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**RESEARCH ARTICLE**

# FORMULATION AND EVALUATION OF FAST DISSOLVING ORAL FILM OF PROCHLORPARAZINE DIMALIATE

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## ABSTRACT

A oral fast dissolving film is a type of multiple new drug delivery system. aim and objective to prepare and evaluate fast Dissolving oral film of Prochlorperazine to reduce the pain like migraine with fast relief. Prochlorperazine oral film quickly disintegrates and dissolves, and can be administered without water, making them particularly suitable for geriatric patients and found faster action. The immediate release layer containing PEG600, HPMC, EC, Citric acid was prepared by solvent casting method and fast release layer containing HPMC, EC, Citric acid (in desired concentrations) was. The drug content of film revealed that the drug was uniformly mixed in the polymers. *In-vitro* dissolution studies revealed that formulation has showed the initial release of immediate release layer dose. The kinetic data showed that drug release from film follow Zero order, Higuchi plot indicated that the formulation follow Diffusion controlled release mechanism.

## INTRODUCTION

Oral drug strip oro-dispersible film to administer drugs via absorption in the mouth (buccally or sublingually) and/or via the small intestines. A film is prepared using hydrophilic polymers that rapidly dissolves on the tongue or buccal cavity, delivering the drug to the systemic circulation via dissolution when contact with liquid is made. Thin-film drug delivery has emerged as an advanced alternative to the traditional tablets, capsules and liquids often associated with prescription and OTC medications. Similar in size, shape and thickness to a postage stamp, thin-film strips are typically designed for oral administration, with the user placing the strip on or under the tongue (sublingual) or along the inside of the cheek (buccal). These drug delivery options allow the medication to bypass the first pass metabolism thereby making the medication more bio-available. As the strip dissolves, the drug can enter the blood stream, buccally or sublingually (1). Evaluating the systemic transmucosal drug delivery, the buccal mucosa is the preferred region as compared to the sublingual mucosa. Different buccal delivery products have been marketed or are proposed for certain diseases like trigeminal neuralgia, Meniere's disease, diabetes, and addiction. The FDFs technology continues to be viewed as an alternative for FDT products that would afford a superior barrier to generic entry and product differentiation to over-the-counter brands. From the marketing perspective, a patented ODF technology would be beneficial. The grant of marketing exclusivity to the new dosage form would help to gain more revenue. The various synonyms used for FDFs include mouth dissolving films (MDFs), orally disintegrating films (ODFs), melt in-mouth films, oro-dispersible, quick dissolving and rapid disintegrating films (2).

**Classification of Oral Films:**

There are three different subtypes

1. Flash release
2. Mucoadhesive melt-away wafer
3. Mucoadhesive sustained-release wafers

**Advantages:**

**1.** Improved bioavailability of poorly soluble compounds.

**2.** During Processing solvents and water are not required.

**3.** Cost-effective process with reduced production time and reduced number of unit operations.

**4.** Homogeneous distribution of fine particle occurs.

**5.** Sustained modified and targeted release capability.

**6.** Superior stability at varying pH and moisture levels (3).

## MATERIALS AND METHODLOGY

Prochlorperazine was obtained as a gift sample from Sun Pharma Ltd, Varodra. Other Excipients were procured from Rankem/SD Fine Chemicals.

**Pre-formulation study**

**A) Organoleptic evaluation**

It refers to the evaluation by sensory characters-taste, appearance, odor etc.

**B) Solubility (at room temp :)**Solubility is determined in different solvents example – water methanol, 0.1 N HCL, Ethyl Alcohol, and Chloroform (4).

**C) Loss on drying:**

Loss on drying directly measuring by IR moisture balance. Firstly calibrate the instrument by knob then take 5.000 gm sample (powder) and set the temp at 100°C to 105°C for 5 minutes and constant reading set the knob and check % moisture.

**D) Determination of pH (1% w/v solution in water)**

pH was determined by digital pH meter. In this method 1gm of the powder was taken and dissolved in 100ml of distilled water with sonication and filtered, pH of the filtrate was checked with standard glass electrode (5).

