apparatus, was operated for fixed number of taps (200). The tapped density was determined by the following formula.

Density = Mass/Tapped Volume

3) Percentage Compressibility (or) Carr's index (%):

Based on the apparent bulk density and the tapped density, the percentage Compressibility of the bulk drug was determined by the following formula.

Carr's index (%) = [(Tapped Density-Bulk Density) / Tapped Density] X 100

Table-5: % Compressibility limits with respect to flow ability

S.no	%Compressibility	Flow ability
1	5-12	Excellent
2	12-16	Good
3	18-21	Fair
4	23-25	Poor
5	33-38	Very poor
6	More than	Very very poor

4) Housner's Ratio:

It indicates the flow properties of powder and is measured by the ratio of tap density to bulk density.

Hausner ratio = Tapped density/Bulk density

Table-6: Hausner ratio limits.

Hausner's ratio	Type of flow
< 1.25	Good flow
> 1.25	Poor flow

5) Angle of Repose:

The flow property was determined by measuring the Angle of Repose. In order to determine the flow property, the Angle of Repose was determined. It is the maximum angle that can be obtained between the free standing surface of a powder heap and the horizontal.

Angle of repose= $\tan^{-1}$ (h/r) Where, h = height r = radius

Procedure:

- 20gms of the sample was taken
- The sample was passed through the funnel slowly to form a heap.
- The height of the powder heap formed was measured.
- The circumference formed was drawn with a pencil on the graph paper.

The radius was measured and the angle of repose was determined. This was repeated three times for a sample.

Table-7: Flow properties with Angle of repose.

Flow properties	Angle of repose (θ)
Excellent	25-30
Good	31-35
Fair	36-40
Passable	41-45
Poor	46-55
Very poor	56-65
Very very poor	> 66

Evaluation of Tablets:

The quantitative evaluation and assessment of a tablets chemical, physical and bioavailability properties are important in the design of tablets and to monitor product quality. There are various standards that have been set in the various pharmacopoeias regarding the quality of pharmaceutical tablets. These include the diameter, size, shape, thickness, weight, hardness, Friability and invitro-dissolution characters.

1. Physical Appearance:

The general appearance of a tablet, its identity and general elegance is essential for consumer acceptance, for control of lot-to-lot uniformity and tablet-to-tablet uniformity. The control of general appearance involves the measurement of size, shape, colour, presence or absence of odour, taste etc.

2. Size & Shape:

It can be dimensionally described & controlled. The thickness of a tablet is only variables. Tablet thickness can be measured by micro-meter or by other device. Tablet thickness should be controlled within a ± 5% variation of standard value.

3. Weight variation test:

This is an in process quality control test to ensure that the manufacturers control the variation in the weight of the compressed tablets, different pharmacopoeia specify these weight variation tests.. These tests are primarily based on the comparison of the weight of the individual tablets (xi) of a sample of tablets with an upper and lower percentage limit of the observed sample average (x-mean). The USP has provided limits for the average weight of uncoated compressed tablets. These are applicable when the tablet contains 50mg or more of the drug substance or when the latter comprises 50% or more, by weight of the dosage form.

Method:

Twenty tablets were weighed individually and the average weight was calculated. The individual tablet weights are then compared to the average weight. Not more than two tablets should differ in their average weight by more than percentages stated in USP. No tablet must differ by more than double the relevant percentage.

Table-8: Limits for Tablet Weight variation test:

Average weight of tablet (mg)	% Difference allowed
130 or less	10 %
From 130 to 324	7.5 %
> 324	5 %

4. Content Uniformity:

The drug content of the matrix tablets was determined by standards and it meets the requirements if the amount of the active ingredient in each of 10 tested tablets lies within the range of 90% to 110% of the standard amount.

Ten tablets were weighed and taken into a mortar and crushed into fine powder. An accurately weighed portion of the powder equivalent to about 10mg of Candesartan cilexetil was transferred to 100ml volumetric flask containing 70ml of 7.4 pH phosphate buffer. It was shaken by mechanical means for 1hr then it was filtered through Watsmann filter paper (no.1) and diluted to 100ml with 7.4 pH phosphate buffer. From this resulted solution 1ml was taken, diluted to 50ml with 7.4 pH phosphate buffer and absorbance was measured against blank at 257 nm.

5. Friability:

Friction and shock are the forces that most often cause tablets to chip, cap or break. The friability test is closely related to tablet hardness and designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping. It is usually measured by the use of the Roche friabilator.

Method:

A number of tablets are weighed and placed in the apparatus where they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After four minutes of this treatment or 100 revolutions, the tablets are weighed and the weight compared with the initial weight. The loss due to abrasion is a measure of the tablet friability.

The value is expressed as a percentage. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable and any broken or smashed tablets are not picked.

The percentage friability was determined by the formula:

$$\% \text{ friability} = (W_1 - W_2) / W_1 \text{ X } 100$$

W_1 = Weight of tablets before test

W_2 = Weight of tablets after test

In vitro drug release study:

In vitro drug release was studied using USP II apparatus, with 900 ml of dissolution medium maintained at 37±1°C for 15 h, at 50 rpm. 0.1 N HCl (pH 1.2) was used as a dissolution medium for the first 2 h, followed by pH 7.4 phosphate buffers for further 10 h. 5ml of sample was withdrawn in different time intervels, and was replaced by an equal volume of fresh dissolution medium of same pH. Collected samples were analyzed spectrophotometrically at 257 nm, and cumulative percent drug release was calculated. The study was performed in triplicate.

Kinetic-models:

In order to describe the DS release kinetics from individual tablet formulations, the corresponding dissolution data were fitted in various kinetic dissolution models: Zero order, first order, and Higuchi respectively.

$$Qt = Q0 + K0\ t$$

Where, Qt is the amount of drug released at time t; Q0 the amount of drug in the solution at t = 0, (usually, Q0 = 0) and K0 the zero order release constant.

$$\log Qt = \log Q\alpha + (K1 / 2.303)\ t$$

Qα being the total amount of drug in the matrix and K1 the first order kinetic constant.

$$Qt = KH.\ t^{½}$$

Where, KH is the Higuchi rate constant.

