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# Formulation and evaluation of hydrogel beads of flecainide

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## Abstract

This study focuses on creating and assessing hydrogel beads containing Flecainide. Hydrogels are polymer networks that absorb and retain significant amounts of water. Within this network, hydrophilic groups become hydrated in aqueous environments, forming a hydrogel structure. The primary goal was to evaluate the formulation of hydrogel beads with Flecainide. Preliminary studies, including solubility and UV analysis, confirmed the formulation's requirements. FTIR spectra indicated no interaction between Flecainide and the polymers, suggesting that the distribution of Flecainide within the beads was appropriate and within acceptable limits.Additionally, the study demonstrated that as the polymer concentration increases, the amount of medication released decreases. The Flecainide hydrogel beads exhibited controlled and extended drug release in vitro. The dissolution data for the optimal formulation (F12) were analyzed using three kinetic models: the Higuchi and Korsmeyer-Peppas equations, zero-order, and first-order kinetics. The $r^2$ value for the optimized formulation F12 is 0.974, indicating compliance with zero-order release kinetics. Furthermore, the Korsmeyer-Peppas analysis supports the mechanism of drug release. For formulation F12, the "n" value is 1.021, indicating a supercase transport mechanism.

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## INTRODUCTION

Hydrogels are polymeric networks that can absorb and hold vast amounts of water. A hydrogel structure is created by the hydrophilic groups in the polymeric network hydrating in aqueous surroundings. It can alternatively be described as a polymeric material that has the ability to swell and retain a significant amount of water inside its structure despite not dissolving in water. They resemble natural tissue because they are somewhat flexible due to their high water content. Hydrogels are resistant to dissolution because of

crosslinks between network chains, and they can absorb water because of hydrophilic functional groups attached to the polymeric backbone [1]. A hydrogel comprises a three-dimensional (3D) network of hydrophilic polymers that have been crosslinked chemically or physically to allow the polymer chains to swell in water and retain a significant amount of water while retaining their structure. In the beginning, Wichterle and Lím reported on hydrogels. To qualify as a hydrogel, a material's weight (or volume) must include water at least 10% of the total. Hydrogels possess an extraordinarily close-to-natural tissue degree of elasticity, primarily attributed to their high water content. The hydrophilicity of the network is explained by the presence of hydrophilic groups such as -NH2, -COOH, -OH, -CONH2, -CONH -, and -SO3H. Hydrogels undergo a significant volume phase change, also known as a gel-sol phase transition, in response to particular physical and chemical stimuli [2].

## METHODOLOGY

### PREFORMULATION STUDY:

### FTIR study:

Fourier transform infrared spectroscopy was used in drug-polymer compatibility studies to verify that the drug's entrapment within polymeric systems is solely a physical process and that there is no ongoing interaction between the drug and polymer combination. To verify the identity of the drug and identify any interactions between it and the excipients, FTIR absorption spectra of the pure drug, all of the polymers utilized, and the combination of drug and polymers were obtained [3].The drug's compatibility with the formulation was verified using FTIR spectrum analysis. Using the Shimadzu FT-IR 8300 spectrophotometer and the potassium bromide pellet method, the FTIR spectra of Flecainide and formulation comprising all polymers were determined in the wavelength range of 4,000 to 400 cm-1. The process involved distributing a sample of potassium bromide and compressing it into discs using a hydraulic press set to five tonnes of pressure for five minutes. The spectrum was acquired after inserting the pellet into the light path [4].

### Methodology

### Formulation of Hydrogel Beads:

Ionotropic gelation is the process used to make hydrogel beads. A precise amount of polymer was dissolved in 25 milliliters of purified water and mixed to create a dispersion. The drug was added to the dispersion mentioned above and mixed once more to ensure uniform distribution and create a homogenous mixture. Using a 23G syringe needle, the mixture was extruded into a 1% w/v calcium chloride solution. The beads were left in the same solution for thirty minutes to increase their mechanical strength. After the beads were created, they were separated, given a water wash, and left to dry overnight at room temperature [5].

