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# DESIGN, PREPARATION AND CHARACTERIZATION OF HOLLOW MICROSPHERE (MICROBALLOON OF KETOPROFEN)

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## ABSTRACT

The objective of the present work was to formulate floating hollow microspheres of Ketoprofen which is soluble and shows better absorption in gastric pH. Microspheres were prepared by emulsion solvent diffusion technique. Using various such as ethyl cellulose and Eudragit polymers. The formulations were evaluated for Micromeritic properties, in vitro, buoyancy time, % yield, entrapment efficiency and in vitro studies. They were characterized by FT-IR. FT-IR and studies indicated that there was no interaction between the drug and polymers. SEM photographs showed the outer surface of microspheres was smooth and dense where as internal surface was porous which helped to prolong floating to increase residence time in stomach. The results showed that floating microspheres could be successfully prepared with better yield. Results showed larger the particle size, longer was the floating time. In vitro drug release studies showed controlled release of Ketoprofen for over 8 h. The release behaviour best fitted mostly in peppas and zero order equations.

**KEYWORDS:** Ketoprofen, Polymers, Ionotropic Gelation Technique, Floating Time, In Vitro Drug Release Studies.

## INTRODUCTION

Gastric retention is an approach to overcome the several problems associated with the oral formulations such as; first pass metabolism, ionization in gastric pH etc.[1] Floating microspheres are the systems which are based on the concept of low density system to provide gastric retention to the drugs having instability problem in intestinal medium. It can be formulated by using gas generating agents or hydrocolloids (swelling agents)[2] The main goal behind designing sustained release dosage is to prolong the release of the drug and maintain an almost linear drug level for a definite period to achieve the least side effects and maximum effectiveness of the drug.[3,4] The microsphere is microparticles that are spherical, with a diameter in micrometres. Floating microspheres of drug provide evidence of a prolonged and constant therapeutic effect while reducing the frequency of dose[5] Ketoprofen, (RS) 2-(3-benzoylphenyl)-propionic acid is one of the propionic acid class of non-steroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic effects. It potently inhibits the enzyme cyclooxygenase resulting in prostaglandin synthesis inhibition. It also prevents formation of thromboxane A2 by platelet aggregation.[6] The present research was to develop floating microspheres of Ketoprofen by ionotropic gelation method to give prolonged drug release resulting in reduced dosing frequency.

## MATERIALS

Ketoprofen was obtained from Alkem Pvt Mumbai, Ethyl cellulose, Carbopol 934 and Eudragit procured from SD fine chemicals Mumbai. Other chemicals and the reagents used were of analytical grade.

## METHODOLOGY

### Drug Excipient Compatibility Studies

Drug excipients compatibility studies were performed to know the compatibility of excipient with drug at accelerated conditions. The study was conducted by preparing homogenous mixture of excipients with drug and filled in HDPE bags and LDPE bags. Glass vials were exposed to 600 C and 400C/75 %RH for 4 weeks and LDPE bags were exposed to 400C±75 %RH for 4

weeks. Samples were observed periodically for any physical change.

**Preparation and Evaluation of Ketoprofen Hollow Microspheres**

**Table 1: Formulation table.**

| Ingredients | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 |
|---|---|---|---|---|---|---|---|---|
| Drug | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| Carbopol 934 | - | 1000 | - | 500 | | 800 | 200 | |
| Ethyl Cellulose | 1000 | - | - | 500 | 500 | 200 | 800 | 800 |
| Eudragit | - | - | 1000 | - | 500 | - | - | 200 |

**Method of Preparation[7]**

Floating microspheres with of Ketoprofen was prepared by using emulsion solvent diffusion evaporation technique. Accurately weighed quantities of drug, polymers were dissolved in mixture of ethanol and dichloromethane (1:1 solvent ratio). Above prepared solution was poured into 150ml distilled water containing poly vinyl alcohol and maintained at temperature of 30-40$^0$c. The resultant emulsion was stirred with propeller type agitator at 400 rpm for 1 hr to allow the volatile solvent to evaporate.

**Evaluation of Hollow Microspheres[8,9,10]**

**Particle Size Analysis**

Particle size analysis plays an important role in determining the release characteristics and floating property. The sizes of hollow microspheres were measured by using a set of standard sieves ranging from 14, 16, 18, 22, 30 and pan. The sieves were arranged in increasing order from top to bottom. The hollow microspheres were passed through the set of sieves and amount retained on each sieve was weighed and calculate the % weight of hollow microspheres retained by each sieve. Mean particle size for all formulation was determined by dividing the total weight size of formulation to % total weight of hollow microspheres.

