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Original Article

FORMULATION AND EVALUATION OF NEVIRAPINE SUSTAINED RELEASE MATRIX TABLETS USING MUCILAGE OF ABELMOSCHUS ESCULENTUS AS RELEASE MODIFIER

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ABSTRACT

The present study was aimed to develop generic formulation of sustained release matrix tablets of Nevirapine using okra gum as a matrix forming hydrophilic polymer. Okra gum was extractedfrom the fruits of *Abelmoschus esculentus* using different organic solvents. The nevirapine matrix tablets were prepared by wet granulation technique using starch as binder and okra gum as a release retarding polymer. Six formulations of different polymer percentages were formulated, F1(10%), F2(15%), F3(20%), F4(25%), F5(30%) and F6(35%). The fabricated matrix tablets were evaluated and it was found that all the parameters are within the limits. The dissolution studies were performed using USP apparatus using pH 6.8 phosphate buffer as dissolution medium. These studies showed that formulation F5 consisting of 30% of polymer was found to sustain the release of nevirapine over a period of 12hrs. The optimized formulation was subjected to different kinetic models including zero order, first order, Higuchi model and Korsemeyer Peppa's model and the formulation was found to follow first order release kinetics.

Keywords: Nevirapine, Sustained release, Okra gum, Non-nucleoside reverse transcriptase inhibitors (NNRTI's).

INTRODUCTION

Over the past few decades, significant medical advances have been made in the area of drug delivery with the development of controlled release dosage forms. The purpose of the controlled release systems is to maintain drug concentration in the blood or in target tissues at a desired value as long as possible. Numerous sustained release oral dosage forms such as membrane controlled system, matrices with water soluble/insoluble polymers or waxes and osmotic systems have been developed. Intense research has recently focused on the designation of sustained release systems for poorly water soluble drugs. Introducing the technique of formulating matrix tablet as sustained release (SR) has given a new breakthrough for novel drug delivery system in the field of Pharmaceutical technology[1]. Sustained release formulation constitutes any dosage form that provides medication over an extended period of time or denotes that the system is able to provide some actual therapeutic control whether this is of a temporal nature, spatial nature or both. The basic objective of sustained release drug delivery system is to optimise the biopharmaceutical, pharmacokinetic and pharmacodynamic properties of a drug in such a way that its utility is maximised, side effects are reduced and the cure of the disease is achieved effectively[2].

The materials most widely used in preparing matrix systems include both hydrophilic and hydrophobic polymers. Commonly available hydrophilic polymers include Hydroxy propyl methyl cellulose (HPMC), Hydroxy propyl cellulose (HPC), Hydroxy ethyl cellulose (HEC), Xanthan gum and Sodium alginate. Okra gum obtained from the fresh pods of *Abelmoschus esculentus* is a hydrophilic polymer which can be used as a matrix forming material[3,4].

Drug release retarding polymers are the key performers in sustained release drug delivery systems for which various natural, semi-synthetic and synthetic polymeric materials are being investigated[5]. The natural polymers are more superior to the synthetic polymers in respect of their highly organized macroscopic[6] and molecular structure which adds to their strength and biocompatibility.

The main aim of the present work is to design and evaluate nevirapine sustained release matrix tablets using okra gum so as to investigate the release controlling propertyof the natural hydrophilic polymer i.e mucilage of *Abelmoschus esculentus*. The intention of choosing a natural polymer[7]in this study mainly lies in non toxicity, free availability, eco friendly and compatible nature of gums.

Nevirapine is an important NNRTI (non nucleoside reverse trascriptase inhibitor) class of anti retroviral drug acting through inhibition of HIV-1 reverse transcriptase enzyme subsequently causing stoppage of viral replication. A study conducted on comparison of Nevirapine SR formulation versus nevirapine immediate release in treatment naive patients, it was found that nevirapine sustained release formulations dosed once daily has more clinical efficacy[8] than nevirapine immediate release formulation dosed twice daily. Hence nevirapine can be suitably formulated as a sustained release matrix tablets owing to its high clinical efficacy when compared to nevirapine immediate release formulation.

MATERIALS AND METHODS

Materials

The drug sample was procured from Cipla ltd. (Mumbai), Magnesium stearate, Lactose and starch were purchased from S.D. Fine Chem Ltd., Mumbai, India. Okra fruits were obtained from the local market. All the other chemicals were of laboratory grade.