**Table 1 Formulation Design for Flecainide hydrogel beads**

| Ingredients | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 | F11 | F12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Flecainide | 150 | 150 | 150 | 150 | 150 | 150 | 150 | 150 | 150 | 150 | 150 | 150 |
| Sodium Alginate | 150 | 300 | 450 | 600 | 150 | 300 | 450 | 600 | 150 | 300 | 450 | 600 |
| Sodium CMC | 150 | 300 | 450 | 600 | - | - | - | - | - | - | - | - |
| HPMC K4M | - | - | - | - | 150 | 300 | 450 | 600 | - | - | - | - |
| Carbopol | - | - | - | - | - | - | - | - | 150 | 300 | 450 | 600 |
| Calcium chloride (%) | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |

### Evaluation of Hydrogel Beads

### Surface Morphology (SEM)

Particle size distribution, surface topography, texture, and the morphology of shattered or sectioned surfaces have all been studied using scanning electron microscopy. SEM is arguably the most widely used technique for characterizing drug delivery systems since it is easy to use and requires little material preparation [6].SEM research was conducted on a JEOL JSM T-330A scanning microscope. An electron microscope brass stub was coated with dry flecainide gel

beads using an ion sputter. Random stub scanning was used to capture images of the flecainide hydrogel beads [7].

**Percentage Yield**

The % practical yield of flecainide hydrogel beads was computed to determine the efficiency or yield percentage of any given process, which aids in selecting the most suitable manufacturing technique [8].The weight of Flecainide beads recovered from each batch divided by the total starting material was used to compute the practical yield. Using the formula, the % yield of prepared flecainide beads was ascertained.

$$\textbf{Percentage yield} = \frac{\textbf{Practical yield}}{\textbf{Theoretical yield}} \textbf{ X 100}$$

**Drug Content**

A porcelain mortar and pestle were used to smash 40 mg of beads, which were then dispersed in an appropriate solvent to measure the beads' drug concentration and encapsulation efficiency. It was filtered after the dispersion was allowed overnight for 24 hours and sonicated for 15 minutes. A UV-visible spectrophotometer with a λmax of 232 nm was used to measure the drug content of a 1 ml sample diluted with an appropriate solvent. Each formulation's medication content was stated as mg / 200 mg of gel beads [9].

**Drug Entrapment Efficiency**

The following formula was used to calculate the drug entrapment efficiency of the produced beads [10].

$$\textbf{EE}\ (\%) = \frac{\textbf{Actual Drug Content}}{\textbf{Theoretical Drug Content}} \textbf{ X 100}$$

## In-vitro dissolution studies

## Procedure for In-vitro Dissolution Study

The paddle method of USP XXIII equipment II was utilized to ascertain the release rate of Flecainide Hydrogel beads. The dissolution test was run with 900 milliliters of 0.1N HCL for two hours and a 6.8 pH buffer for ten hours at 50 rpm, 37 ±0.5°C. For the investigation, 40 mg of flecainide hydrogel beads were employed [11]. Five milliliters of the sample solution were taken out of the dissolving device for up to twelve hours at different times (hourly). A new dissolution medium was added to the samples. After filtering the samples, the absorbance at λmax232nm was calculated. A cumulative percentage drug release versus time plot was used to analyze the dissolution profiles of the formulations. Kinetic treatment was also applied to the collected data [12] to comprehend the release process.

**Mathematical modeling for drug release profile**

**Zero-order kinetics**: It explains the mechanism wherein the drug release rate is unaffected by concentration.

$$\textbf{Qt} = \textbf{Q}_o + \textbf{K}_o\textbf{t}$$

## First order kinetics

The drug release from systems where the release rate depends on concentration is described [13].

$$\textbf{Log Qt} = \frac{\textbf{Log Q}_o\textbf{K}_1\textbf{t}}{\textbf{2.303}}$$

## Higuchi model

It explains how the square root of time determines the proportion of drug release from a matrix.

