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# INVESTIGATION OF HYDROXY PROPYL METHYL CELLULOSE K4M AND ETHYL CELLULOSE FOR DEVELOPMENT AND CHARACTERIZATION OF GASTRO RETENTIVE DRUG DELIVERY SYSTEM OF CEFUROXIME AXETIL

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## ABSTRACT

*The objective of the present study was to develop floating microspheres of Cefuroxime Axetil in order to achieve an extended retention in the upper gastrointestinal tract, which may result in enhanced absorption and thereby improved bioavailability. In present work microspheres of Cefuroxime Axetil were prepared in six batches using hydroxy propyl methyl cellulose (K4M) and ethyl cellulose in different drug and polymer ratio by using non-aqueous solvent evaporation method. The buoyancy percentage was determined in dissolution apparatus (TDT 06L, Electro lab), drug entrapment studies were done by solubilizing finely powdered microspheres in hydrochloric acid buffer pH 1.2 at room temperature. In-vitro release study of each formulation was carried out in dissolution apparatus (TDT 06L, Electro lab) using hydrochloric acid buffer pH 1.2 and simulated gastric fluid. Various results were inferred such as percentage yield value (78.8% to 92.14%), particle size (244µm to 294.8µm), drug entrapment efficiency (32.9% to 60.6%) and buoyancy percentages (52.5% to 70%). The best drug release profiles were seen with formulation $A_2$ at the ratio of drug: ethyl cellulose of 1:2.5.*

## KEY WORDS

*Floating Microsphere, Cefuroxime Axetil, HPMC, Ethylcellulose*

## INTRODUCTION

The present era comprises of devouring challenges in the field of public health care and unresting researches have laid down several queries towards the design of various formulations capably possessing highest possible pharmacodynamic as well as the pharmacokinetic properties to render the particular formulation appreciably significant acceptability to the patient care systems prevailing all across the globe with narrower spectrum of toxicities. Such queries encompass problems of variable intensities and hence invite the attention of manufacturing chemists to devise new techniques which may exert control over the rate of drug delivery, sustain the duration of therapeutic activity and/ or target the delivery of drug to a tissue or particular organ. These are tremendous unending brain hankering thirst which lead to the development of several "Novel Drug Delivery Systems"[1] that could revolutionize the method of medication and provide multifold therapeutic benefits such as reduction of adverse side effects, maximization of efficacy-dose relationship, enhancement of patient compliance, minimization of the need for frequent dose intake and maintenance of drug concentration within an optimal therapeutic range for prolonged duration of treatment.

**Floating drug delivery system:**

The controlled gastric retention of solid dosage forms may be achieved by various mechanisms i.e. mucoadhesion, flotation, sedimentation, expansion, modified shape systems etc. floating drug delivery systems are of two types[2]-

**A) Effervescent floating dosage form**

**B) Non-effervescent floating dosage form**

**Microspheres:**

Between 1940s and 1960s, the concept of microencapsulation technology began as an alternative means of delivering drugs. The term microcapsule is defined as a spherical particle with size varying from 50 nm to 2 mm containing a core substance. Microspheres are, in strict sense, spherical empty particles. In addition some related terms for example "micro beads" and "beads" are used alternatively. Sphere and spherical particles are used for rigid morphology[3]. The microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers which are biodegradable in nature and ideally having a particle size less than 200 µm.

## MATERIALS AND METHODS

**Materials:**

Cefuroxime axetil was kindly gifted by Twenty Century Pharma. Ethyl cellulose and HPMC K4M were procured from Fine Chemical Laboratories, Mumbai and Signet Chemical Corporations, Mumbai respectively. Other chemicals, solvents and reagents were of laboratory and analytical reagent grade as per requirements.

**Equipments:**

All equipments were of good quality procured from different companies well established and reputed in their fields.

**Formulation design:**

The formulation was divided into six batches prepared with different ratio of suitably chosen polymers as depicted in the Table 1.