Extraction and Isolation of Okra Gum

Okra gum was extracted[9,10]from the fruits of *Abelmoschus esculentus* using different organic solvents. Fruits of Abelmoschus esculentus were sliced into thin pieces and the seeds were removed. These slices were then soaked in pH 8 distilled water for 24 hours. They were then squeezed through muslin bags to express the viscous mucilage. To this aqueous extract double the volume of 90% ethanol was added to extract the mucilage. This mucilage was then treated with petroleum ether and diethyl ether to remove the fat soluble impurities and then washed with ethanol. Final precipitation was carried out with acetone. It was then dried in hot air oven at 40^{o}C. It was then milled and passed through sieve number 60.

Characterization of okra gum

Loss on Drying (LOD)[12]:

LOD determines the percentage of moisture present in the gum powder.

- About 1.5g of the powder gum weighed in porcelain dish.

- It was dried in the oven at 100^0 c or 105^0 c, till a constant wt. was observed.
- The dish was cooled in a desiccator and reweighed. The loss in weight indicates the moisture present in it.
- The moisture content was calculated as ratio of wt. of moisture loss to wt. of sample used and it is expressed in percentage.
- LOD of okra gum was found to be 4%

Physicochemical characterization[11]

Table 1: Physicochemical Tests For Okra Gum

S. No.	Test	Observation
1	Colour	Pale yellow to greenish brown was observed
2	Odour	Agreeable odour
3	Test for carbohydrates: Molisch's test :To 2-3 ml aqueous extract add few drops of alpha napthol solution in alcohol and add concentrated sulphuric acid from the sides of the test tube.	Violet ring formed at the junction of two liquids
4	Test for reducing sugars: Fehling's test: mix 1ml of fehling A and 1ml of fehling B solutions boil for 1min,add equal volume of test solution and then heat in boiling water bath for 5-10 mins.	First yellow then brick red preci- -pitate was observed
5	Benedict's test: Mix equal volumes of benedict's reagent and test solution in test tube. Heat in boiling water bath for 5 mins. Solution appears green,yellow or red depending on amount of reducing sugar present	Red colour was observed

Preparation of sustained release matrix tablets

Nevirapine sustained release matrix tablets were prepared by wet granulation technique[13,14]employing starch as a binder, okra gum as a release retarding polymer and lactose as a diluent to maintain the tablet weight. Six formulations F1-F6 using different percentages of okra gum., 5%, 10%, 15%, 20%, 25%, 30% were formulated. All the excipients, drug and gum were weighed, sifted, blended and mixed with binder solution to prepare granules. The granules obtained were compressed into matrix tablets with a compression force of 8-12 KN.

Evaluation of sustained release matrix tablets

Precompressional Parameters[15]

Angle of Repose

Angle of Repose (θ) is the maximum angle between the surface of a pile of powder and horizontal plane. It is determined by using funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained.

The radius of the heap (r) was measured and angle of repose (θ) was calculated using the formula:

$\theta = \tan^{-1}(h/r)$

Bulk Density

Apparent bulk density (Pb) was determined by pouring the blend in to a graduated cylinder. The bulk volume (Vb) and weight of the powder (M) was calculated using the formula:

$Pb = M/Vb$

Tapped Density

The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum volume (Vt) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density (Pt) was calculated by using formula:

$Pt = M/Vt$

Compressibility Index

The simplest way for measuring of free flow of powder is compressibility, an indication of the ease with which a material can be induced to flow is given by compressibility index (I). Compressibility index is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. A material having values of less than 12% is defined as the free flowing material.

$I = (Vo-Vt/Vo) \times 100$

Where, Vo is the bulk volume and Vt is tapped volume.

Hausner's Ratio

Hausner's ratio is an indirect index of ease of powder flow. It is the ratio of tapped density and bulk density. Hausner found that this ratio was related to inter-particle friction and, as such, could be used to predict powder flow properties (Lachman et al., 1987). Generally a value less than 1.25 indicates good flow properties, which is equivalent to 20% of Carr's index.

It can be calculated by:

Hausner's ratio = Tapped density / Bulk density

Post compression parameters

Hardness

Tablet hardness[16] was measured by using Monsantro hardness tester. From each batch six tablets were measured for the hardness and average of six values was noted.

