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FORMULATION AND *IN-VITRO* CHARACTERIZATION OF METFORMIN MICROSPHERE FOR ENHANCED DRUG DELIVERY *VIA* SPRAY DRYING IN TYPE 2 DIABETES MANAGEMENT

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Keywords:

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ABSTRACT: This study focuses on developing and characterizing metformin microspheres using spray drying with hydroxypropyl methylcellulose (HPMC) as a polymer, aiming to enhance gastrointestinal drug delivery, reduce gastric irritation, and lower dosage requirements for type 2 diabetes management. Metformin hydrochloride and HPMC concentrations are varied to generate microspheres with1 to1000µm diameter. These biodegradable polymers were selected because of their efficacy and compatibility with drugs. The thermal analysis and compatibility of the excipients used in microsphere tablet compression are assessed using differential scanning calorimetry and Fourier transform infrared spectroscopy. *In-vitro* drug release behaviour is evaluated over an 8-hour period using a Copley dissolution tester in 0.1 N HCl at 37 ± 0.5°C, with drug release monitored by UV spectroscopy at 228 nm. Results show that metformin release from microspheres is sustained for the first 6 hours, with a decrease noted at the 8-hour mark. The Higuchi model suggested diffusion-controlled release, while the Korsmeyer-Peppas model indicated non-Fickian diffusion. Some other drug release kinetic models, such as zero-order and first-order kinetic models are used to study the drug release mechanism.

INTRODUCTION: Diabetes mellitus is a chronic metabolic disorder resulting from insulin deficiency, characterized by hyperglycaemia, altered metabolism of carbohydrates, protein and lipids, and an increased risk of vascular complications. Millions of people have diabetes. Even children suffer from this disease [1].

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90% of all diabetic patients worldwide have type 2 diabetes mellitus, commonly known as adult-onset or noninsulin-dependent diabetes. It is a metabolic disorder characterized by insulin resistance in muscle, liver and adipose tissue, imbalances, abnormalities affecting multiple organ systems and ongoing decline in b-cell function resulting from the body's ineffective use of insulin.

Metformin, an oral biguanide commonly prescribed drug for T2DM, improves insulin sensitivity and reduces liver glucose production but has limitations in bioavailability and patient compliance [2]. Diabetes significantly contributes to stroke, heart attacks, kidney failure, and blindness, with a

102.9% increase in global cases, emphasizing the need for better treatment and prevention. Fasting plasma glucose levels range from 126-200 mg/dL in diabetics and 100-130 mg/dL in healthy individuals. Metformin's mechanism improves glycemic control without causing hypoglycemia, but its low bioavailability and GI side effects affect up to 25% of patients, with 5% being intolerant.

Despite its efficacy in improving glycaemia control and reducing cardiovascular risks, a notable concern associated with metformin administration is its potential to cause gastric irritation. This issue poses a challenge in ensuring optimal patient adherence and therapeutic outcomes. Metformin HCl, being a hydrophilic biguanide, exhibits poor bioavailability and solubility, which may contribute to its adverse effects on the gastrointestinal tract [3]. The gastric irritation associated with metformin intake often manifests as symptoms such as nausea, vomiting, and abdominal discomfort, leading to suboptimal patient compliance and, consequently, hindered glycemic control. The conventional administration of metformin, typically as an immediate-release tablet, results in a rapid release of the drug in the stomach, potentially exacerbating gastric irritation [4]. Hence, there is a critical need for innovative drug delivery strategies to mitigate these adverse effects while maintaining the therapeutic efficacy of metformin.

This research aims to reduce gastric irritation caused by metformin HCl by formulating microspheres with Hydroxypropyl Methylcellulose (HPMC) *via* spray drying. The encapsulated metformin offers controlled release, minimizing direct contact with the gastric mucosa and improving patient tolerability in Type 2 diabetes management [5]. The proximal small intestine is where metformin HCl is absorbed. It has an oral bioavailability of 50–60% and a half-life of 1.5–1.6 hours. The spray-dried formulation enhances drug availability at the absorption site, improving uptake and reducing gastrointestinal discomfort [6].

Spray drying is used to convert liquid metformin solutions into microspheres, offering advantages over solvent evaporation due to its one-step process, scalability, and minimal residual solvent [7]. In this method, metformin is sprayed into a heated air stream, where the solvent evaporates, leaving metformin in microsphere form **Fig. 1**. Benefits include producing uniform microspheres, ensuring consistent drug release and absorption, improving stability, enhancing drug loading, and extending shelf life with controlled release properties.

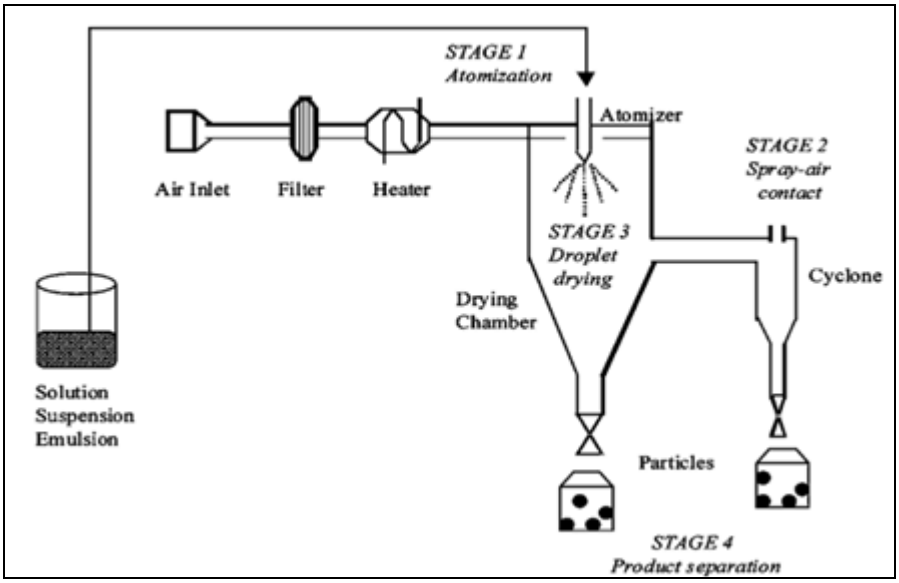

FIG. 1: SCHEMATIC DIAGRAM OF SPRAY DRYER; (ADAPTED FROM PATEL TEJAS *ET AL.*, 2012)

MATERIALS AND METHODS:

Materials: Metformin microsphere hydrochloride was provided by Shanghai Macklin Biochemical Technology Co., Ltd., while HPMC was sourced from Sigma (15mpa). Microcrystalline cellulose and polyvinyl pyrrolidone were also obtained from Shanghai Macklin, and polyethene glycol 8000 came from Across Organics. Magnesium stearate was supplied by the Faculty of Pharmacy, University of Malaya. All materials used were of

analytical grade. These materials were selected based on compatibility, functionality, and regulatory compliance, ensuring quality control and reproducibility in the formulation and characterization processes.