Further, to better characterise the mechanism of drug release from matrices, dissolution data were analyzed using the equation proposed by Korsmeyer and Peppas.

$$Q\ (t-l)\ /Q\alpha = KK\ (t-l)n$$

Where, Qt corresponds to the amount of drug released in time t, *l* is the lag time (*l* = 2 hours), Qα is the total amount of drug that must be released at infinite time, KK a constant comprising the structural and geometric characteristics of the tablet, and n is the release exponent indicating the type of drug release mechanism. To the determination of the exponent n, the points in the release curves where Q (t-*l*)/Qα>0.6, were only used. If n approaches to 0.5, the release mechanism can be Fickian. If n approaches to 1, the release mechanism can be zero order and on the other hand if 0.5<n<1, non-Fickian (anomalous) transport could be obtained. Anomalous (non-Fickian) transport generally refers to the drug release by the summation of both diffusion and erosion of the polymeric matrix. The criteria employed to select the ‘‘best model’’ was the one with the highest coefficient of determination (r2).

Stability studies[42]:

Selected Formulation was subjected to stability studies as per ICHguidelines.

Following conditions were used for Stability Testing.

1. 25^0C/60% RH analyzed every month for period of Two months.
2. 30^0C/75% RH analyzed every month for period of Two months.
3. 40^0C/75% RH analyzed every month for period of Two month.

Table-9: Composition of Candesartan Cilexetil bilayered tablets.

S.NO.	INGREDIENTS	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)
IMMEDIATE LAYER										
1	CANDESARTAN CILEXETIL	4	4	4	4	4	4	4	4	4
2	CROSPOVIDON	8	8	8	8	8	8	8	8	8
3	SORBITOL	85	85	85	85	85	85	85	85	85
4	MAGNESIUM STEARATE	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
5	TALC	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
SUSTAINED LAYER										
1	CANDESARTAN CILEXETIL	16	16	16	16	16	16	16	16	16
2	SODIUM ALGINATE	20	---	20	20	20	---	20	---	20
3	HPMC K100M	---	20	---	---	20	20	---	20	20
4	ETHYL CELLULOSE	20	20	20	20	---	20	20	20	---
5	MICROCRYSTALLINE CELLULOSE	140	140	140	140	140	140	140	140	140
6	MAGNESIUM STEARATE	2	2	2	2	2	2	2	2	2
7	TALC	2	2	2	2	2	2	2	2	2
	TOTAL WT(mg)	300	300	300	300	300	300	300	300	300

Formulation development

Steps in Formulation:

Preparation of Immediate layer:

1. Drug and super disintegrant (Crospovidone) pass through 40 # mesh separately and then transfer it to poly bag and mix it for 3 minutes.
2. Add other excipients to the above mixture. Finally add the Glidant (Magnesium Stearate) to the above blend mix it for 2min.

Preparation of Sustained layer:

1. Drug and polymer (Sodium alginate or HPMC K100 or Ethylcellulose) pass through 40 # mesh separately and then transfer it to poly bag and mix it for 3 minutes.
2. Add other excipients to the above mixture. Finally add the glidant (Magnesium Stearate) to the above blend mix it for 2min.
3. Compressed the above lubricated blend by using 8mm round punches.

Results and Discussion

Table-10: Preformulation

S.NO	API CHARACTERISATION	RESULTS
1	Physical Appearance	Candesartan cilexetil is a white solid
2	Melting point	188 °C
3	Solubility	It is practically insoluble in water and sparingly soluble in methanol.
4	Bulk density	0.27gm/ml
5	Tapped Density	0.31 gm/ml
6	Carr's index Compressibility index	14.81
7	Hausner's Ratio	1.14

Conclusion:

The value of compressibility index is 14.81%, 15-25%, less than 15% indicates poor flowability, optimum flowability and high flowability respectively.

Table-11: List of Micromeritic properties of directly compressible powder.

parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9
Angleof repose	$26^0 35'$	$27^o 31'$	$28^o 33'$	$27^0 85'$	$26^0 62'$	$25^0 71'$	$27^o 35'$	$22^0 53'$	$25^0 62'$
Bulk density	0.46	0.61	0.47	0.60	0.46	0.55	0.63	0.42	0.57
Tapped density	0.51	0.69	0.52	0.64	0.51	0.63	0.66	0.53	0.63
%Compressibility	10.86	13.11	10.63	6.66	10.86	14.54	4.76	26.19	10.52
Hausner's ratio	1.10	1.13	1.10	1.06	1.10	1.14	1.047	1.15	1.10

4.3 Calibration of Standard Graph of Candesartan cilexetil:

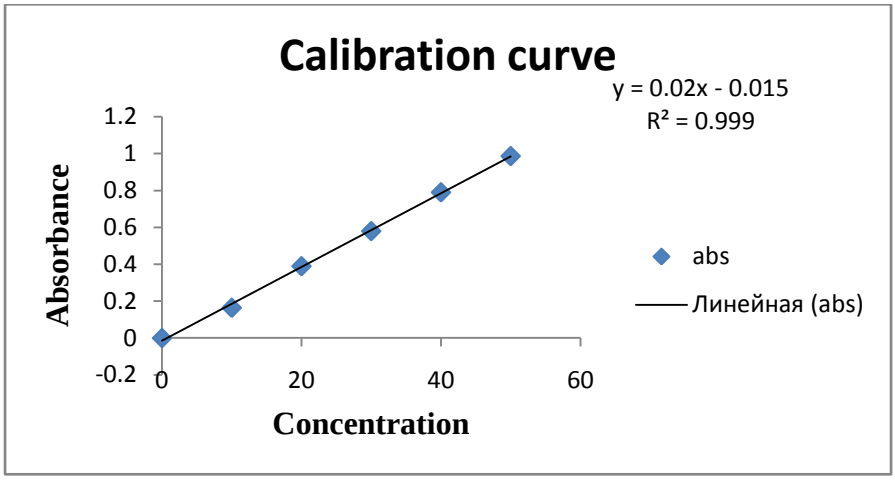
Standard graph of Candesartan cilexetil in 0.1N HCl (1.2 pH buffer):

