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# Formulation, Optimization, and In- Vitro Evaluation of Floating In-Situ Gel of Piroxicam

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**Keywords:** GRDDS, In-Situ Gel, NSAID, Piroxicam.

**ABSTRACT**

The oral drug delivery system is the most popular route of drug administration but, the conventional dosage form has any problems like short Gastrointestinal transit time, fluctuation in blood plasma concentration, low bioavailability, so there was a need of novel drug delivery like GRDDS. In GRDDS most popular one is In-Situ gel. Gastro-retentive In-Situ gel-forming system provides controlled drug delivery within the stomach. In-Situ gel formation occurs due to one or a combination of different stimuli like pH change, Temperature modulation and solvent exchange. This work aimed to formulate and evaluate floating In-Situ gel containing Piroxicam for the treatment of Arthritis. As In-Situ gel has emerged as a promising drug delivery system for the delivery of hydrophobic drugs. Piroxicam is one of the most effective Non-Steroidal Anti-inflammatory drug of the Piroxicam derivative which also has Anti-Pyretic and Analgesic activity in numerous types of pains such as used in the treatment of Rheumatoid Arthritis and Osteoarthritis. All the results indicated that the formulation GI did not undergo any major chemical change/interaction during the study period. Finally concluded that this developed floating In-Situ gel of Piroxicam is an effective alternative to the conventional dosage form of Piroxicam for the treatment of Arthritis and Pain.

## INTRODUCTION

[17,18] Piroxicam is a Non-Steroidal Anti-Inflammatory drug (NSAID) indicated for relief of the signs and symptoms of Osteoarthritis (OA) and Rheumatoid Arthritis (RA). The minimum dose of piroxicam is of 10 mg/day and the maximum dose of Piroxicam is of 20 mg/day. Piroxicam, as in tablet for, has a frequency of a minimum of two tablets a day.

In this study, Piroxicam is used as an Active Pharmaceutical Ingredient (API), HPC K200M was used as a Synthetic Polymer, Propyl Paraben was used as a Preservative, and Sodium Alginate, Calcium Carbonate, Trisodium Citrate, Calcium Chloride, Carbopol were used as Excipients and Distilled Water as Base Material. With the help of Design Expert ® software developed by State Ease Corp. the factorial design of tablet batches was developed and the In-Vitro studies such as dissolution studies on the formulation were studied, and the stability studies of the formulation were studied as per the ICH guidelines on Stability Studies, the objectives of the stability studies is to predict the shelf life of a product by accelerating the rate of decomposition, preferably by increasing the temperature and relative humidity. The Stability Studies for optimized formulation G1 were carried out at [$40^0$ C ± $2^0$, 75% RH ± 5% RH] as accelerated storage conditions for 1 Month, to assess stability these samples were analyzed and checked for changes in physical appearance and drug content at regular intervals. The obtained data is presented in the stability studies table. The results indicated that the formulation G1did not undergo any major chemical change in various parameters like pH, Viscosity, Floating Lag Time, Floating Duration, and In-Vitro Drug release during the study period. All the obtained results were compared with the standard references and were within the standard range.

## MATERIALS AND METHODS

The pure drug “Piroxicam” was a gift sample from *Swami Samarth Ayurvedic Pharmacy. Jalgaon (Allopathic Division).* Sodium Alginate, HPC K200M, Calcium Carbonate, Trisodium Citrate, Propyl Paraben, Calcium Chloride and Carbopol 934 were purchased from *Research Lab Fine Chem Industries, Mumbai*.

College of Pharmacy, Akkalkuwa provided all the Glassware, Equipment and Lab Access. All the chemicals used for this study was of Analytical Grade. Instruments such as dissolution apparatus, electronic weighing balance, FTIR spectrophotometer, differential scanning calorimeter, magnetic stirrer, pH meter, UV spectrophotometer (dual beam),

viscometer, and stability chamber were used. Drug-Excipient interaction study were studied by FTIR and DSC analysis, the melting point of Piroxicam was determined by the *capillary tube method*.

**Preparation of Standard Calibration Curve of Piroxicam:**

The calibration Curve of Piroxicam was taken in media i.e., 0.1 N HCL solution.