Thickness

Twenty tablets from the representative sample were randomly taken and individual tablet thickness was measured by using digital vernier callipers. Average thickness was calculated.

Thickness = MSR + [VSR × 0.01]

Where,

MSR = Main scale reading

VSR = Vernier scale reading

Friability Test

- Ten tablets were accurately weighed and placed in the friability test[16]apparatus (Roche Friabilator).

- Apparatus was operated at 25 rpm for 4 minutes and tablets were observed while rotating. The tablets were then taken after 100 rotations, dedusted and reweighed.
- The friability was calculated as the percentage weight loss.

% Friability can be calculated as follows

$\% F = (W_1 - W_2 / W_1) \times 100$

Where W_1 = Initial weight of the 20 tablets.

W_2 = Final weight of the 20 tablets after testing.

Friability values below 0.8% are generally acceptable.

Weight Variation Test

To study weight variation**[17]** individual weights (W_i) of 20 tablets were noted using electronic balance. Their average weight (W_{avg}) was calculated. Percent weight variation was calculated as follows. Average weights of the tablets were calculated.

Percentage deviation (PD) **=** $[(W_{avg}) - (W_i) / (W_{avg})] \times 100$

Where,

PD = Percentage deviation,

W_{avg} = Average weight of tablet,

W_i = Individual weight of tablet.

According to IP 1996, out of twenty tablets ±5 % variation can be allowed for not more than two tablets.

According to USP 2004, ±5% weight variation can be allowed for not more than two tablets out of twenty tablets.

Assay

Five tablets were weighed and powdered. An accurately weighed portion of the above mixture equivalent to 400mg of nevirapine is transferred to a 100ml volumetric flask containing buffer solution. The concentration is measured at λmax (284.40nm).

In vitro Dissolution Studies

In vitro dissolution studies[16] were performed using the USP dissolution apparatus at 50 rpm. The dissolution medium consisted of 900 ml of pH 6.8 phosphate buffer maintained at 37±0.5ºC. An aliquot was withdrawn at specific time intervals and drug content was determined by UV-visible spectrometer at 284.40 nm.

RESULTS AND DISCUSSION

In the present study the sustained release matrix tablets of Nevirapine were successfully developed in order to sustain the drug release rate by okra gum as a release retarding hydrophilic polymer.

FTIR spectra of nevirapine, okra mucilage, magnesium stearate, lactose and their physical mixture was taken.

FTIR of pure Nevirapine:

FTIR of nevirapine exhibits characteristic peaks for amide group at 3188.21cm-1 and 1650.29 cm^{-1} due to N-H and C=O stretching respectively, at 3061.45 cm^{-1} (C-H stretch, pyridines), 1288.87 cm^{-1} (Aromatic amine group, C-N stretch).

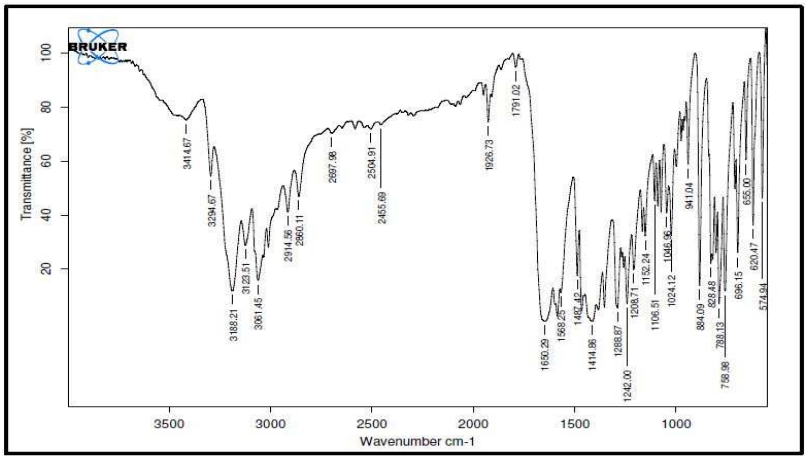

Fig. 1: FTIR of Pure Nevirapine

FTIR of okra mucilage

FTIR Spectra of okra mucilage revealed a stretching band at 3361.36 cm^{-1}, O-H, carboxylate group, 2927.27 cm^{-1} due to C-H, methylene group,1614.76 cm^{-1} C=O, carboxylate group.