**E) Melting point:**

A small quantity of powder was placed into a fusion tube. That tube is placed in the melting point determining apparatus containing castor oil. The temperature of the castor oil was gradual increased automatically and read the temperature at which powder started to melt and the temperature when all the powder gets melted.

**F) Moisture Content Determination**

The titrimetric determination of water is based upon the quantitative reaction of water which is present on sample with KF reagents and record % of water (6).

**G) Determination of $\lambda_{max.}$**

The absorption maxima of Prochlorperazine dimaleate were determined by Accurately weighed 10 mg of drug was dissolved in 10 ml of 6.8 pH phosphate Buffer in 10 ml of volumetric flask and prepare suitable dilution to make it to a concentration of 10µg/ml make adequate of sample with concentration range of 5-25µg/ml. The spectrum of this solution was run in 200-400 nm range in U.V spectrophotometer (Labindia UV 3000 +) (7).

**Formulation**

The method of solvent casting technique involves preparation of the film base which involves the mixing of suitable film forming excipients along with drug in a suitable solvent or solvent system. Once the solution is prepared, the film casting process is performed wherein a film of desired thickness is casted onto a moving inert substrate, where suitable rollers are employed for guiding the solution onto the substrate (8).

formulation of oral fast dissolving films of Prochlorperazine dimaleate done by solvent casting methodformulation done by combining the polymers in different ratios. HPMC and EC films were prepared by dissolving HPMC in measured volume of chloroform. Then added EC and mixed thoroughly to get a homogeneous mixture. To this, specified quantities of dibutyl phthalate and isopropyl myristate were added. The polymeric solution of EC and HPMC were prepared by dissolving separately in methanol- chloroform (1:1) mixture. A weighed amount of drug was dissolved in DM water and dispersed in polymer mixture, then added PEG-600, SSG , CCS Citric Acid, and poured in to the glass mould placed in a hard rigid and uniformly leveled surface. Solvent evaporation was controlled by covering with a funnel in its inverted position. After 24 hours the films were removed, cut in circular disc with 3.8cm diameter and kept in desiccators for further studies (9). The composition of various polymeric combinations is given in the Table. 1

| Name of Ingredients | Composition |
|---|---|
| Prochlorperazine dimaleate | 120mg |
| HPMC | 200 |
| EC | 100 |
| PEG-600 | 0.5 |
| SSG | 10 |
| CCS | 10 |
| Citric Acid | 10 |
| DM Water | 20 ml |

## EVALUATION PARAMETERS [10, 11]

**A) Thickness**

The thickness of patches was measured at three different places using a absolute outside micrometer.

**B) Weight uniformity**

For each formulation, three randomly selected patches were used. For weight variation test, 3 films from each batch were weighed individually by digital electronic balance and the average weight was calculated (10).

The tensile testing gives an indication of the strengthand elasticity of the film, reflected

by the parameters- tensile strength, elastic modulus, % strain, and loadat yield.

**C) Folding Endurance**

This was determined by repeatedly folding one film at the same place until it broke. The number of times the film could be folded at the same place without breaking / cracking gave the value of folding endurance (11).

**D) Percentage of Moisture Content**

The films were weighed individually and kept in desiccators containing activated silica at room temperature for 24 hrs. Individual films were weighed repeatedly until they showed a constant weight. The percentage of moisture content was calculated as the difference between initial and final weight with respect to final weight (12).

**E) Drug Content Analysis**

The film of specified area were taken into a 10 ml volumetric flask and dissolved I in methanol and volume was made up with 10 ml methanol. Subsequent dilutions were made and analyzed by UV spectrophotometer (13-14).

**F) Disintegrating time**

The most important criteria of present work are to that dosage form should be dissolved within few seconds. The incorporation of super disintegrating agent to minimizes the disintegrating time. Three super disintegrating agent were selected for this work (15).