**The standard plot of Piroxicam in 0.1 N HCL:**

An accurately weighed quantity of Piroxicam (100 mg) was dissolved in small amount of 0.1 N HCL and made upto 100 ml with 0.1 N HCL to generate a primary stock solution having a concentration of 1000 mcg/ml. 1 ml of primary stock solution was further diluted to 100 ml to produce a secondary stock solution having a concentration of 10 µg/ml. pipette out 2,4,6,8 and 10 ml from the secondary stock solution were further diluted to 10 ml to produce standard solutions having concentrations of 2,4,6,8, and 10 µg/ml. the absorbance of the solutions was measured at 242.0 nm using a dual beam UV-Visible spectrophotometer against 0.1 N HCL as blank. The plot of Absorbance vs Concentration (µg/ml) was plotted and data was subjected to linear regression analysis in Microsoft excel.

**Design of factorial batches and preparation of formulations:**

All the batches i.e., G1-G9, were designed with the help of Design Expert software.

A specified quantity of Piroxicam, Trisodium Citrate, Sodium Alginate, Calcium Carbonate, Calcium Chloride, Propyl Paraben, Carbopol 934 and HPMC K200M were weighed accurately. Accordingly, in about 30 ml of deionized water, HPMC K200M was allowed to hydrate overnight Piroxicam was then dissolved in the HPMC K200M solution and Calcium Carbonate (gas generating agent) was added to it while stirring to facilitate dispersion. Sodium Alginate solutions were prepared by adding the remaining amount of deionized water (up to 50 ml) containing Sodium Citrate and Calcium Chloride and heating to $60^0$ C while stirring on a heating magnetic stirrer after cooling to below $40^0$ C, it was added to the HPMC K200M solution while stirring to achieve uniform dispersion. Solution of Methyl Paraben and Carbopol 934 were added and mixed properly finally, the formulations were adjusted to volume, filled and stored in amber-colored bottles until further tests were done.

**Table 1: Factorially Designed Batches**

| INGREDIENTS | BATCHES | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | G1 | G2 | G3 | G4 | G5 | G6 | G7 | G8 | G9 |
| PIROXICAM (mg) | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| SODIUM ALGINATE (% w/v) | 1.0 | 1.0 | 1.0 | 2.0 | 2.0 | 2.0 | 3.0 | 3.0 | 3.0 |
| HPMC K200M (% w/v) | 0.5 | 1.0 | 1.5 | 0.5 | 1.0 | 1.5 | 0.5 | 1.0 | 1.5 |
| CALCIUM CARBONATE (% w/v) | 2.0 | 1.0 | 2.0 | 1.0 | 1.0 | 2.0 | 1.0 | 2.0 | 1.0 |
| TRISODIUM CITRATE (% w/v) | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |
| PROPYL PARABEN (% w/v) | 0.5 | 0.2 | 0.4 | 0.6 | 0.8 | 1.0 | 1.2 | 1.4 | 1.6 |
| CALCIUM CHLORIDE (% w/v) | 0.15 | 0.15 | 0.15 | 0.15 | 0.15 | 0.15 | 0.15 | 0.15 | 0.15 |
| CARBOPOL 934 (% w/v) | - | 0.5 | - | 0.7 | - | 0.5 | - | 0.7 | - |
| DISTILLED WATER (ml) | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 |

## RESULTS AND DISCUSSION

### A. Determination of pH:

The pH values of all In-Situ gel formulations of Piroxicam were measured using a calibrated digital pH meter. The pH of formulations was found in the range of 6.8 to 7.9.

### B. Floating Lag Time:

All the formulations exhibited a very short floating time most of the formulations floated within 1 minute after they were placed in the dissolution medium formulation G1 showed the least lag time of about 25 Seconds. The results showed that as the concentration of calcium carbonate increased, the floating lag time decreased.

### C. Gelation Lag Time:

From the data obtained it was found that formulation G1 which contained the 2% concentration of Calcium Carbonate showed the least gelation time and gelation lag time of 2 and 104 sec respectively among four formulations (G6 to G9).