Preparation of the Metformin Microsphere Powder: Metformin HCl and HPMC were used to form metformin microspheres through spray drying. Different ratios of metformin to HPMC (1:0.5, 1:1, 1:1.5 wt/wt) were dissolved in distilled water and mixed using a magnetic stirrer at 300-500 RPM and 60°C. The mixtures were spray-dried with an inlet temperature of 160°C ± 20°C, outlet temperature of 80°C ± 20°C, 100% aspiration, and 70% pump capacity. The resulting microparticles were collected for use in tablet production.

Formulation of the Metformin Tablet: The tablet formulation process employed direct compression, where powdered metformin microspheres were combined with specific excipients to optimize the tablet's properties.

The formulation included 850 mg of metformin microspheres as the active ingredient, along with PEG 8000 as a plasticizer, PVP as a binder, magnesium stearate as a lubricant, and microcrystalline cellulose as a filler. Achieving uniform particle size through sieving was a key step, ensuring consistency in the tablet composition. This process streamlined production while enhancing the structural integrity and uniformity of the final tablets.

TABLE 1: METFORMIN HCL ORAL DISPERSIBLE TABLETS: FORMULATION AND DESIGN

Ingredients	Formulation 1 (1:0.5)	Formulation 2 (1:1)	Formulation 3 (1:1.5)
Metformin HCl	150mg	150mg	150mg
HPMC	75mg	150mg	225mg
PEG 8000	10mg	10mg	10mg
PVP	30mg	30mg	30mg
Mg. Stearate	10mg	10mg	10mg
Microcrystalline cellulose	575mg	500mg	425mg
Total	850mg	850mg	850mg

Pre-compression Evaluations:

Tapped Density: The maximum packing density of a granular or powdered material after tapping or vibration. It is calculated using a tap density volumeter and is the ratio of initial to tapped volume.

Tapped density = (weight of the powder formulation) / (tapped volume)

Bulk Density: The bulk density of a material, defined as its mass per unit volume, including both the solid and interparticle space, was determined using the weight-to-volume ratio of untapped powder [8].

Bulk density = M / (V°) or (weight of the powder formulation / (apparent volume of the powder)

Angle of Repose: The angle of repose measures the stability of a granular material pile, influenced by particle size and type. To assess this, the maximum angle between the microsphere pile surface and the horizontal plane was measured using a funnel.

$$\theta = \tan^{-1}(h/r)$$

Hausner's Ratio: The Hausner ratio assesses the flowability of powdered materials by comparing tapped and loose bulk densities. A ratio of 1.25–1.30 in Metformin HCl formulations focused indicates good flow, ensuring uniformity during tablet production.

Hausner's ratio = (tapped density) / (bulk density)

Carr's Compressibility Index: Carr's index measures a powder's compressibility, indicating how much volume it loses under pressure [9]. For metformin HCl microspheres, a Carr's index between 20% and 23% reflects good flow properties.

Carr's index = (tapped density-bulk density) / (tapped density) × 100

Compatibility Studies: Fourier Transform Infrared Spectroscopy (FTIR) and Differential Scanning Calorimetry (DSC) were used to assess the compatibility of metformin HCl with polymers and excipients. FTIR was performed using an IR spectrophotometer to analyze the physical and chemical interactions between the pure drug,

HPMC polymer, excipients, and microsphere formulations. Samples were examined in the attenuated total reflectance mode, scanning a range of 400–4000 cm^{-1} to evaluate chemical integrity and compatibility [10]. DSC analysis, conducted with a DSC6000 (Perkin Elmer), was employed to study thermodynamic properties and interactions between drugs and excipients by measuring phase transitions and conformational changes in the formulations [11].

Post-compression Evaluations:

Weight Variation: Twenty tablets from each formulation were randomly selected and individually weighed. The mean and standard deviation were calculated. For an 850 mg tablet, the individual mass should not deviate by more than ±5% from the average.

Hardness Test: The hardness of each Metformin HCl microsphere tablet is optimized to demonstrate strong mechanical strength for good handling. A Monsanto hardness tester is used to assess ten tablets per formulation, with means and standard deviations calculated.

Friability Test: The friability of twenty tablets was tested using a Roche Friabilator at 25 rpm for four minutes. Tablets were weighed before and after dedusting to calculate the percentage weight reduction. A friability of less than 1% was considered acceptable and mechanically stable according to USP and IP standards.

Thickness and Dimension: The thickness and diameter of all three formulations of Metformin Hydrochloride microspheres are to be evaluated and are expected to fall within standard acceptance criteria. This will demonstrate that the microsphere tablets have good dimensional consistency.

***In-vitro* Kinetic Studies and Kinetic Modelling of Drug Release Profile:** *In-vitro* dissolution studies for all tablet formulations were conducted using the USP Paddle method (instrument: Coplet Dissolution Tester DIS8000) at 50 rpm in 900 mL of 0.1N HCl at 37±0.5ºC over eight hours. Samples (5 mL) were taken at predetermined intervals (0, 1, 2, 3, 4.5, 6, and 8 hours) and analyzed spectrophotometrically at 228 nm. Fresh medium replaced the withdrawn samples. Kinetic models, including zero-order, first-order, Higuchi, and Korsmeyer-Peppas, were fitted to the drug release data, and the best-fit model was identified by comparing correlation coefficients [12].

Zero-order Kinetics: The following equation can be used to depict how the drug dissolves in dosage forms that release the drug slowly and do not disintegrate.

$$Qt = Q0+K0t$$

Where, Q0 is the initiating drug concentration in the solution, K0 is the zero-order release rate constant, and Qt is the quantity of drug dissolved in time t. Data Kt was used to investigate the kinetics of release.

First-order Kinetics: This model has been applied to explain how drugs get absorbed or released. The drug release, demonstrating first-order kinetics, can be represented using the subsequent formula.

$$LogC = logC0 - Kt/ (2.303)$$

Where, C0 is the total quantity of drug in the solution, C is the amount of drug released in time t, and K is the first-order release rate constant. The release kinetic data from the *in-vitro* drug release studies were shown as log% drug unreleased vs. time.

Higuchi Model: This model explains drug release from solid or semisolid matrix systems for both water-soluble and low-solubility compounds. The model is mathematically represented as

$$Qt = KH.\ t\ 1/2$$

Where, Qt is the drug released over time t, and KH is the Higuchi dissolution constant. Release kinetics are analyzed by plotting % CDR versus the square root of time using *in-vitro* drug release data.