$Mt/M\alpha = K_H t^{1/2}$

## Korsemayer-Peppas model (Power law)

The potent law effectively characterizes the release of drugs from slabs, cylinders, and spheres by stating that the fractional amount of drug release is exponentially related to the release time [14]

$$\frac{\textbf{Mt}}{\textbf{M}\infty} = \textbf{Ktn}$$

$$\textbf{Log}\left(\frac{\textbf{Mt}}{\textbf{M}\infty}\right) = \textbf{log K} + \textbf{n log t}$$

**Stability Conditions**

For one month and three months, the following temperatures were used to examine the stability of tablets containing Flecainide.

1. Extended testing period: 1 month at 25 °C and 60% relative humidity (3 months)
2. Quick testing: 1 month at 40°C and 75% relative

humidity (3months) Estimated parameters: drug content [15].

## RESULTS AND DISCUSSION

### PREFORMULATION STUDY

### Drug polymer interaction study

It was discovered from the spectra of Flecainide, Flecainide and blank beads, and Flecainide and polymer mixture that all of Flecainide's distinctive

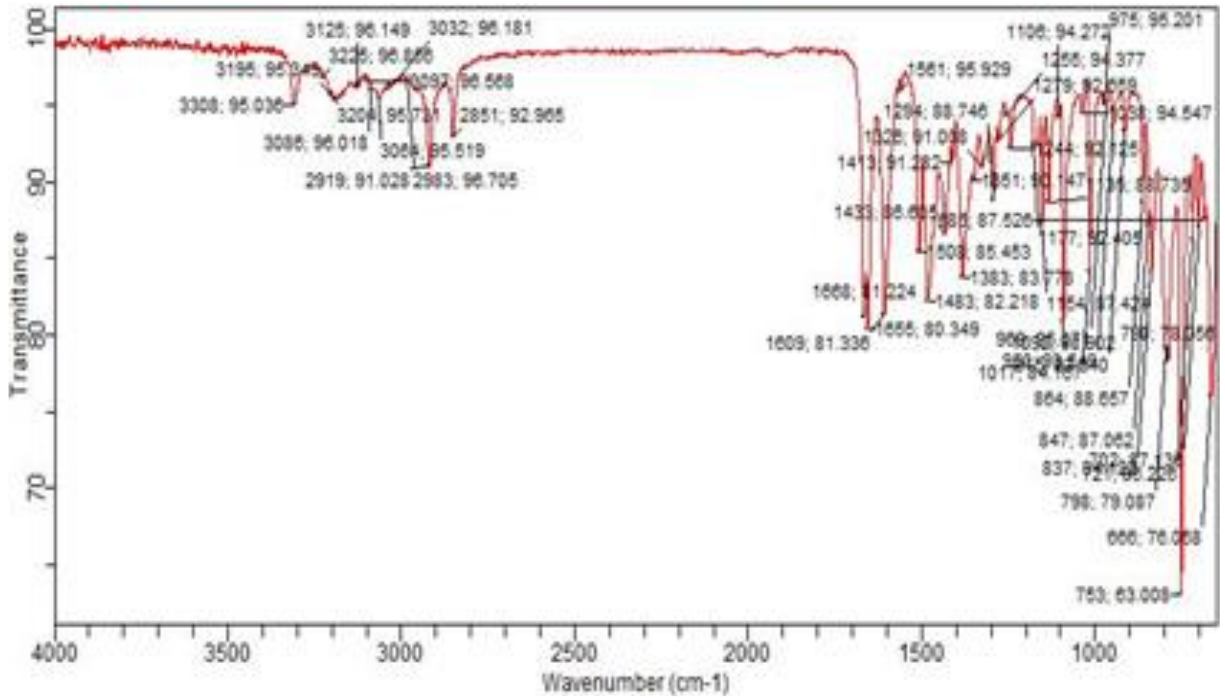


Figure 1 FTIR spectra of Flecainide

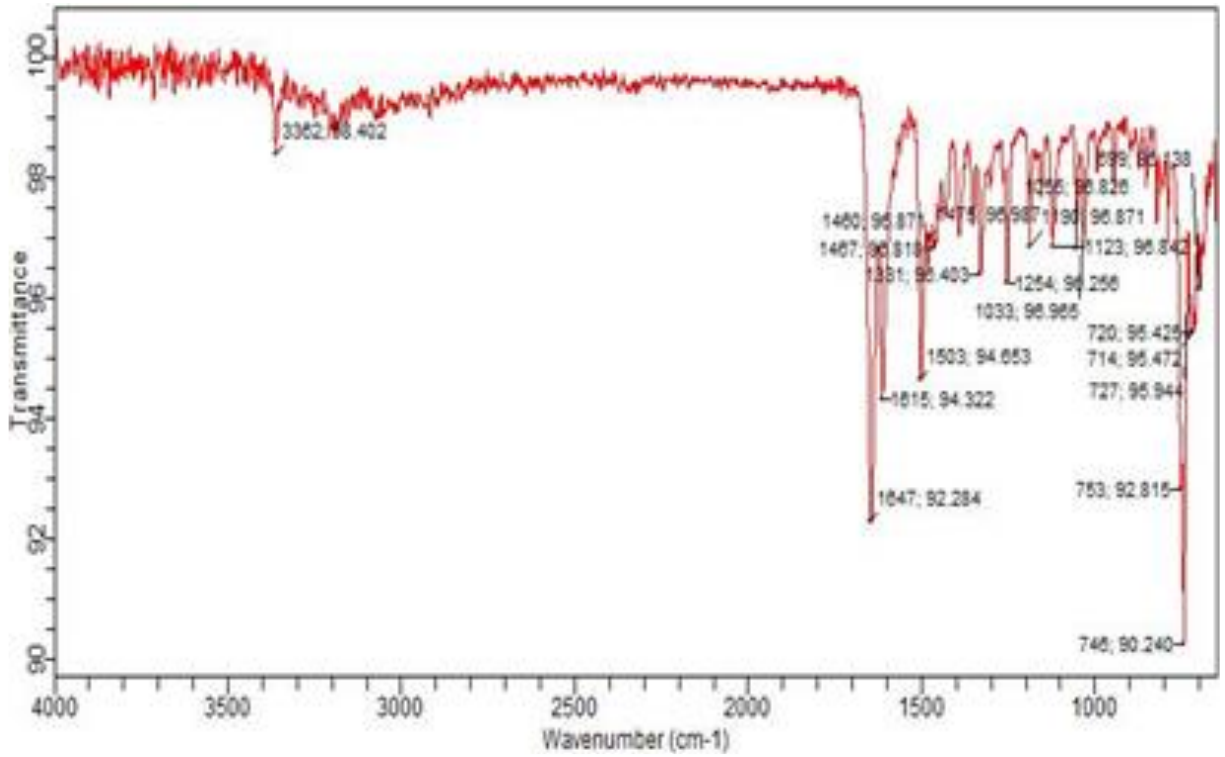