### D. Viscosity Determination:

Viscosity determination was done for all the formulations using Brookfield Viscometer at 3 different rpm (20, 30, and 40 rpm) using Spindle no. 63 at $25^0$ C, from the observations it was noticed that there was an increase in viscosity with an increase in the concentration of Gellan. This increase in viscosity can be attributed to a consequence of increasing chain interaction with polymer concentration. Formulation G4 contained the highest concentration of HPMC and hence exhibited higher viscosity (101.96 ± 0.81) and G1 shown the lowest viscosity (49.46 ± 0.55).

### E. Floating Duration (Hr.):

All the formulations showed 12 Hr. floating duration time.

### F. % Drug Content:

G1 showed the highest % drug content (99.63 ± 0.09) and G7 showed the lowest % drug content (97.82 ± 0.25).

### G. Standard Calibration Curve of Piroxicam in 0.1 N HCL:

A standard plot of Piroxicam in 0.1 N HCL is shown in the figure. The data on absorbance is shown in the table. The correlation coefficient obtained was 0.996 in the equation of the regression line was Y=MX+C. the absorbance values were determined at 242 nm.

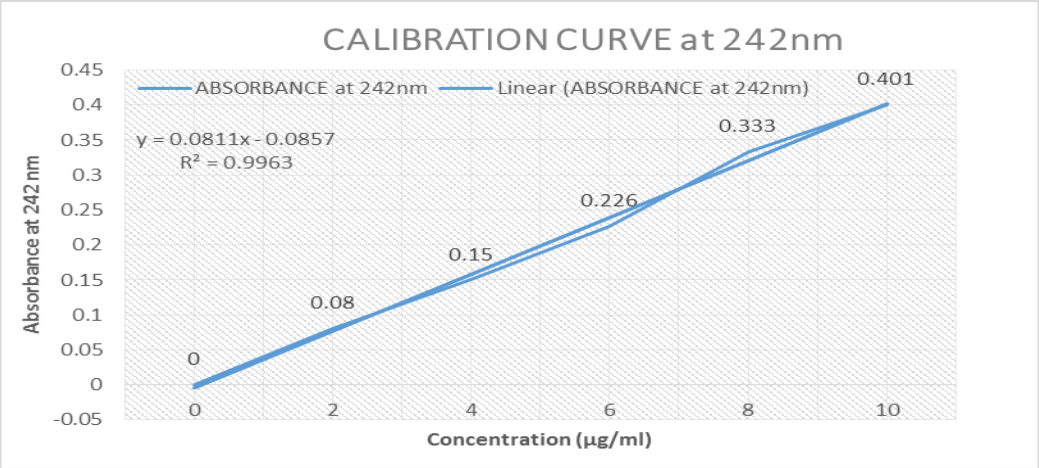


**Figure 1: Standard Calibration Curve of Piroxicam in 0.1 N HCL**

**Table 2: Standard Calibration Curve of Piroxicam in 0.1 N HCL**

| SR.NO | CONCENTRATION (µg/ml) | ABSORBANCE at 242 nm |
|---|---|---|
| 1 | 0 | 0 |
| 2 | 2 | 0.08 |
| 3 | 4 | 0.150 |
| 4 | 6 | 0.226 |
| 5 | 8 | 0.333 |
| 6 | 10 | 0.401 |

