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# Preparation and evaluation of sustained release microspheres for the treatment of diabetic neuropathy

Pathloth Nandini *, M. Sunitha Reddy and K. Anie vijetha

*Department of Pharmaceutics, Centre for Pharmaceutical Sciences, JNTUH UCESTH, JNTUH, Hyderabad, Telangana-500085, India.*

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## Abstract

This study aimed to prepare and evaluate sustained release microspheres for the treatment of diabetic neuropathy using Various polymers including sodium alginate, ethyl cellulose, HPMC K100, Carbopol 934, and Eudragit L-100-55. Polymers were employed to assess their impact on several crucial parameter's entrapment efficiency, production yield Particle size analysis, swelling index, in vitro dissolution, and release kinetics. The production yield of microspheres varied depending on the polymer used, with some polymers performing in advanced yields. Entrapment effectiveness was set up to be optimal with certain polymer combinations. Particle size analysis indicated that the microspheres were within the asked range for controlled release operations. The swelling index showed polymer-dependent lump actions. In vitro dissolution studies demonstrated sustained medicine release over time, with different polymers impacting both the release rate and profile. medicine release kinetics analysis revealed that the release followed specific models, reflecting the commerce between the microsphere matrix and the medicine.

**Keywords:** Microsphere; Sodium Alginate; HPMC K100; Carbopol 934; Eudragit L-100-55

## 1. Introduction

Microspheres are round particles that extend in measure from 1µm to 1000µm. In some cases, called microparticles, they can be made from a assortment of normal, manufactured, and semi-synthetic materials.[1]

The use of microspheres in parenteral and oral controlled medication delivery systems has become widely accepted. They frequently need both a core material and a polymer as a carrier. The solvent evaporation method has attracted significant attention among the different approaches established for the formulation of microspheres since it is simple to fabricate without sacrificing the drug's action.[2]

Ethyl cellulose is a non-ionic, inert, hydrophobic, non-biodegradable, biocompatible polymer with minimal toxicity. For the regulated release of drugs, it is one of the encapsulating materials that has undergone extensive research. The non-ionic polymer HPMC can swell. Because of their adaptability, hydrophilic polymer gel lattice frameworks are habitually utilized in controlled medicate conveyance to accomplish a wanted medicate discharge profile and fetched adequacy. As the amount of hydroxypropyl content rises, so does the HPMC hydration rate. Carbopol is a polymer made by divinyl glycol, ether cross-linked with acrylic acid. It swells and becomes hydrated quickly after absorbing water. Apart from its water solubility, Because of its ability to attract water and cross-linked structure, Carbopol is an anionic polymer and may be used as a controlled release drug. [2]

* Corresponding author: Pathloth Nandini

### 1.1. Advantages

- Microspheres have persistent and ongoing effects.
- By lowering dosage frequency, it enhances patient compliance.
- Their spherical form allowed them to fit inside the body due to their size.
- The microspheres' architecture allows for regulated changes in the medication's release and deterioration.
- Surface area increases with reduced size, which can help a drug's poor solubility.
- The largest drug distribution occurs when a medication is polymer-coated to stop enzymatic cleavage.
- A smaller particle has more surface area and can increase the efficiency of a substance that is difficult to dissolve.[3]

### 1.2. Disadvantages

The regulated dose mechanism of release has a different release rate depending on a number of factors, including transfer levels through the stomach and nutrition.

- Variation in discharge rate between doses
- With these dosage forms, chewing is not allowed.
- A decrease in reproducibility.

Environmentally hazardous consequences of polymer matrix breakdown can be produced by light, heat, hydrolysis, oxidation, and biological activities.

From time to time, there was a chance that the drug composition would vary while being prepared. [1, 3]

Types of microspheres

- Bio adhesive microsphere.
- Magnetic microsphere.
- Floating microsphere.
- Radioactive microsphere.
- Bio degradable microsphere.