The construction of standard calibration curve of Candesartan cilexetil was done by using 0.1N HCl as the medium. Candesartan cilexetil was found to have the maximum absorbance at 257 nm. The standard graph of Candesartan cilexetil in 0.1N HClwas constructed by making the concentrations of 10µg/ml, 20µg/ml, 30 µg/ml, 40µg/ml and 50 µg/ml solutions. The absorbance of solutions was examined under UV- spectrophotometer at an absorption maximum of 257 nm. The standard graph of Candesartan cilexetil was constructed by taking the absorbance on Y-axis and concentrations on X-axis.

Table 12: Standard graph of Candesartan cilexetil in 0.1N HCl:

S. No.	CONCENTRATION(µg/ml)	ABSORBANCE
1	0	0
2	10	0.179
3	20	0.401
4	30	0.612
5	40	0.836
6	50	1.056

Fig 10: Calibration curve of Candesartan cilexetil in 0.1N HCl (1.2 pH buffer).



Standard graph of Candesartan cilexetil in 7.4 pH Phosphate buffer:

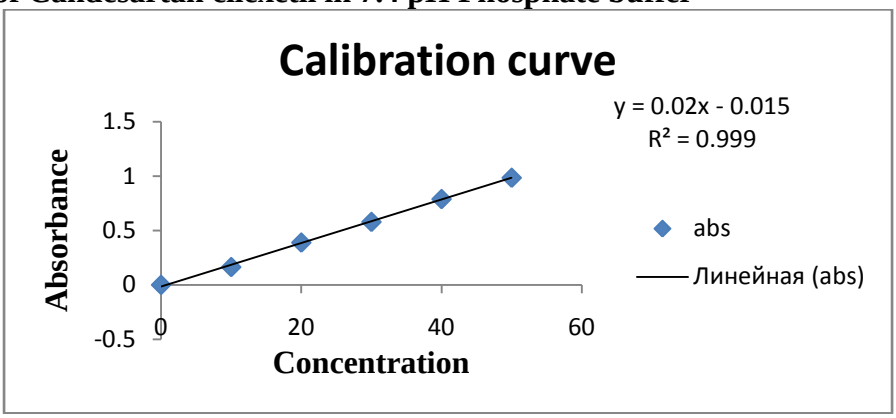
The construction of standard calibration curve of Candesartan cilexetil was done by using 7.4 pH Phosphate buffer as the medium. Candesartan cilexetil was found to have the maximum absorbance at 257 nm. The standard graph of Candesartan cilexetil 7.4 pH Phosphate bufferwas constructed by making the concentrations of 10µg/ml, 20µg/ml, 30 µg/ml, 40 µg/ml and 50 µg/ml solutions. The absorbance of solutions was examined under UV- spectrophotometer at an absorption maximum of 257 nm. The standard graph of Candesartan cilexetil was constructed by taking the absorbance on Y-axis and concentrations on X-axis.

Table 13: Standard graph of Candesartan cilexetil in 7.4 pH Phosphate buffer at λ_{max}= 257 nm

S. NO.	CONCENTRATION(µg/ml)	ABSORBANCE
1	0	0
2	10	0.164
3	20	0.389
4	30	0.579
5	40	0.789
6	50	0.985

Standard graph of Candesartan cilexetil

Fig 11: Calibration curve of Candesartan cilexetil in 7.4 pH Phosphate buffer



Fourier Transformation Infra-red (FTIR) analysis:

Infra-red spectroscopy analysis was performed by Fourier Transformation Infrared Spectrophotometer Alpha Brooker FTIR (Tokyo, Japan).The instrument was calibrated by using polystyrene film.

Fig-12: FT-IR sample for Candesartan cilexetil (pure drug).

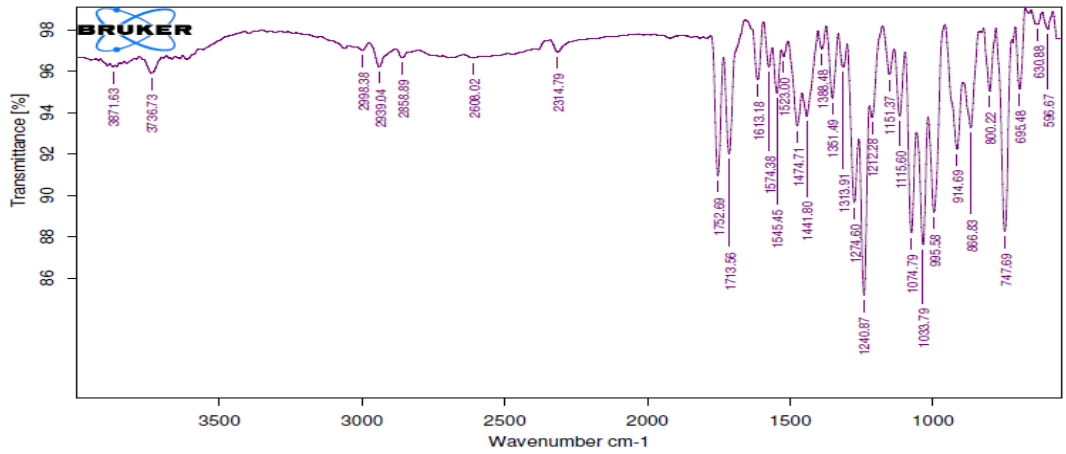


Fig-13: FT-IR Sample for Crospovidone.