Korsmeyer-Peppas Model: The model is used to describe drug release from polymeric systems, especially when the release mechanism is unclear or involves multiple phases. The model is expressed

$$(Mt)/M\infty = Kt\hat{}n$$

Where, K is the release rate constant, t is the release time, n is the release exponent, and $Mt/M\infty$ is the fraction of the drug released. To assess

release kinetics, *in-vitro* data are plotted as log% CDR vs. time, with the n-value indicating different release mechanisms.

RESULT AND DISCUSSION:

Pre-compression Evaluations: All three formulations demonstrated suitable bulk and tapped densities, good flowability, and acceptable compressibility. The Hausner's ratios and Carr's index values indicated favorable flow behavior and compressibility for all formulations. The angles of repose for all three formulations were within acceptable limits, confirming their good flow properties as shown in the **Table 2.** These characteristics make the formulations well-suited for further development and preparation of metformin microsphere tablet formulations.

TABLE 2: EVALUATIONS OF POWDER MIXTURES

Formulation	Bulk density (gm/ml)	Tapped density (gm/ml)	Hausner's ratio	Carr's index (%)	Angle of repose(⁰)
1	0.3950	0.4981	1.26	20.69	25.04
2	0.3672	0.4642	1.27	20.89	28.76
3	0.2495	0.3214	1.28	22.37	27.9

Drug Polymer Compatibility Study: For pure metformin HCl**,** Metformin HCl's FTIR spectra show distinctive peaks: around 3300 cm^{-1} for N-H stretching, 1600-1700 cm^-1. for C=O stretching, and 1500-1600cm^-1 for N-H bending. Peaks at 1000-1300cm^-1 indicate C-N stretching, confirming the drug's molecular identity. From the **Fig. 3**; indicate the Key peaks include 3367.37cm^{-1} for N-H stretching and 1621.92cm^-1. For C=O stretching and also C-N stretching at different regions between 1000-1300cm^-1 like 1059.32, 1079.94 and 1166.24cm^-1. Furthermore, the peaks at 1548.36cm^-1 could be assigned to N– H bending as indicate the amine group. In **Fig. 2**, the absence of unaccounted peaks and the presence of expected absorption bands confirm the purity of the metformin HCl sample.

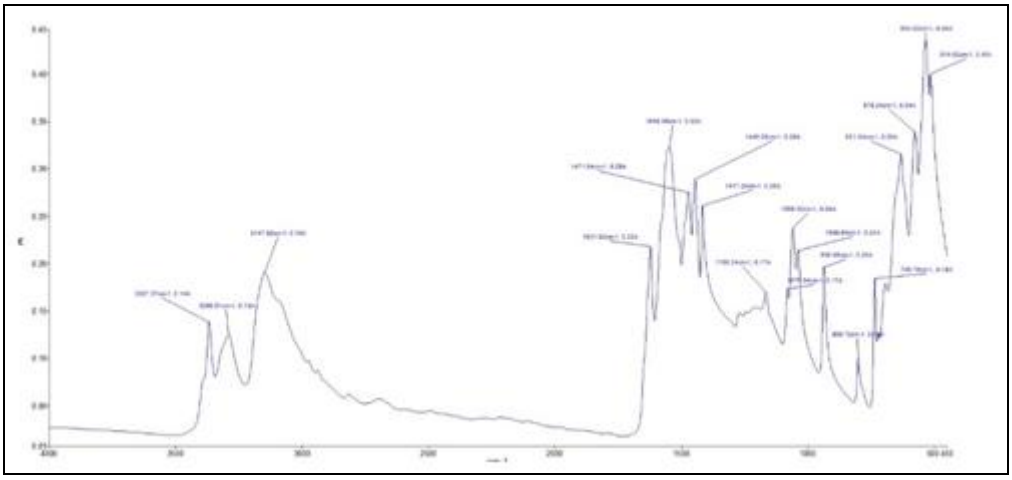

FIG. 2: FTIR SPECTRAFOR METFORMIN HCL (ABSORBANCE)

For Hydroxy propyl methyl cellulose (HPMC), the FTIR spectrum of Hydroxypropyl Methylcellulose (HPMC) shows key peaks corresponding to its chemical structure. From **Fig. 3**, the broad peak at 3437.03cm^-1 indicates O-H stretching vibrations, while the peak at 2899.07cm^-1 represents C-H bond stretching. The C-O stretching vibration is identified at 1050.66cm^-1. Other notable peaks include water bending vibrations at 1643.13cm^-1 and CH2 wagging at 1373.45cm^-1, confirming HPMC's functional groups and molecular structure. The FTIR analysis confirmed no chemical interactions between metformin HCl and HPMC, indicating compatibility through physical interactions like hydrogen bonding [8]. Formulation 1 showed a superimposed spectrum of the drug and polymer, while formulations 2 and 3 retained all characteristic metformin bands, indicating no significant changes or interactions with excipients [13]. Peaks for PEG (1100-1150 cm^-1, C-O stretching), PVP (1550-1650 cm^-1, N-H bending), microcrystalline cellulose (1050-1150 cm^-1, C-O

stretching; 2800-3000 cm^-1, C-H stretching), and magnesium stearate (400-600 cm^-1, Mg-O stretching) confirmed the presence of excipients, maintaining the drug's chemical integrity.

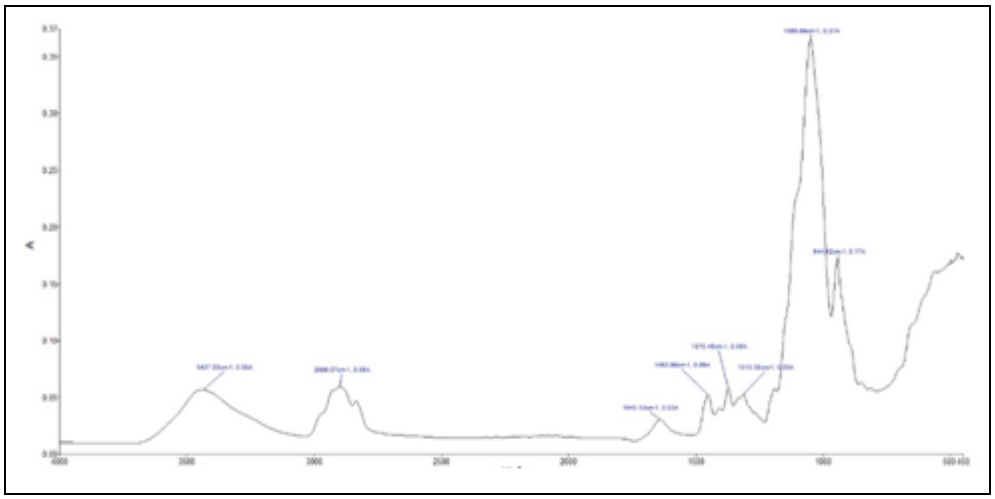

FIG. 3: FTIR SPECTRA FOR HPMC POLYMER (ABSORBANCE)