**Table 1: Formulation design of Microspheres:**

| Sr. no. | Ingredients | A1 | A2 | A3 | B1 | B2 | B3 |
|---|---|---|---|---|---|---|---|
| 1 | Cefuroxime Axetil (mg) | 1 | 1 | 1 | 1 | 1 | 1 |
| 2 | Ethyl cellulose (gm) | 2 | 2.5 | 3 | ----- | ------ | ------ |
| 3 | HPMCK4M (gm) | ------ | ------ | ------ | 2 | 2.5 | 3 |
| 4 | Ethanol (ml) | 25 | 25 | 25 | 25 | 25 | 25 |
| 5 | DCM (ml) | 25 | 25 | 25 | 25 | 25 | 25 |
| 6 | Tween-80 (ml) | 0.18 | 0.18 | 0.18 | 0.18 | 0.18 | 0.18 |
| 7 | Liquid paraffin (ml) | 60 | 60 | 60 | 60 | 60 | 60 |
| 8 | RPM | 1200 | 1200 | 1200 | 1200 | 1200 | 1200 |

**Preparation of cefuroxime Axetil floating microspheres:**

Microspheres containing Cefuroxime Axetil as a core material were prepared by a non-aqueous solvent evaporation method. Drug and polymer were dispersed in the solvent (dichloromethane and ethanol in ratio 1:1). The slurry was slowly introduced into 30 ml of light liquid paraffin containing Tween-80 (0.01% w/v) as emulsifier with continuous stirring at 1200 rpm using a propeller type mechanical stirrer at room temperature. The solution was stirred for 2 hrs for complete evaporation of solvent and filtered. The microspheres thus obtained were washed[4].

**Evaluation of microspheres:**

**Percentage yield (% yield):**

The percentage yield was determined on the basis of method as reported by Amitava et.al.[5]. The yield was calculated as the weight of the microspheres recovered from each batch divided by total weight of drug and polymer used in the preparation of the particular batch.

$$Percentage\,Yield = \frac{Practical\,Yield}{Theoretical\,Yield} * 100$$

**Particle size analysis:**

The analysis of particle size was carried out using a photomicroscope (QUASMO, Quality Scientific, Ambala) fitted with micrometric tools (Winzoe). The particle size distribution was determined and the average diameter was calculated for each batch of microspheres[6].

**Bulk density:**

The principle involved in such determination was derived from the text reference[7].The Bulk density was calculated by manual tapping method introducing microspheres in 10 ml graduated cylinder. The ratio of weight of particles to that of its volume gave the bulk density as mentioned below:

$$Bulk\ Density = \frac{Weight\ of\ Microspheres}{Volume\ of\ Microspheres}$$

**Buoyancy percentage:**

The experiment to determine this parameter was performed as reported by **Anand et. al.[8].** The microspheres (0.3 g) were spread over the surface of USP (TDT 06L) dissolution apparatus (Type II) filled with 900 ml of 1.2 pH HCl buffer containing 0.01% of Tween 80. The medium was agitated with a paddle rotating at 100 rpm for 12 h. The floating and the settled portions of microspheres were recovered, dried and weighed separately. Buoyancy percentage was calculated as the ratio of the mass of particles that remained floating and the total mass of the recovered microspheres.

**Drug Entrapment Studies:**

The practical drug content was determined by UV analysis and entrapment efficiency was calculated[9].

$$Drug\ Entrapment\ Efficiency = \frac{\Pr actical\ Drug\ Content}{Theoretical\ Drug\ Content} * 100$$

**Surface Morphology:**

The morphology and surface characteristics of microspheres were studied by Scanning electron microscopy (Quanta FEI 200F). The dried microspheres were coated with gold foil (100 A°) under an argon atmosphere in a gold coating unit and micrographs were obtained at both higher and lower resolutions[10] (Fig. 1 and 2).

***In-Vitro* Release Studies:**

In vitro drug release studies were carried out for all batches by using USP (TDT 06L) type I USP dissolution rate test apparatus. The sample of Microspheres equivalent to 150 mg of the pure cefuroxime axetil was used for the study. 5 ml sample were withdrawn, diluted suitably and analyzed for the drug content spectrophotometrically at $\lambda_{max}$ 281nm using dissolution media (pH 1.2 HCl Buffer and SGF) as blank[11].

## RESULTS AND DISCUSSION:

**Particle size analysis:**

The analysis was performed for all six batches by Photomicroscope using micrometric tools. The results were as shown in table no- 8. The mean diameters of particles for all batches were found to be 244, 266, 269.2, 272, 269.2 294.8 µm (Table 2).