Figure 2 FTIR Spectrum of Mixture of compounds

peaks were present in the combination spectrum, demonstrating the drug and polymer's compatibility. IR spectra of each polymer and Cefotaxime combination with each polymer are displayed in **Figures 1** and **Figure 2**, using data from **Table 2**.

**Table 2 FTIR interpretation data of Drug and Mixture of Compounds**

| Functional Groups | Flecainide | Mixture of compounds |
|---|---|---|
| (s)= C-H bend (Alkenes) | 1000-650 | 1000-650 |
| (m)O-H bend (Carboxylic Acid) | 950-910 | 3300-2500 |
| (s, b) N-H wag ($1^o$,$2^o$ amines) | 910-665 | 910-665 |
| (m) C-Br stretch (Alkyl halides) | 725-720 | 1300-1150 |
| (s)C-O stretch (Alcohol, carboxylic acid, esters, ethers) | 1320-1000 | 1320-1000 |
| (m)C-N stretch (Aliphatic amines) | 1250-1020 | 1250-1020 |
| (m) C-C stretch (in-ring) (Aromatics) | 1500-1400 | 3100-3000 |

## Evaluation Parameters

### Surface Morphology

SEM was used to examine the Flecainide beads' surface morphology. SEM images displaying the enhanced mixture. Surface smoothness was observed with guar gum incorporated Flecainide beads.