**Floating Property of Hollow Microsphere**

100 mg of the hollow microsphere were placed in 0.1 N HCI (300 ml) containing 0.02% Tween 20. The mixture was stirred with paddle at 100rpm. The layer of buoyant micro balloons was pipetted and separated by filtration at 1, 2, 4 and 6 hours. The collected micro balloons were dried in a desiccator overnight.

The percentage of micro balloons was calculated by the following equation:

$$\% \text{ hollow microsphere} = \frac{\text{Weight of hollow microsphere}}{\text{Initial weight of hollow microsphere}} \times 100$$

**Drug Entrapment Efficiency**

The various formulations of the hollow microspheres were subjected for drug content. 50 mg of hollow microspheres from all batches were accurately weighed and crushed. The powdered of microspheres were dissolved with 10ml ethanol in 100ml volumetric flask and makeup the volume with 0.1 N HCl. This resulting solution is than filtered through Whatmann filter paper No. 44. After filtration, from this solution 10 ml was taken out and diluted up to 100 ml with 0.1 N HCl. Again from this solution 2 ml was taken out and diluted up to 10 m1 with 0.1 N HCI and the absorbance was measured at 265 nm against 0.1 N HCI as a blank.

The percentage drug entrapment was calculated as follows.

$$\% \text{ Drug entrapment} = \frac{\text{Calculated drug concentration}}{\text{Theoretical drug concentration}} \times 100$$

**Percentage Yield**

The percentage yield of different formulations was determined by weighing the hollow microspheres after drying. The percentage yield was calculated as follows.

$$\% \text{ Yield} = \frac{\text{Total weight of hollow microspheres}}{\text{Total weight of drug and polymer}} \times 100$$

**Shape and Surface Characterization by Scanning Electron Microscopy**

From the formulated batches of hollow microspheres, formulation which showed an appropriate balance between the buoyancy and the percentage release were examined for surface morphology and shape using scanning electron microscope Hitachi, Japan. Sample was fixed on carbon tape and fine gold sputtering was applied in a high vacuum evaporator. The acceleration voltage was set at 20KV during scanning. Microphotographs were taken on different magnification and higher magnification (200X) was used for surface morphology.

***In vitro* Release Studies**

The drug release rate from floating micro spheres was carried out using the Franz diffusion cell apparatus. A weighed amount of floating micro spheres equivalent to 100 mg drug were dispersed in 10 ml of 0.1 N HCI (pH 1.2) maintained at 37 ± 0.5°C and stirred at 100 rpm. At preselected time intervals one ml sample was withdrawn and replaced with equal amount of 0.1 N HCI (pH 1.2). The collected samples were suitably diluted with 0.1 N HCI and analyzed spectrophotometrically at 265 nm to determine the concentration of drug present in the dissolution medium. The dissolution studies were repeated using buffer pH 1.2 as dissolution medium.

**Release Kinetics**[11]

Drug release mechanisms and kinetics are the two important characteristics of a drug delivery system in describing drug dissolution profile. Mathematical models are used to evaluate the kinetics and mechanism of drug release from the tablets. The model that best fits the release data was selected based on the correlation coefficient(R) value in various models. The models that have shown high 'R' value was considered as the best fit on the release data.

**1. Zero Order Release Equation**

The equation for zero order release is

$$Q_t = Q_o + K_o t$$

Where,

$Q_o$ = Initial amount of drug

$Q_t$ = Cumulative amount of drug release at time "t"

$K_o$= Zero order release constant

T= Time in hours

**2. First Order Release Equation:**

The first order release equation is

$$\text{Log } Q_t = \text{Log } Q_o + K_t / 2.303$$

Where,

$Q_o$ = Initial amount of drug

$Q_t$ = Cumulative amount of drug release at time "t"

K= First order release constant

T= Time in hours

**Higuchi Release Equation**

The Higuchi release equation is

$$Q_t = K_H \sqrt{t}$$

Where,

Q = Cumulative amount of drug release at time "t"

$K_H$ = Higuchi constant

T = Time in hrs

**Korsmeyer -Peppas Release Equation**

Korsmeyer –Peppas equation is

$$F = M_t / M = K_m t^n$$

Where,

F = fraction of drug released at time't'

$M_t$ = amount of drug released at time 't'

M = total amount of drug in dosage form

$K_m$= kinetic constant

n = diffusion or release exponent

t = time in hrs

'n' = Linear regression of log ($M_t$ / M) versus log t

**Stability studies**[12]

Selected Formulation was subjected to stability studies as per ICH guidelines.

