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# Formulation and In-Vitro Evaluation of Repaglinide

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## ABSTRACT

**The present study aimed to develop and evaluate mucoadhesive microspheres of Repaglinide to achieve sustained drug release and reduce dosing frequency in the management of type-II diabetes mellitus. Microspheres were prepared using Acacia nilotica and sodium alginate as mucoadhesive polymers by ionic gelation using calcium chloride as a crosslinking agent. Eight formulations (F1–F8) were developed by varying polymer ratios, keeping the drug content constant. Preformulation studies including solubility, melting point, FTIR, and DSC confirmed the identity and compatibility of the drug with excipients. Prepared microspheres were evaluated for particle size, percentage yield, swelling index, drug content, micromeritic properties, and in-vitro drug release. Particle size increased with increasing polymer concentration, while drug content and yield varied according to polymer composition. FTIR and DSC analyses revealed no interaction between Repaglinide and formulation excipients. In-vitro release studies conducted in 0.1N HCl (pH 1.2) demonstrated sustained drug release over 12 hours. Formulation F? (as per thesis conclusion) showed optimal release behavior and micromeritic properties. Stability studies indicated no significant changes in appearance, drug content, or release profile after 3 months. The study concluded that Acacia–alginate mucoadhesive microspheres provide a promising sustained-release system for Repaglinide.**

**Keywords: Repaglinide; Mucoadhesive microspheres; Sodium alginate; Acacia nilotica; Ionic gelation; Sustained release; Type-II diabetes.**

## INTRODUCTION

### Microspheres and Their Importance

Microspheres are small spherical particles ranging from 1–1000 µm in diameter, prepared using natural or synthetic materials such as polymers, glass, or ceramics. Their structural versatility, biocompatibility, and ability to incorporate a wide variety of drugs make them highly valuable in pharmaceutical technology. Microspheres offer several benefits including enhanced stability of labile drugs, improved bioavailability, sustained and controlled drug release, reduced dosing frequency, and minimized side effects. Because they distribute uniformly in the gastrointestinal tract and avoid dose dumping, microspheres are preferred over single-unit dosage forms for controlled drug delivery.

### Types of Microspheres

A variety of microsphere systems have been developed to meet different therapeutic needs. Bioadhesive microspheres adhere to mucosal surfaces such as the gastrointestinal, nasal, buccal, and ocular mucosa, thereby prolonging residence time and promoting sustained drug absorption. Magnetic microspheres utilize an external magnetic field to localize the carrier at specific sites in the body, offering targeted delivery of chemotherapeutics and peptides. Floating microspheres, with their low density, remain buoyant in gastric fluid and extend gastric residence time, making them useful for drugs primarily absorbed in the stomach. Radioactive microspheres are designed to deliver site-specific radiation for cancer therapy. Polymeric microspheres, which may be biodegradable or synthetic, are widely used for controlled release due to their safety, stability, and predictable release characteristics.

**Advantages and Limitations of Microsphere Systems**
Microspheres offer numerous advantages including continuous and prolonged drug action, improved solubility of poorly soluble drugs, protection of drugs from enzymatic or photolytic degradation, minimized dosing frequency, enhanced patient compliance, and reduced gastrointestinal irritation. However, certain limitations exist. Manufacturing and processing costs can be high, reproducibility may be challenging, and polymer degradation products may cause concerns depending on environmental or physiological conditions. Additionally, formulation stability can be affected by variables such as pH, temperature, and solvent evaporation during preparation.

**Techniques Used for the Preparation of Microspheres**
Several formulation techniques are commonly used depending on the nature of the drug and polymer. These include solvent evaporation, single and double-emulsion methods, phase separation–coacervation, spray drying, solvent extraction, and quasi-emulsion solvent diffusion. Each method influences particle size, encapsulation efficiency, morphology, and drug-release behavior. Among these, ionotropic gelation is particularly suitable for natural polymers such as sodium alginate, as it does not require organic solvents or harsh processing conditions.

**Need for Controlled and Mucoadhesive Drug Delivery**
Although oral administration is the most convenient route for drug delivery, many drugs suffer from low bioavailability, short half-life, and rapid clearance from the gastrointestinal tract. Controlled-release and gastro-retentive systems such as mucoadhesive microspheres are designed to overcome these challenges. By adhering to the mucosal lining of the stomach or upper intestine, these systems prolong residence time, maintain a constant drug concentration at the absorption site, and improve overall therapeutic efficacy. This is especially useful for drugs absorbed primarily in the upper gastrointestinal tract or requiring sustained plasma levels for optimal action.

**Repaglinide and Its Limitations**
Repaglinide is an oral hypoglycemic agent belonging to the meglitinide class and acts by stimulating insulin secretion through inhibition of ATP-dependent potassium channels in pancreatic β-cells. Despite its effectiveness, Repaglinide has a short biological half-life of about one hour, low bioavailability (approximately 63%), and requires frequent administration before meals. These pharmacokinetic limitations result in fluctuating blood glucose levels and reduced patient adherence, indicating the need for a sustained-release formulation that can provide prolonged therapeutic action with fewer daily doses.

**Rationale for Polymer Selection**
Sodium alginate is a natural, biocompatible, and biodegradable polymer composed of β-D-mannuronic and α-L-guluronic acid residues. It has the unique ability to undergo gelation in the presence of calcium ions due to the formation of crosslinked networks through the “egg-box” model. This property makes it an excellent candidate for microsphere formation using ionic gelation. Acacia nilotica, a natural gum composed of arabinose, galactose, and rhamnose units, possesses good emulsifying, stabilizing, film-forming, and bioadhesive characteristics. Its compatibility with alginate and its ability to prolong drug release make it suitable for developing mucoadhesive sustained-release microspheres.

**Aim of the Present Study**
The present work focuses on the formulation and evaluation of Repaglinide-loaded mucoadhesive microspheres using sodium alginate and Acacia nilotica through ionotropic gelation. The study includes preformulation analysis, compatibility testing using FTIR and DSC, formulation development, evaluation of micromeritic properties, particle size determination, drug content analysis, swelling studies, in-vitro drug-release profiling, kinetic modeling, and stability assessment. The ultimate objective is to develop a sustained-release mucoadhesive microsphere system capable of improving the therapeutic performance of Repaglinide in the management of type-II diabetes mellitus.

## MATERIALS AND METHODS

**Materials**
Repaglinide was procured from Biocon Ltd., while sodium alginate and calcium chloride were obtained from SDFCL Fine Chem Ltd. Acacia nilotica gum was supplied by Loba Chemie Ltd., and all these materials were used as received without any further purification. The study also involved the use of various analytical and processing instruments, including a Lab India dissolution test apparatus, a Systronics 117 UV–visible spectrophotometer, a Shimadzu AX200 digital analytical balance, a pH meter from Optics Ltd., an FTIR spectrophotometer from Sipra Labs, a magnetic stirrer manufactured by Rolex Ltd., differential scanning calorimetry equipment from Poornayu Labs, an optical microscope from Rolex Ltd., a hot air oven from Shital Scientific Industries, and a tapped density tester from Electro Labs. All chemicals, reagents, and solvents used throughout the study were of analytical grade and suitable for pharmaceutical research.

## METHODOLOGY

**Preformulation Studies**

**λmax Study:**

A total 10 mg drug was weighed in a volumetric flask dissolved in 10ml phosphate buffer. This was filled into 10ml calibrated flasks along with sample extraction, a 1ml solution followed by subsequently dilution by 100 ml phosphate buffer to acquire a concentration of 10µg /ml. A wavelength range of 200-400nm was studied using double-beam UV-visible spectrophotometer

**Solubility studies:**

The pure drug (repaglinide) was dissolved in different solvents to check their solubility until it formed a precipitate and was recorded. The solvents used are water, methanol, ethanol and dimethyl formamide.