### Frequency distribution analysis

The mean particle size of the Flecainide beads also decreased when the polymer ratio increased (**Table 3**). The rise in droplet viscosity could be the cause of the notable decrease. Obtaining flecainide beads with a normal frequency distribution and a size range of 1. to 1. mm was possible.

### Percentage yield

The % practical yield of flecainide hydrogel beads has been calculated to determine the efficiency or percentage yield for any given process, which aids in selecting the most suitable manufacturing technique. The weight of the flecainide beads recovered from each batch divided by the total starting material was used to compute the practical yield, as shown in **Table 3**.

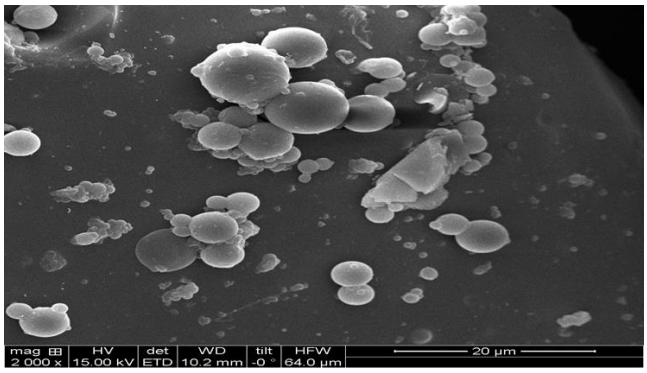


**Figure 3 SEM photographs of hydrogel beads**

## Drug Content

As the polymer concentration increased, the drug content correspondingly increased. The data suggest that the distribution of Flecainide in the beads is appropriate, and the deviations are within allowable bounds, as Table 3 demonstrates.

## Percentage of drug entrapment efficiency

As the concentration of polymer increased, its entrapment efficiency correspondingly increased. According to the findings, Flecainide has an appropriate distribution in the beads, and any deviations are within allowable bounds. Increasing the polymer concentration enhanced encapsulation efficiency [**Table 3**]. The effectiveness of trapping of highly concentrated beads made with carbopol.

## *In vitro* dissolution studies

The Flecainide hydrogel beads' in vitro performance demonstrated a prolonged and regulated release of Flecainide. The in vitro dissolution trials' outcomes demonstrated predictable, regulated release. It was discovered that the medication release from the hydrogel beads decreased as the polymer content rose. Carbopol more successfully delayed drug release

**Table 3 Average particle size of Flecainide Hydrogel beads**

| Formulation code | Average size (mm) | Percentage Yield | Entrapment efficiency (%) | Drug Content (%) |
|---|---|---|---|---|
| F1 | 1.1 | 83.32 | 73.23 | 75.42 |
| F2 | 1.3 | 86.16 | 67.12 | 65.32 |
| F3 | 1.4 | 88.41 | 81.78 | 79.38 |
| F4 | 1.1 | 83.19 | 77.85 | 82.36 |
| F5 | 1.2 | 85.17 | 82.83 | 89.43 |
| F6 | 1.4 | 89.38 | 85.61 | 87.67 |
| F7 | 1.2 | 88.49 | 77.54 | 90.32 |
| F8 | 1.4 | 91.54 | 84.21 | 95.76 |
| F9 | 1.1 | 92.66 | 83.24 | 94.34 |
| F10 | 1.2 | 93.45 | 77.14 | 96.68 |
| F11 | 1.2 | 94.32 | 89.18 | 97.77 |
| F12 | 1.2 | 95.41 | 97.19 | 98.82 |

than HPMC K4M and sodium CMC; hydrogel beads reached their maximum release by the end of the 12th hour. **Table 4** and **Figure 4** exhibit every formulation's in vitro release profiles (F1 to F12).