Following conditions were used for Stability Testing.

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

**RESULTS AND DISCUSSION**

**FT-IR Spectrum of Ketoprofen**

FT-IR Spectra of Ketoprofen and F5 formulation were recorded. All these peaks have appeared in formulation and physical mixture, indicating no chemical interaction between Ketoprofen and polymer. It also confirmed that the stability of drug during microencapsulation process.

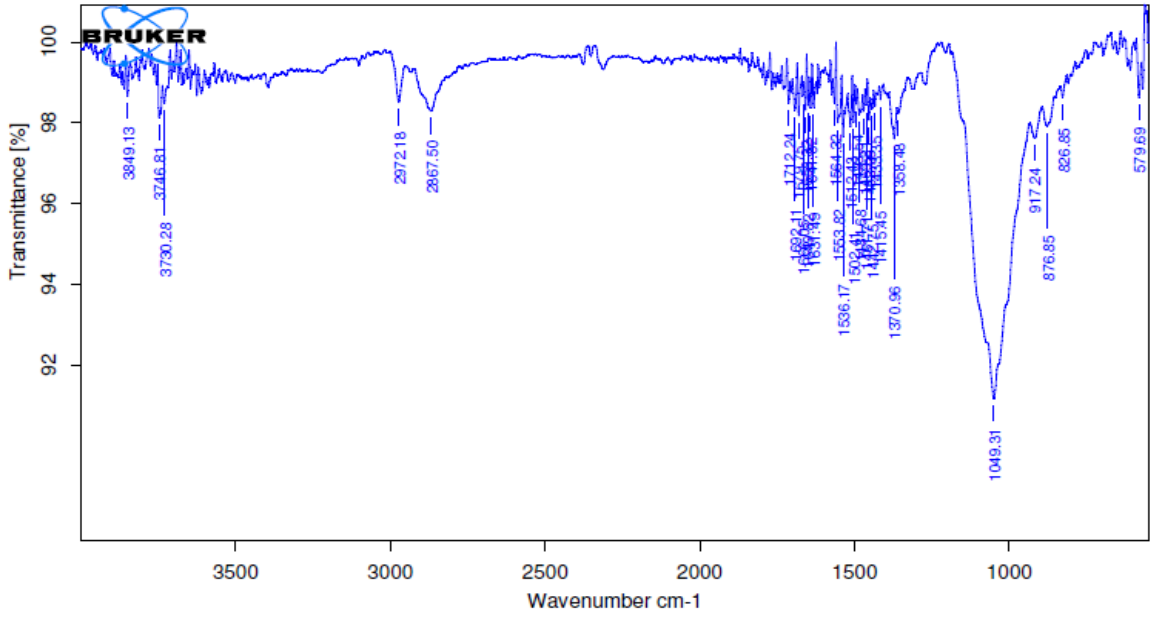


**Fig. 1: FTIR Studies of Ketoprofen.**

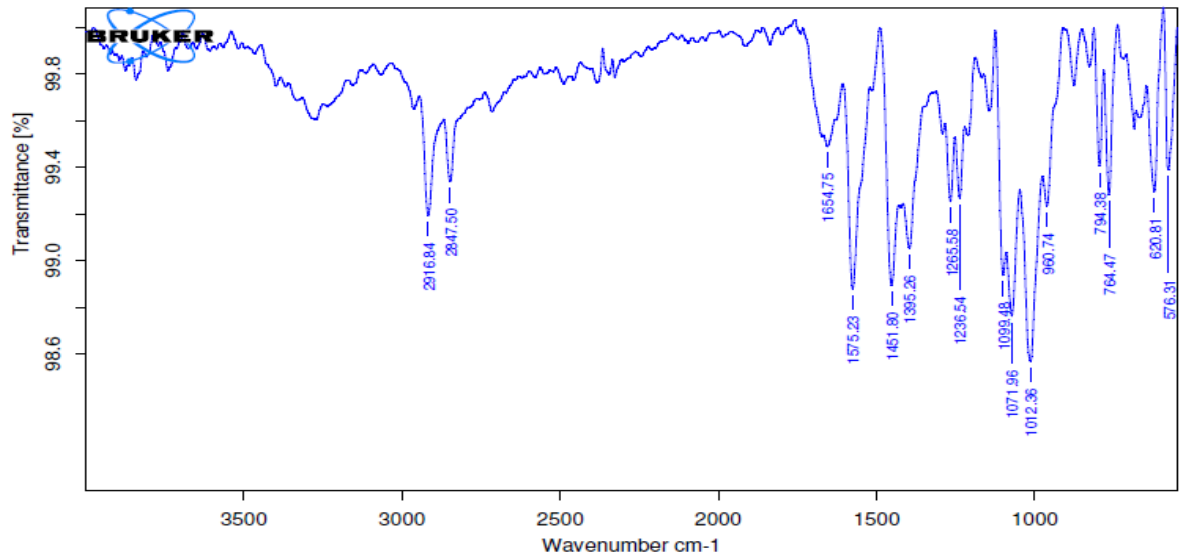


**Fig. 2: FTIR Studies of Optimized Formulation.**

**Evaluations of Hollow Microspheres**

**Particle Size Analysis**

Particle size was determined by sieving method it plays important role in floating ability and release corrected of drug from micro balloon. If size of micro balloons less than 500 mm so release rate of drug will be high and floating ability will reduce, while micro balloons range between 500mm - 1000mm, floating ability will be more and release rate will be in sustained manner. The mean particle size of hollow microsphere was in range 799 - 864mm.

**Table 2: Mean Particle Size of Different Batches of Hollow Microsphere.**

| S. No. | Formulation code | Mean particle size* (mm) |
|---|---|---|
| 1 | F1 | 756 |
| 2 | F2 | 735 |
| 3 | F3 | 789 |
| 4 | F4 | 765 |
| 5 | F5 | 782 |
| 6 | F6 | 802 |
| 7 | F7 | 758 |
| 8 | F8 | 769 |

**Particle Size**

The particle size values ranged from 735µm to 802 µm for all formulations. The particle size of all formulations Carbopol 934, ethyl cellulose, Eudragit was found to be 735µm to 802 µm. With increase in the polymer concentrations an increase in the particle size of the particles was observed.

**Floating Property of Hollow Microsphere**

Hollow Microsphere were dispersed in 0.1 N HCl to simulate gastric fluid. Floating ability of different formulation were found to be differed according to polymer ratio.

**Table-3: Percentage Buoyancy for Different Formulation.**

| Formulation | 1 hour | 2 hours | 4 hours | 6 hours |