**Table 1** Various Types of Microspheres

| Types | Description |
|---|---|
| Bio-adhesive microsphere. | Since of their bio adhesive properties, these microspheres cause hint contact with the retention location and keep up persistent medicine discharge, coming about in a delayed home term at the location. |
| Magnetic microsphere. | Releasable supramolecular particles that can be controlled by magnetism, known as magnetic microspheres, are small enough to pass through capillaries without causing embolic blockage (<5μm), yet they are also sufficiently susceptible to Microspheres: as carriers for innovative drug delivery systems that are drawn into micro vessels and into surrounding tissues by a magnetic field weaker than 1.0 tesla.[1] |
| Floating microsphere. | Gastro-retentive floating microspheres, which are low- consistency bias, give sufficient buoyancy to float above stomach contents and remain in the stomach for dragged ages of time without causing the stomach to empty more slow. The medicine is administered gradationally and at the listed rate. |
| Radioactive microsphere. | When radioactive microspheres are injected into the arteries that lead to tumours of interest, they effectively target the tumour cells and deliver a high dosage of radiation there while causing minimal damage to the surrounding normal tissues. |
| Bio-degradable microsphere. | Biodegradable polymeric microspheres have a tall degree of swelling in a fluid media that causes gel arrangement, which expands the home period when in contact with mucous layers. The polymer concentration and the maintained discharge design direct the drug's discharge rate and extent.[1] |

### 1.3. Techniques used in microsphere preparation

- Single emulsion technique
- Spray drying technique
- Use of double emulsion technique.
- Phase separation coacerative.
- Solvent evaporation technique.

*1.3.1. Single emulsion technique:*

The natural polymers are broken down in an aqueous medium (oil, for example) and then dispersed in a non-aqueous medium while being constantly agitated. Using heat or chemical cross-linking agents such as formaldehyde, diacid chloride, etc. are the two methods available for achieving cross-linking. [1,5]

*1.3.2. Spray drying technique:*

A suitable unpredictable organic solvent, like as acetone or dichloromethane, is used to dissolve the polymer. After being homogenized at a high speed, the medication in its solid state is either dissolved or distributed throughout the polymeric solution. The dispersion is subsequently atomized in an opposite-flowing stream of hot, dry air, which causes tiny droplets to form. The solvent then instantly evaporates from these droplets, forming microspheres, which eventually settle to the spray dryer's bottom [1,21]

*1.3.3. Double emulsion method:*

The most suitable candidates for the double emulsion method are water soluble drugs, proteins, peptides, and vaccines. A lipophilic organic continuous phase is used to dispense the aqueous protein solution containing the active medication while concurrently providing continuous sonication. In the continuous phase, the primary emulsion is produced by the polymer solution that finally envelops the protein present in the scattered aqueous phase. The substance is along these lines homogenized or sonicated earlier to being included to the polyvinyl liquor (PVA) fluid arrangement, shaping a twofold emulsion. Subsequently, the solvent is extracted from the emulsion using low-pressure solvent evaporation. The solid microspheres are then produced through filtration and acetone washing. [1,5]

*1.3.4. Phase separation coacerative:*

This technique encapsulates pharmaceuticals that are soluble in water, such as proteins and peptides. The procedure comprises dissolving the polymer in an appropriate solvent and then dispersing the medication. Subsequently, phase separation is achieved by modifying the solution conditions through the addition of salt, odd-solvent, incompatible polymer, or PH change. [5,21]

*1.3.5. .Solvent evaporation technique:*

Using an organic solvent to remove the organic phase is the process by which microparticles are produced. The organic phase is eliminated during the process since water is a miscible organic solvent. The drug is inserted directly into the body as one procedure. The volume of the emulsion in proportion to a polymer's solubility profile in water, the amount of solvent, the water's temperature, and other factors are some of the factors that affect elimination. [1,3,5].