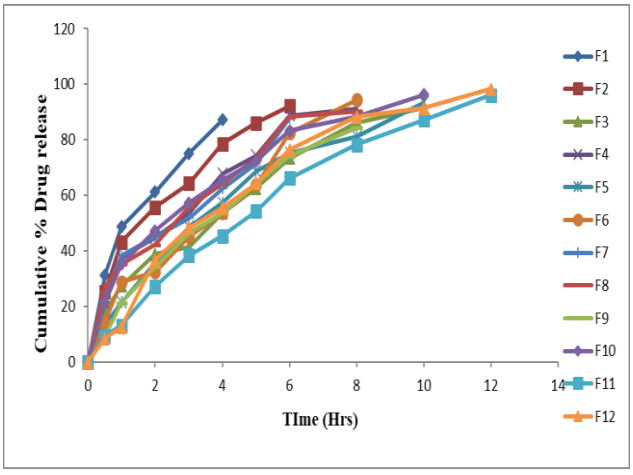


**Figure 4 Flecainide hydrogel beads made of sodium alginate: in vitro release data**

## Release Order Kinetics of Flecainide Hydrogel Beads

The best formulation F9 in vitro dissolution data were fitted using various kinetic models, including the zero order, first order, Higuchi, and Korsemeyer-Peppas equations. It is confirmed as it follows the zero-order release because its value is closer to the '1' [Table 9]. The Korsmeyer and Peppas plot

[**Figure 5**,**Figure 6**, **Figure 7**,**Figure 8**] confirms the drug release mechanism.