|---|---|---|---|---|
| **F1** | 97.20 | 96.15 | 92.49 | 95.25 |
| **F2** | 96.15 | 96.46 | 95.23 | 93.25 |
| **F3** | 97.55 | 95.51 | 90.96 | 91.49 |
| **F4** | 96.62 | 92.42 | 92.68 | 93.16 |
| **F5** | 97.72 | 90.95 | 91.63 | 89.15 |
| **F6** | 94.50 | 91.65 | 89.90 | 93.18 |
| **F7** | 92.49 | 89.56 | 92.53 | 85.99 |
| **F8** | 90.18 | 90.18 | 93.15 | 93.20 |

**Drug Entrapment Efficiency**

The drug entrapment efficiency of different formulations were in range of 68.18% - 78.20 % w/w. Drug entrapment efficacy slightly decrease with increases Carbopol 934 content and decreases Eudragit ratio in micro balloons. This is due to the permeation characteristics of Carbopol 934, which could facilitate the diffusion of part of entrapped drug to surrounding medium during preparation of hollow microspheres.

**Table-4: Drug Entrapment for Different Formulation.**

| Formulation | Drug Entrapment (% w/w) |
|---|---|
| **F1** | 74.25 |
| **F2** | 71.58 |
| **F3** | 82.36 |
| **F4** | 68.18 |
| **F5** | 75.62 |
| **F6** | 72.38 |
| **F7** | 70.15 |
| **F8** | 78.20 |

The entrapment efficiency values ranged from 68.18 to 82.36 for all the formulations. For selected formulation (Eudragit) entrapment was found to be more in F3. So it is indicated only optimum concentration is suggestible. From the above result F3 (drug and polymer) was selected as a optimized formulation.

**Percentage Yield**

Percentage yield of different formulation was determined by weighing the micro balloons after drying. The percentage yield of different formulation were in range of 55.10 - 84.67% as shown in Table.

**Table 5: Percentage Yield for Different Formulation.**

| Formulation | Percent Yield*(%) |
|---|---|
| **F1** | 82.96 |
| **F2** | 81.70 |
| **F3** | 86.52 |
| **F4** | 82.56 |
| **F5** | 86.34 |
| **F6** | 78.03 |
| **F7** | 79.44 |
| **F8** | 75.10 |

**Percent Yield**

The percentage (%) yield values ranged from 75.10 to 86.52 for all the formulations.