## H. FTIR Studies:

### 1. FTIR of Piroxicam (Pure Drug):

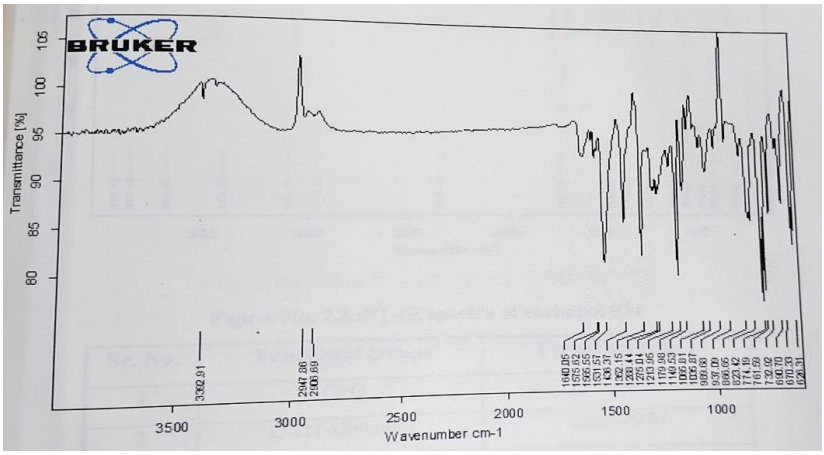


**Figure 2: FTIR of Piroxicam (Pure Drug)**

**Table 3: Interpretation of FTIR of Piroxicam (Pure Drug)**

| FUNCTIONAL GROUP | FREQUENCY ($cm^{-1}$) |
|---|---|
| C=C | 1630-1635 |
| C=O | 1800-1810 |
| N-H | 3392-3400 |
| C-H (Aromatic) | 3050-3065 |
| C-N | 1149-1155 |

## 2. FTIR Spectra of Carbopol 934:

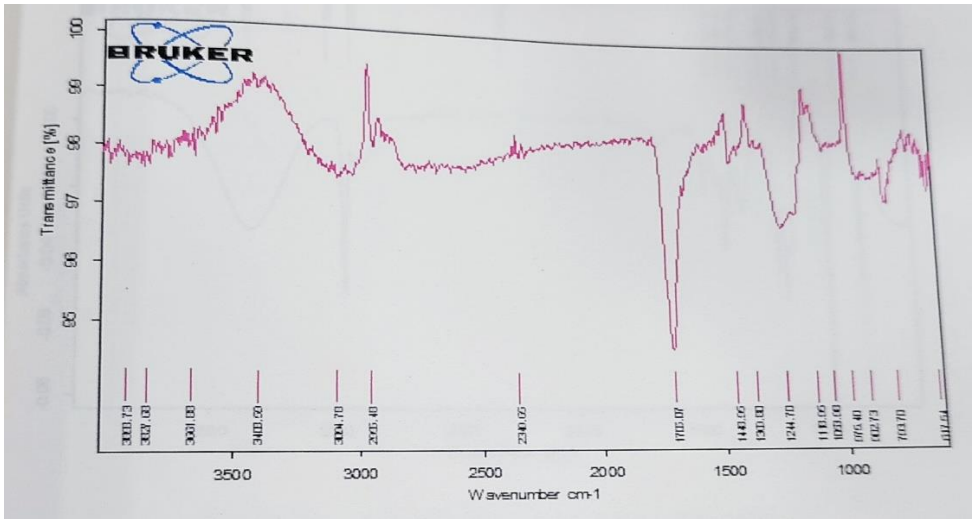


**Figure 3: FTIR of Carbopol 934**

**Table 4: Interpretation of FTIR of Carbopol 934**

| FUNCTIONAL GROUP | FREQUENCY ($cm^{-1}$) |
|---|---|
| C=O | 3300 |
| C-H (Aliphatic) | 2966-2970 |
| CH2 | 1485-1489 |