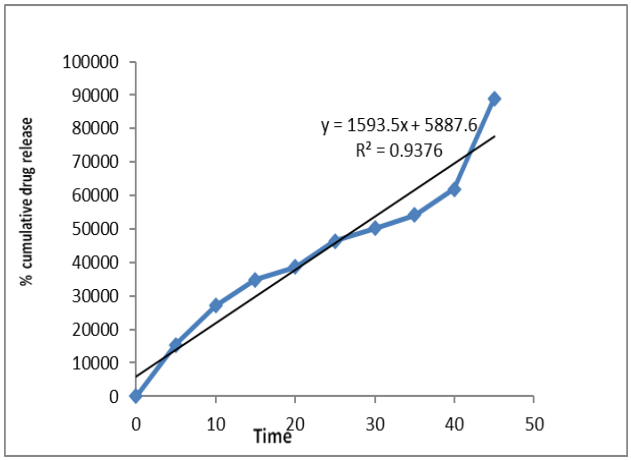


**Figure 5 F12 of Zero Order Kinetics In vitro Dissolution Studies**

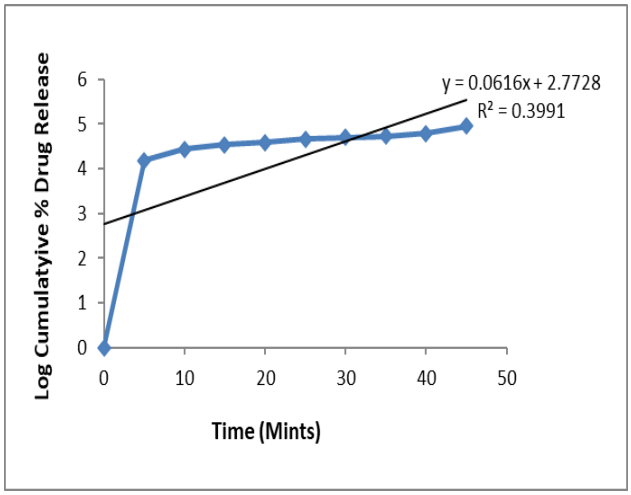


**Figure 6 F12 of First Order Kinetics In vitro Dissolution Studies**

**Table 4 Flecainide hydrogel beads made of sodium alginate: in vitro release data**

| TIME (hrs) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 | F11 | F12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0.5 | 31.43 | 25.28 | 18.36 | 21.32 | 13.51 | 14.45 | 25.35 | 27.43 | 9.18 | 21.62 | 9.52 | 8.54 |
| 1 | 48.65 | 43.17 | 27.41 | 37.45 | 21.52 | 28.81 | 38.32 | 35.32 | 21.32 | 35.18 | 13.18 | 12.48 |
| 2 | 61.21 | 55.81 | 38.91 | 44.82 | 35.81 | 32.51 | 45.32 | 42.32 | 34.43 | 47.32 | 27.34 | 36.49 |
| 3 | 75.15 | 64.31 | 41.42 | 53.71 | 48.72 | 45.33 | 51.85 | 55.75 | 46.51 | 57.28 | 38.44 | 48.52 |
| 4 | 87.31 | 78.64 | 53.87 | 67.88 | 57.34 | 53.65 | 62.51 | 64.34 | 53.56 | 65.58 | 45.38 | 55.61 |
| 5 | - | 86.22 | 62.61 | 74.34 | 68.81 | 63.88 | 71.65 | 73.34 | 64.32 | 72.31 | 54.32 | 64.42 |
| 6 | - | 92.25 | 73.56 | 88.87 | 75.33 | 82.34 | 87.92 | 88.32 | 74.32 | 83.33 | 66.34 | 76.42 |
| 8 | - | - | 86.21 | 91.41 | 81.33 | 94.54 | - | 90.44 | 84.43 | 88.32 | 78.26 | 88.28 |
| 10 | - | - | 91.32 | - | 93.53 | - | - | - | - | 96.32 | 87.29 | 91.22 |
| 12 | - | - | - | - | - | - | - | - | - | - | 96.18 | 98.31 |

**Table 5 Drug Release Kinetics.**

| Batch Code | Zero Order $r^2$ | First Order $r^2$ | Higuchi $r^2$ | Peppas $r^2$ | Peppas n |
|---|---|---|---|---|---|
| F1 | 0.966 | 0.822 | 0.948 | 0.623 | 1.032 |
| F2 | 0.978 | 0.816 | 0.949 | 0.632 | 1.022 |
| F3 | 0.976 | 0.822 | 0.966 | 0.612 | 1.023 |
| F4 | 0.962 | 0.843 | 0.964 | 0.633 | 1.032 |
| F5 | 0.951 | 0.811 | 0.987 | 0.621 | 1.018 |
| F6 | 0.962 | 0.843 | 0.945 | 0.624 | 1.013 |
| F7 | 0.964 | 0.832 | 0.963 | 0.618 | 1.017 |
| F8 | 0.977 | 0.811 | 0.977 | 0.617 | 1.018 |
| F9 | 0.967 | 0.388 | 0.888 | 0.776 | 1.012 |
| F10 | 0.979 | 0.812 | 0.945 | 0.637 | 1.021 |
| F11 | 0.973 | 0.824 | 0.963 | 0.615 | 1.022 |
| F12 | 0.841 | 0.841 | 0.961 | 0.974 | 1.021 |