**Scanning Electronic Microscopy**

Shape and surface characteristic of hollow microspheres examine by Scanning Electronic Microscopy analysis as shown in Fig. Surface morphology of F3 formulation examine at different magnification 40X and 200X, which illustrate the smooth surface of floating micro balloons and small hollow cavity present in microsphere which is responsible for floating property.

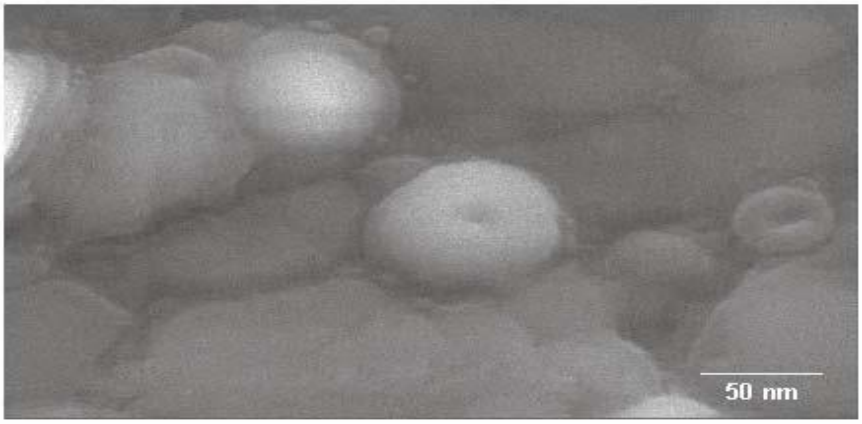


**Fig-3: Micro Photographs of Formulation F4.**

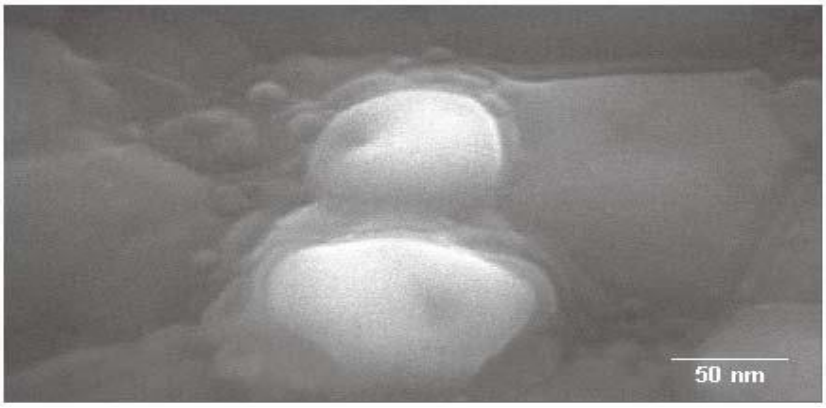


**Fig-4: Cross Section.**

The optimized formulation F3 was evaluated for its surface morphology by using SEM analysis. The particle size was found to be 789 µm. The hollow microspheres were found to be smooth and spherical in shape.

### *IN-VITRO* Drug Release Study

*In-vitro* drug release study of micro balloons was evaluated in pH 1.2 buffer. Eudragit RS100 which is present in all formulation, have low permeability in acid medium. Since Eudragit is less soluble in acidic pH, release of drug in 0.1 N HCl was generally low.

**Table-6: Comparative *In-Vitro* Drug Release Profile for Formulation in 6.8 Phosphate.**

| S. No. | TIME (hrs) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 |
|---|---|---|---|---|---|---|---|---|---|
| **1** | **0** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **2** | **1** | 15.18 | 16.50 | 18.62 | 15.12 | 12.05 | 16.20 | 18.15 | 17.48 |
| **3** | **2** | 28.15 | 26.75 | 26.60 | 27.53 | 25.12 | 28.15 | 29.21 | 21.88 |
| **4** | **3** | 35.11 | 40.14 | 38.29 | 36.82 | 31.61 | 32.88 | 32.85 | 34.25 |
| **5** | **4** | 43.08 | 56.03 | 51.74 | 45.15 | 48.03 | 44.15 | 48.22 | 50.14 |
| **6** | **5** | 55.75 | 67.25 | 69.92 | 58.05 | 70.96 | 59.18 | 56.29 | 69.29 |
| **7** | **6** | 69.50 | 72.65 | 77.63 | 69.89 | 76.66 | 66.63 | 62.22 | 75.18 |
| **8** | **7** | 80.15 | 84.92 | 83.33 | 86.48 | 81.14 | 74.16 | 79.18 | 83.85 |
| **9** | **8** | 91.25 | 92.53 | 96.90 | 90.89 | 88.32 | 85.90 | 89.25 | 90.12 |