**Melting Point:**

The melting point of repaglinide was analysed using the open capillary method with Thiel's tube. A small quantity of repaglinide was placed in a thin -walled capillary tube that was 10-15nm long and had an inside diameter of approximately 1nm, with one end closed.

**FT-IR spectroscopy**

This study is carried out to find the compatibility between the drug and the various excipients, which will be used in the formulation of a dosage form.

**Procedure:**

The Attenuated total reflection-Fourier transform infrared spectrometry (ATR-FTIR) Infrared spectra of all the samples were recorded in Bruker ATR alpha kept at an ambient temperature of 25.0 ± 0.5oC. The analytical procedure was simple and did not need any special sample preparation. Few mg of sample was placed on the Zinc solenoid crystal plate, Anvil was rotate to fix the sample and the spectra were recorded by scanning the samples in region of 4000-400 cm-1 to determine various functional groups.

**Differential Scanning Calorimetry**

Differential Scanning Calorimetry (DSC) is a thermos analytical technique in which the difference in the amount of heat required to increase the temperature of a sample and reference material are measured as a function of temperature. Both the sample and reference are maintained at nearly the same temperature throughout the experiment.

**Procedure**

**DSC (Shimadzu 60 series)** experiments were carried out in order to characterize the physical state of the drugs. Samples of formulation were placed in aluminium pans and thematically sealed. The heating rate was 10°C per minute using nitrogen as the purge gas. The sample will be run from ambient temperature up to 400oC depending on the melting point of the given compound.

**Formulation Studies**

The microspheres containing Repaglinide were formulated utilizing inotropic gelation system. The measured amount of Acacia nilotica gum and sodium alginate was measured. The taken ingredients were stirred using distilled water with the help of magnetic stirrer for 1hour and required quantity of Repaglinide was measured and stirred well for required time. The resultant mixture was pushed out drop wise with the help of syringe and needle inti 50ml of calcium chloride solution at 50rpm. After 60 min prepared microspheres were washed with distilled water and dried at 50ºC for 6hours the prepared microspheres are stored in a dessicators36

**Table 1: List of formulations prepared for microspheres.**

| Formulations | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 |
|---|---|---|---|---|---|---|---|---|
| Repaglinide(mg) | 16 | 16 | 16 | 16 | 16 | 16 | 16 | 16 |
| Ac. Nilotica(mg) | 80 | 160 | 240 | 320 | 400 | 480 | 560 | 640 |
| Sodium alginate(mg) | 320 | 320 | 320 | 320 | 320 | 320 | 320 | 320 |
| Calcium chloride (%) | 1.6 | 1.6 | 1.6 | 1.6 | 1.6 | 1.6 | 1.6 | 1.6 |
| Water up to(ml) | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

**Bulk characteristics**

**Angle of repose:**

The prepared microspheres, when only gravity acts upon it, will tend to forma conical mount. One limitation exists, the angle to the horizontal cannot exceed a certain value and this is known as the angle of repose (0). 20 gm of beads were

allowed to flow freely through a funnel having orifice of diameter of 0.95cm, from a height of 10cm from the base. As the heap was formed a circular line was drawn around the heap of granules and diameter was measured with scale. Height of the heap was measured with the help of scale.

$$\text{Tan } Ø = h/r$$

**Carrs index :**

Flow ability of microspheres is evaluated by comparing the bulk density and repose (0) was calculated from the equation given below tapped density of a microspheres and the rate at which it packed down. The following formula were utilized for obtaining Cam's index and Hausner's ratio.

$$\text{Carr's index} = \frac{\text{tapped density} - \text{bulk density}}{\text{tapped density}} \times 100$$

**Table 2.: Relationship between % carr's index and flowability**

| Carr's Index | Flowability |
|---|---|
| 5-15 | Excellent |
| 12-16 | Good |
| 18-21 | Fair to passable |
| 23-35 | Poor |
| 33-38 | Very poor |
| >40 | Extremely poor |

**Hausner ratio:**

Hausner's ratio is another parameter to estimate microspheres flow characteristics. It is the ratio of tapped density to bulk density.

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

**Table 3.: Relationship between Hausner's Ratio and flowability**

| Hausner's Ratio | Flowability |
|---|---|
| Less than 1.25 | Good flow |
| Greater than 1.5 | Poor flow |
| Between 1.25-1.5 | The addition of glidant normally improves the flow |

**Evaluation of drug microspheres:**

**Particle size analysis:**

The particle size was determined by using an optical microscope under regular polarized light, and the mean microsphere size was calculated by measuring 100 particles with the help of a calibrated ocular micrometre. 1 mm of the stage micrometres scale is equal to 65 eyepiece division. Therefore 1 eyepiece division is equal to (1/65) x100 µm i.e. 1.53 µm. The microspheres were uniformly spread on a slide. The particle size of the microparticles was measured, along the longest axis and the shortest axis (cross-shaped measurement) Average of these two readings was given as the mean diameter of particles. The diameter of a minimum number of 100 microspheres in each batch was calculated.

**Percentage Yield of Microspheres**

The production yield of microspheres of each batch was calculated using the weight of the final product after drying concerning the initial total weight of the drug and polymers used for the preparation of microspheres, and the percentage yield was calculated using equation

$$\text{Percentage yield} = \frac{\text{practical yield}}{\text{theoretical yield}}$$

**Swelling index studies:**

The swelling behaviour of a dosage unit was measured by studying its weight gain. The swelling index of microspheres was determined by placing the microspheres in the basket of a dissolution apparatus (USP type, Rotating Basket) using 0.1N HCl as the dissolution medium at 37±0.5 °C. Every 30 min, up to 6 h, microspheres were withdrawn, blotted with tissue paper to remove the excess water and weighed using an electronic balance (BL-220H, Shimadzu, Japan). The experiment was performed in triplicate, every time. Swelling index was calculated by using the following.

$$\text{Swelling index} = \frac{\text{Wet wt.of microspheres} - \text{Dry wt.of microspheres}}{\text{Dry wt.of microspheres}}$$

**Drug content:**

From the given data it could be observed that again sodium alginate microspheres gave the highest drug content and percentage yield while those made from chitosan provided less drug content and percentage entrapment efficiency. Polymers based on drug content and % EE could be arranged in the following order: Sodium alginate guar gum chitosan. Thus, it was analysed drug content are directly proportional to each other. Calculated drug content have been mentioned.

**Drug Content (%)=Theoretical amount of drug in the sampleAmount of drug actually present in the sample×100**

**Dissolution drug release :**

A USP type II (paddle) dissolution apparatus was used to study the in vitro drug release of the microspheres. Accordingly, an amount of the microspheres equivalent to 10 mg of Repaglinide filled in a hard gelatine capsule (size 0) was placed in the dissolution medium containing 900 ml of 0.1 N HCl and 0.02% of Tween 80 maintained at 37±0.5°C with paddle rotating at 100 rpm. Samples of 10 ml were withdrawn at 0.5, 1, 2, 4, 6, 8, 10 and 12 h and filtered. An equal volume (10 ml) of the dissolution medium was replaced in the vessel after each withdrawal to maintain sink condition. Then, each of the sample solutions was analysed spectrophotometrically for the drug content at 290 nm and the percentage of drug release was calculated and plotted as a function of time

**Kinetics studies :**

**Zero-order kinetics**

The following formula can represent drug dissolution from pharmaceutical dosage forms that do not break down and release the drug gradually as long as the area stays constant and no equilibrium requirements are achieved

**.Qt=Qo+Kot**

**First order kinetics**

First-order release kinetics was examined by fitting the following equation into the release rate data.

**Log Qt = log Qo + Kt/2.303**

**Higuchi model**

Higuchi developed several theoretical models to study the release of drugs integrated into solid matrices or either low soluble or water-soluble semisolids. Mathematical formulas were developed for drug particles dispersed in a homogenous matrix serving as the diffusion media; the equation is

**Qt=KH · t1/2**

**Kosemeyer and Peppas Release model:**

The release rate data is fitted to the following equation for analysis of this model.