The FTIR analysis of optimized metformin microsphere formulation F1 showed no interaction between metformin, HPMC, and excipients (PEG, PVP, microcrystalline cellulose, and magnesium stearate **Fig. 4**. Metformin HCl was identified by peaks at 3367.82 cm^-1 (N-H stretching), 1623.36cm^-1 (C=O stretching), and while HPMC showed peaks at 3292.66cm^-1 (O-H stretching) [14] and 1057.52cm^-1 (C-O stretching). PEG at 1159.57cm^-1, PVP at 1565.98cm^-1 (N-H bending), for microcrystalline cellulose indication at 1034.65 cm^-1 (C-O stretching), 2916.22cm^-1(C-H stretching) and magnesium stearate at 582.79cm^-1 Mg-O stretching) respectively and some other peak indicating characteristic peak for drug, polymer and excipients compounds confirming compatibility.

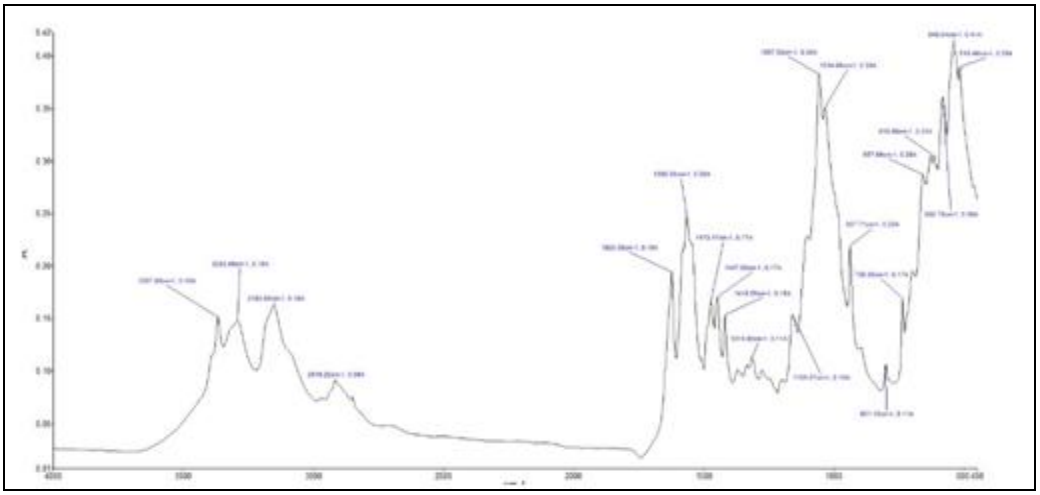

FIG. 4: FTIR SPECTRA FOR METFORMIN MICROSPHERE FORMULATION MIXTURE 1 (METFORMIN MICROSPHERE POWDER + EXCIPIENTS) ABSORBANCE

The FTIR spectrum of metformin microsphere formulation 2 confirmed the presence of key components: metformin HCl showed peaks at 3367.79cm^-1 (N-H stretching), 1623.44 cm^-1 (C=O stretching) **Fig. 5**. HPMC contributed peaks at 3292.66 cm^-1 (O-H stretching) and 1057.26cm^-1 (C-O stretching). PVP had a peak at1566.38 cm^-1 (N-H stretching), PEG showed C-O stretching between 1100–1160 cm^-1, microcrystalline cellulose had peaks in the 1000–1050 cm^-1 (C-O stretching), 2916.52 cm^-1 (C-H stretching). Then 582.3cm^-1(Mg-O stretching) for magnesium stearate, confirming the formulation composition in **Fig. 5.**

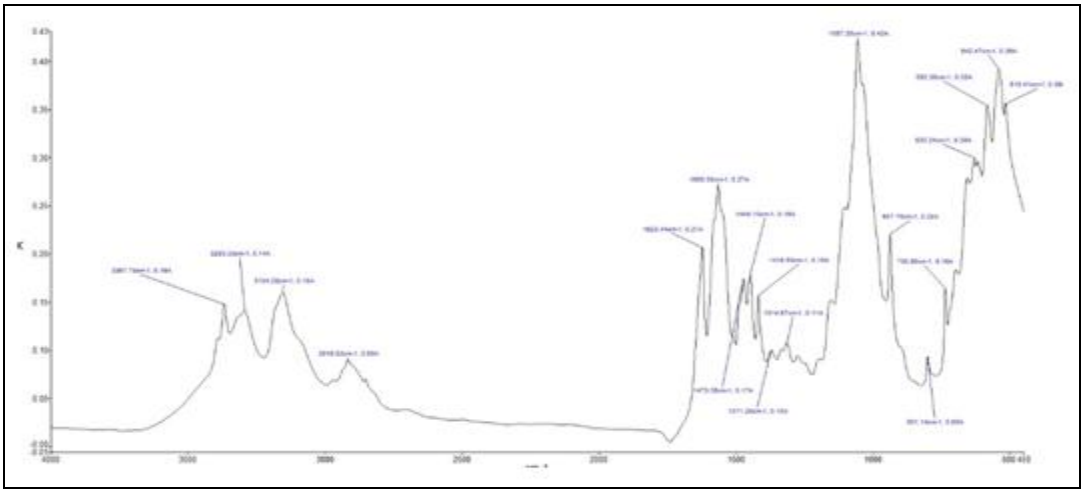

FIG. 5: FTIR FOR METFORMIN MICROSPHERE FORMULATION MIXTURE 2 (METFORMIN MICROSPHERE POWDER + EXCIPIENTS) TRANSMITTANCE

The FTIR spectrum of metformin microsphere tablet formulation mixture 3confirmed that key peaks for metformin HCl at 3367.96 cm^-1 (N-H stretching), 1623.54 cm^-1 (C=O stretching. HPMC contributed peaks at 3294.40 cm^-1 (O-H stretching) and 1057.12 cm^-1 (C-O stretching). [14]. PEG was identified by peaks at 1100-1200 cm^-1 (C-O stretching), PVP at 1565.74cm^-1 (N-H stretching), microcrystalline cellulose between 1000–1100 cm^-1 for (C-O stretching) and 2916.44 cm^-1(C-H stretching), and magnesium stearate at 2916.44 cm^-1 and 583.42cm^-1. No additional peaks were observed except characteristic peaks of ingredients, confirming the absence of other compounds in the formulation, as shown in **Fig. 6.**