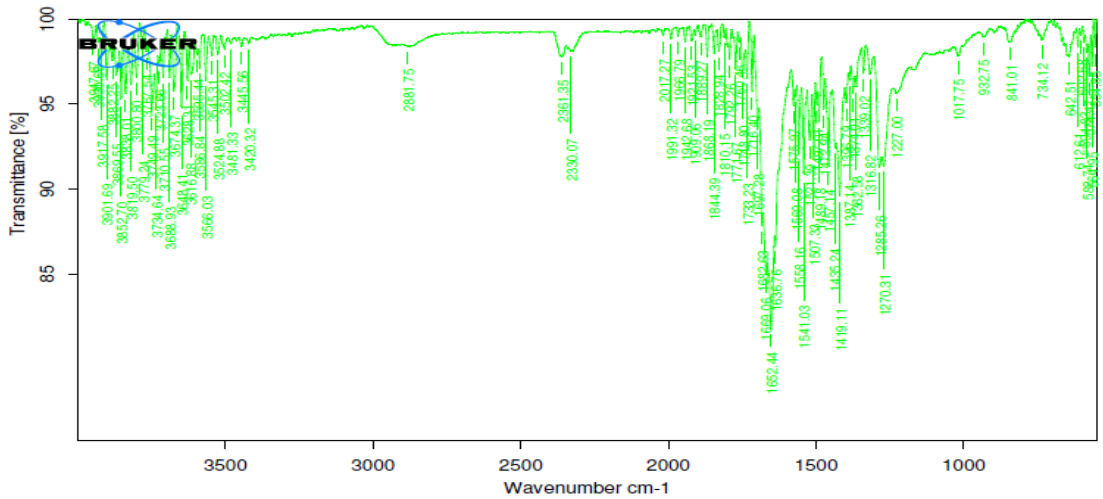


Fig-14: FT-IR Sample for best formulation for immediate release.

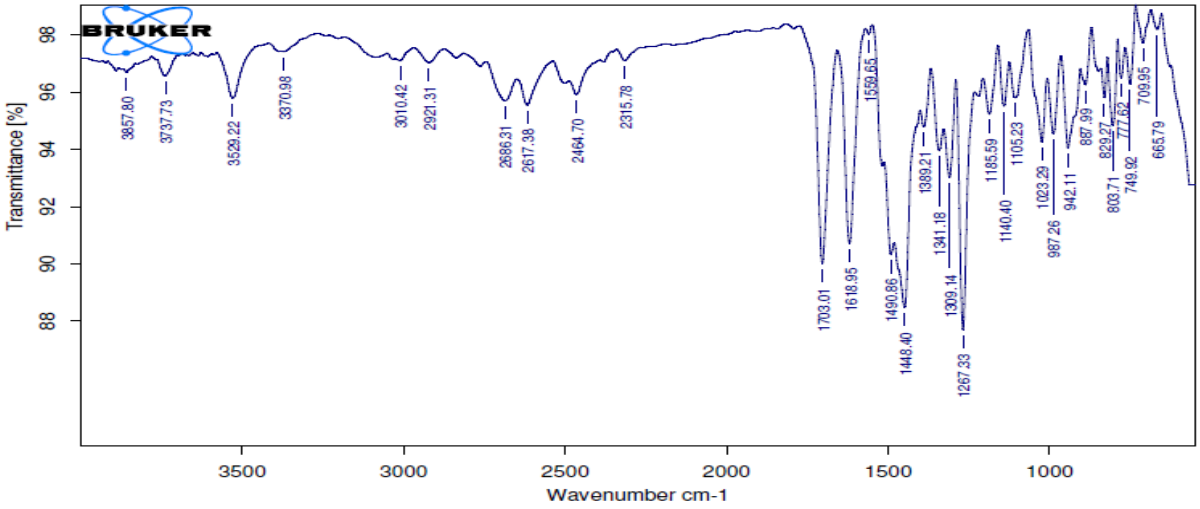


Fig-15: FT-IR sample for sodium alginate.

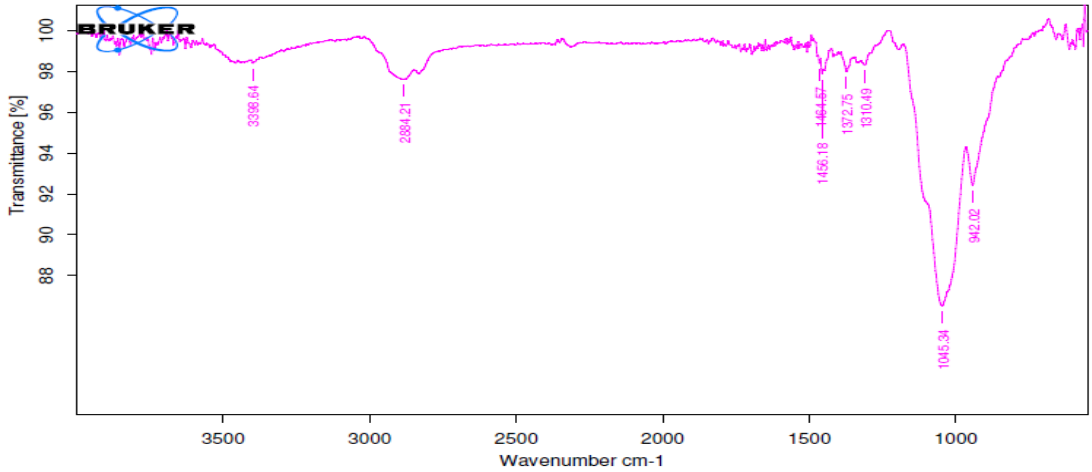


Fig-16: FT-IR sample for ethyl cellulose.