**F=Mt/M = K·tn**

**Stability studies:**

The stability of a drug has been defined as the capability of a specific formulation, in an explicit container, to persist within its chemical, physical, toxicological and therapeutic specifications. Stability testing aims to make available the proof regarding how the quality of a drug ingredient or dug final product differs with time under the effect of diverse environmental aspects such as humidity, temperature, light, and permits the suggested retest periods, storage conditions, and shelf life to be established. Temperature-dependent stability testing was performed on the optimized batch. Accelereted testing at temperature 40±2ºC and relative humdity 75%± 5% RH. The optimised formulation of the drug loaded Acacia-Sodium alginate microspheres was tested after 3 months of storage at room temperature.The stability test indicates no significant change in the appearance,drug content and dissolution microspheres.Therefore these studies demonstrate excellent stability results over the period of month .

## RESULTS AND DISCUSSION

**Result Of Pre-Formulation Studies**

**Determination of λmax**

The standard solution of repaglinide (10µg/ml) scanned in the range of 200nm to 400nm showed maximum absorbance at 243nm as shown below.

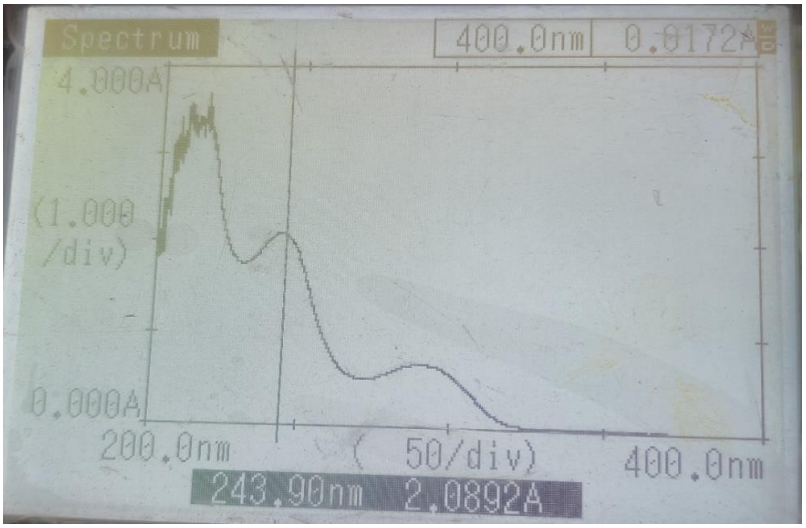


**Fig 1.Absorbance maxima of repaglinide**

**Oraganoleptic properties:**
The sample was observed to be white or almost white powder, which is typical for propranolol hydrochloride. The sample was odourless, aligning with its expected physical properties. Upon evaluation, the sample had a bitter taste, characteristic of repaglinide.

These physical and organoleptic properties support the identity and purity of the drug sample.

**Caliberation curve**
The calibration curve for repaglinide was constructed by plotting the concentration of repaglinide (in µg/ml) on the x-axis against the corresponding absorbance values on the y-axis. The relationship between concentration and absorbance follows Beer-Lambert's law, which shows a strong linear correlation. This linearity indicates that absorbance increases proportionally with concentration, and the curve can be used to determine the concentration of repaglinide in unknown samples based on their absorbance measurements.

The plotted points on the graph exhibit a straight line, confirming that repaglinide obeys Beer's law within the tested concentration range (0-30 µg/ml). This linear behaviour ensures the accuracy and reliability of the calibration curve for quantitative analysis. The value was found to be 0.9998, indicating an almost perfect linear fit. The equation of the line (slope) of the curve is 0.0194x + 0.0686, which further confirms the strong linear relationship between concentration and absorbance. This high regression value and the equation of the curve validate that the calibration curve is highly precise and can be confidently used for determining the concentrations of repaglinide in various samples. The Standard Calibration Curve of repaglinide is shown in Table 3.1.3.

**Table 4. Standard Curve Of Repaglinide**

| Concentration (µg/ml) | Absorbance |
|---|---|
| 2 | 0.0398 |
| 4 | 0.0796 |
| 6 | 0.1200 |
| 8 | 0.1601 |
| 10 | 0.1998 |

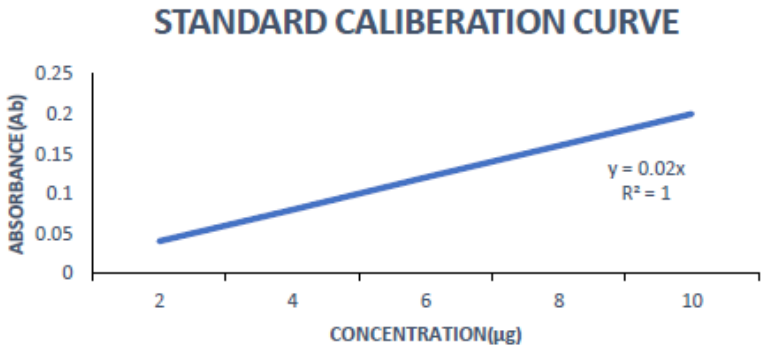


**Fig 2: Graphical representation of standard caliberation curve of repaglinide**

**Solubility studies:**
The solubility of DRUG was determined using the equilibrium solubility method. An excess amount of the drug was added to individual test tubes containing 10ml of various solvents, including distilled water, ethanol, methanol, dimethyl sulfoxide and phosphate-buffered saline. The test tubes were sealed and agitated on an orbital shaker at 25ºC ±2ºC for 24 hours to achieve equilibrium. The suspension was then centrifuged at 3000 rpm for 10 minutes, and the supernatant was carefully collected and filtered through a 0.45µm membrane filter. The concentration of DRUG in each filtrate was analysed using a UV-visible spectrophotometer at the λmax of 210 nm. All measurements were conducted in triplicate, and the mean solubility values were reported. This analysis provided essential data for optimizing the formulation parameters of the developed chrono modulated drug delivery system

**Table 5. Solubility of Repaglinide**

| SOLVENT | INFERENCE |
|---|---|
| Water | Insoluble |
| Ethanol | Soluble |
| Methanol | Soluble |
| Dimethyl formamide | Soluble |

**Melting Point:**
The melting point of Repaglinide was determined to be **130ºC ± 0.66ºC**, which is consistent with the standard values for this drug. This finding confirms the purity of the propranolol hydrochloride sample.

**Table 6 Melting point of Repaglinide**

| **MELTING POINT** | | |
|---|---|---|
| 131ºC | 130ºC | 131ºC |
| Average=130ºC ± 0.66ºC | | |

**FT-IR spectroscopy**
This study is carried out to find the compatibility between the drug and the various excipients, which will be used in the formulation of a dosage form. The characteristic peaks and streaks of the pure drug repaglinide is shown