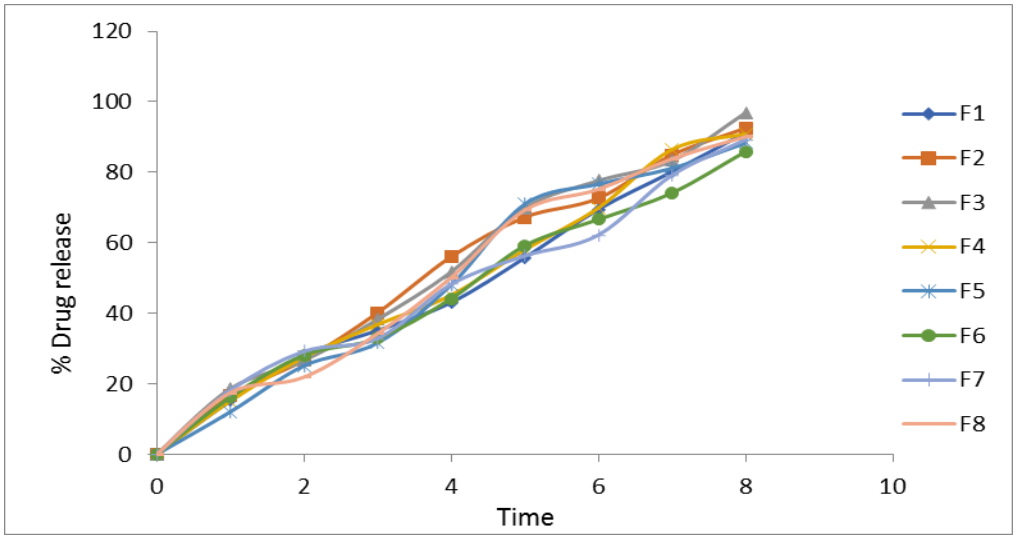


**Fig. 5: Comparative In-Vitro Drug Release Profile of (F1-F8) Formulations.**

All the 8 formulations of hollow microspheres were subjected to dissolution studies. Dissolution was carried out in Franz diffusion cell apparatus at 100 rpm in the volume of 10 ml dissolution media of 0.1N HCL for 8 hours. F3 showed a release rate of 96.90 by end of 8$^{th}$ hour of dissolution study.

### Drug Release Kinetics

Kinetics and mechanism of drug release from all formulation was evaluated on the basis of zero order, Higuchi equation and Pappas model. Correlation coefficient ($r^2$) and slop value for each equation was calculated from Microsoft excel. Zero order plot for all formulations were found to be linear in both dissolution medium. That indicates it may follow zero order mechanism. Higuchi plot was found to be linear, which indicates diffusion may be the mechanism of drug release for each formulation. Peppas plot was found good linear, n > 0.5 for all formulations, indicated that drug release may follow anomalous diffusion. Zero order plot for F3 formulation was found to be linear in both dissolution medium, it considered as a best fit for drug release.