**G) *In vitro* dissolution study**

The *in vitro* dissolution test was performed using the USPXXX dissolution apparatus II (Paddle with sinker). The dissolution studies were carried out at 37±0.5° C; with stirring speed of 75 rpm in 900 ml 0.1 N Hydrochloric acid. Film size required for dose delivery (2.5×2.5 cm2) was used. Five ml aliquot of dissolution media was collected at time intervals of 1, 2, 5, 10 and 15 minutes and replaced with equal volumes of 6.8 N HCl. The collected samples were filtered through 0.45 µm membrane filter and the concentration of the dissolved Prochlorperazine dimaleate was determined using UV-Visible spectrophotometer at 256 nm. The results were presented as an average of three such concentrations (16-18).

## RESULTS AND DISUSSION

Solubility studies of Prochlorperazine dimaleate has been done in various solvent such as water, Chloroform, Ethanol, Methanol, and 0.1N HCL solution. We were found that a solubility of Prochlorperazine dimaleate is good in a Methanol solution.

The melting point of the drug sample range of the drug is 140-142$^{o}$C. Hence complies

with IP standards thus indicating the purity of the drug sample.

The **partition coefficient** is a ratio of concentrations of un-ionized compound between the two solutions. To measure the **partition coefficient** of ionizable solutes, the pH of the aqueous phase is adjusted such that the predominant form of the compound is un-ionized.

The percentage of loss on drying of Prochlorperazine dimaleate was found to be **0.92%** w/w respectively.

The pH of Prochlorperazine dimaleate was determined by Digital pH meter and found to be 7.6. The Moisture content of Prochlorperazine maleate is 0.56 %.

Accurately weighed 10 mg of Prochlorperazine dimaleate separately and dissolved in 10 ml of 6.8 pH buffer in 10 ml of volumetric flask and prepared suitable dilution to make it to a concentration of 10µg/ml make adequate of sample with concentration range of 5-25µg/ml Prochlorperazine dimaleate. The spectrum of this solution was run in 200-400 nm range in U.V spectrophotometer. the $\lambda_{max}$ found for Prochlorperazine dimaleate is 256.0 nm.

The mechanical properties of the film give idea about to what extent the film can withstand the force or stress during processing, packaging, transport and handling. The desirable characteristics of film are moderate tensile strength, low elastic modulus, high% strain and high load at yield. From the above table, the polymer should give soft but tough film. disintrigation time of this batch also suitable fast disintegration oral film aimed about 25 sec.

The most important criteria of present work are to that dosage form should be dissolved within few seconds. The incorporation of super disintegrating agent to minimizes the disintegrating time. Three super disintegrating agent were selected for this work.

The In vitro drug release data of the optimized formulation was subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetic equsation in order to determine the mechanism of drug release. When the regression coefficient values of were compared, it was observed that ‘r’ values of first order was maximum 0.949 hence indicating drug release from formulations was found to follow First order release kinetics.

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**Table No. 2 Organoleptic property of Prochlorperazine Dimaleate**

| | | |
|---|---|---|
| **Color** | : | **Light yellow powder** |
| **Odor** | : | **Odorless** |
| **Taste:** | : | **Bitter** |

**Table No. 3. Solubility studies of Prochlorperazine dimaleatein different solvent**

| **S. No.** | **Solvent used** | **Solubility** |
|---|---|---|
| **1.** | Water | Insoluble |
| **2.** | 0.1 N HCL | Sparingly soluble |
| **3.** | Ethanol | Sparingly soluble |
| **4.** | Methanol | Freely Soluble |
| **5.** | Chloroform | Sparingly soluble |
| **6.** | 6.8 pH buffer | Freely soluble |

**Table No. 4 Description of IP-Index**

| **Descriptive term** | **Parts of solvent required for Parts of soluble** |
|---|---|
| Very soluble | Less than 1 |
| Freely soluble | From 1to 10 |
| Soluble | From 10 to 30 |
| Sparingly soluble | From 30to 100 |
| slightly soluble | From 100 to1000 |
| Very slightly soluble | From 1000 to 10000 |
| Practically insoluble | 10000 or more |