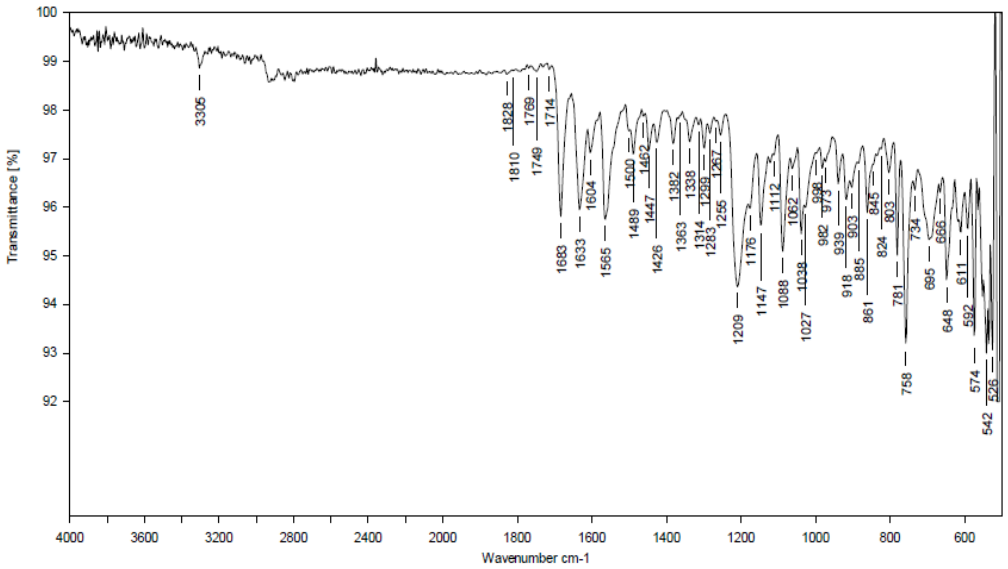


**Fig: 3 FT-IR Spectrum of pure drug (Repaglinide)**

The characteristic peaks and stretches obtained in the pure drug were found undisturbed in the drug excipient spectra indicating the compatibility of PNL with the excipients used. The FT-IR spectrum repaglinide is shown

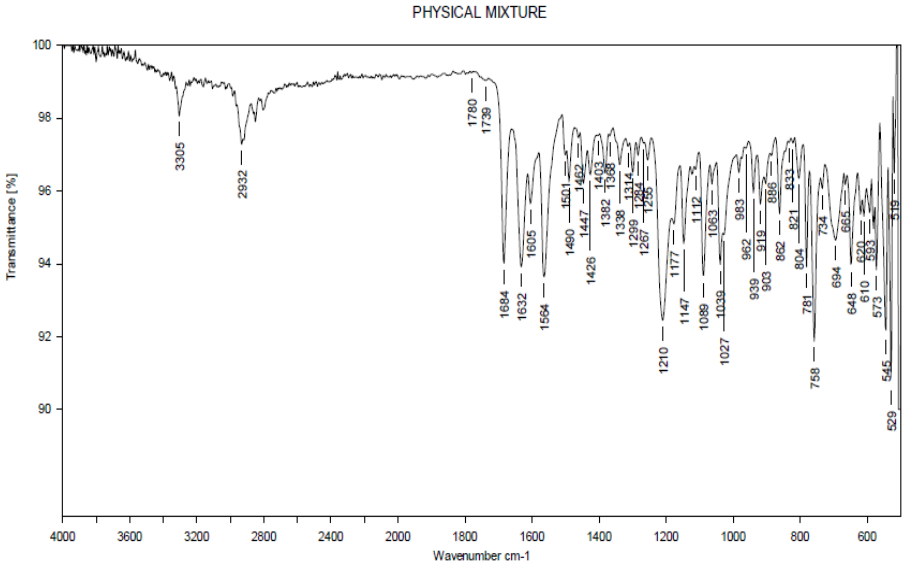


**Fig4 FT-IR Spectrum of Drug + Excipients**

**Table 7 Interpretation of FT-IR Spectrum of drug and excipients**

| FUNCTIONAL GROUP | FREQUENCY RANGE ($cm^{-1}$) | OBSERVE FREQENCY ($cm^{-1}$) | | STRECHING /BENDING |
|---|---|---|---|---|
| | | DRUG | DRUG + EXCIEPIENTS | |
| C=C aromatic | 1680-1690 | 1683 | 1684 | Stretching |
| C=O amide | 1630-1710 | 1633 | 1632 | Stretching |
| N-H amine | 3200-3500 | 3305 | 3305 | Stretching |
| O-H bending | 1210-1320 | 1314 | 1314 | Bending |
| C=OOH acid | 1690-1760 | 1749 | 1739 | Stretching |
| -CH=$CH_2$ aliphatic | 1200-1275 | 1267 | 1267 | Bending |
| R-O-R' ether | 1060-1150 | 1112 | 1112 | Bending |
| C-O ether | 1000-1260 | 1209 | 1209 | Stretching |

**DSC STUDIES**

The DSC theogram of Repaglinide exhibited an edothermal peak at 144.82 ºC corresponding to its recorded melting point.

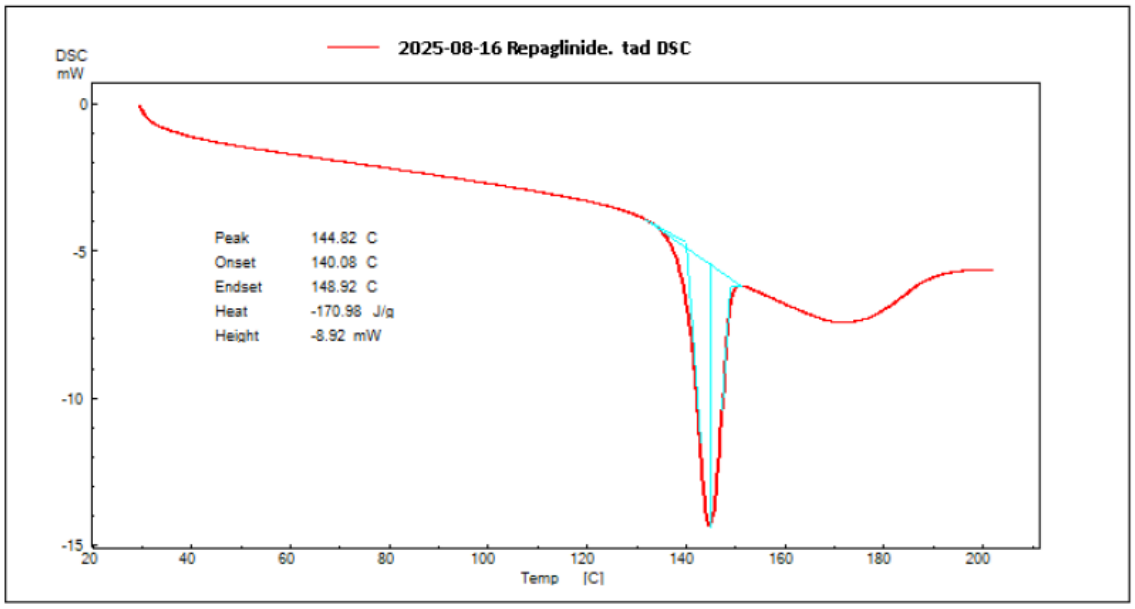


**Fig:5. DSC Theo gram of pure drug**

**Evaluation Of Formulation Studies**

**Angle of repose:**

The angle of repose for all formulations ranges from 19.52±0.08° to 27.19±0.52°, indicating that the formulations have well to excellent flow properties. Generally, angles below 30° are considered indicative of good flowability, which is essential for uniform mixing and ease of filling during manufacturing.

**Carr's index:**

Carr's index values are relatively low across all formulations, ranging from 1.43±0.08% to 7.03±0.01%, which further confirms the good flow properties. Lower Carr's index values (below 10%) suggest excellent compressibility and flowability, which is desirable for the manufacturing of dosage forms like microspheres.

**Hausner ratio:**

The Hausner's ratio values for all formulations ranged from 1.01±0.04 to 1.07±0.01, indicating minimal inter-particle friction and good flowability. Ratios closer to 1.0 are preferred, as they suggest less particle cohesion and good flow characteristics.