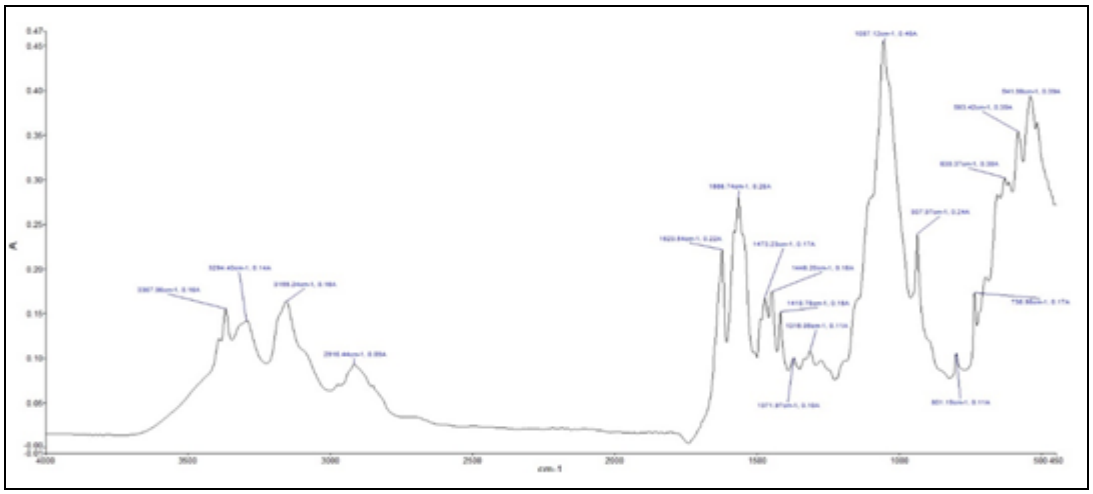

FIG. 6: FTIR FOR METFORMIN MICROSPHERE FORMULATION MIXTURE 3 (METFORMIN MICROSPHERE POWDER + EXCIPIENTS)

As seen in **Fig. 7**, the DSC thermogram of pure metformin HCl shows a strong endothermic peak at 235.56°C, indicating the drug's melting point and crystalline structure deterioration occurs above 300°C, important for formulation considerations. This thermogram also aids in assessing formulation interactions. From this study, revealed that there is no chemical interaction between metformin HCl and the polymer based on the DSC spectra. Metformin HCl exhibited a strong endothermic peak at 231°C, its melting point, indicating no significant interactions. Samples were heated at a rate of 10°C per minute from 30 to 300°C in a nitrogen environment. For HPMC, Figure 8 displays a broad endothermic transition between 50°C and 90.99°C, with a peak at 62.66°C, indicating its thermal properties. DSC analysis was performed on pure metformin HCl, HPMC, and their physical mixtures (F1, F2, F3 microspheres).

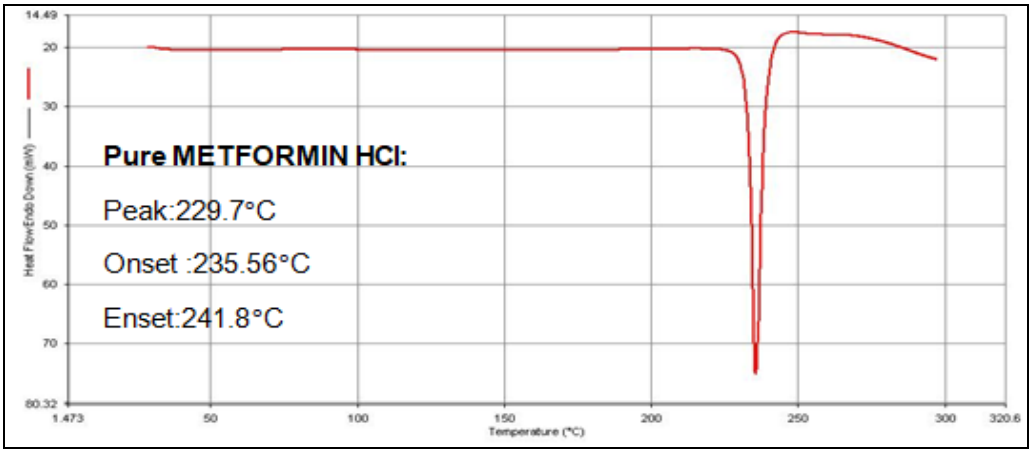

FIG. 7: DSC THERMOGRAM FOR PURE METFORMIN HCL

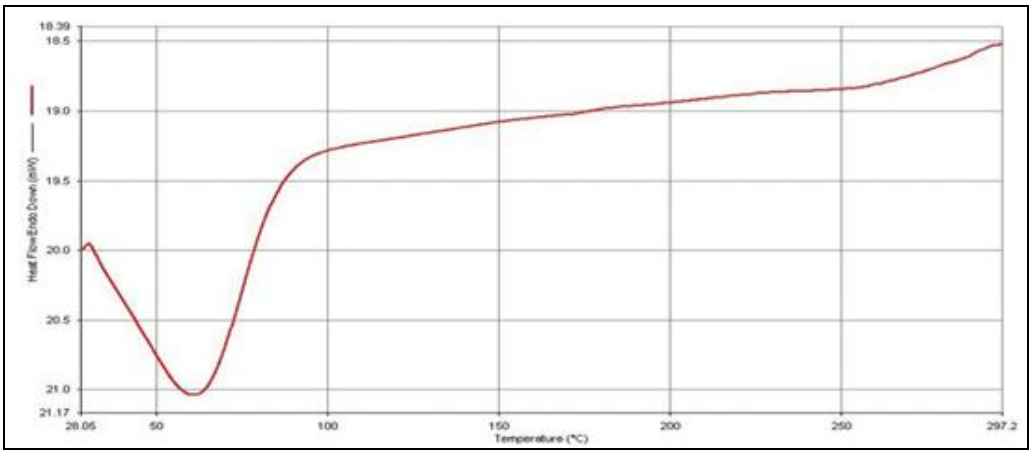

FIG. 8: DSC ANALYSIS FOR HPMC POLYMER

For excipients, PEG showed an endothermic peak at 63.15°C, PVP at 167.49°C (melting or decomposition), magnesium stearate at 60.75°C with an exothermic transition at 116.91°C (crystallisation), and microcrystalline cellulose exhibited a peak around 120°C (dehydration) and then confirmed the excipients' stability in the formulation. In the three formulation mixtures based on the drug: polymer concentration, from **Fig. 9, 10, 11**, DSC revealed that the endothermic peak of metformin HCl is around 230-231℃ which indicates that there is no interaction between the excipients and metformin HCl and microsphere formulation. The DSC results for formulation mixes showed that there was no discernible interaction between the excipients utilized in the investigation and metformin HCl.