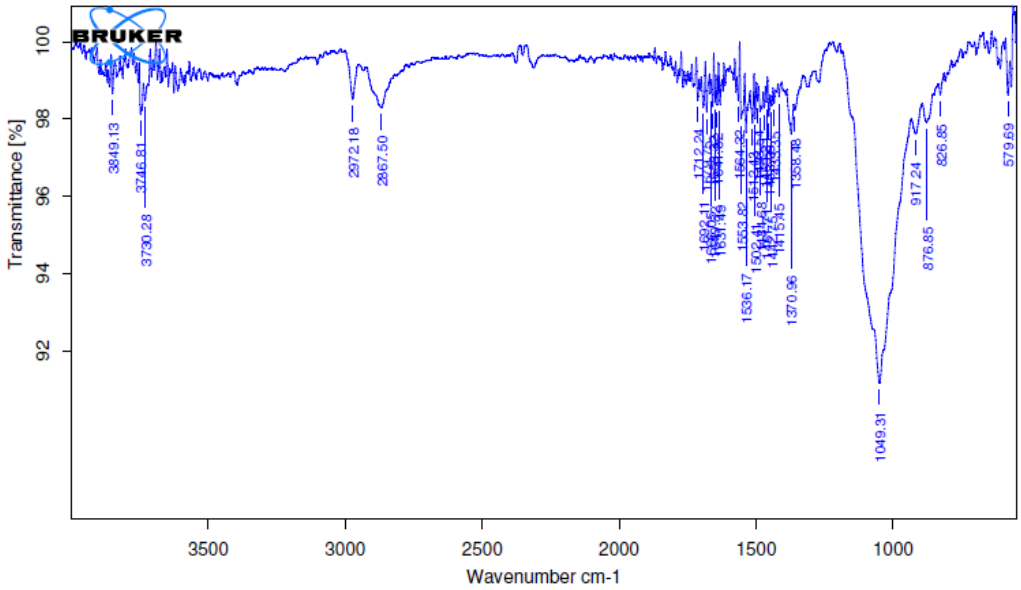


Fig-17: FT-IR sample for magnesium stearate

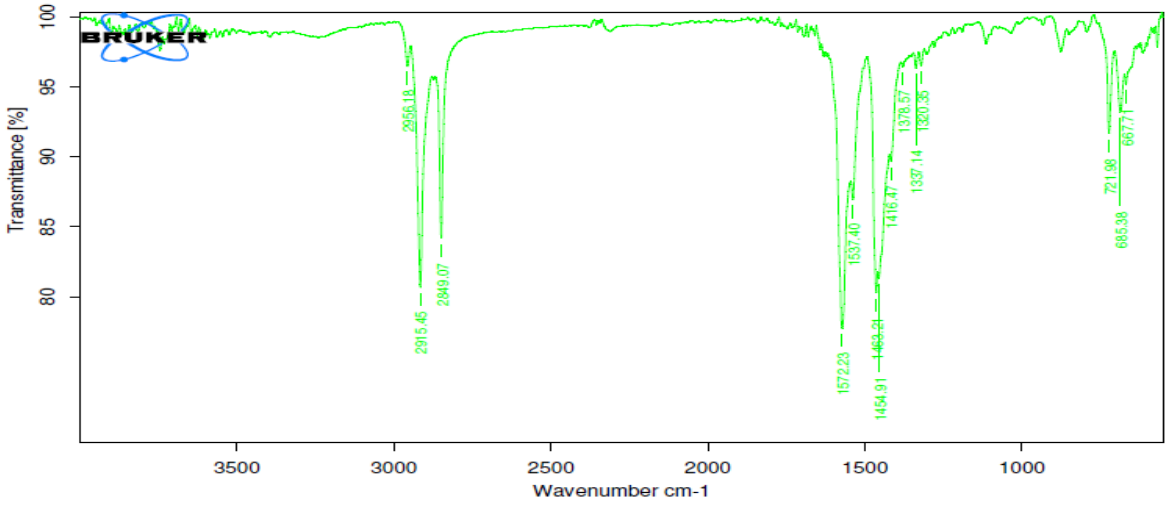
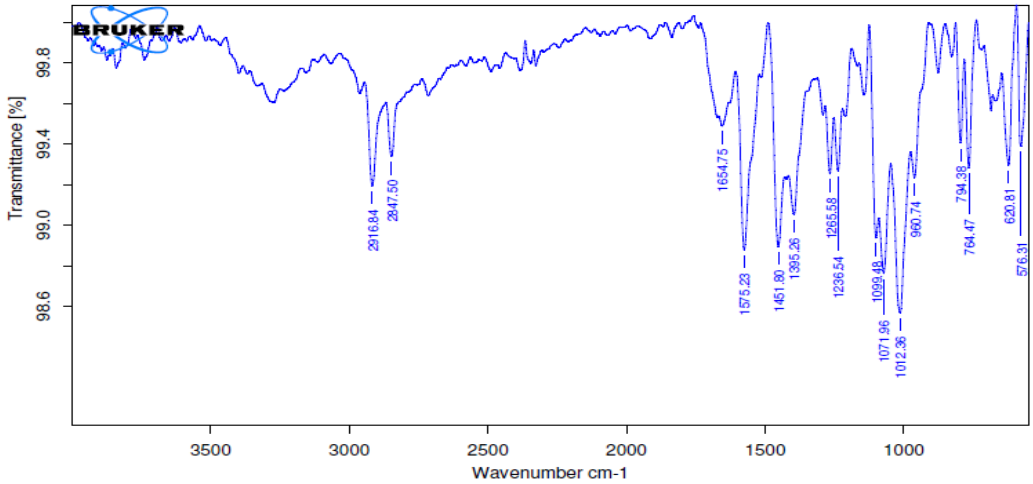


Fig-18: FT-IR sample for best formulation sustained release formulation.