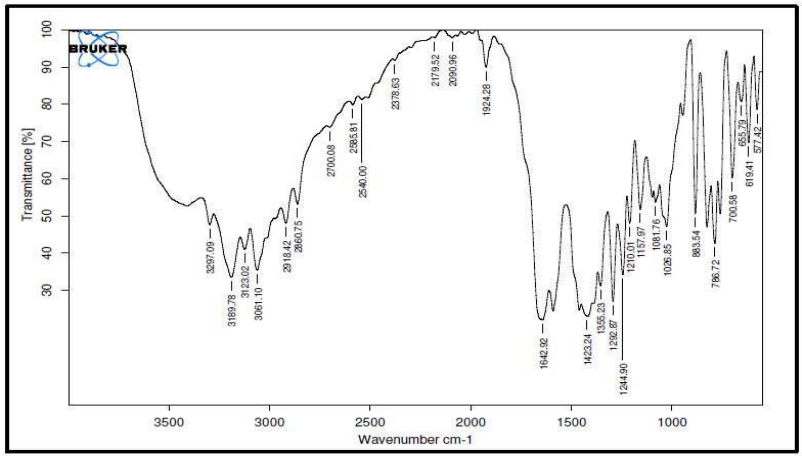

Fig. 2: FTIR of okra gum

FTIR of Nevirapine with Okra Gum

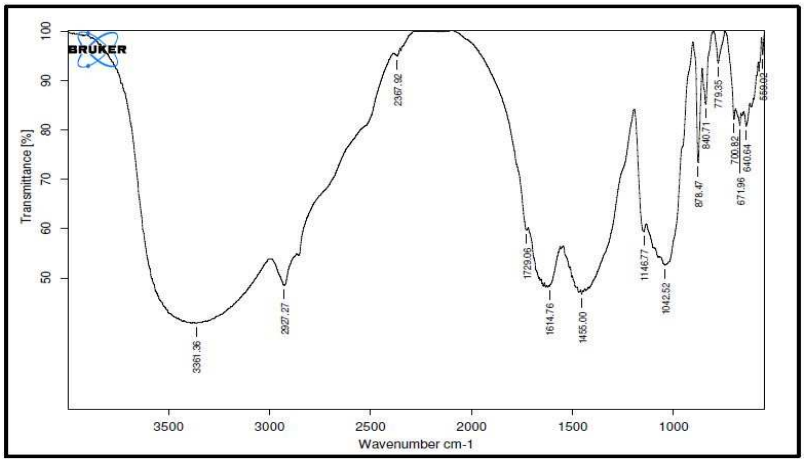

Fig. 3: FTIR of Nevirapine and okra gum

FTIR of the optimized formulation

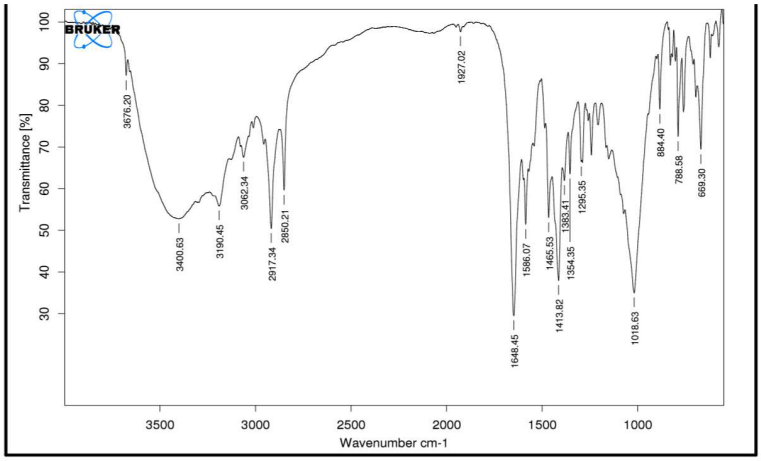

Fig. 4: FTIR of Optimized Formulation

All the characteristic peaks of pure drug were observed in the spectrums of drug nevirapine with okra gum, and all other excipients. This indicated that there is no interaction between drug and excipients used in formulation.