## 2. Materials and method

- Chemicals: Sodium alginate, HPMCK100, Eudragit RL-100, Ethyl cellulose, Carbopol 931, Acetone,
- Buffer made of phosphate: Dihydrogen phosphate of potassium and hydrogen phosphate of sodium.
- Equipments: UV spectroscopy, Stirrer, Magnetic stirrer, weighing balance.
- Preformulation studies: Organoleptic properties
- Colour: Yellow to orange
- Odour: Odourless
- Taste: Tasteless

### 2.1. Preparation of pH Phosphate Buffer:

Add 13.872 grams of potassium dihydrogen phosphate and 35.084 grams of disodium hydrogen phosphate in enough water to make 1000 millilitres, then store in a cold area.

### 2.2. Determination of λ max:

An individual µg/ml solution of API was checked in the spectrum mode from 200 nm to 400 nm in order to choose an analytical wavelength.

### 2.3. Standard curve of API

100 mg of the API reference standard, precisely weighed, was transferred to a 1000 ml volumetric flask, dissolved, and diluted with acetone to create a stock solution with a strength of 1000 µg/ml. By diluting 1 millilitre of stock solution with 10 millilitres of acetone, 100µg/ml of regular working solution was created. A working solution of 10µg/ml was created by diluting 1 millilitre of stock solution with 10 millilitres of acetone. Prepare serial dilutions of 3 ppm, 6 ppm, 9 ppm, 12 ppm, and 15 ppm from the aforementioned solution.

### 2.4. Preparation of Microspheres:

- Microsphere are prepared by solvent evaporation method
- Weigh different quantity of polymer were dissolved in 10ml of chloroform and dichloromethane by using a stirrer.
- Drug was mixed with polymer solution and stir for 10mins.
- The dispersion was poured into 500ml beaker containing PVA (Continuous phase) and 2% of SLS.
- Mechanical stirrer with 3 blades paddle was used for stirring at 1000rpm for 2-3hours until chloroform is evaporated.
- Microsphere are sifted utilizing channel paper and washed with water and dried for 24hrs.

**Table 2** Formulation table with different polymers

| Formulations | Drug | Ethyl cellulose | Eudragit L 100-55 | Sodium alginate | Carbopol 934 | HPMC K100 | Amount of chloroform & DCM (ml) | SLS (%) |
|---|---|---|---|---|---|---|---|---|
| F1 | “500 mg” | “600 mg” | “400 mg” | - | - | - | 5:5 | 2 |
| F2 | “500 mg” | “600 mg” | - | “400 mg” | - | - | 5:5 | 2 |
| F3 | “500 mg” | “600 mg” | - | - | “400 mg” | - | 5:5 | 2 |
| F4 | “500 mg” | “600 mg” | - | - | - | “400 mg” | 5:5 | 2 |

### 2.5. Evaluation of microspheres:

*2.5.1. Determination of Encapsulation efficiency (EE)*

By performing an analysis on the drug concentration in the produced microspheres, the EE of the microspheres was ascertained. All batch's microspheres were taken. Twenty-five milligrams of the powder were added to a 10-milliliter volumetric flask after the microspheres had first been crushed in a crushing device. After to begin with smashing the microspheres in a crushing device, 25 mg of the powder was included to a 10-milliliter volumetric jar. By using 100% encapsulation efficiency, a further dilution was created. The samples were examined at 390 nm with a UV-visible spectrophotometer. (16)

% EE was calculated by

$$\% \text{ (EE)} = \frac{\text{Drug amount encapsulated}}{\text{Total amount of medication added}} \times 100$$

*2.5.2. Production yield:*

Percentage abdicate of microspheres is calculated by isolating genuine weight of item to add up to sum of all components that are utilized in the arrangement of microsphere. (16)

$$\text{Production yield} = \frac{\text{weight of microsphere}}{\text{Weight of all polymers + weight of medication taken}}$$

*2.5.3. Particle size analysis*

optical microscope was used to measure the microspheres' size. Using this procedure, the eye component micrometer is checked using the stage micrometer. A fixed line that is selected to cross the center of each particle is used to measure stage micrometers. Each division of one millimeter is equal to ten millimeters because one millimeter is divided into 100 equal divisions. The average diameter of was calculated using the formula below. (16)

$$\text{Avg diameter} = \frac{\Sigma nd}{n} \times \text{C.F.}$$

here n = number of microspheres, d =distance across of microspheres, C.F =calibration Calculate.

