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Formulation and Evaluation of Tolmetin Sodium Floating Micropshere for Sustained Delivery

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ABSTRACT

Objective: The aim of this study was to prepare sustained-release microspheres for tolmetin sodium utilizing ethyl cellulose and HPMC. **Methods:** The microspheres were prepared using the solvent evaporation method. Microspheres were characterized for particle size, encapsulation efficiency, and in vitro drug release. The influence of the processing variables on the characteristics of the prepared microspheres was studied. **Results and Discussion:** The results described in the context of the current work illustrated the suitability of the water-oil-oil system in the preparation of sustained-release microspheres for tolmetin sodium. This formula produced microspheres particle size in the range 190-500 µm, with 48-98yield, and 45-95% encapsulation efficiency. Drug release from the microspheres was found to be diffusion controlled, with a pH-independent behavior. **Conclusion:** The current work presented a successful attempt to fabricate a sustained-release microsphere comprising tolmetin sodium. This will help overcome the frequent dosing problems with conventional pregabalin dosage forms and improve product performance.

INTRODUCTION

Various routes of drug delivery, oral route is the most convenient, easily preferred and patient compliance one. However, drugs administrated orally undergoes hepatic first-pass metabolism and enzymatic degradation in the gastrointestinal tract (GI) or both (1). A type of gastro-retentive medication delivery system known as floating microspheres is composed of solid, roughly spherical particles with a size between 1 and 1000 µm (2). These have a bulk density lower than the gastric content. They remain floating in the stomach for a prolonged period of time, with the possibility of a continuous release of the drug. Eventually, the residual system empties from the stomach. (3) Gastric emptying is much faster in the fasting state, and floating systems rely heavily on the presence of food to delay emptying and provide sufficient fluid for effective buoyancy. SRDDS is employed to give patients their medications. SRDDS is made to release a drug at a predetermined rate by maintaining a constant drug level for a specific period of time with maximum therapeutic efficacy and minimal side effects. (4, 5) Its goal is to maintain consistent levels of medication over an extended period without allowing for fluctuations in absorption or metabolism (6).

The gastric retention system can stay in the stomach for several hours, greatly extending the amount of time that medications are present there, increasing their bioavailability, and minimizing drug loss. Gastro-retentive systems can also be used to administer medications locally to the stomach and proximal small intestine. Better access to novel products with novel therapeutic potential and significant patient benefits may result from this (7).

Tolmetin sodium is an effective anti-inflammatory and analgesic drug in clinical practice. Tolmetin sodium inhibits both isoforms of cyclo-oxygenase enzyme. The inhibition of cyclo-oxygenase enzyme COX–I results in a number of undesirable effects such as gastrointestinal complaints. Moreover, tolmetin sodium has a short plasma half life (about1–2 hours) that necessitates three–times a day administration of the drug. Therefore, tolmetin sodium is highly recommended to be prescribed in controlled release form. Furthermore, it would contribute to retain encapsulant during emulsification, decrease its loss during microspheres recovery, and may provide a controlled release effect. (8-10) Hence, the aim of this work was to formulate tolmetin sodium in controlled release oral dosage form.

2. MATERIALS AND METHODS

2.1 Materials: Drug (Tolmetin sodium) was acquired from Yarrow Chem Pvt. Ltd., Mumbai, India and Ethyl cellulose and HPMC was obtained from Sigma-Aldrich Chemicals Private Limited, Bangalore (India). Polyvinyl alcohol, acetone and dichloromethane were purchased from Merck Pvt. Ltd., Mumbai, India. All other chemicals and reagents used were of analytical grade and purchased from Loba Chemie Pvt. Ltd., Mumbai (India).

2.2 IR Spectroscopy: Drug identification was determined via infrared spectroscopy. By compressing 3-5 mg of each medication with 100-150 mg of potassium bromide in a KBr press, a pellet with a diameter of around 1 mm was created. A FTIR (Brukers Alpha) was used to scan the pellet between wave numbers 4000-600 cm^{-1} while it was positioned in an 80 IR compartment. (11)

2.3 Formulation Of Floating Microspheres: In this investigation, the preparation of the microsphere formulation was done using the solvent evaporation technique. Polymer EC and HPMC were dissolved in ethanol and DCM to create tolmetin microparticles. The polymer solution was then supplemented with the medication tolmetin. After that, the liquid was continually stirred and added drop by drop to 0.1% SLS. Until the organic solvent completely evaporated, the stir ring rate was maintained at 900 rpm for 30 minutes.