**Figure no. 1 DETERMINATION OF $\Lambda_{max}$ BY UV-VISIBLE SPECTROSCOPY**

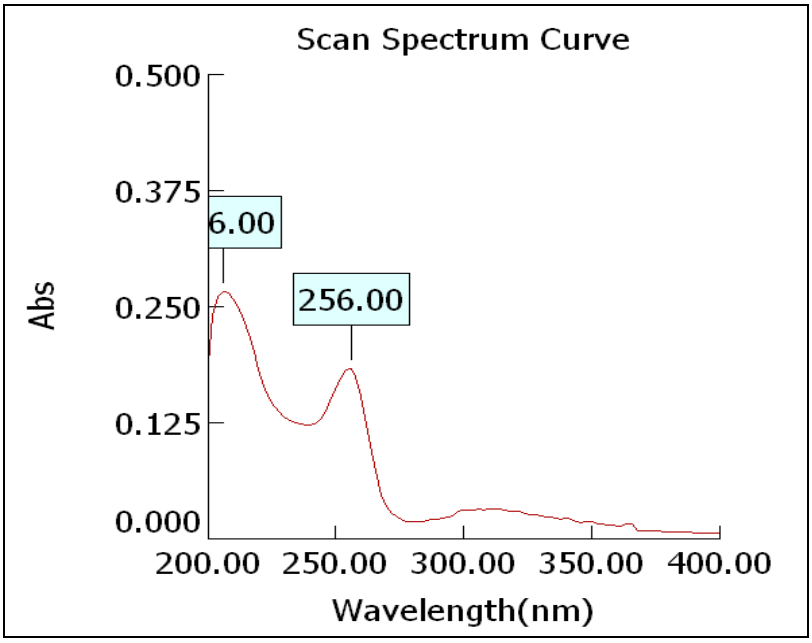


**Fig No.1 Determination of $\lambda_{max}$ of Prochlorparazine dimeliate**

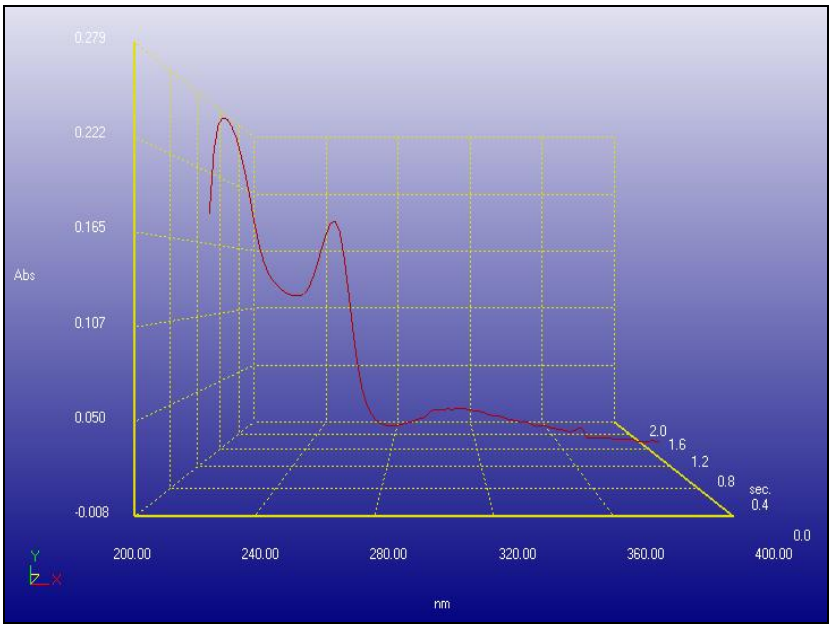


**Fig no. 2 Spectrum of Prochlorparazine dimeliate**

**Table No. 5 Calibration Curve of Prochlorperazine Dimaleate**

| Replicate | 2 | 4 | 6 | 8 | 10 |
|---|---|---|---|---|---|
| **1** | 0.241 | 0.529 | 0.737 | 0.980 | 1.33 |
| **2** | 0.243 | 0.527 | 0.736 | 0.982 | 1.30 |
| **3** | 0.241 | 0.530 | 0.736 | 0.981 | 1.32 |
| **Mean** | 0.241 | 0.528 | 0.736 | 0.981 | 1.31 |
| **S.D.** | 0.001 | 0.001 | 0.0005 | 0.001 | 0.0002 |
| **% RSD** | 0.414 | 0.189 | 0.068 | 0.101 | 0.015 |