**Table 8: Values of pre formulation studies:**

| Formulation | Angle of repose | Bulk density | Tapped density | Carr's index | Hausner's ratio |
|---|---|---|---|---|---|
| F-1 | 23.51±0.04 | 0.515±0.01 | 0.546±0.02 | 5.67±0.08 | 1.06±0.01 |
| F-2 | 24.01±0.73 | 0.568±0.02 | 0.597±0.01 | 4.85±0.07 | 1.05±0.03 |
| F-3 | 19.52±0.08 | 0.502±0.03 | 0.538±0.03 | 6.69±0.03 | 1.07±0.01 |
| F-4 | 24.15±0.54 | 0.368±0.05 | 0.389±0.02 | 5.39±0.04 | 1.05±0.04 |
| F-5 | 26.28±0.14 | 0.658±0.04 | 0.678±0.04 | 2.94±0.09 | 1.03±0.03 |
| F-6 | 27.19±0.52 | 0.357±0.04 | 0.384±0.05 | 7.03±0.01 | 1.07±0.07 |
| F-7 | 25.87±0.62 | 0.582±0.02 | 0.598±0.02 | 2.67±0.05 | 1.02±0.05 |
| F-8 | 24.12±0.82 | 0.685±0.03 | 0.695±0.03 | 1.43±0.08 | 1.01±0.04 |

All values mentioned as mean ± SD

**Particle Size:**

The particle size of the prepared mucoadhesive microspheres ranged from 198.24±0.31µm to 275.12±0.34µm. Formulation F7- exhibited the largest particle size at 275.12±0.34 µm, while F-3 had the smallest particle size at 198.24±0.08 µm. Larger particle sizes, such as those seen in F-6 and F-7, may be attributed to higher concentrations of polymers or variations in the cross-linking process, which can result in the formation of larger microspheres. These differences in particle size can impact the drug release rate and mucoadhesion properties, with larger particles generally providing a slower release due to a reduced surface area-to-volume ratio.

Particle size plays a crucial role in determining both the mucoadhesion properties and the drug release profile. Larger particles, such as those in F-7, tend to have a slower drug release, making them suitable for sustained-release formulations. Smaller particles, like those in F-3, might offer faster drug release, which could be advantageous for immediate therapeutic effect.

**Table 9. Physiochemical Assets of prepared microspheres**

| FORMU-LATION | PARTICLE SIZE (µm) | PERCENTAGE YIELD | SWELLING INDEX | % CDR IN 12hrs |
|---|---|---|---|---|
| F1 | 204.61±0.14 | 89.98±2.18 | 88.63±2.13 | 89.18 ±1.94 |
| F2 | 205.03±0.23 | 91.43±1.25 | 93.76±1.05 | 90.56± 2.98 |
| F3 | 198.24±0.31 | 92.67±1.76 | 89.34±1.98 | 95.25± 2.54 |
| F4 | 248.15±0.28 | 88.78±2.65 | 87.87±2.03 | 97.02±2.31 |
| F5 | 240.15±0.16 | 90.58±1.98 | 94.76±1.78 | 89.82 ±3.03 |
| F6 | 264.64±0.56 | 95.56±2.76 | 88.56±1.54 | 87.25±1.46 |
| F7 | 275.12±0.34 | 93.76±2.03 | 89.45±1.58 | 85.64±4.24 |
| F8 | 236.43±0.26 | 89.72±1.87 | 87.35±1.88 | 89.43±1.98 |

**Percentage Yield:**

The percentage yield of the mucoadhesive microspheres ranged from 88.35±6.25% to 95.62±2.84%. Formulation F-6 achieved the highest yield at 95.56±2.76%, indicating an efficient microsphere preparation process with minimal material loss. High yield is crucial for industrial scalability and cost-effectiveness. In contrast, F-4 had the lowest yield at 88.78±2.65%, which could suggest inefficiencies in the manufacturing process, such as loss of material during filtration or incomplete cross-linking.

The percentage yield of the microspheres is an indicator of the efficiency of the manufacturing process. A higher yield, as seen in F-6, suggests that the preparation method was efficient and that the formulation process minimized material loss. This is critical for scaling up production and ensuring cost-effectiveness in a commercial setting.

**Swelling Index:**

The swelling index of the microspheres, which measures their ability to absorb water and swell, varied from 88.63±2.31% in F-1 to 95.47±2.05% in F-5. A higher swelling index, as observed in F-5, indicates that the microspheres can absorb more water, which may enhance their mucoadhesive properties and facilitate sustained drug release. Swelling is a critical factor in the performance of mucoadhesive drug delivery systems, as it can directly influence the drug release rate and the duration of adhesion to mucosal surfaces.

The swelling index directly influences the mucoadhesive properties and drug release kinetics of the microspheres. Formulations with a higher swelling index, such as F-5, demonstrate enhanced mucoadhesion and the potential for prolonged drug release. This is because swollen microspheres adhere better to mucosal surfaces and release the drug more slowly as they gradually decompose.

**Cumulative Drug Release In 12 Hours:**

The CDR after 12 hours ranged from 85.07±4.24% in F-1 to 97.14±2.31% in F-8. Formulations F-4 and F-3 demonstrated the highest drug release rates, suggesting that these microspheres are well-suited for applications requiring rapid or complete drug release within a specified time frame. This high release rate could be beneficial for conditions where immediate drug availability is critical. Conversely, formulations like F-4, may be more suitable for sustained-release applications, where a gradual release over an extended period is preferred. Finally, the CDR over 12hours provides insight into the release profile of the microspheres. Formulations like F-3and F-4, which exhibit high CDR, are ideal for applications where rapid drug release is necessary. In contrast, formulations with lower CDR, such as F-4, might be better suited for conditions requiring sustained drug release over an extended period. Overall, the study demonstrates that by carefully adjusting the formulation parameters, it is possible to optimize the mucoadhesive microspheres for specific therapeutic needs balancing factors like particle size, yield, swelling, mucoadhesion, EC, and drug release profile.