*2.5.4. Swelling index*

The microspheres were placed in 5 mL of USP-simulated stomach fluid (pH 1.2) in order to calculate the swelling index. Using an optical magnifying lens, a microscopy method was used to view the molecules every hour. The microspheres' increase in molecular measure was observed for a maximum of eight hours. The rate of swelling was determined at different times within the microspheres by calculating the difference between the microspheres' breadth at time t (Dt, which is) and introduction time (t = 0 [D0]), as determined by the following condition:

$$S\ I = Dt - DoDt$$

*2.5.5. In-vitro dissolution studies*

In vitro dissolve studies were conducted for the generated microspheres condition by a USP II dissolving apparatus. The dissolving medium's bowel contained the microspheres. The 6.8 phosphate buffer was utilized as the disintegration media, and it was kept at 37.5°C and turned at a speed of 100rpm. At foreordained intervals, a 2-milliliter aliquot was expelled and sifted through a 0.45µ Millipore channel. Following the proper dilution, the samples were examined, and the cumulative percentage of drug release was determined.

*2.5.6. Drug release kinetics*

- Kinetics of zero order:

Systems in which the drug release rate is independent of its concentration are described by the zero-order rate. (19)

$$Qt = Ko + Qo.$$

Qo= Initial dosage of medication

The total medication released at time 't' is denoted by Qt.

Ko is constant.

‘t’ represents the total number of hours.

- Rate of drug release
- Not dependent on focus.
- A straight line and %CDR vs. Time are obtained in the graph.

Zero order examples include:

Release of oral control, suspension, tablets in the matrix with limited drug solubility, depots implantable, Transdermal The pressure in the mouth

- Kinetics of first order:

The medicate discharge from a framework where the discharge rate depends on concentration.

$$\text{Log } Qt + Kt/2.303 = \text{Log } Qo$$

Initial dosage of medication is Qo

Qt is the total of medication released at time t.

K is constant

‘t’ represents the total number of hours.

The concentration determines the drug release rate.

Visual representation: log of medication percentage left over time

First-order examples include:

Matrix dissolution-controlled release, solution, sustained release, and diffusion-controlled release.

- The Higuchi Model

The Higuchi formula for medication release via matrix.

$$Q = KHt1/2.$$

Q is the total of medication released at time 't'.

Higuchi constant is KH.

‘t’ represents total number of hours.

Drug release amount vs. square root of time is shown graphically.

Importance of the Higuchi equation or model

The dependent on time square root of Fick's law is used to explain the drug release as a diffusion process(20).

- Hixson Crowell:

The equation for the Hixson Crowell release

$$3-Qo - 3-Qt = KHC.t$$

‘Qo’ Initial dosage of medication

‘Qt’ Cumulative Release of Drug

KHC is constant

t = hrs

A few instances of Hixson Crowell

Drug release through solubility Diffusion is not the cause of surface area changes, particle diameter changes, or release.

- The Korsmeyer-Peppas formula

F = (Mt/M) = Km t n

'F' is the % of medication released at time t.

'Mt' amount of medication released at t.

'M' The total dose form medication quantity

Kinetic constant is Km.

n = Exponent of diffusion or release

t = Hours in a day

Visual representation: log percentage CDR vs log time

Log (Mt/M) linear regression is used to estimate n'. Compared to log t

**Table 3** Release mechanism of drug.

| Diffusion exponent (n) | Overall solute diffusion mechanism |
|---|---|
| 0.45 | Fickian diffusion |
| 0.45 < n < 0.89 | Anomalous (non-Fickian) diffusion |
| 0.89 | Case-II transport |
| n > 0.89 | Super case-II transport |

## 3. Results and discussion

### 3.1. Preformulation studies:

- Organoleptic properties:
- Colour: Yellow to orange
- Odour: Odourless
- Taste: Tasteless

λ max of API: UV spectrum analysis of epalrestat revealed that the drug has a maximum absorbance at 390 nm

Standard Curve of Epalrestat: A linear relationship between concentration and absorbance is shown by the regression coefficient of 0.9906, which indicates a high degree of precision and accuracy in the measurements.