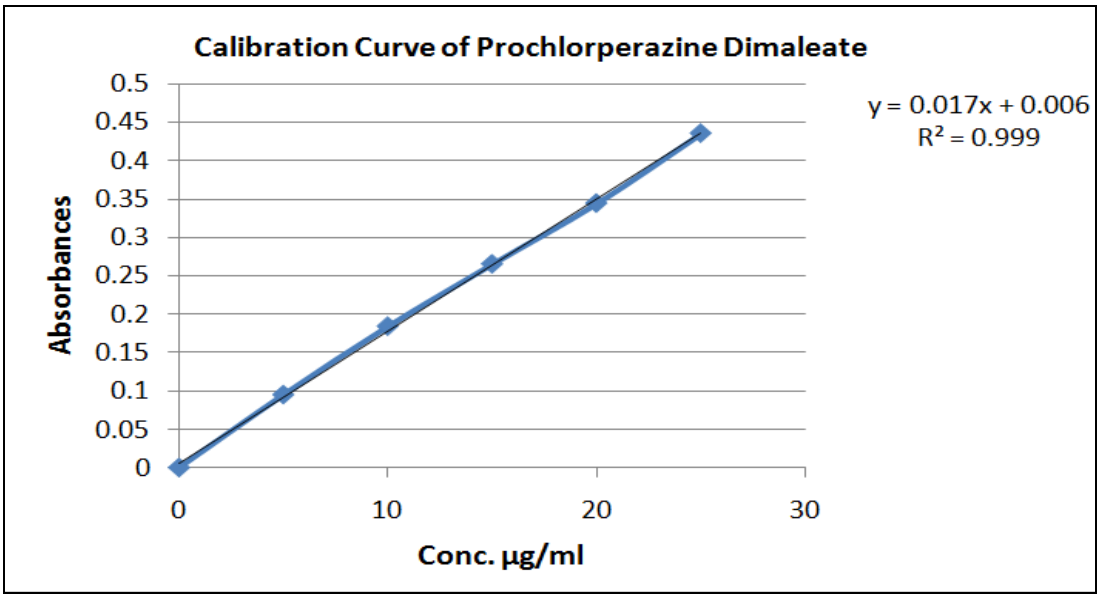


**Fig. 3 Calibration Curve of Prochlorperazine Dimaleate at 256 .0 nm**

**Table No. 6 Stastical Data For Linearty**

| S.No. | Parameter | Remark |
|---|---|---|
| **1** | Linearty Range | 5-25 µg/ml |
| **2** | Regression Equation | 0.017+0.006 |
| **3** | Correlation Cofficient | 0.999 |

**Table No. 7 Formulation Development**

| Formulation code | General Appearance | Thickness in µm | Weight mg |
|---|---|---|---|
| **F1** | TP | 23.56 | 40.25 |
| **F2** | TP | 24.54 | 44.25 |
| **F3** | TP | 25.45 | 48.56 |

***TP – Transparent, TL - Translucent**

**Table No 8 Result of Folding Endurance, Tensile strength & % Age Elongation**

| Formulation code | Folding endurance | Tensile strength in Kg/cm2Kg |
|---|---|---|
| **F1** | 350±35 | 0.758 |
| **F2** | 548±32 | 0.869 |
| **F3** | 586±22 | 1.056 |

**Table No. 9 Results of disintegrating**

| Formulation code | Disintegrating time (sec.) |
|---|---|
| **F1** | 46 |
| **F2** | 35 |
| **F3** | 25 |