## 3. FTIR of HPMC K200M:

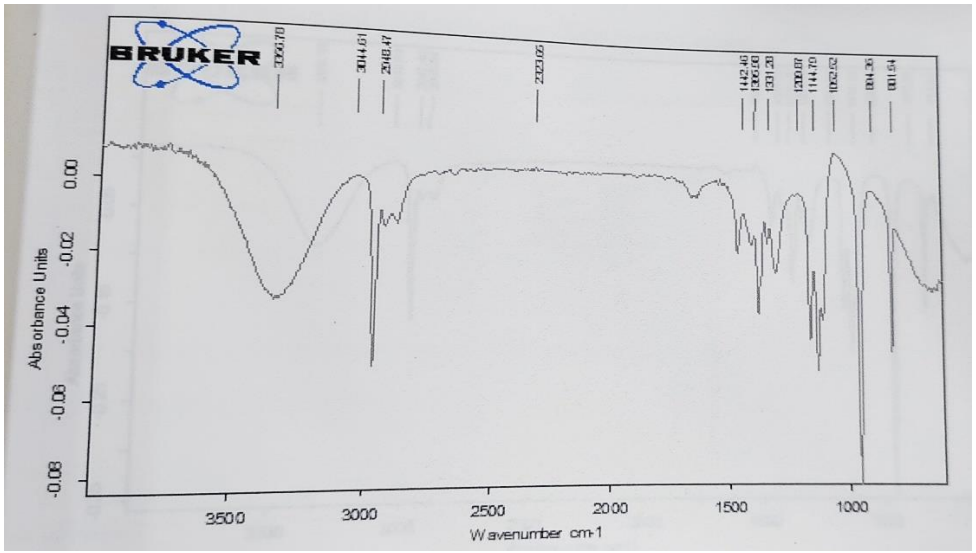


**Figure 4: FTIR of HPMC K200M**

**Table 5: Interpretation of FTIR of HPMC K200M**

| FUNCTIONAL GROUP | FREQUENCY ($cm^{-1}$) |
|---|---|
| O-H | 3273-3278 |
| C-O | 1050-1055 |
| C=O | 1663-1666 |

**4. FTIR of Piroxicam + Carbopol 934:**

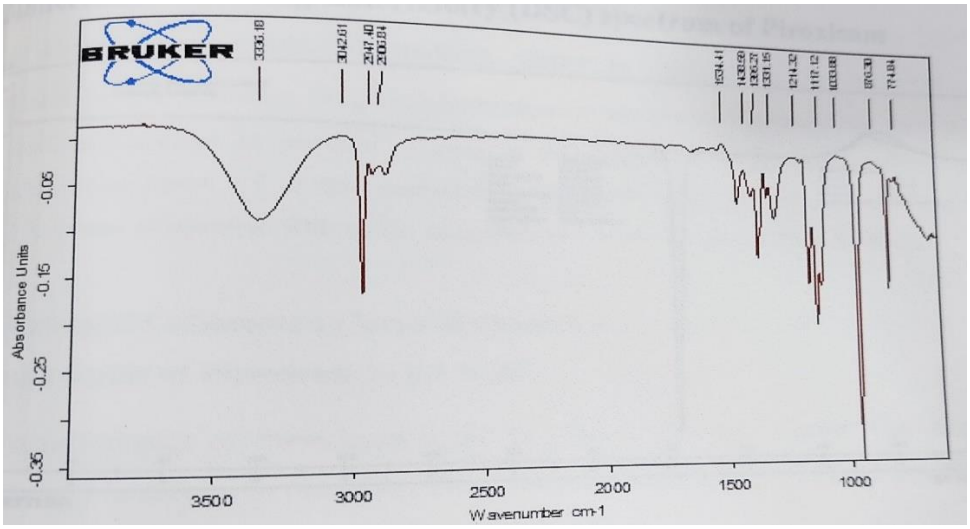


**Figure 5: FTIR of Piroxicam + Carbopol 934**

**5. FTIR of Blend (Drug + HPMC K200M + Carbopol 934):**

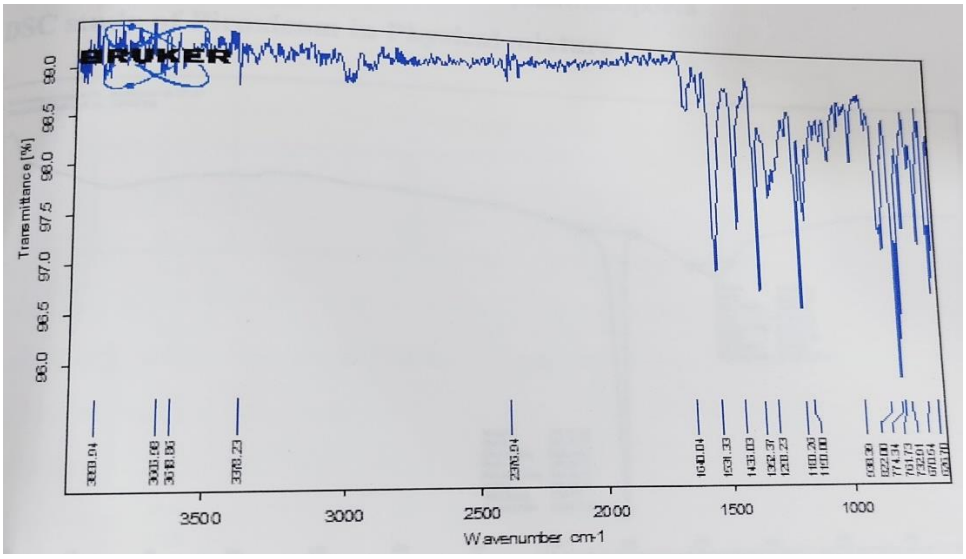