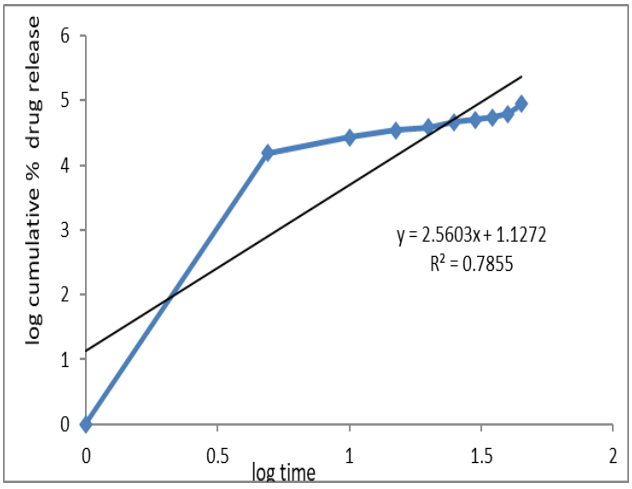


**Figure 7 F12 of the Korsmeyer peppas in vitro dissolution studies**

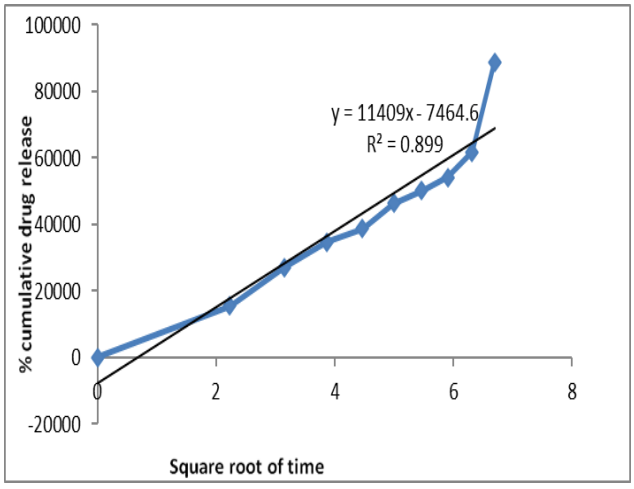


**Figure 8 F12 of the Higuchi in vitro dissolution studies**

**STABILITY STUDY:**

Formulation optimized for one to three months, F12 underwent stability trials, and the tablets' pharmacological content was examined. The outcomes are shown in **Table 6**.

**Table 6 Studies on the stability of the optimized F12 formulation**

| Time in hrs | Drug Content | | |
|---|---|---|---|
| | F12 | After 1 Month | After 3 Month |
| 1 | 75.43 | 75.41 | 74.31 |
| 2 | 65.43 | 65.31 | 64.31 |
| 3 | 79.22 | 79.14 | 80.38 |
| 4 | 82.24 | 82.43 | 81.61 |
| 5 | 89.41 | 89.45 | 90.43 |
| 6 | 87.28 | 87.14 | 86.46 |
| 7 | 90.27 | 90.32 | 91.65 |
| 8 | 95.67 | 94.34 | 94.61 |
| 9 | 94.34 | 93.25 | 93.54 |
| 10 | 96.49 | 95.88 | 95.68 |
| 11 | 97.32 | 96.77 | 96.32 |
| 12 | 98.67 | 97.77 | 96.79 |

**CONCLUSION**

Studies conducted before formulation, such as solubility and UV analysis, met the requirements. Flecainide and polymers did not interact, according to the FTIR Spectra. By using SEM, the flat surface of the Flecainide beads was verified. The Flecainide hydrogel beads' mean particle size decreased as the polymer ratio increased. Ordinary frequency distribution hydrogel beads containing fluorescein were produced. As the concentration of polymer developed, its entrapment efficiency correspondingly increased. The results suggest that the distribution of Flecainide in the beads was appropriate and that the variation remained within allowable bounds. The research findings also indicate that an increase in polymer concentration leads to a decrease in drug release. The Flecainide Hydrogel beads' in vitro performance demonstrated a sustained and regulated drug release. The in vitro dissolution data for the optimal formulation F12 were fitted using various kinetic models, including the Higuchi, Korsemeyer-Peppas, zero-order, and first-order equations. The optimized formulation F12 displays a 0.974 r2 value. It conforms when approaching the zero-order release since its value is closer to the '1'. The scenario involving Korsmeyer and Peppas further confirms the drug release mechanism. When the 'n' value for the optimized formulation (F12) is 1.021, the n value was more significant than 0.89, indicating Super case transport.

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**Conflict of Interest**

The authors declare no conflict of interest, financial or otherwise.

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