4.4 Evaluation of the Prepared Tablets for Physical Parameters:

All formulations were tested for Physical parameters like Hardness, thickness, Weight Variation, Friability and found to be within the Pharmacopoeial limits. The results of the tests were tabulated. The drug content of all the formulations was determined and was found to be within the permissible limit. This study indicated that all the prepared formulations were good.

Table-14: Results for Evaluation parameters of all formulations.

Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9
Weight variation	300±0.4	299±0.3	298±0.7	300±0.1	299±0.3	300±0.2	299±0.9	300±0.8	399±0.1
Thickness (mm)	2.5±0.4	2.6±0.4	2.3±0.4	2.6±0.4	2.5±0.4	2.5±0.3	2.5±0.2	2.5±0.1	2.5±0.2
Hardness (kg/cm^2)	7.9±1.4	7.2±1.2	7.2±1.2	7.9±0.9	7.4±1.9	7.1±1.7	7.2±1.5	7.3±1.6	7.2±1.4

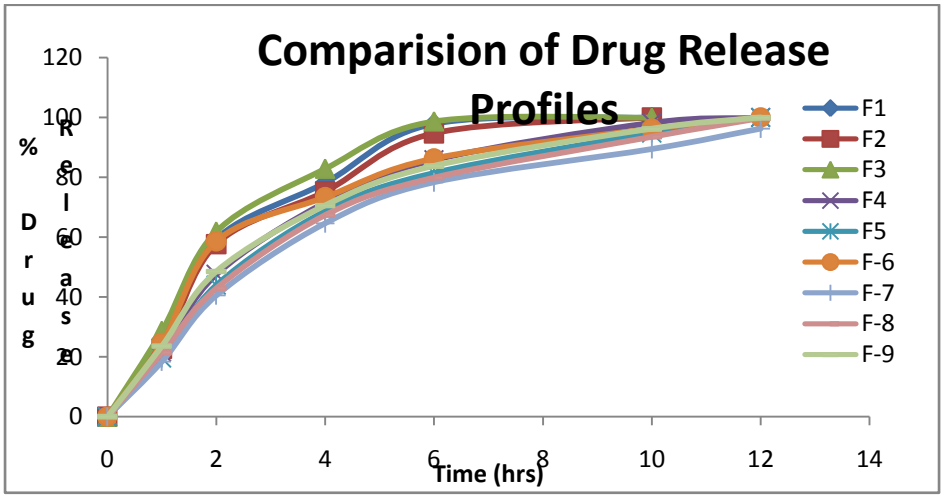
Friability	0.19% ±0.2	0.26%± 0.23	0.19% ±0.19	0.17%± 0.26	0.18%± 0.22	0.15%± 0.1	0.10%± 0.4	0.18%±0. 5	0.13%± 0.7
Content uniformit y	95.01% ±0.2	96.4%± 0.4	98.7% ±0.3	98.8%± 0.2	99.8%± 0.3	99.19% ±0.2	99.98% ±0.2	99.56%± 0.2	99.46% ±0. 2

In vitro Dissolution studies:

Table-15: Result of dissolution profile for F1-F9:

Time in hrs	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	25.92	22.67	28.67	21.61	19.61	24.57	18.43	21.41	23.61
2	59.36	57.67	61.91	47.56	43.96	58.63	40.54	42.94	48.56
4	78.21	75.24	82.91	71.62	68.65	73.35	64.65	67.43	70.62
6	97.92	94.72	98.72	85.83	81.44	86.29	78.37	79.94	83.83
10	100	100	100	98.26	94.83	96.21	89.47	93.59	96.26
12	100	100	100	100	100	100	96.28	99.86	100

Fig 19: Comparison of drug release profiles.



Stability Studies:

There were no significant changes in physical and chemical properties of capsule of formulation F-7 after 2 months. Parameters quantified at various time intervals were shown

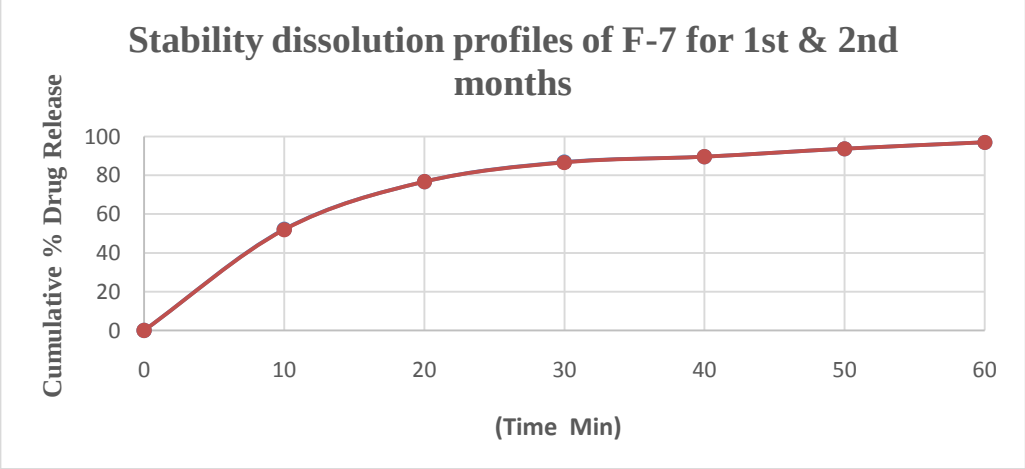
Table-16: Results of stability studies of optimized formulation F7:

Formulation code	Parameters	Initial	1st Month	2nd Month	Limits as per specifications
F7	25˚C/60%RH% Release	96.11	95.87	95.65	Not less than 85%
F7	30˚C/75%RH % Release	96.05	95.89	95.88	Not less than 85%
F7	40˚C/75%RH % Release	96.11	95.88	95.63	Not less than 85%
F7	25˚C/60%RH Assay value	97.16	97.10	97.12	Not less than 90% Not more than 110%
F7	30˚C/75%RH Assay value	97.12	97.11	97.10	Not less than 90% Not more than 110%
F7	40˚C/75%RH Assay value	97.16	97.10	97.10	Not less than 90% Not more than 110%

Table-17: Stability dissolution profile of F7 for 1st and 2nd month.