**Table 4** Standard curve of Epalrestat

| **Concentration(µg/mL)** | **Absorbance at 390nm** |
|---|---|
| 2 | 0.322 ± 0.022 |
| 4 | 0.455 ± 0.038 |
| 6 | 0.659 ± 0.053 |
| 8 | 0.819 ± 0.041 |
| 10 | 0.926 ± 0.062 |

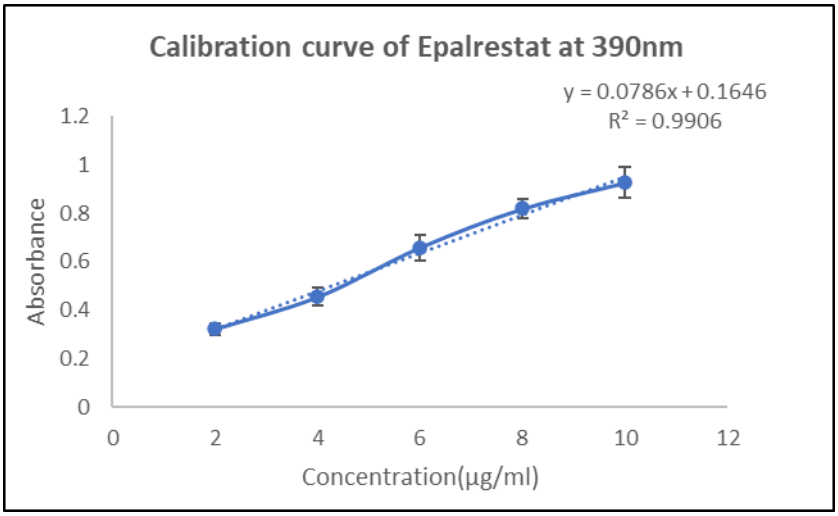


**Figure 1** Calibration curve of Epalrestat at 390nm

**Table 5** Flow properties of microspheres

| Formulations | Bulk density | Tapped density | Carr's Index | Hausner's ratio | Angle of repose |
|---|---|---|---|---|---|
| F1 | 0.34 | 0.39 | 12.82 | 1.14 | 20.32 |
| F2 | 0.30 | 0.37 | 18.91 | 1.23 | 23.15 |
| F3 | 0.32 | 0.36 | 11.11 | 1.12 | 25.23 |
| F4 | 0.34 | 0.38 | 10.52 | 1.11 | 22.19 |

**Table 6** Production yield, Particle size, Entrapment efficiency and swelling index of microsphere of Epalrestat by solvent evaporation method

| Formulations | Production yield (%) | Entrapment efficiency (%) | Particle size | Swelling Index |
|---|---|---|---|---|
| F1 | 80 | 84 | 169 | 89 |
| F2 | 79 | 94 | 171 | 92 |
| F3 | 75 | 72 | 122 | 88 |
| F4 | 69 | 78 | 135 | 85 |

**Table 7** Invitro Dissolution studies

| Time(hrs) | F1 | F2 | F3 | F5 |
|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 |
| 0.5 | 27 | 32 | 9 | 24 |
| 1hr | 34 | 38 | 18 | 32 |
| 2hr | 48 | 46 | 24 | 39 |
| 3hr | 59 | 52 | 28 | 45 |
| 6hr | 64 | 68 | 36 | 47 |
| 8hr | 72 | 76 | 39 | 50 |

| | | | | |
|---|---|---|---|---|
| 10hr | 78 | 82 | 43 | 58 |
| 12hr | 89 | 96 | 58 | 69 |