Table 2: Evaluation of Granules

Formulation (F)	Angle of repose(ϴ)	Bulk density (gm / cm3)	Tapped density (gm / cm3)	Hausner's ratio	Compressibility index(%)
F-1	25.5±0.5	0.41±0.03	0.46±0.07	1.20±0.06	13.46±0.62
F-2	31.5±0.6	0.39±0.01	0.45±0.04	1.15±0.09	13.34±0.43
F-3	26.2±0.4	0.37±0.02	0.45±0.05	1.09±0.02	13.32±0.34
F-4	33.1±0.3	0.46±0.08	0.49±0.04	1.19±0.04	14.01±0.56
F-5	25.7±0.4	0.34±0.07	0.40±0.03	1.01±0.08	13.02±0.21
F-6	29.2±0.5	0.37±0.06	0.41±0.02	1.11±0.06	13.40±0.89

Values ± SD, n = 3

Evaluation of Tablets

Precompressonal Parameters

Six batches of granule formulations were prepared using different polymer percentages and various evaluation parameters like Angle of repose, Bulk density, Tapped density and Hausner's ratio. All the results of pre-compressional evaluation parameters of the formulations were found to be satisfactory and complied with the official limits.

Post Compressional Parameters

Tablet evaluation for the optimized formulation was done.

Table 3: Evaluation of Tablets

Formulation (F)	Hardness (kg/cm2)	Thickness (mm)	Friability (% w/w)	Content uniformity(%)	Weight variation(mg)
F-1	6.2	3.5	0.52	98.94	745
F-2	6.5	4.6	0.46	98.95	710
F-3	7.2	5.4	0.62	99.05	695
F-4	6.7	5.8	0.54	101.2	735
F-5	6.8	5.2	0.37	99.52	689
F-6	6.4	5.0	0.44	98.79	723

In vitro drug release study

Dissolution studies were performed using 0.1 N Hcl and pH 6.8 phosphate buffer. In order to investigate the effect of polymer concentration on drug release profile, different formulations containing various percentages of *Abelmoschus esculentus* mucilage was used. The drug release was found to retard as concentration of gum increases in the formulation. The natural gum is hydrophilic which is used as a retarding release of drug in controllable manners up to 10 hrs. The formulations F3, F4, F5 containing polymer concentrations (20%.25%,30%) were able to sustain the drug release up to 8-12 hrs with percentage drug release as (97.1%, 97.8%, 98.5%)respectively indicate that rate of release decreases as The concentration of gum increases

Among all the formulations, formulation F5 (30% of polymer) is able to sustain drug release for more time period compared to other formulations evident from dissolution studies. Hence formulation F5 is considered as an optimized formulation.

Table 4: In Vitro Dissolution Study Data of F1-F6 Formulations

Time(hrs)	F1(10%)	F2(15%)	F3(20%)	F4(25%)	F5(30%)	F6(35%)
0	0	0	0	0	0	0
1	37.2	31.1	9.1	8.4	6.5	4.8
2	59.1	40.2	18.2	15.7	15.8	12.4
3	75.7	69.5	30.6	28.5	27.9	22.6
4	80.2	70.6	56.8	54.2	45.0	43.8
6	95.5	80.2	72.8	69.6	56.3	55.7
8	-	96.3	97.1	78.9	71.6	64.3
10	-	-	-	97.8	87.2	78.5
12	-	-	-	-	98.5	87.9

Comparative in Vitro dissolution profiles of formulations (F1-F6)