## KINETICS GRAPHS

**GRAPHS FOR F1 FORMULATION:**

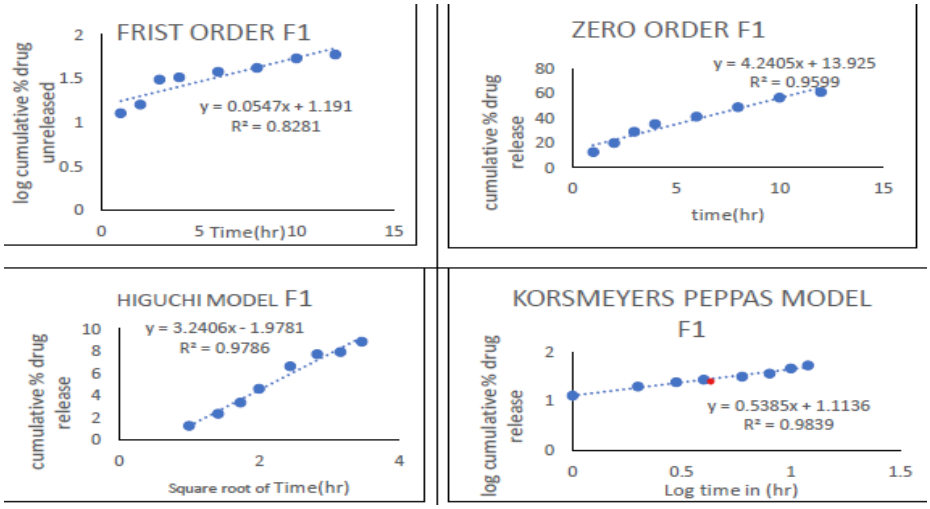


**Fig 6 Graphical representation of cumulative drug release profile of formulation**

**GRAPHS FOR F2 FORMULATION:**

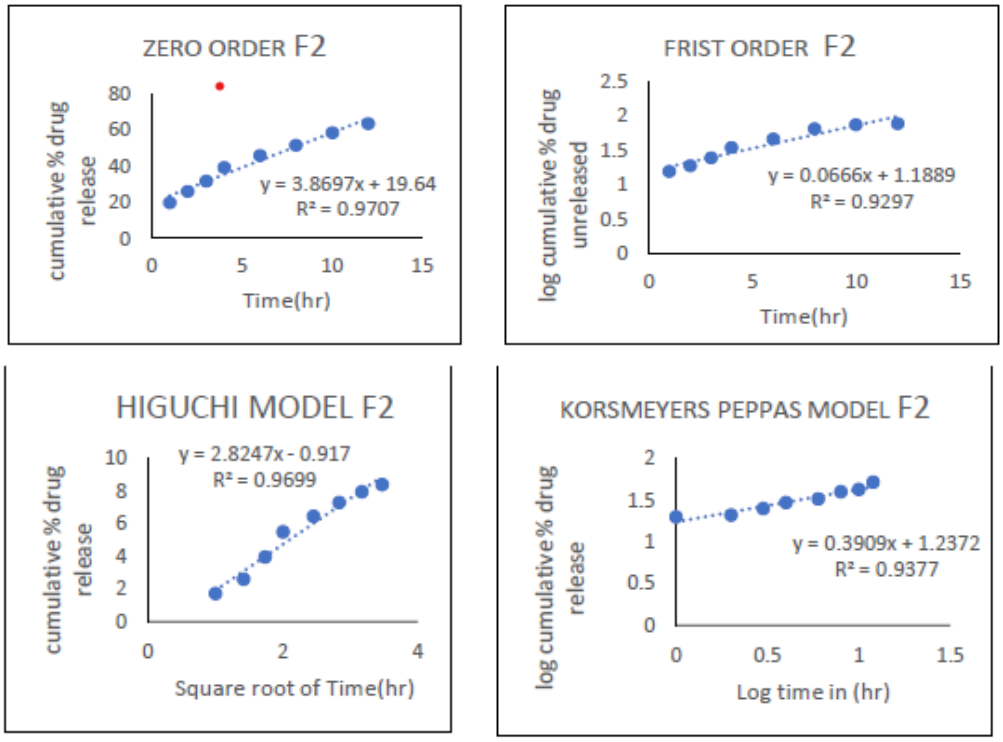


**Fig 7 Graphical representation of cumulative drug release profile of F2 formulation**

**GRAPHS OF F3 FORMULATION:**

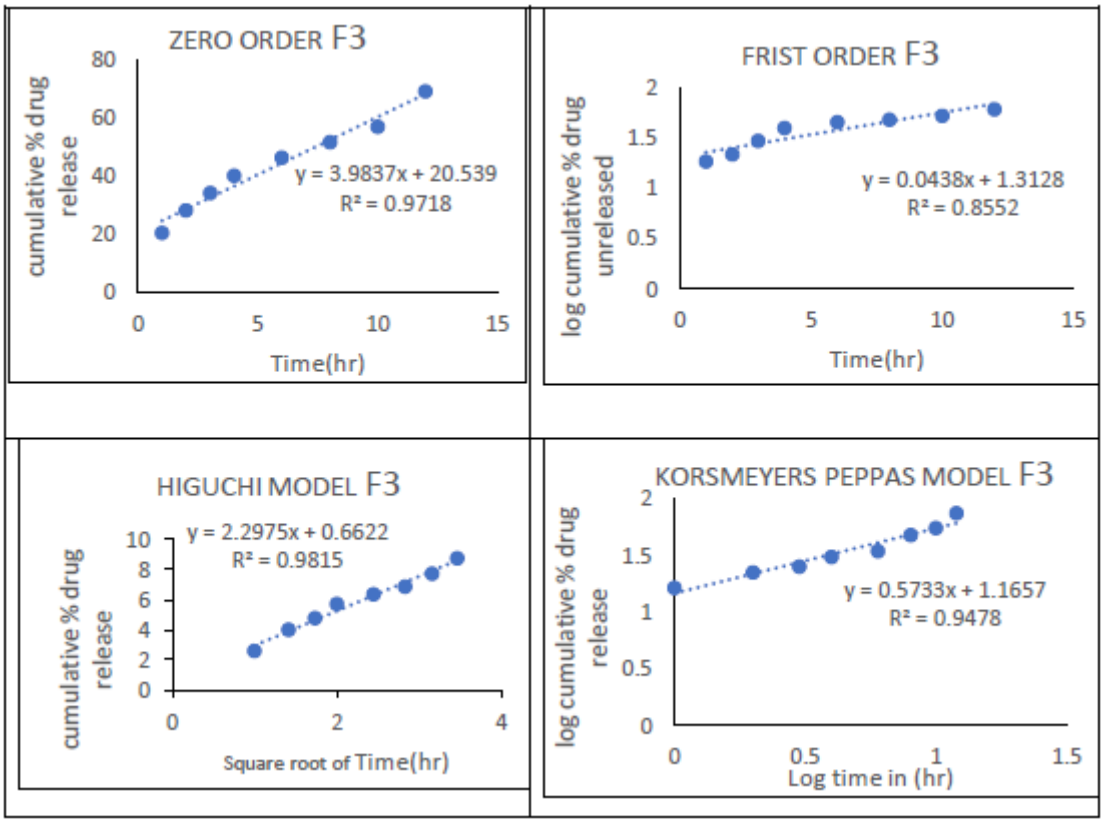


**Fig 8 Graphical representation of cumulative drug release profile of F3 formulation**

**GRAPHS OF F4 FORMULATION**:

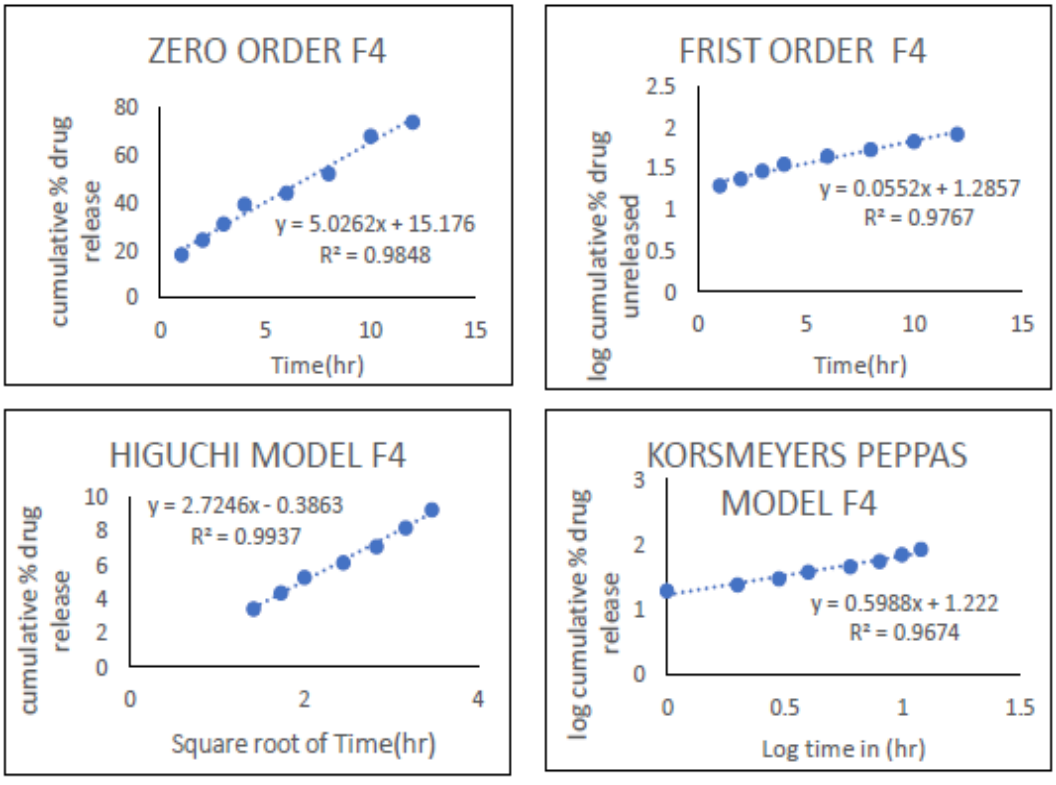


**Fig 9 Graphical representation of cumulative drug release profile of F4 formulation**

**GRAPHS OF F5 FORMULATION:**

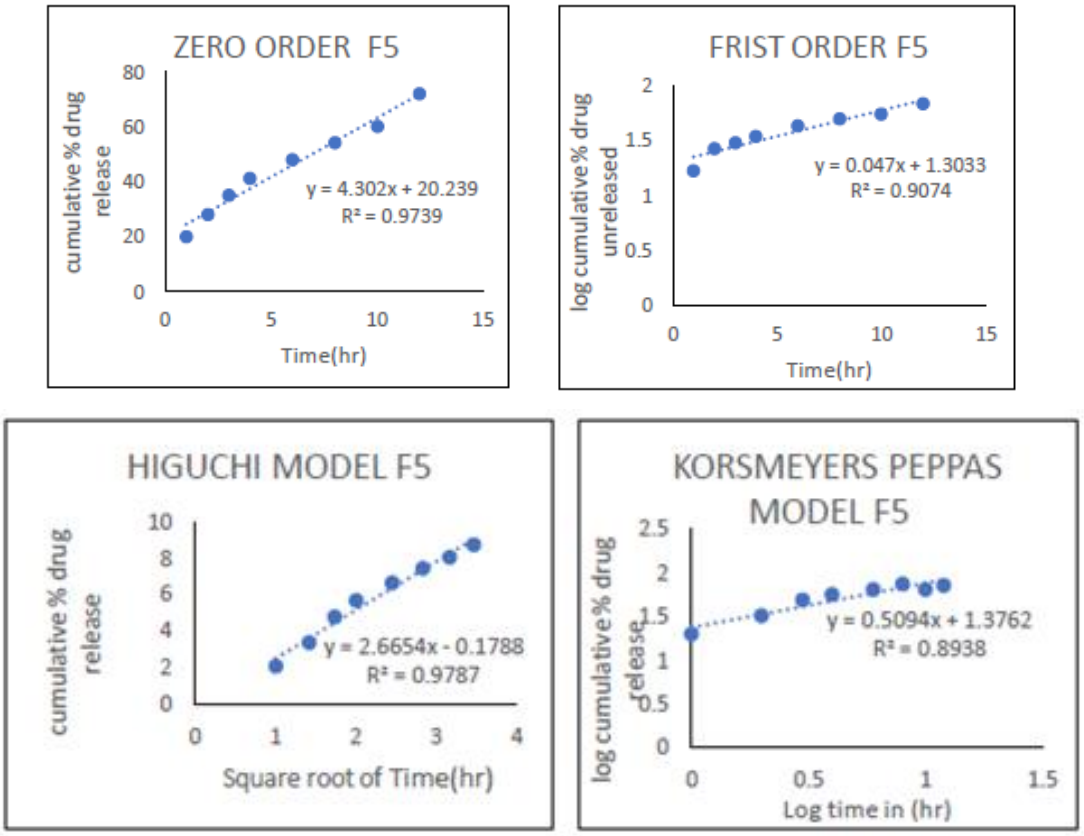


**Fig 10 Graphical representation of cumulative drug release profile of F5 formulation**

**GRAPHS OF F6 FORMULATION:**

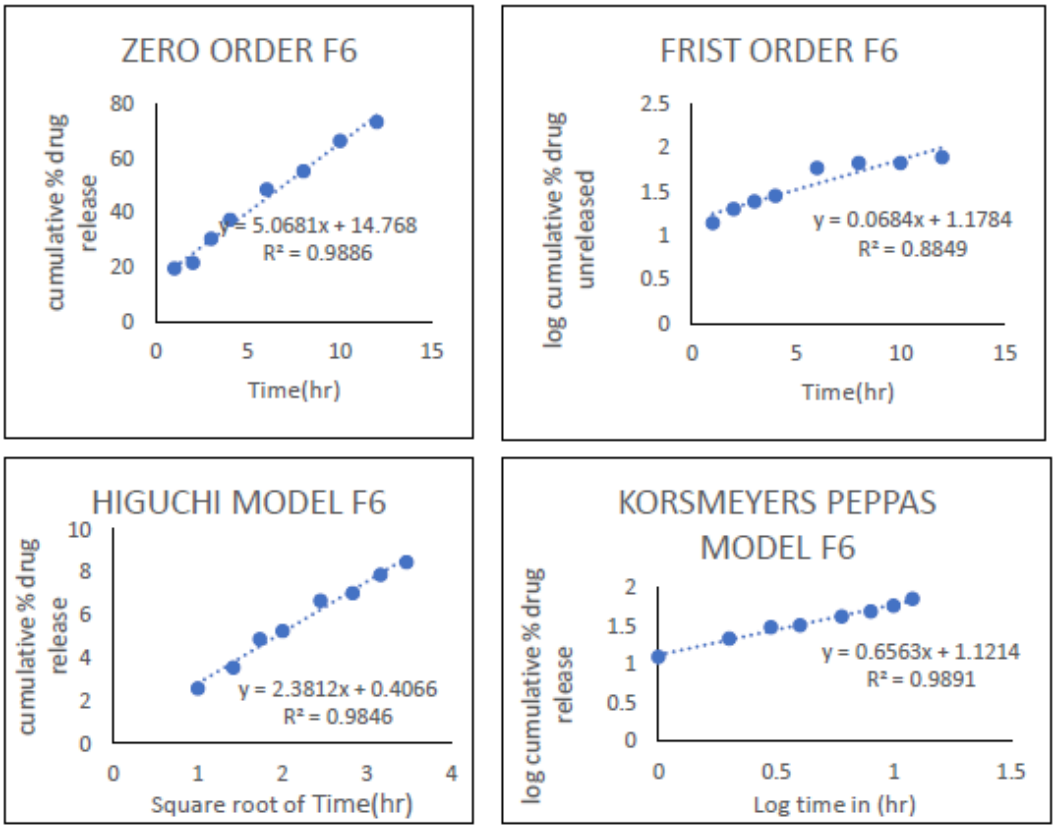


**Fig 11 Graphical representation of cumulative drug release profile of F6 formulation**

**GRAPHS OF F7 FORMULATION:**

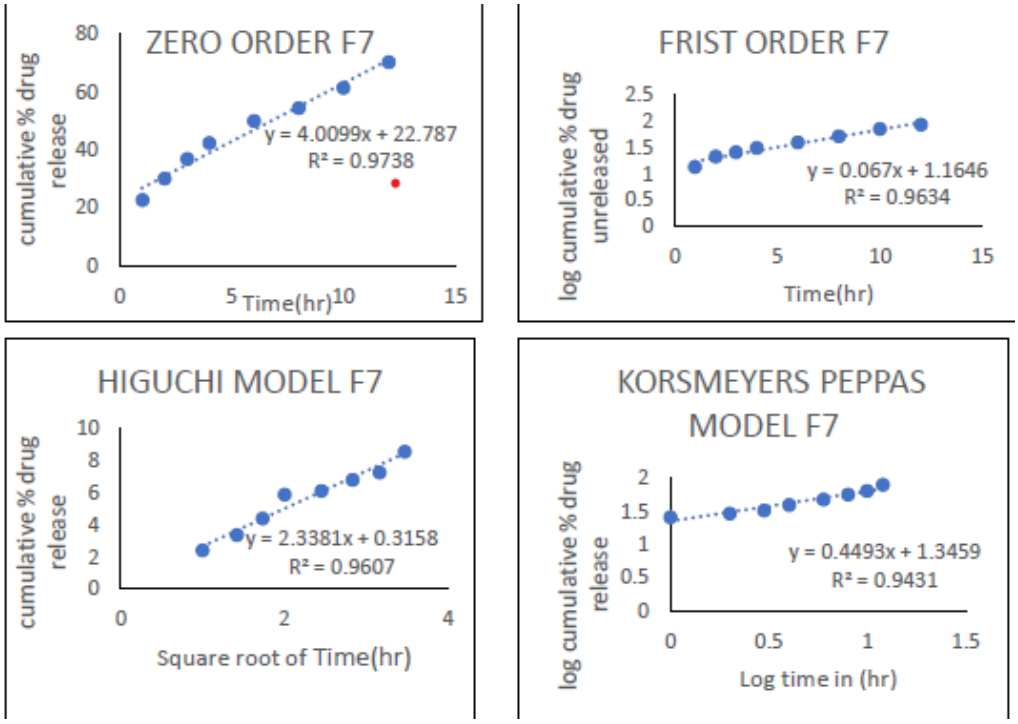


**Fig 12 Graphical representation of cumulative drug release profile of F7 formulation**

**GRAPHS OF F8 FORMULATION:**

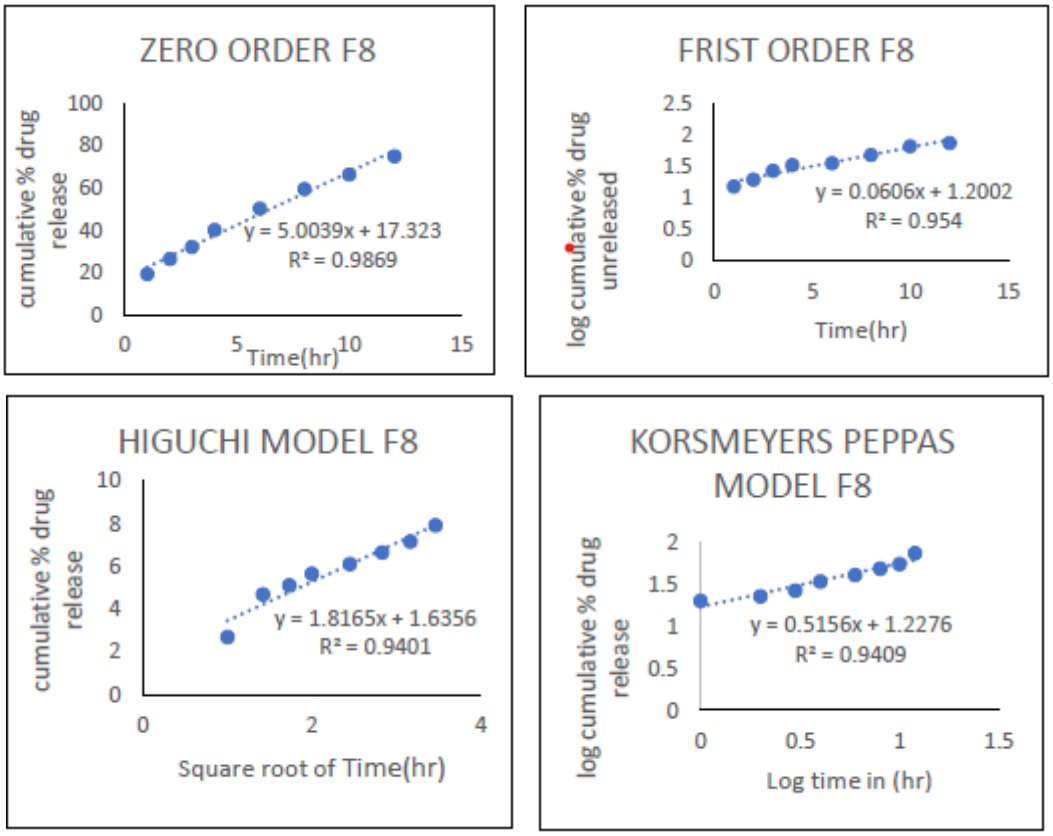


**Fig 13 Graphical representation of cumulative drug release profile of F8 formulation**

The majority of the formulations (F1, F3, F4, F5, F6, F8) exhibit Non-Fickian or Anomalous Transport, indicating that the drug release is controlled by a combination of both diffusion of the drug and the relaxation or erosion of the polymer matrix.