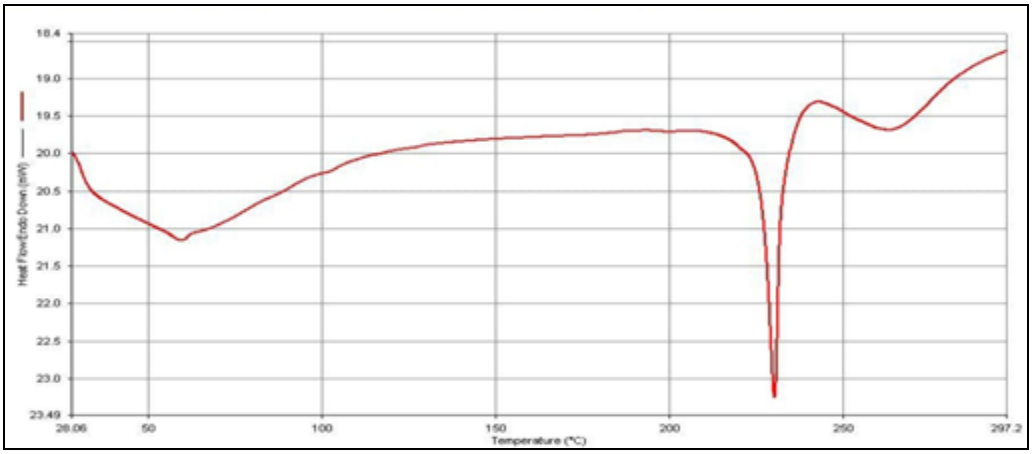

FIG. 9: DSC ANALYSIS FOR METFORMIN MICROSPHERE FORMULATION MIXTURE 1 (METFORMIN MICROSPHERE POWDER + EXCIPIENTS)

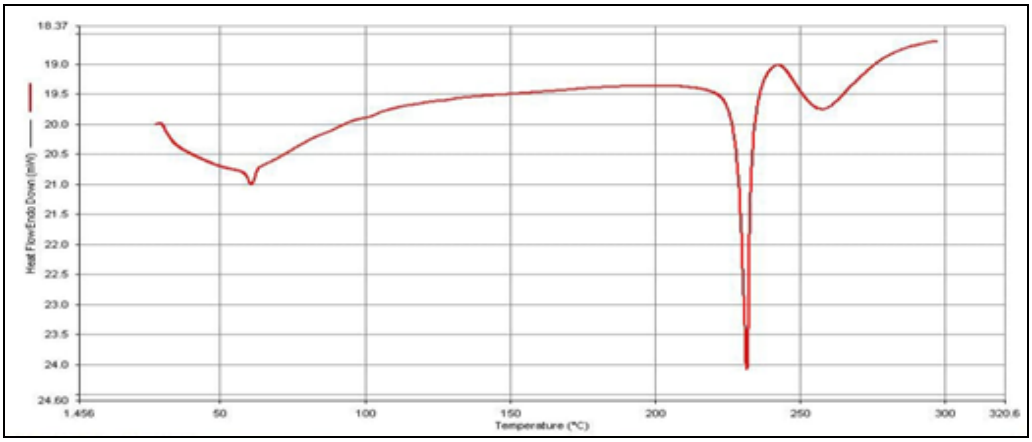

FIG. 10: DSC ANALYSIS FOR METFORMIN MICROSPHERE FORMULATION MIXTURE 2 (METFORMIN MICROSPHERE POWDER WITH EXCIPIENTS)

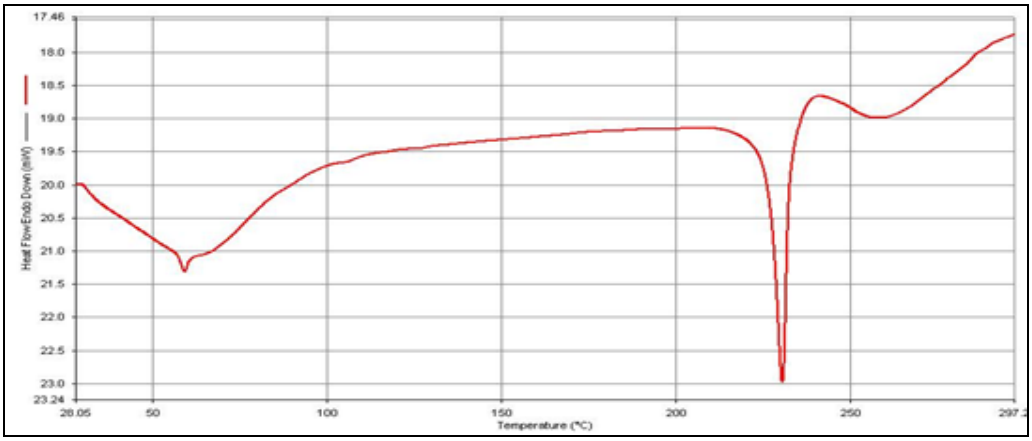

FIG. 11: DSC ANALYSIS FOR METFORMIN MICROSPHERE FORMULATION MIXTURE 3 (METFORMIN MICROSPHERE POWDER WITH EXCIPIENTS)

Post-compression Evaluations: The metformin microsphere tablets displayed uniform thickness (2.02 mm, 1.96 mm, 1.99 mm) and diameter (6.5 mm) across all formulations, ensuring consistent drug release. Weight variation met pharmacopeial standards (850 mg), confirming dose accuracy. Hardness ranged from 12.14 to 13.1 kg, indicating suitable robustness, and friability was below 1%, showing good mechanical strength.

TABLE 3: POST COMPRESSION EVALUATIONS

Evaluations	Formulation 1	Formulation 2	Formulation 3
Thickness (mm) ± SD	2.02±0.08	1.96±0.02	1.99±0.09
Diameter (mm)±SD	6.5±0.04	6.50±0.06	6.49±0.07
Weight variation (mg)±SD	850.17± 1.15	851.22±1.60	850.30± 1.54
Tablet hardness (kg)±SD	12.14±0.028	12.69 ±0.018	13.10±0.022
Friability (%)	0.79	0.88	0.81

This dissolution study revealed that as polymer viscosity increased, resistance to drug diffusion and polymer erosion also rose, impacting drug release rates [12]. Three metformin microsphere formulations were tested, with formulations 2 and 3 showing the highest drug release (99.24% and 91.4% at 6 hours). Drug release increased up to 6 hours and then slowed, with higher polymer concentrations leading to slower release. The study was performed in triplicate over eight hours in 0.1N HCl. During the *in-vitro* dissolution test of Metformin microspheres, a technical error was identified in Formulation 1, significantly affecting the first-order kinetic release profiles. The issue, caused by equipment calibration discrepancies, led to variations in dissolution rates. This deviation may impact the accuracy of the release kinetics data. Additionally, potential errors in sample dilution preparation due to variations in dilution ratios could introduce inaccuracies in the results.