**Table 2: Particle size analysis of batch $A_1$ to $B_3$**

| No | Formulation Codes | Mean Particle Size (µm) |
|---|---|---|
| 1 | $A_1$ | 244 |
| 2 | $A_2$ | 269.6 |
| 3 | $A_3$ | 292 |
| 4 | $B_1$ | 266 |
| 5 | $B_2$ | 272 |
| 6 | $B_3$ | 294.8 |

**Surface morphology:**

The surface morphology of microspheres belonging to optimized batches i.e. $A_2$ and $B_3$ was examined by scanning electron microscopy. Scanning electron micrographs of the optimized formulation are shown in Fig. 1 and 2.

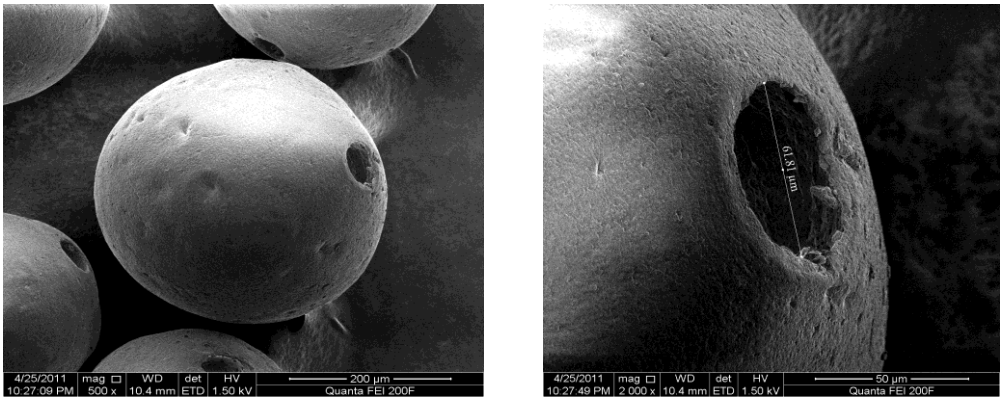


**Fig. 1. Scanning Electron Microscopy of formulation $A_2$**

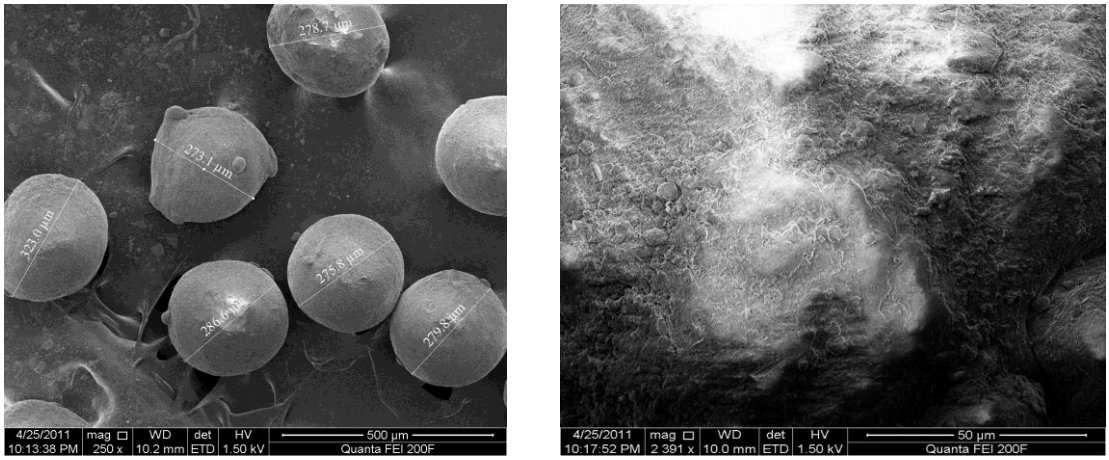


**Fig. 2. SEM image of formulation $B_3$**

**Bulk density of the Microspheres:**

The Bulk density determination was performed for all six batches by hand tapping method using measuring cylinder. Results were as shown in Table 3. The bulk densities for all samples were found to be in the range of 0.750 to 0.833 respectively.