The drug release from the F1 to F8 formulations is best described by the Higuchi diffusion model overall. The analysis by the Korsmeyer-Peppas model further clarifies that the predominant release mechanism for most formulations is Non-Fickian (Anomalous Transport), where both diffusion and polymer-related processes (swelling/erosion) contribute to the drug release kinetics. Formulations F2 and F7 show a mechanism closer to purely Fickian diffusion. The highest R2 values for the Zero Order model in F7 and F8 suggest these formulations are the most successful at achieving a constant-rate, sustained release profile.

**Table 10 Pharmacokinetics data from F1 to F8 formulations**

| FORMUL-ATION | ZERO ORDER | | FRIST ORDER | | HIGUCHI MODEL | | KOSMEYERS PEPPAS MODEL | |
|---|---|---|---|---|---|---|---|---|
| | SLOPE | $R^2$ | SLOPE | $R^2$ | SLOPE | $R^2$ | Diffusion coefficient | Type of Diffusion |
| F1 | 4.2405 | 0.9599 | 0.0547 | 0.8281 | 3.2406 | 0.9786 | 0.5385 | Non-Fickian |
| F2 | 3.8697 | 0.9707 | 0.0666 | 0.9271 | 2.8247 | 0.9699 | 0.3909 | Fickian |
| F3 | 3.9837 | 0.9718 | 0.0438 | 0.8552 | 2.2975 | 0.9815 | 0.5733 | Non-Fickian |
| F4 | 4.0099 | 0.9848 | 0.0552 | 0.9767 | 2.7246 | 0.9937 | 0.5988 | Non-Fickian |
| F5 | 4.302 | 0.9739 | 0.047 | 0.9074 | 2.6654 | 0.9787 | 0.5094 | Non-Fickian |
| F6 | 5.0681 | 0.9886 | 0.0684 | 0.8849 | 2.3812 | 0.9846 | 0.6563 | Non-Fickian |
| F7 | 5.0262 | 0.9738 | 0.067 | 0.9634 | 2.3381 | 0.9607 | 0.4493 | Fickian |
| F8 | 5.0039 | 0.9869 | 0.0606 | 0.954 | 1.8165 | 0.9401 | 0.5156 | Non-fickian |