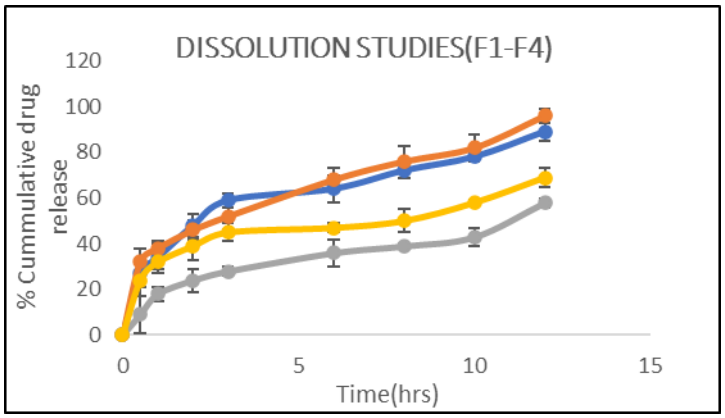


**Figure 2** In vitro Dissolution studies (F1-F4)

### 3.2. Drug release kinetics of (F2)

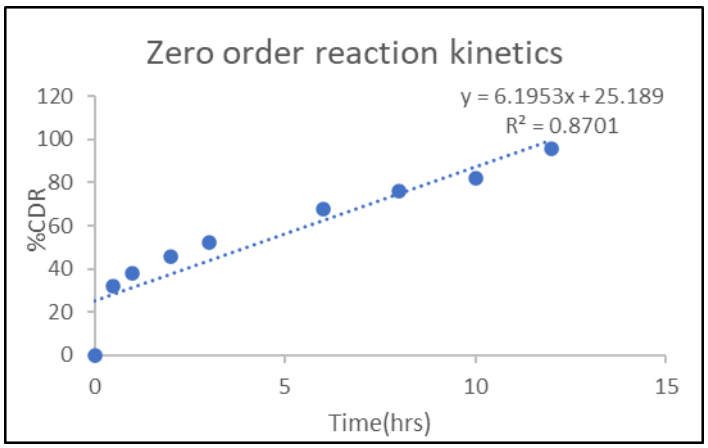


**Figure 3** Zero order kinetics of F2

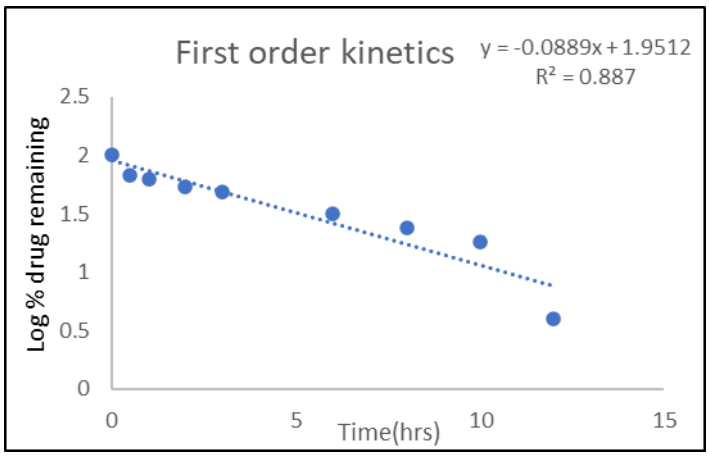


**Figure 4** First order kinetics of F2

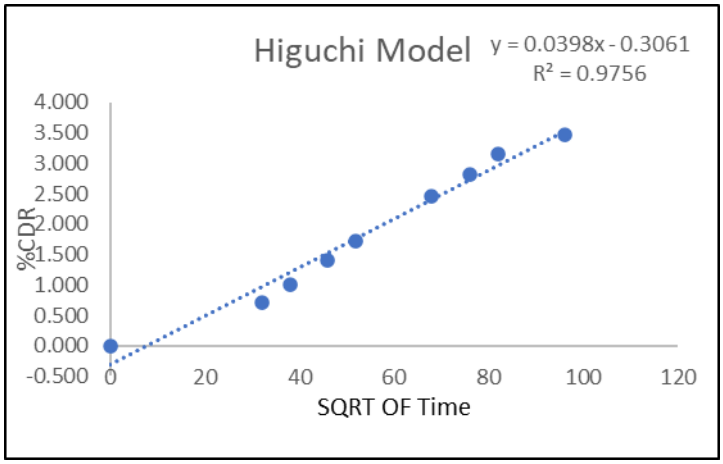


**Figure 5** Higuchi Model of F2

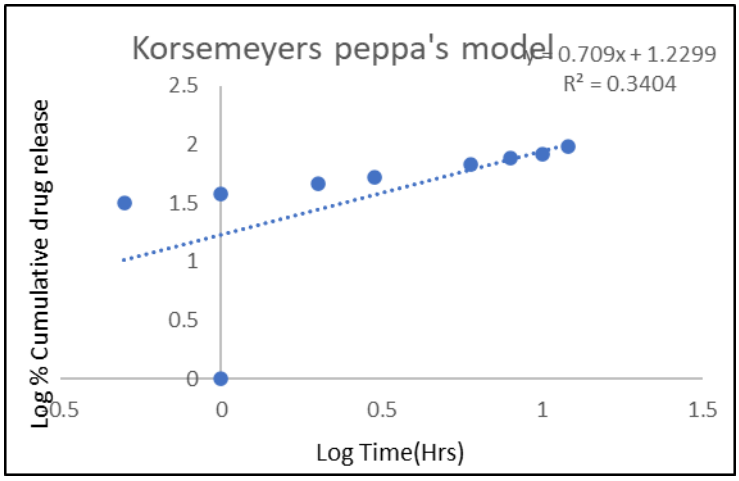


**Figure 6** Korsemeyers peppas's Model of F2

## 4. Discussion

The API is freely soluble in acetone. Preformulation studies, including organoleptic characteristics, were performed. Its spectrum was observed at 390 nm using UV spectroscopy.

Microspheres were prepared by the solvent evaporation method. In the formulation of the microspheres, In the detailing of the microspheres, the angle of repose was watched to be in the extend of 20-25°, showing great stream properties For Carr's index, it was observed that the microspheres exhibited good flow, with a Hausner's ratio of < 1.23, concluding good flow properties.

### 4.1. Evaluation of Microspheres

Production yield: Various polymers were used in the preparation of microspheres. The production yield for different Formulations was found to be in the range of 69 to 80%.

Entrapment efficiency: Polymers positively affected the entrapment efficiency of the microspheres. Formulation 2 had a higher entrapment efficiency 94% due to the presence of sodium alginate.

Particle size: The particle size for different microsphere formulations ranged from 122 to 169 µm.

Swelling Index: The swelling capacity of the developed microspheres was determined in gastric fluid (pH 1.2). The swelling list of the microspheres was found to be between 85 and 92%.