**Table 3: Bulk density of the prepared batches**

| Sr. no. | Formulation | Bulk density (mg/ml) |
|---|---|---|
| 1 | $A_1$ | 0.833 |
| 2 | $A_2$ | 0.769 |
| 3 | $A_3$ | 0.757 |
| 4 | $B_1$ | 0.750 |
| 5 | $B_2$ | 0.769 |
| 6 | $B_3$ | 0.833 |

**Percentage yield:**

The maximum percentage yield was found to be 92.14% with batch $A_2$ and minimum of 78.8% with batch $A_3$. The results are shown in Table 4.

**Table 4: Percentage yield of the prepared batch $A_1$ to $B_3$**

| Formulation | Theoretical Yield (g) | Practical Yield (g) | Percentage Yield (%) |
|---|---|---|---|
| $A_1$ (g) | 6 | 5.31 | 88.5 |
| $A_2$ (g) | 7 | 6.45 | 92.14 |
| $A_3$ (g) | 8 | 6.31 | 78.8 |
| $B_1$ (g) | 6 | 5.450 | 90.8 |
| $B_2$ (g) | 7 | 6.29 | 89.8 |
| $B_3$ (g) | 8 | 6.35 | 79.37 |

**Buoyancy percentage:**

The purpose of preparing floating microspheres was to extend the gastric residence time of the drug. The buoyancy test was carried out to investigate the floatability of the prepared microspheres. The particles were spread over the surface of a simulated gastric fluid and the fraction of microspheres settled down as a function of time was quantitated. The fraction of floating microspheres reduced up to 12 hrs suggesting that the absorption of the drug in vivo pertaining to sustained release would be linear with time. Buoyancy of Batch $A_2$ was found to be 70% which indicated that most of the microspheres were still floatable even after 12 hrs. The results are presented in the Table 5.

**Table 5. Buoyancy percentage of batch $A_1$ to $B_3$**

| Formulation | Total mass (mg) | Total mass remained floating (mg) | Buoyancy Lag time (sec) | Buoyancy percentage (%) |
|---|---|---|---|---|
| $A_1$ | 200 | 125 | 8 | 62.5 |
| $A_2$ | 200 | 140 | 5 | 70 |
| $A_3$ | 200 | 130 | 7 | 65 |
| $B_1$ | 200 | 105 | 9 | 52.5 |
| $B_2$ | 200 | 115 | 10 | 57.5 |
| $B_3$ | 200 | 123 | 8 | 61.5 |

**Drug entrapment efficiency:**

The microspheres of batch $A_2$ and $B_3$ formulations showed entrapment of 60.6% and 57.2% respectively while formulation $A_1$ and $B_1$ particles were least entrapped (Table 6). It attributed to the permeation characteristics of each polymer.

**Table 6: Percentage drug entrapment of batch $A_1$ to $B_3$**

| Formulations | Absorbance | % drug content |
|---|---|---|
| $A_1$ | 0.302 | 41.7 |
| $A_2$ | 0.208 | 60.6 |
| $A_3$ | 0.195 | 56.6 |
| $B_1$ | 0.148 | 32.9 |
| $B_2$ | 0.164 | 42.7 |
| $B_3$ | 0.213 | 57.2 |

***In-Vitro* Release Studies:**

The release profiles were fitted in various in vitro release models like Zero order, Higuchi plot and Korsmeyer peppas model for the prepared formulations. The results are shown in Tables 7 and 8, and Fig. 3-8.

**Table 7: Estimation value of $r^2$, k and n by the regression of log ($M_t$ / $M_\infty$) on log (t) for 1.2 pH HCl buffer data**

| Formulation | Zero order | | Higuchi | | Korsmeyer-Peppas | |
|---|---|---|---|---|---|---|
| | $r^2$ | $K_0$ | $r^2$ | $k_h$ | $r^2$ | N |
| A1 | 0.808 | 0.068 | 0.919 | 2.091 | 0.959 | 0.594 |
| A2 | 0.910 | 0.059 | 0.959 | 1.825 | 0.968 | 0.576 |
| A3 | 0.969 | 0.071 | 0.962 | 2.144 | 0.992 | 0.6 |
| B1 | 0.974 | 0.119 | 0.934 | 3.494 | 0.948 | 0.705 |
| B2 | 0.993 | 0.108 | 0.936 | 3.141 | 0.972 | 0.677 |
| B3 | 0.996 | 0.09 | 0.919 | 2.585 | 9.962 | 0.644 |