**Table No. 10 Results of Optimized Formulation**

| F. code | Dis. Time | General appearance | Thickness in µm | weight in mg | Folding endurance | Tensile strength in Kg/cm2Kg | Drug Content |
|---|---|---|---|---|---|---|---|
| **F3** | 25 | Transparent | 25.45 | 48.56 | 586±22 | 1.056 | 99.6±0.6 |

**Table No. 11: *In-vitro* drug release data of formulation F3**

| S. No. | Time (min) | Square Root of Time | Log Time | Cumulative* Percentage Drug Release±SD | Log Cumulative Percentage Drug Release | Cumulative Percent Drug Remaining | Log cumulative Percent Drug Remaining |
|---|---|---|---|---|---|---|---|
| 1 | 1 | 1.000 | 0.000 | 33.2 | 1.521 | 66.800 | 1.825 |
| 2 | 2 | 1.414 | 0.301 | 44.5 | 1.648 | 55.500 | 1.744 |
| 3 | 5 | 2.236 | 0.699 | 86.12 | 1.935 | 13.880 | 1.142 |
| 4 | 10 | 3.162 | 1.000 | 93.65 | 1.972 | 6.350 | 0.803 |
| 5 | 15 | 3.873 | 1.176 | 99.56 | 1.998 | 0.440 | -0.357 |
| 6 | 20 | 4.472 | 1.301 | 99.89 | 2.000 | 0.110 | -0.959 |
| 7 | 25 | 5.000 | 1.398 | 99.87 | 1.999 | 0.130 | -0.886 |