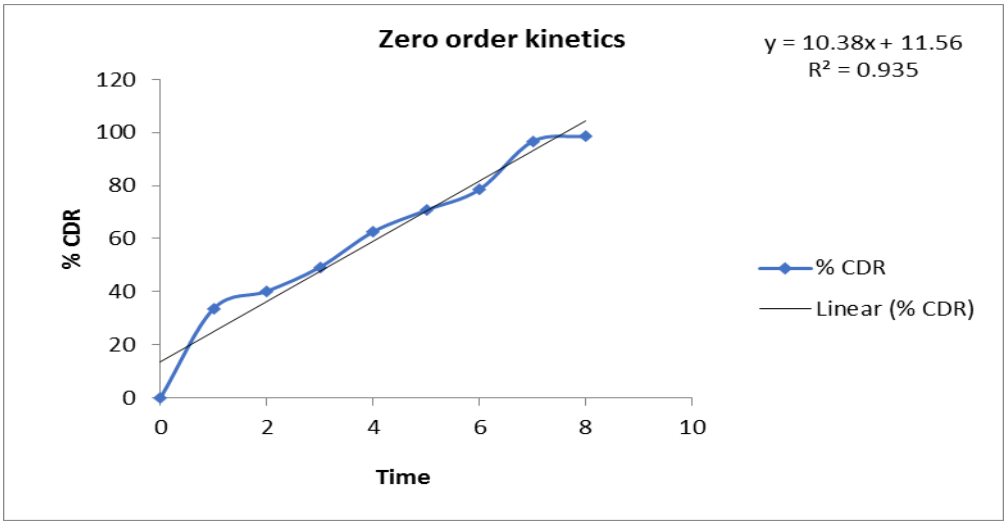


**Fig. 6: Zero Order Kinetics of Optimized Formulation.**

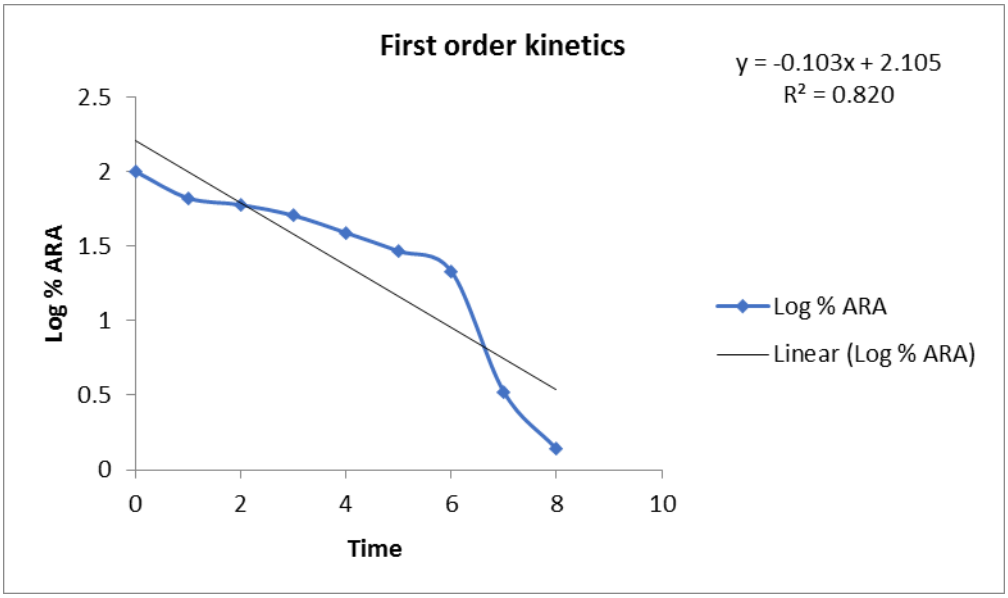


**Fig. 7: First Order Kinetics of Optimized Formulation.**

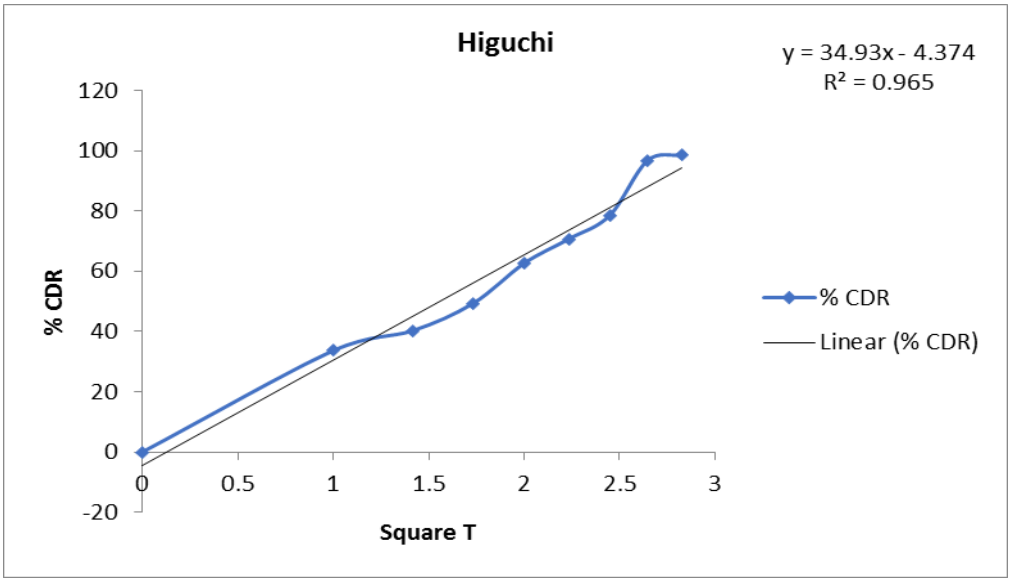


**Fig. 8: Higuchi Model of Optimized Formulation.**

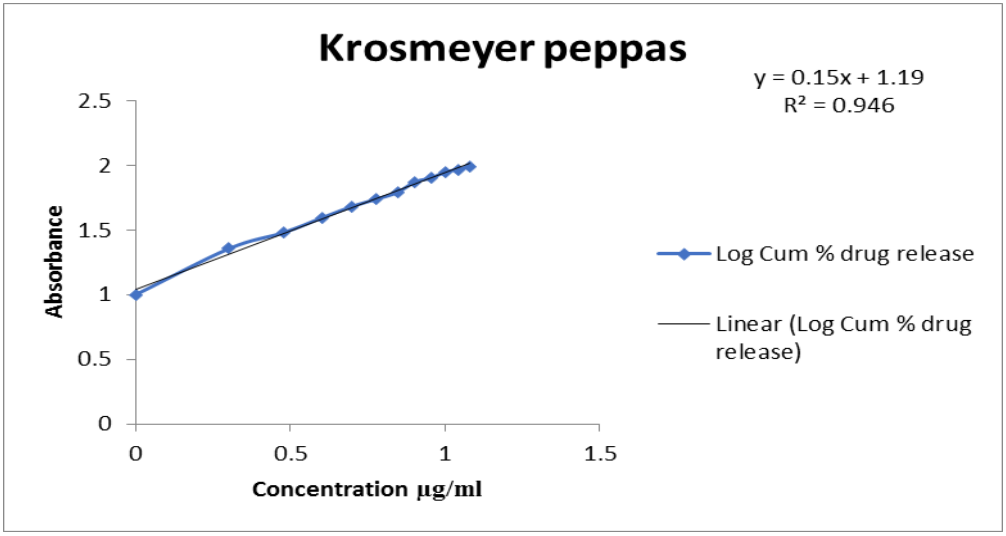


**Fig. 9: Krossmayer Peppas of Optimized Formulation.**

**Table 7: Regression Equations of Ketoprofen Microspheres F3.**

| Film Code | In Vitro Release in Phosphate Buffer $P^H$ 7.4 Regression Values | | | |
|---|---|---|---|---|
| | Zero order | First Order | Higuchi Plot | Kross Mayer Peppas |
| $F_3$ | 0.935 | 0.820 | 0.965 | 0.946 |

The table indicates that $r^2$ values are higher for Higuchi's model compared for all the microspheres. Hence Ketoprofen release from all the films followed diffusion rate controlled mechanism.

**Stability Study**

Stability study was carried out for the F3 formulation by exposing it to different temperature 25°C, 30°C and 40°C for 90 days. The sample was analyzed for drug content at the regular intervals. It was found that no remarkable change in the drug content of F3 formulation. This indicates that F3 was stable for following temperature.

**Table 8: Results of Stability Studies of Optimized Formulation F-3.**

| S. No. | Time in Days | Physical Changes | Mean % Drug Release | | |
|---|---|---|---|---|---|
| | | | Ketoprofen | | |
| | | | $25^0$C/60% | $30^0$C/75% | $40^0$C/75% |
| 1. | 01 | No Change | 96.90 | 96.90 | 96.90 |
| 2. | 30 | No Change | 96.85 | 96.86 | 95.82 |