**Table 8: Estimation value of $r^2$, k and n by the regression of log ($M_t$ / $M_\infty$) on log (t) for SGF data**

| Formulation | Zero order | | Higuchi | | Korsmeyer-Peppas | |
|---|---|---|---|---|---|---|
| | $r^2$ | $K_0$ | $r^2$ | $k_h$ | $r^2$ | N |
| A1 | 0.864 | 0.069 | 0.919 | 2.15 | 0.953 | 0.599 |
| A2 | 0.892 | 0.06 | 0.957 | 1.884 | 0.962 | 0.582 |
| A3 | 0.958 | 0.073 | 0.967 | 2.202 | 0.988 | 0.604 |
| B1 | 0.973 | 0.120 | 0.943 | 3.552 | 0.969 | 0.699 |
| B2 | 0.992 | 0.109 | 0.946 | 3.20 | 0.986 | 0.674 |
| B3 | 0.995 | 0.091 | 0.932 | 2.643 | 0.981 | 0.641 |

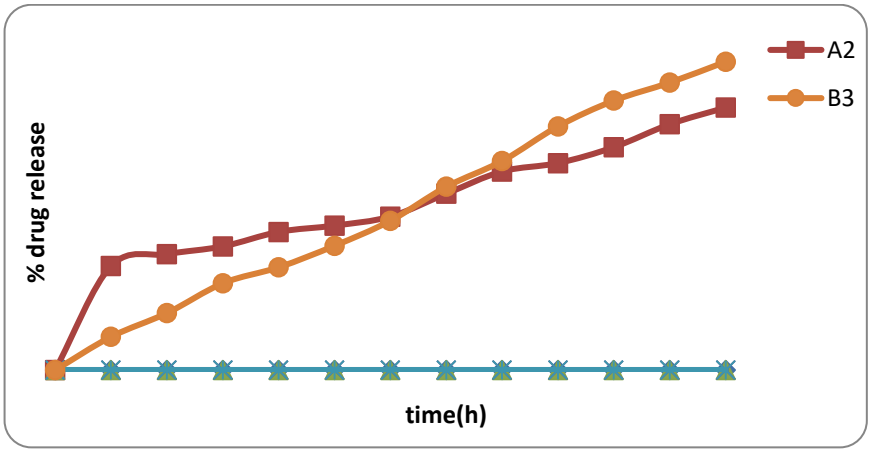


**Fig. 3. Comparative Kinetic Zero order release of batch $A_2$, $B_3$ in HCl buffer pH 1.2**

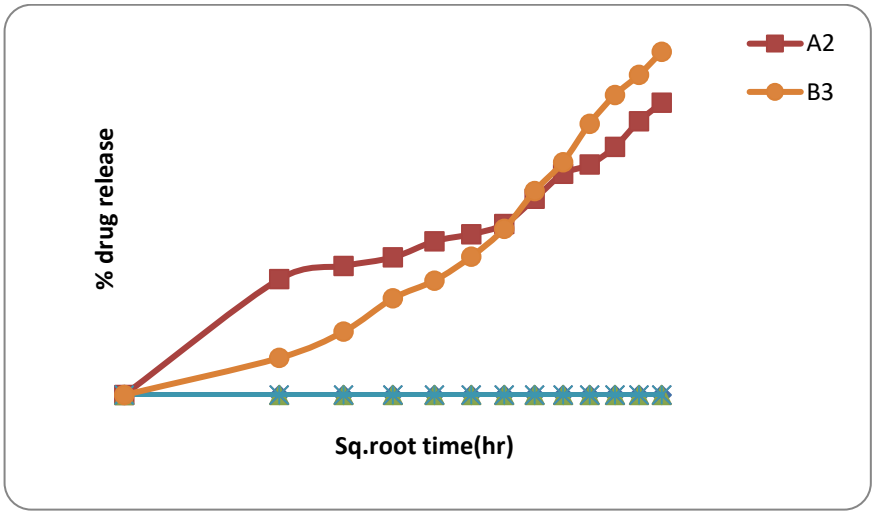


**Fig. 4. Comparative Higuchi plot of batch $A_2$, $B_3$ in HCl buffer pH 1.2**

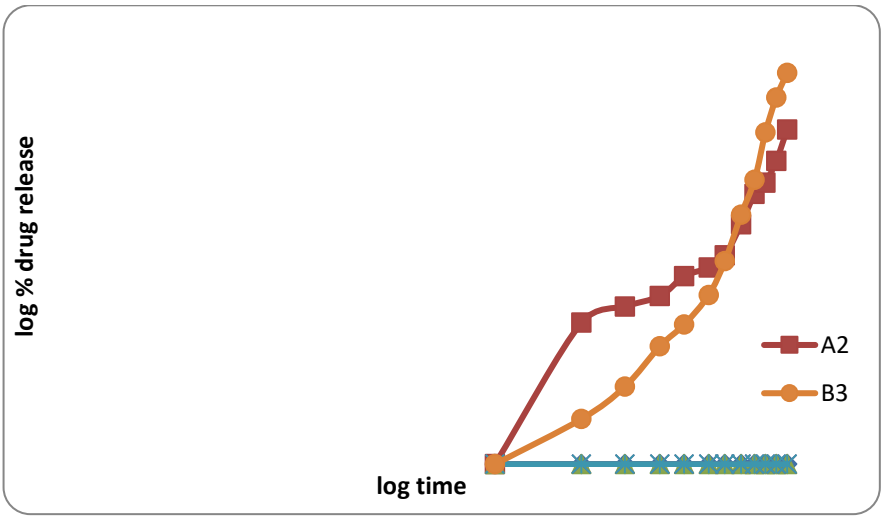


**Fig. 5. Comparative Korsmeyer peppas model of batch $A_2$, $B_3$ in HCl buffer pH 1.2**

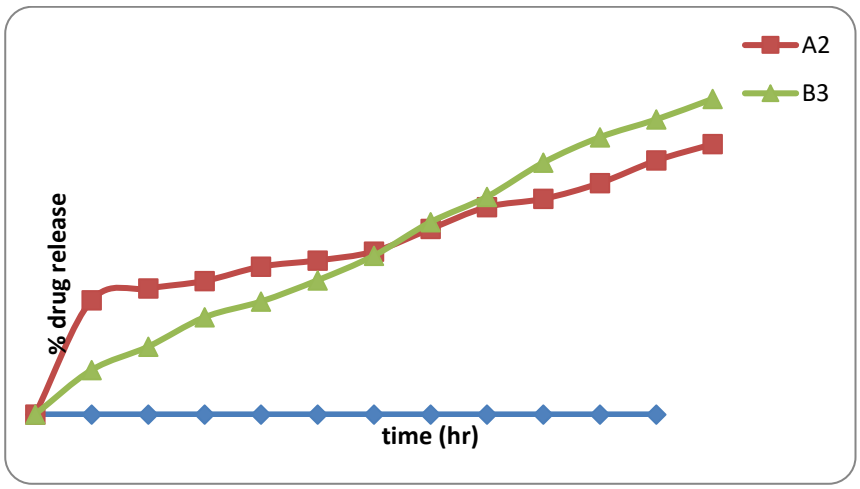


**Fig. 6. Comparative Kinetic Zero order release of batch $A_2$, $B_3$ in simulated gastric fluid**

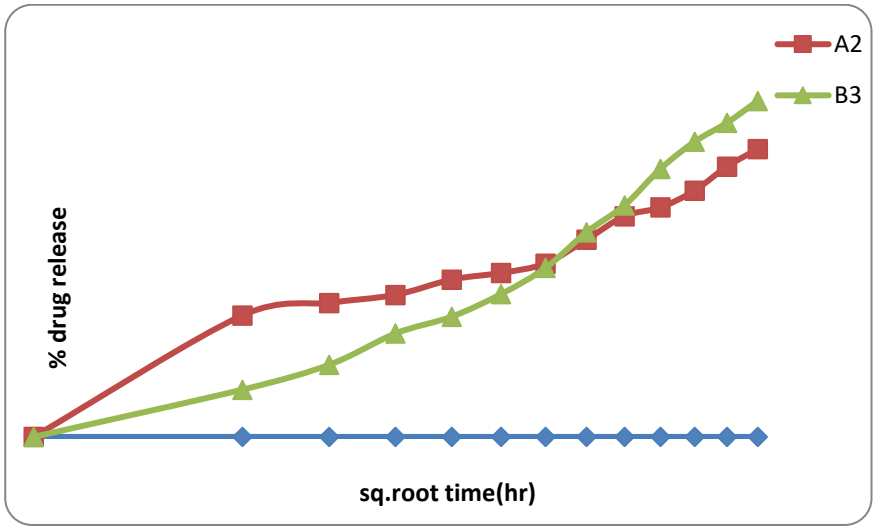


**Fig. 7. Comparative Higuchi plot of batch $A_2$, $B_3$ in simulated gastric fluid**

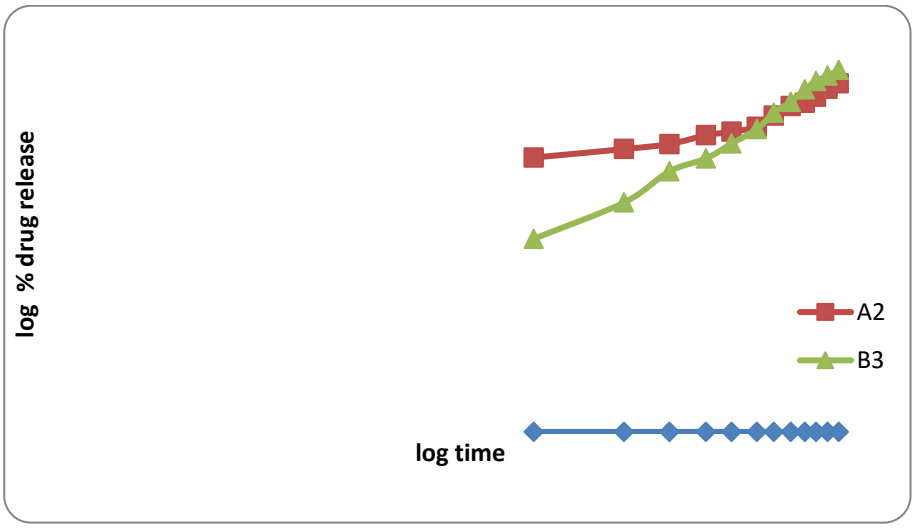