Drug release kinetics and in vitro dissolution investigations: Using various polymers, in vitro dissolution investigations were carried out for all formulations (F1-F4). In comparison to the other features, Formulation F2 appeared to have a 90% moderate discharge.

For Formulation F2, drug release kinetics were performed. t indicated drug release by diffusion and was in accordance with first-order kinetics($R^2$=0.887) and the Higuchi model($R^2$=0.9756). Anomalous diffusion was indicated by the Korsmeyer-Peppas model with an exponent (n) of 0.70.

## 5. Conclusion

The study successfully developed and evaluated microspheres using various polymers. The preformulation studies confirmed the API's solubility and appropriate organoleptic characteristics. Microspheres prepared by the solvent evaporation method exhibited good flow properties, with a production yield ranging from 69% to 80% and a particle size range of 122-169 µm. The use of sodium alginate in Formulation 2 enhanced the entrapment efficiency, resulting in a higher drug loading capacity. Swelling index studies indicated that the microspheres had significant swelling capacity in gastric fluid. In vitro dissolution studies showed that Formulation F2 achieved the highest drug release (90%) among all formulations. The release kinetics for Formulation F2 followed first-order kinetics ($R^2$=0.887) and the Higuchi model ($R^2$=0.9756) with the Korsmeyer-Peppas model (n=0.70) suggesting anomalous diffusion, indicating that the drug release occurred through a combination of diffusion and erosion mechanisms.

## Compliance with ethical standards

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### *Disclosure of conflict of interest*

All the authors declare no conflict of interest.

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