| 3. | 60 | No Change | 96.81 | 96.79 | 96.75 |
| 4. | 90 | No Change | 96.65 | 96.69 | 96.72 |

The optimized formulation was stored in different conditions to check the stability. Drug content of the optimized formulation F3 initially was 96.90%. From the above result it can be concluded that there was no significant change in physical and chemical properties of the hollow microspheres of formulation F-3 after 3 Months.

## CONCLUSION

Hollow microspheres of Ketoprofen were prepared by emulsion solvent diffusion technique and performances of this formulation were evaluated. It increases the bioavailability of dosage form with prolong effect hence improves the patients compliances. Mean particle size for all formulations were varied, due to change in drug and polymer ratio. Drug entrapment efficiency slightly decreases with increasing the polymer content. Drug release pattern was evaluated in 0.1 N HCl. In order to increase the release rate of drug the ratio of Carbopol 934 and Eudragit is decreased and increased respectively. Ideal property of hollow microsphere includes high buoyancy and sufficient release of drug in pH 1.2. It is necessary to select an appropriate balance between buoyancy and drug release rate from all developing hollow microsphere. F3 formulation showed best appropriate balance between buoyancy and drug release rate, it considered as a best fit for drug release. Zero order plots for F3 formulation was found to be linear in dissolution medium, that indicates it may follow zero order mechanism.

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