S.no	Time (in minutes)	F-7 1st Month	F-7 2nd Month
1	0	0	0
2	10	51.15	51.05
3	20	75.71	75.67
4	30	85.78	85.71
5	40	88.60	88.56
6	50	92.79	92.78
7	60	96.11	96.10

Fig 20: Stability studies.



Kinetic Models:

Dissolution data of above two methods was fitted in Zero order, First order and Higuchi equations. The mechanism of drug release was determined by using Higuchi equation[43].

Table-18: Release kinetics data.

S.NO	Time (hr)	log T	Square root of Time	%CR	%Drug remaining	log %CR	LOG% DRUG RETAINED	cube root of %drug remaining
0	0	0	0	0	100	0	2	4.641589
1	1	0	1	18.43	81.57	1.265525	1.91153	4.336874
2	2	0.30103	1.414214	40.54	59.46	1.607884	1.774225	3.903088
3	4	0.60206	2	64.65	35.35	1.810569	1.548389	3.281934
4	6	0.778151	2.44949	78.37	21.63	1.89415	1.335057	2.786242
5	10	1	3.162278	89.47	10.53	1.951677	1.022428	2.191843
6	12	1.079181	3.464102	96.28	3.72	1.983536	0.570543	1.549462

Fig-21: Zero order plot for optimized formula.

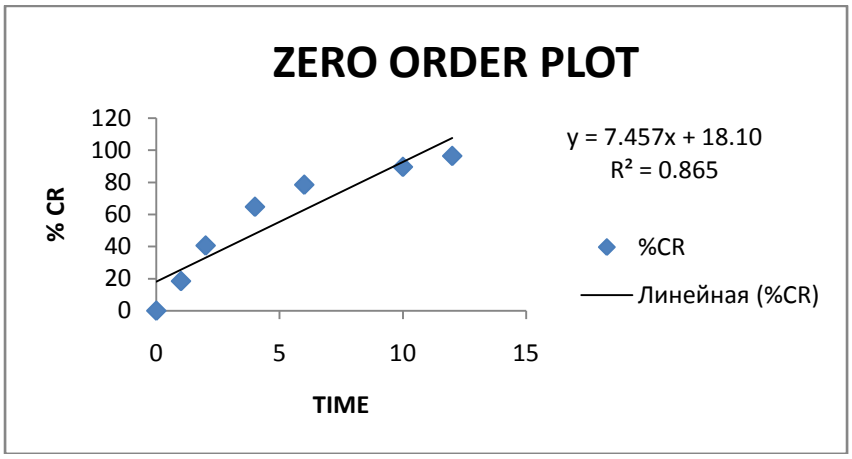


Fig-22: First order for optimized formula.

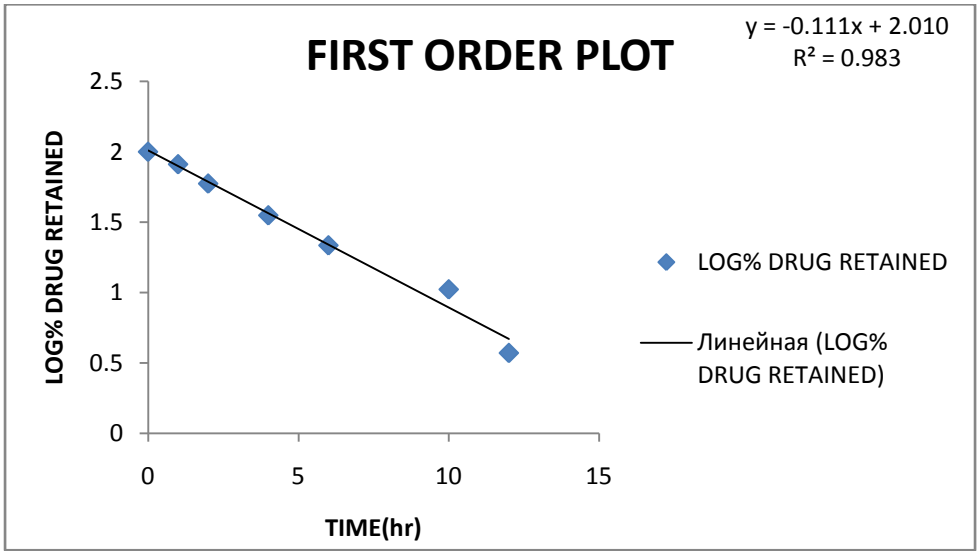


Fig-23: Higuchi plot for optimized formula.

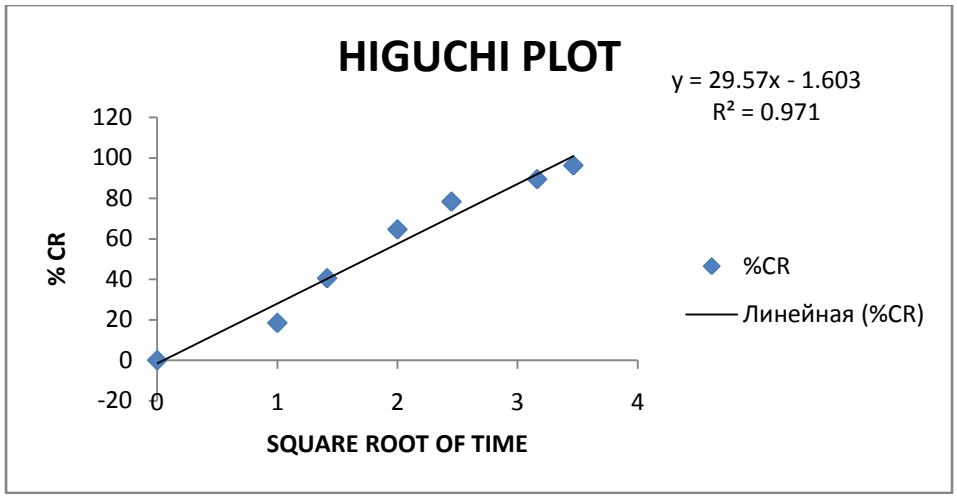


Fig-24: korsmayer peppas plot for optimized formula.