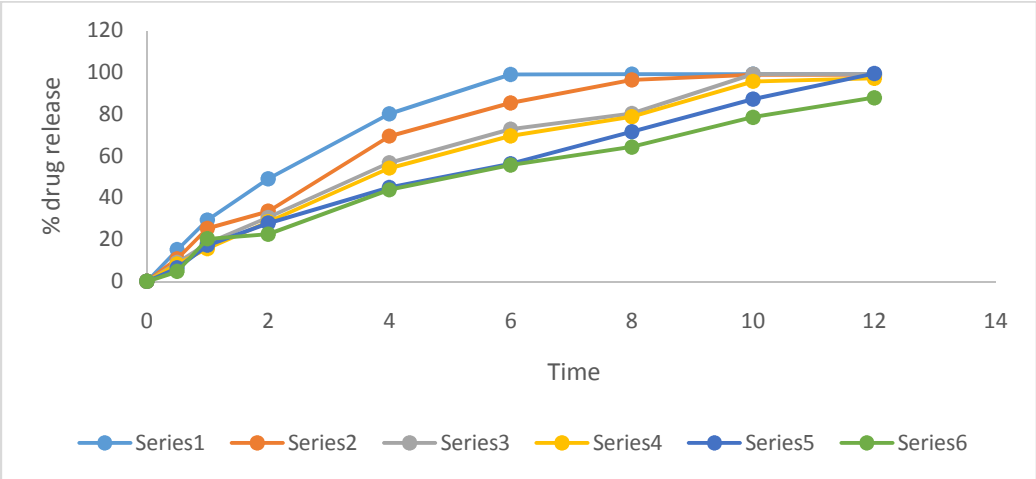

Fig. 5: Plot for comparative dissolution profiles of formulations F1-F6

Kinetic modelling for the optimized formulation

To know the drug release kinetics for the optimized formulation, the dissolution data was subjected to different kinetic model such as Zero order, First order and Higuchi's square root and Korsmeyer-Peppa's. Results of these models are shown the figures: 6,7,8,9,10. The line of equations and regression coefficient of kinetic study for all the formulations are shown in table 11. The regression coefficient was considered as main parameter to interpret release kinetics

The kinetic treatment of the drug release data of the optimized formulation(F5) was done. On comparing equation of line and regression coefficient (R^2) for different models it was found that the optimized formulation F5 follows first order drug release (value of $R^2$is **0.9803**). Formulation F5 releases 6.5 % of drug in the first one hour and prolongs the release of remaining drug upto 12 hours whereas other formulations do not prolong the release upto 12 hours. The formulation F6 also prolongs the drug release upto 12 hours but has poor pre-compressional and post-compressional parameters. Hence considering the dissolution studies and all other evaluation parameters formulation F5 was considered as an optimized formulation.

Accelerated Stability Studies

There was no significant change in physical properties of the tablets of formulation F5 after 3 Months, parameters like % drug release and Drug content values at various conditions as per ICH guidelines quantified at various time intervals were shown in table no 6.