* Average of three determinations

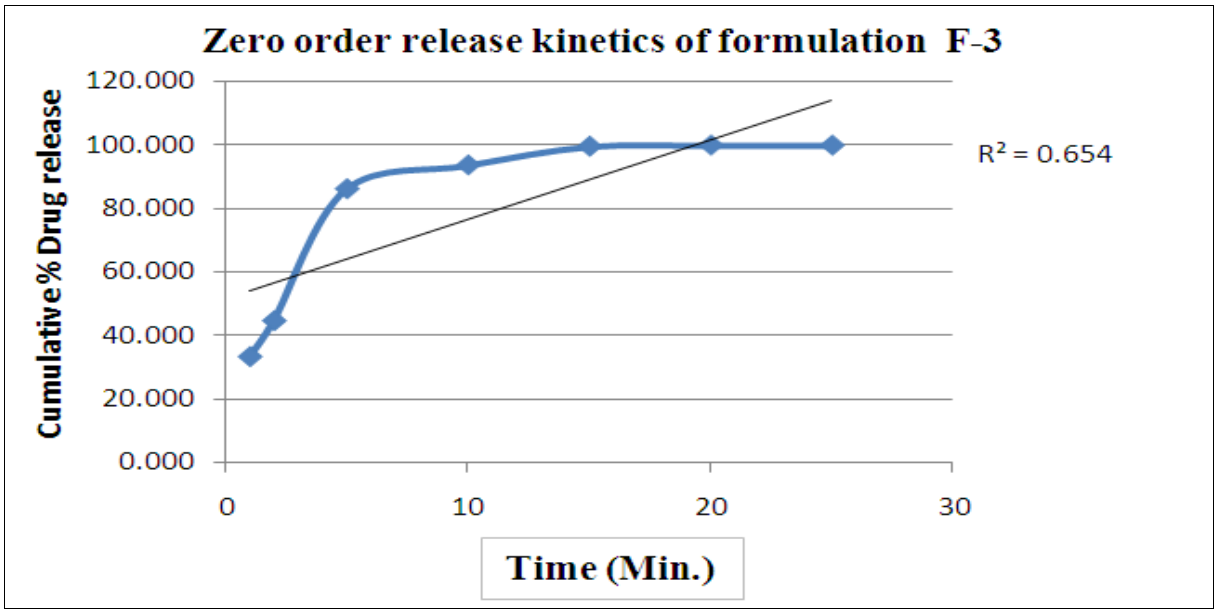


**Fig. 4 Zero order release kinetics of optimized formulation F3**

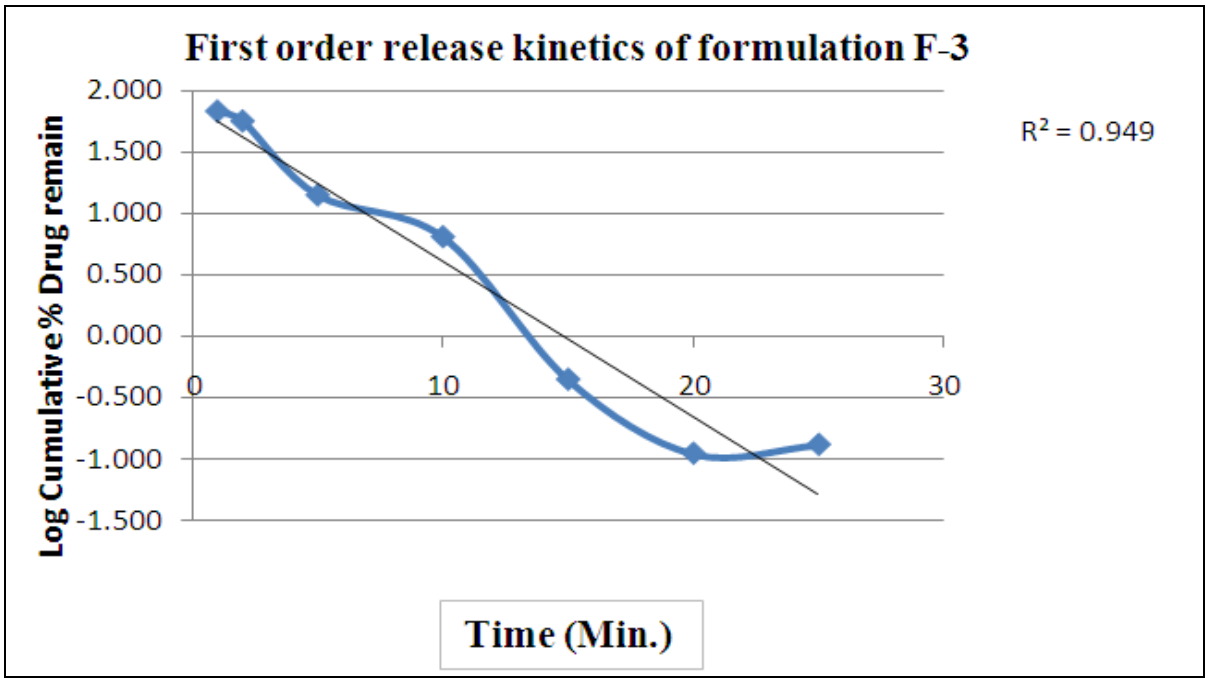


**Fig. 5 First order release kinetics of Optimized Formulation F3**

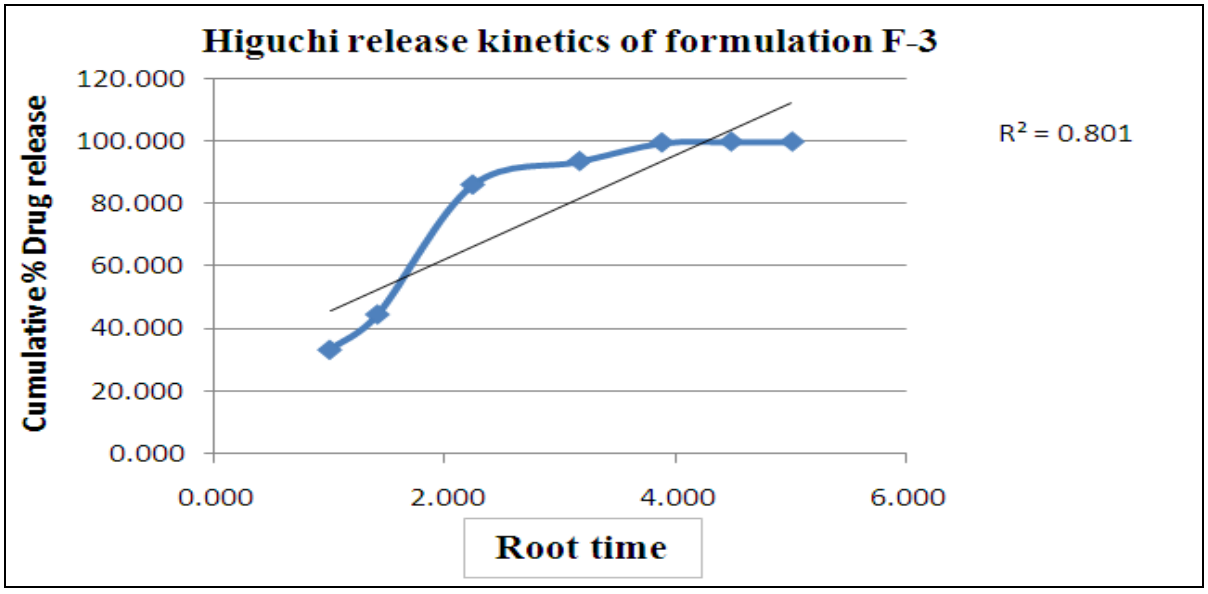


**Fig. 6 Higuchi release kinetics of Optimized Formulation F3**

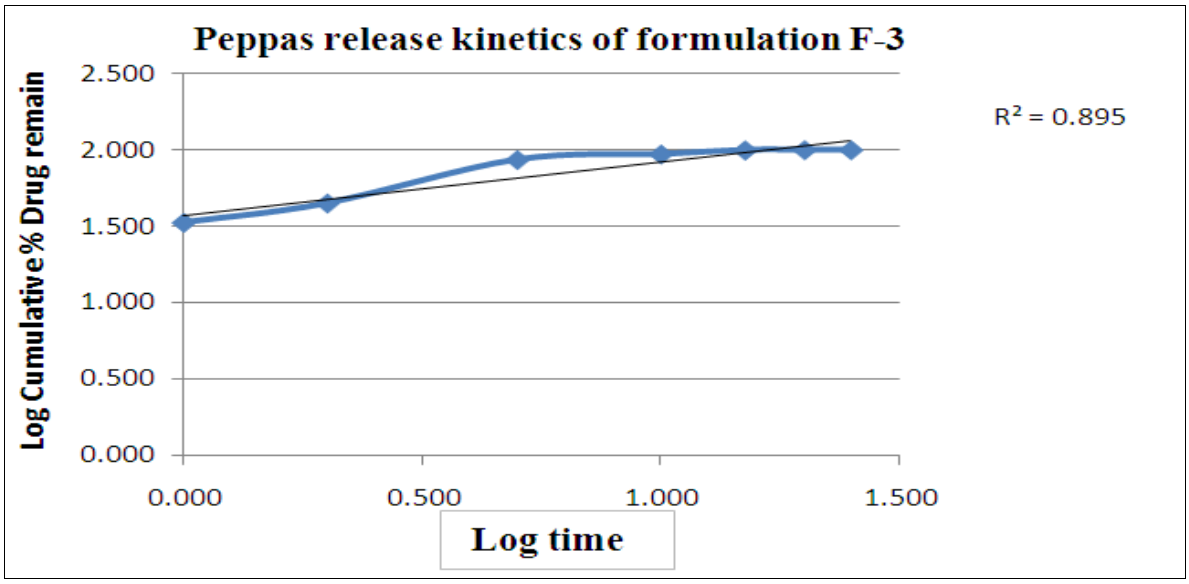


**Fig. 7 Higuchi release kinetics of Optimized Formulation F3**

**Table No. 12 Kinetics data of Optimized Formulation F3**

| **Formulation** | **Regration Cofficient** | **Zero order** | **First order** | **Higuchi** | **Peppas** |
|---|---|---|---|---|---|
| F6 | $r^2$ | 0.654 | 0.949 | 0.801 | 0.895 |