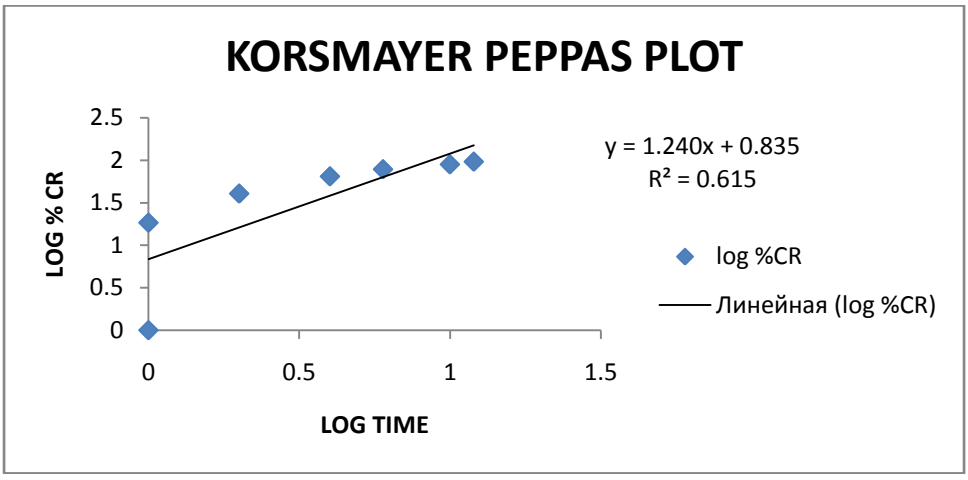
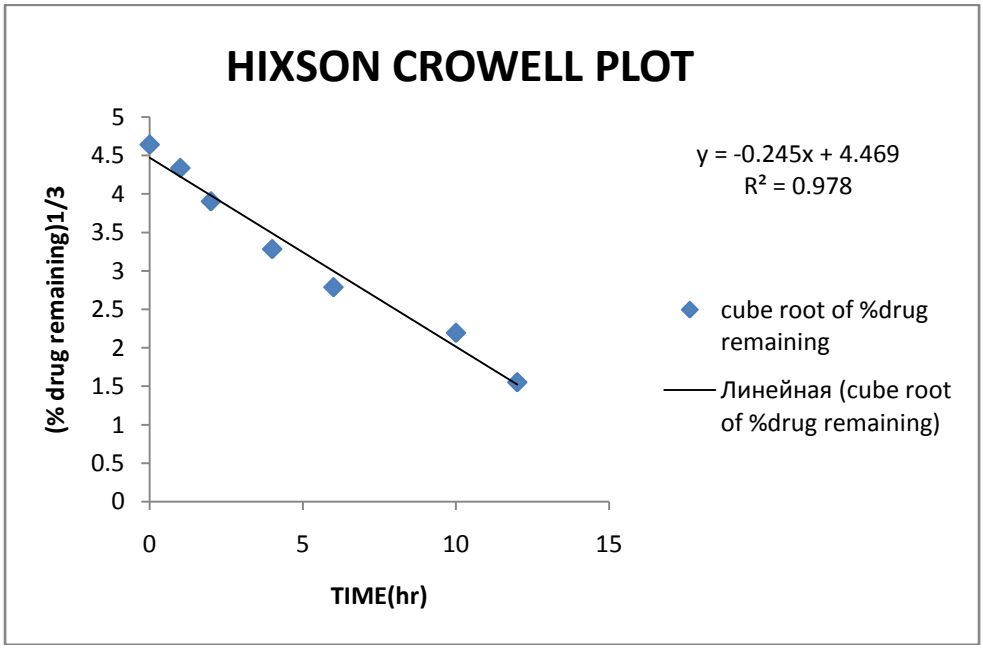


Fig-25: Hixson Crowell plot for optimized formula



Conclusion

Systematic studies were conducted using different concentration of rate releasing polymer slike Sodium alginate, HPMC K100 and Ethyl cellulose for extending the drug release up to 12 hrs.And immediate layer prepared by using croscarmellose sodium as a super disintegrant. All the prepared systems were evaluated for the different properties. Before the preparation of tablets, preformulation studies to find out the micromeritic properties to assess flowability, compressibility properties and solubility studies. And all the formulations gave good results for above preformulation studies.

Formulated tablets gave satisfactory results for various physical tablet evaluation parameters like tablet dimensions, hardness, friability, weight variation, content uniformity, all the formulations were found within the permissible range.

Finally it was concluded that: Among all the formulations (F1-F9), it was observed that formulation-7 has shown better dissolution profile. So Formulation-7 was found to be the best formulation when compared with other prepared formulations. All the polymers were used at the different concentrations in the formula, much difference were observed in the release characteristics of the bilayered tablets prepared. The release data were analyzed as per zero order, first order, Higuchi, Hixson Crowell and Korsemeyer-peppas models.

The correlation coefficient (r^2) values in the analysis of release data as per various models are mentioned. Analysis of the release data as per zero order and first order kinetic models indicated that the drug release from bilayered tablets formulated followed first order kinetics. The correlation coefficient (r^2) values were higher in first order model when compared to zero order models. As per Peppas equation of F-7 shows the release exponent ‘n’ was found 1.240 in the case of bilayered indicating super case-II transport as the release mechanism from these tablets.

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Corresponding author:

B Raja Narender,

Email: *rajanarenderbongoni@gmail.com*