**Figure 6: FTIR of Blend (Drug + HPMC K200M + Carbopol 934)**

## I. DSC Studies:

### 1. DSC Graph of Piroxicam (Pure Drug):

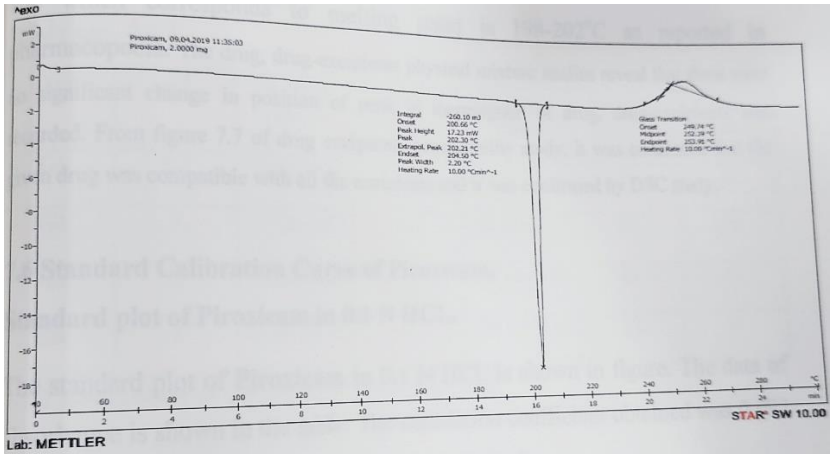


**Figure 7: DSC Graph of Piroxicam (Pure Drug)**

Endothermic peak of the Pure Drug was found to be $200^0$ C and which corresponds to Melting Point of 198-$202^0$ C as per the official standards.

### 2. DSC Graph of Piroxicam in Physical Mixture:

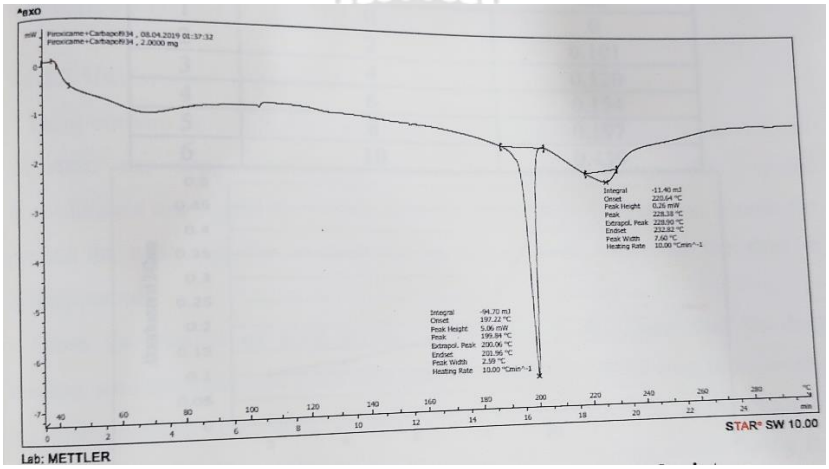


**Figure 8: DSC Graph of Piroxicam in Physical Mixture**

The endothermic peak of the drug was found to be $200^0$ C which corresponds to its Melting point of 198-$202^0$ C as per the official standards.