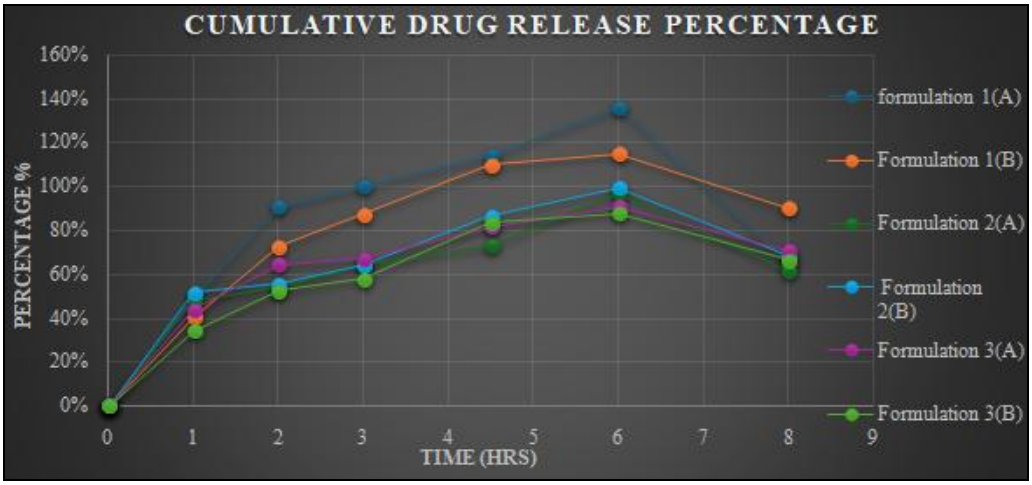

FIG. 12: CUMULATIVE DRUG RELEASE PERCENTAGE FOR METFORMIN MICROSPHERE TABLET FORMULATIONS

TABLE 4: CUMULATION DRUG RELEASE PERCENTAGE

Cumulative Drug Release %						
Time (hrs)	**F1(A)**	**F1(B)**	**F2(A)**	**F2(B)**	**F3(A)**	**F3(B)**
0	0%	0%	0%	0%	0%	0%
1	49.33%	40.43%	48.47%	51.23%	43.91%	34.15%
2	91.07%	72.80%	54.38%	55.67%	64.31%	52.04%
3	99.95%	87.40%	64.67%	64.19%	67.07%	57.83%
4.5	114.20%	109.50%	72.83%	86.27%	81.47%	83.47%
6	136.19%	114.90%	97.40%	99.24%	91.07%	87.71%
8	65.15%	89.87%	61.67%	67.91%	70.48%	66.11%

The *in-vitro* release experiments demonstrated an increase in drug release up to 6 hours, as shown in **Fig. 17.** The percentage cumulative release of metformin HCl decreased with higher HPMC polymer concentrations. Increased HPMC (F1: 0.5:1, F2: 1:1, F3: 1:1.5) leads to a denser polymer matrix within the microspheres, extending the diffusional pathway and delaying drug release. According to the dissolution studies, metformin HCl release at 6 hours was approximately 136% (due to technical error), 99.24%, and 91.07% for formulations F1, F2, and F3, respectively. By the 8th hour, cumulative release decreased for all formulations.

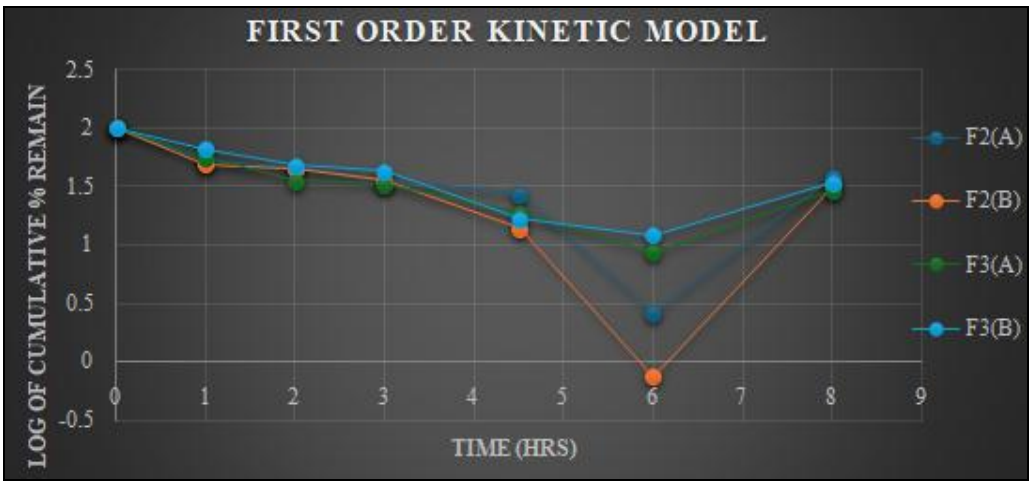

FIG. 13: FIRST ORDER KINETIC MODEL FOR METFORMIN TABLET FORMULATIONS

TABLE 5: FIRST ORDER KINETIC MODELLING

Log of cumulative % remain				
Time (hrs)	**F2(A)**	**F2(B)**	**F3(A)**	**F3(B)**
0	2	2	2	2

1	1.712	1.688	1.748	1.818
2	1.659	1.647	1.552	1.68
3	1.548	1.554	1.51	1.625
4.5	1.434	1.137	1.267	1.218
6	0.414	-0.119	0.95	1.089
8	1.583	1.506	1.47	1.53

FIG. 14: ZERO ORDER KINETIC MODEL FOR METFORMIN MICROSPHERE TABLET FORMULATIONS

TABLE 6: ZERO ORDER KINETIC MODELLING

Time (hrs)	F1(A)	F1(B)	F2(A)	F2(B)	F3(A)	F3(B)
0	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
1	49.33%	40.43%	48.47%	51.23%	43.91%	34.15%
2	91.07%	72.80%	54.38%	55.67%	64.31%	52.04%
3	99.95%	87.40%	64.67%	64.19%	67.07%	57.83%
4.5	114.29%	109.50%	72.83%	86.27%	81.47%	83.47%
6	136.19%	114.9%	97.40%	99.24%	91.07%	87.71%
8	65.15%	89.87%	61.67%	67.91%	70.48%	66.11%