Zero Order Plot

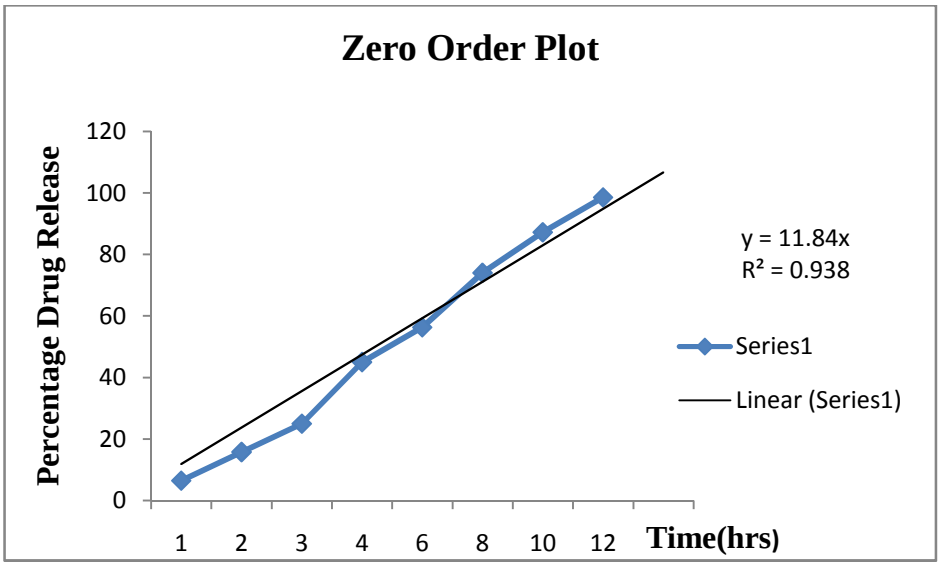

Fig. 6: Zero Order Plot for the formulation F5

First Order Plot

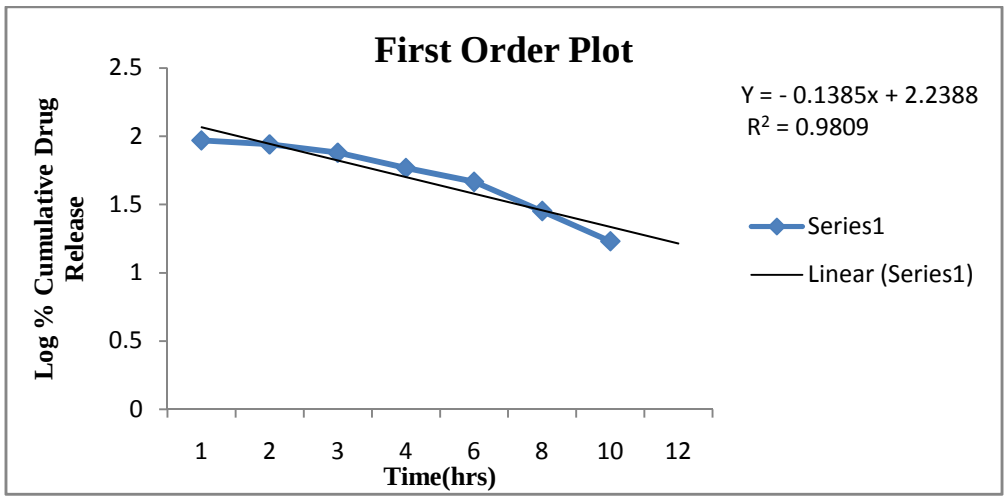

Fig. 7: First Order Plot for the formulation F5

Higuchi Plot

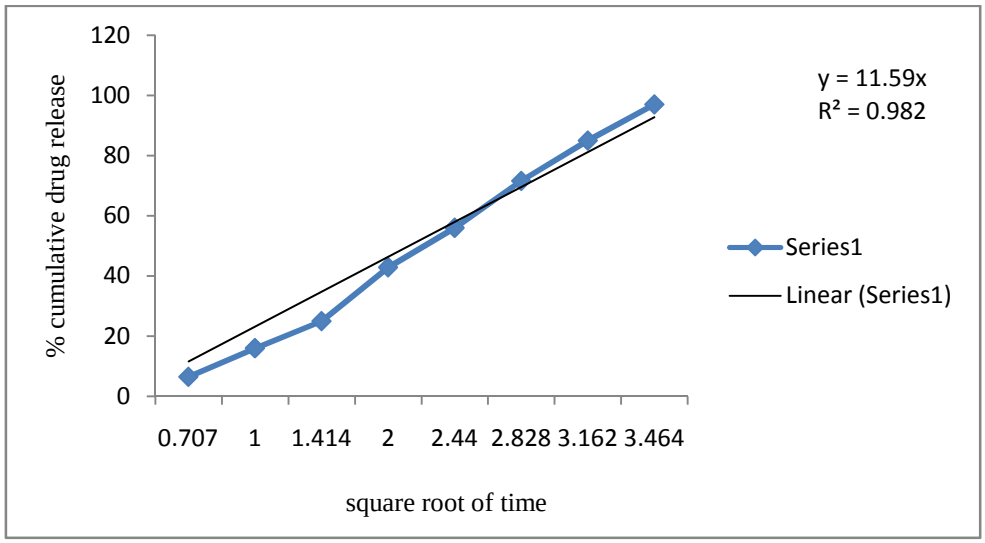

Fig. 8: Higuchi Plot for the formulation F5

Korsemeyer Peppa's Plot

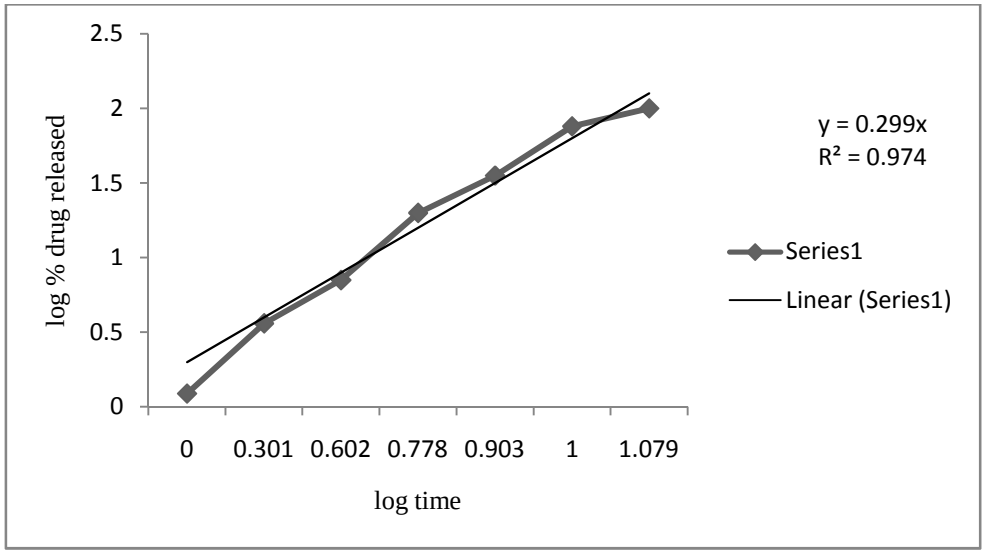

Fig. 9: Korsemeyer Peppa's plot for the formulation F5

Hixon Crowell Plot

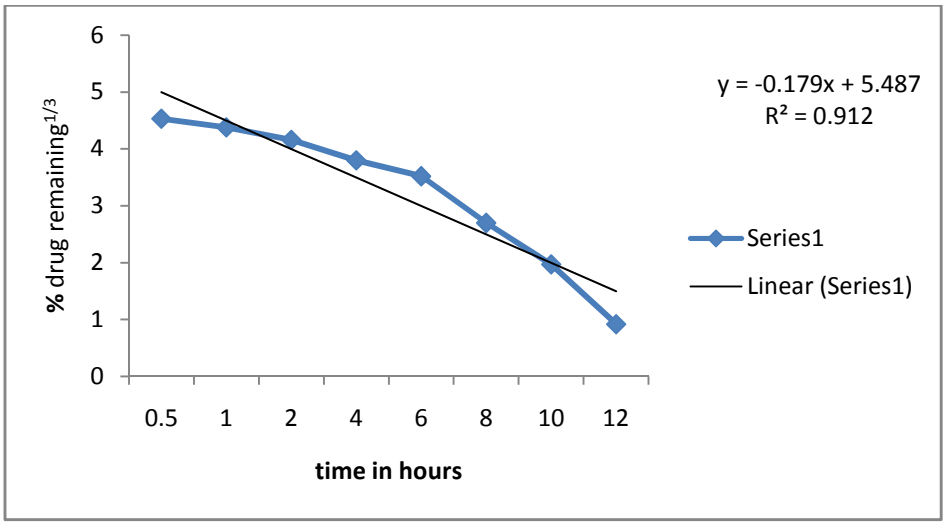

Fig. 10: Hixon Crowell plot for the formulation F5

Table 5: Release Kinetics For F5 Formulation

S. No.	Kinetic model	R^2	n(slope)
1	Zero order	0.938	11.84
2	First order	0.980	-0.138
3	Higuchi plot	0.972	11.59
4	Korsmeyer-Peppa's plot	0.974	0.299
5	Hixon Crowell plot	0.912	-0.179

Table 6: Drug Release And Assay Values For F5

Formulation (F)	Parameters	Initial	After 1 month	After 2 months	After 3 Months	Limits as per Specifications
F5	40⁰C/ 75%RH %Drug Release	99.50	99.35	99.23	99.02	Not less than 85 %
F5	40⁰C/ 75% RH Assay Value	99.52	99.36	99.14	98.91	Not less than 90 % Not more than 110 %

CONCLUSION

Six formulations were prepared using different polymer percentages and were evaluated. All the evaluation parameters were found to be satisfactory. Among all the formulations F5 (30% of polymer) showed the better release pattern compared to other formulations evident from dissolution studies.

The kinetic treatment of the drug release data of the optimized formulation (F5) was done. On comparing equation of line and regression coefficient (R^2) for different models it was found that the optimized formulation F5 follows first order drug release (value of $R^2$is **0.9803**). Hence considering the dissolution studies and all other evaluation parameters formulation F5 was considered as an optimized formulation. The stability studies were carried out for period of 3 months as per ICH guidelines and were in acceptable limits.

From the above study conducted on investigation of okra gum as a release retarding polymer, it can be concluded that okra gum efficiently produces the sustaining effect in the matrix tablets and it can also be used as a matrix forming polymer in sustain release dosage forms besides being used as a binder.

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