## J. In-Vitro Drug Release Study of Optimized batches:

The In-Vitro Dissolution Studies of the Factorially designed formulation batches were studied for 12 Hr. in 0.1 N HCL, the results obtained were given in the table and figure below.

**Table 6: In-Vitro drug release (0-12 Hr.) of optimized formulation (G1-G9)**

| TIME (Hrs) | CUMULATIVE % DRUG RELEASE (% CDR) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | G1 | G2 | G3 | G4 | G5 | G6 | G7 | G8 | G9 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 11.1 | 11.7 | 12.1 | 11.3 | 10.5 | 13.0 | 12.2 | 11.7 | 9.8 |
| 2 | 23.2 | 26.1 | 24.2 | 22.1 | 24.4 | 25.2 | 23.1 | 22.7 | 20.1 |
| 3 | 38.38 | 36.82 | 34.75 | 30.60 | 42.70 | 36.82 | 34.10 | 34.13 | 41.07 |
| 4 | 41.09 | 40.92 | 42.15 | 32.60 | 46.12 | 39.71 | 46.18 | 41.16 | 46.32 |
| 5 | 55.93 | 49.05 | 45.51 | 38.55 | 55.97 | 50.72 | 48.26 | 43.43 | 51.62 |
| 6 | 68.65 | 58.10 | 52.93 | 49.35 | 68.00 | 61.29 | 59.24 | 57.10 | 60.65 |
| 7 | 76.38 | 69.53 | 60.77 | 55.42 | 76.35 | 70.60 | 68.49 | 66.11 | 72.73 |
| 8 | 80.55 | 76.51 | 70.59 | 64.67 | 81.68 | 77.25 | 75.55 | 71.76 | 80.43 |
| 9 | 88.50 | 83.21 | 76.02 | 72.03 | 86.21 | 83.51 | 81.38 | 77.93 | 82.60 |
| 10 | 92.91 | 89.11 | 85.49 | 82.76 | 93.10 | 89.19 | 87.26 | 84.31 | 83.90 |
| 11 | 95.87 | 94.66 | 90.50 | 88.12 | 96.42 | 93.19 | 91.77 | 85.46 | 84.73 |
| 12 | 99.86 | 96.88 | 96.2 | 96.22 | 99.53 | 99.00 | 94.88 | 87.44 | 88.90 |

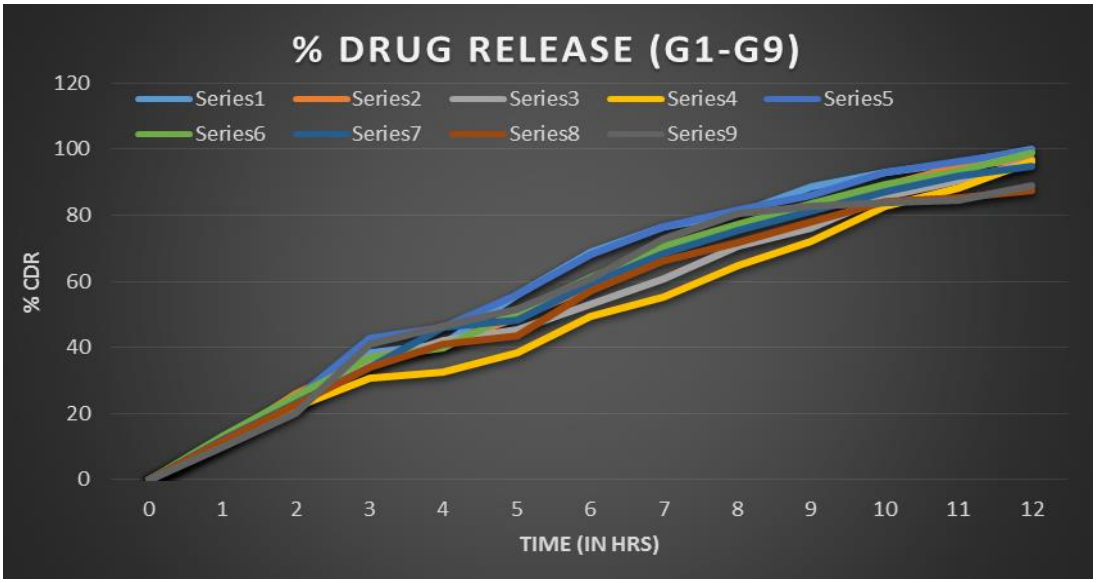


**Figure 9: In-Vitro Drug Release (0-12 Hr.) of Optimized formulation (G1-G9)**

The release of all formulations was companied and evaluated. The results showed that the formulations that give more drug release in a linear form were considered as optimized and further studied for stability studies.