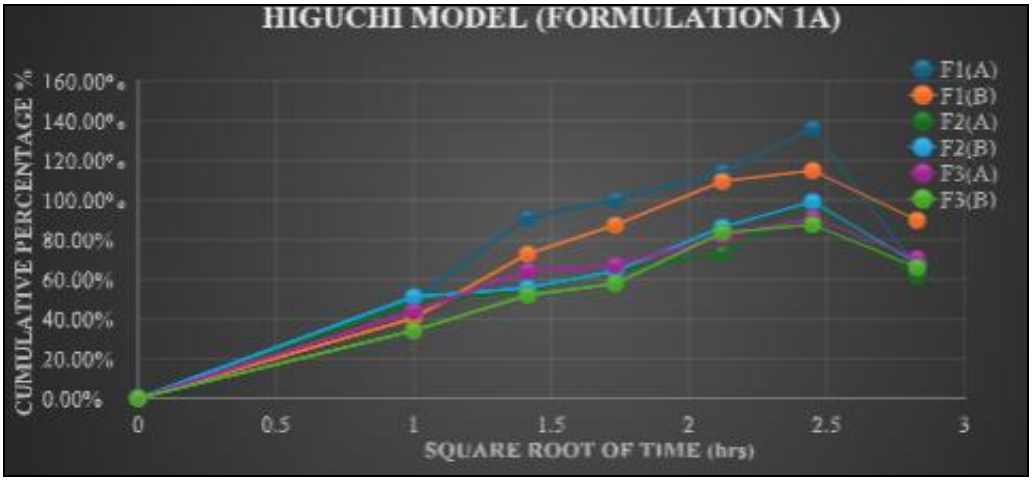

FIG. 15: HIGUCHI KINETIC MODEL FOR METFORMIN MICROSPHERE TABLET FORMULATIONS

TABLE 7: HIGUCHI KINETIC MODELLING

Sq. Root of Time	F1(A)	F1(B)	F2(A)	F2(B)	F3(A)	F3(B)
0	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
1	49.33%	40.43%	48.47%	51.23%	43.91%	34.15%
1.414	91.07%	72.80%	54.38%	55.67%	64.31%	52.04%
1.732	99.95%	87.40%	64.67%	64.19%	67.07%	57.83%
2.121	114.20%	109.50%	72.83%	86.27%	81.47%	83.47%
2.449	136.19%	114.90%	97.40%	99.24%	91.07%	87.71%
2.828	65.15%	89.87%	61.67%	67.91%	70.48%	66.11%

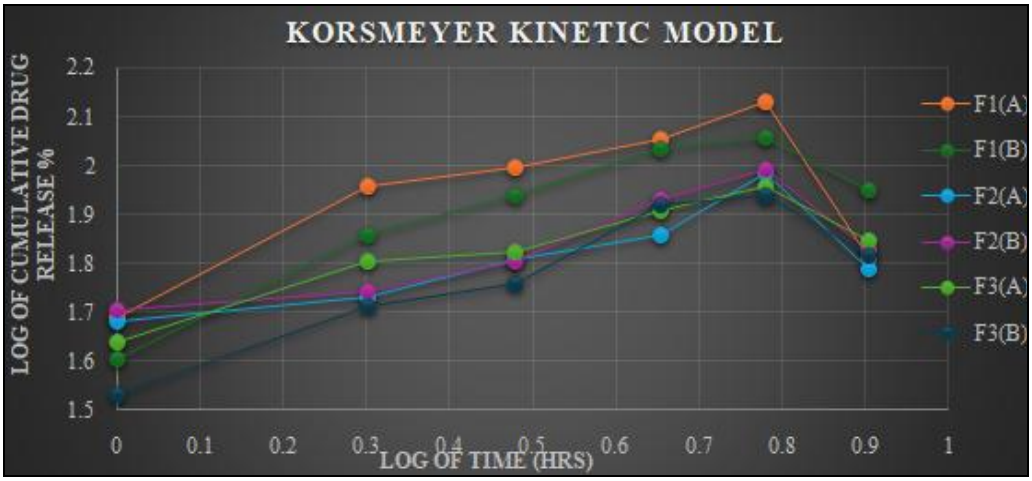

FIG. 16: KORSMEYER KINETIC MODEL FOR METFORMIN MICROSPHERE TABLET FORMULATIONS

TABLE 8: KORSMEYER-PEPPAS KINETIC MODELLING

Log of Time (hrs)	F1(A)	F1(B)	F2(A)	F2(B)	F3(A)	F3(B)
0	1.693	1.606	1.685	1.709	1.642	1.533
0.301	1.959	1.862	1.735	1.745	1.808	1.716
0.477	1.999	1.941	1.81	1.807	1.826	1.762
0.653	2.057	2.039	1.862	1.935	1.91	1.921
0.778	2.134	2.06	1.988	1.996	1.959	1.943
0.903	1.813	1.953	1.79	1.831	1.848	1.82

TABLE 9: R^2 VALUE FOR DRUG RELEASE KINETIC MODELLING OF METFORMIN MICROSPHERE FORMULATIONS

	R^2 Value			
Formulation	First Order	Zero Order	Higuchi Model	Korsmeyer Peppas Model
F1(A)	_	0.8688	0.9823	0.9394
F1(B)	_	0.8868	0.9849	0.9612
F2(A)	0.8117	0.8543	0.9669	0.9001
F2(B)	0.8318	0.8679	0.9762	0.8972
F3(A)	0.9783	0.8227	0.9807	0.9720
F3(B)	0.9734	0.9087	0.9865	0.9865

The drug release mechanism for optimized metformin microsphere formulations F2 and F3 was determined by fitting *in-vitro* release data to kinetic models like zero order, first order, Higuchi, and Korsmeyer-Peppas. Due to a technical error in formulation F1, its first-order kinetic data was inaccurate, emphasizing the need for precise calibration.

Formulations 2 and 3 exhibited consistent release profiles, suitable for sustained drug delivery in type 2 diabetes management. Kinetic models such as zero-order, first-order, Higuchi, and Korsmeyer-Peppas were applied, with strong linearity observed for all formulations. Regression (r^2) analysis confirmed that the release mechanism fits the Higuchi kinetic model, indicating a diffusion-controlled process governed by Fickian diffusion, with the polymer matrix effectively regulating the release rate.

CONCLUSION: The study successfully prepared metformin microspheres using HPMC polymer via spray drying. Post-formulation and micrometric studies confirmed the formulations met the acceptance criteria. FTIR analysis showed no interaction between excipients and the microsphere formulation, while DSC confirmed the stability of all compounds. *In-vitro* characterization and drug release, kinetics were assessed using a Copley dissolution tester and UV spectrometry, with Higuchi modelling indicating diffusion-controlled release. The metformin microsphere tablets, formulated in three drug concentrations, may reduce gastric irritation and provide controlled, enhanced drug release for effective type 2 diabetes management.

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