## CONCLUSION

In conclusion, the study successfully developed and optimized Repaglinide-loaded sodium alginate and acacia microspheres using the ionotropic gelation method, achieving an efficient controlled drug delivery system. The purity and calibration studies confirmed the integrity and quantitative reliability of Repaglinide, while FTIR analysis demonstrated the absence of any drug–excipient interactions, ensuring formulation compatibility. DSC analysis further validated the thermal stability of the drug with its characteristic melting peak. The microspheres exhibited excellent micrometric properties, including optimal flowability, compressibility, and density parameters, indicating their suitability for large-scale pharmaceutical processing. Among the nine formulations developed, variations in particle size, yield, and swelling index influenced drug release performance. The high percentage yield (up to 95.62%) and favorable swelling behavior confirmed the efficiency of the formulation process. Cumulative drug release studies over 12 hours demonstrated that the formulations could be tailored for either rapid or sustained release, depending on the therapeutic requirement. The release kinetics analysis revealed that most formulations followed the Higuchi model, confirming diffusion-controlled release through a polymeric matrix, while some exhibited non-Fickian mechanisms due to matrix swelling and erosion.

Overall, the optimized microspheres provide a promising platform for the sustained and controlled release of Repaglinide, potentially enhancing patient compliance and therapeutic efficacy in diabetes management. The study's findings highlight the importance of formulation parameters in achieving targeted and efficient drug delivery outcomes.

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