## STABILITY STUDIES

A stability study was carried out on the formulation batch G1 according to ICH guidelines the In-Situ gel did not show any physical changes during the study period. The obtained data is presented in the table given below. The results indicated that formulation G1 did not undergo any Major physical and chemical changes in various parameters like pH, Viscosity, Floating Lag Time, Floating Duration, and In-Vitro drug release during the study period.

**Table 7: Stability Study of Optimized Batch (G1)**

| SR. NO | EVALUATION PARAMETERS | BEFORE STABILITY STUDY | AFTER STABILITY STUDY |
|---|---|---|---|
| 1 | pH | 7 | 6.8 |
| 2 | VISCOSITY | 49.46 | 44.30 |
| 3 | GELLING CAPACITY | + | ++ |
| 4 | FLOATING LAG TIME (sec) | 24 | 26 |
| 5 | FLOATING DURATION (Hr) | 12 | 12 |
| 6 | IN-VITRO DRUG RELEASE | 99.86 % | 96.93 % |

## CONCLUSION

This study aimed to Formulate, Optimize and Evaluate the floating In-Situ gel of Piroxicam for the treatment of Arthritis as In-Situ gel has emerged as a promising drug delivery system for the delivery of hydrophobic drugs. Piroxicam is one of the most effective non-steroidal anti-inflammatory drug of the Piroxicam derivative which also has Anti-Pyretic and Analgesic activity in numerous types of pains such as used in the treatment of Rheumatoid Arthritis and Osteoarthritis.

The Drug-Polymer interaction study was done by FTIR, and DSC analysis of physical mixtures of drug and polymer. The compatibility of Piroxicam with Polymers Carbopol 934 the studies of FTIR and DSC shows that all above functional groups characteristic peaks of Piroxicam were observed near their respective values. So, it has been concluded that there is no incompatibility between polymer and pure drug. An optimization study was carried out by using $3^2$factorial designs. The concentration of polymers was considered as an independent variable whereas floating lag time, % CDR of the gel were utilized as dependent variables.

All the formulations exhibited a very short floating lag time, most of the formulations floated within 1 minute after they were placed in the dissolution medium. Formulation G1 showed the least lag tie of 24 seconds. Formulation G4 contained the highest concentration of HPMC K200M and hence exhibited higher viscosity amongst all other formulations. But, the formulations G1 and G9 showed the formation of slimy and scattered gel on contact with 0.1 N HCL due to their low viscosity. As the concentration of polymer is increased, the amount of drug release decrease from the formulations. The drug release from the formulation G1 and G9 released the drug completely at the end of 10 Hr. whereas other formulations retard the drug release even at the end of 12 Hr. formulation G1 showed a drug release of about 99.86 % at the end of 12 Hr. $3^2$full factorial design and optimization technique successfully used in the development of In-Situ gel. The objective of the stability study is to predict the shelf-life of a product by accelerating the rate of decomposition, preferably by increasing the temperature and relative humidity. The stability studies of optimized formulation G1 was carried out at 40 ± $5^0$ C and 75 ± 5 % RH as accelerated storage conditions for 30 days respectively. To assess stability, these samples were analyzed and checked for changes in physical appearance and drug content at regular intervals. The results indicated that formulation G1 did not undergo any major physical or chemical interaction during the study period. Finally, it can be concluded that this developed floating In-Situ gel of Piroxicam is an effective alternative to the conventional dosage form of Piroxicam for the treatment of Arthritis, Osteoarthritis, Rheumatoid Arthritis and Pain.

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**CONFLICTS OF INTEREST**

The Author(s) Declares "No Conflict of Interest".

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