**Fig. 8. Comparative Korsmeyer peppas model of batch $A_2$, $B_3$ in simulated gastric fluid**

**Correlation coefficient ($r^2$), constant (k) and diffusion exponent (n) after fitting of dissolution data (1.2 ph HCl buffer) into various releases kinetic models:**

**Discussion:**

All the release data were fitted into various kinetic models like, zero order, Higuchi, and Korsmeyer-Peppas in order to find out the mechanism of drug release from polymeric spheres. The correlation coefficients, rate constants and diffusion coefficients were calculated as summarized in Table 7.

Analysis of the release data as per zero order kinetic model best suited to describe the release rate of drug from the microspheres. When the release data was analyzed as per peppas equation, the release exponent 'n' was in the range of 0.576 to 0.705 with all the microspheres indicating non-fickian diffusion. Higuchi's plots resulted in linearity ($r^2$>0.919) indicating non-fickian diffusion mechanism.

**Correlation coefficient ($r^2$), constant (k) and diffusion exponent (n) after fitting of dissolution data (SGF) into various releases kinetic models:**

All the release data was fitted into various kinetic models i.e. zero order, Higuchi, and Korsmeyer-Peppas, in order to find out the mechanism of drug release from polymeric spheres. The correlation coefficients rate constants and diffusion coefficients were calculated as summarized in Table 8.

Analysis of the release data as per zero order kinetic model best suited to describe the release rate of drug from the microspheres. When the release data was analyzed as per peppas equation, the release exponent 'n' was in the range of 0.582 to 0.699 with all the microspheres indicating non-fickian diffusion. Higuchi's plots resulted to be linear ($r^2$>0.919) indicating non-fickian diffusion mechanism.

## CONCLUSION:

In present work microspheres of Cefuroxime Axetil were prepared in six batches using hydroxy propyl methyl cellulose (K4M) and ethyl cellulose in different drug and polymer ratio by using non-aqueous solvent evaporation method. The investigation revealed that the combination of hydrophilic and hydrophobic cellulosic polymers can used successfully to achieve sustained release of Cefuroxime Axetil. The best drug release profiles were seen with formulation $A_2$ at the ratio of drug: ethyl cellulose of 1:2.5.

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