The medication and polymer were dissolved and then added to tiny droplets. As the solvent evaporated, the droplets became hardened microparticles. The resulting microparticles were filtered, collected, and then cleaned four to five times with distilled water before being left to dry for twenty-four hours at room temperature. Nine batches of drug-loaded microparticles with formulation codes MF1–MF9 were made by varying the polymer with varying ratios while maintaining a constant drug ratio.(12-14)

Table 1: Formulation Design

Formulation	MF1	MF2	MF3	MF4	MF5	MF6	MF7	MF8	MF9
Drug (gm)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
EC (gm)	1	0.5	1	0.5	1	0.5	1	0.5	1
HPMC E50 (gm)	0.5	1	0.5	1	0.5	1	0.5	1	0.5
Chitosan (gm)	-	2	-	2	-	2	-	2	-
PVP (gm)	2	-	2	-	2		2		-
Eudragit (gm)	-	-	-	-	-	-	-	-	0.2
SLS (0.1%)	70	70	70	70	70	70	70	70	70
Ethanol (ml)	15	15	15	15	15	15	15	15	15
DCM (ml)	15	15	15	15	15	15	15	15	15

EC= Ethyl cellulose, HPMC= Hydroxy propyl methyl cellulose, PVP= Polyvinyl pyrrolidone
SLS= Sodium lauryl sulphate

2.4 Characterization And Evaluation Of Microsphere

i) Determination of microsphere Production yield: The weight of the manufactured microspheres was divided by the initial quantity of the polymer and medicine used in triplicate to measure the microspheres' yield, and the data was summarized in this formula.

$$\%Yield = (\text{Actual weight of product} / \text{Total weight of excipient and drug}) \times 100$$

ii) Determination of microsphere Particle size: A USP standard sieve was used to weigh and size the dried microspheres. The percentage value of the prepared microspheres have passed with each size of sieve and arrange according to the ascending order; average particle size of the sieve employed allowed for the determination of the mean particle size of the microspheres, which was determined by collecting the proportion of microspheres that remained on each sieve. Every experiment was run three times. (15, 16)

iii) Determination of drug content: The studies were conducted in triplicate, and the content of drug in formulation was measured by the digestion process. We have using the solution of phosphate buffer and the 100 mg of drug was dissolved. Then the solution was taken in 50 ml volumetric flask and it will shaken to 5-6 hrs after the preparation. Now filter the solution, filtrate was used and measure drug concentration in UV spectroscopy at 325 nm. The solution was compare with blank solution.

iv) Entrapment Efficiency: Using a UV spectrophotometer, the microparticles' actual drug content was found. After dissolving 50 mg of drug-loaded microsphere in solution like chloroform and extracting the material using 50 ml of phosphate buffer 7.4, the material was measured at 360 nm. (17, 18, 19)

$$\text{Entrapment efficiency (\%)} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$$

v) Swelling Index: The formulated microparticles' swelling indices were measured for eight hours at 37.5 ± 0.5°C in phosphate buffer pH 7.4 and pH 1.2. Microparticles loaded with drugs were allowed to equilibrate in several test tubes. After an hour, the microparticles were removed, filtered, put into a tiny beaker, and weighed. The following expression was used to compute the swelling ratio.

$$\text{Swelling index} = \frac{W_f - W_0}{W_0} \times 100$$

Where, W1 = weight of micro particle observed at every time interval

W0 = initial weight of micro particles.

vi) Flow property: (20, 21)

Angle of Repose: It is a useful tool for measuring flow properties. “Friction between the particles is the cause of improper flow; the angle surface of the powder pile and the horizontal plane are used to quantify these forces and he following table shows the angle of repose and the powder flow”.

$$\Theta = \tan^{-1} h/r$$

Where Θ is angle of repose, r is radius and h is the height

Bulk density: Using this technique, floating microparticles are moved to a measuring cylinder and manually tapped until a consistent volume is reached. This volume, which is known as bulk volume, comprises the microparticle void space as well as the actual volume of the powder.

$$\text{Bulk density} = \text{Mass of microparticle} / \text{Bulk volume}$$

Tapped density: This technique involved moving floating microparticles to a measuring cylinder and tapping them 100 times. The microparticle volume was visually assessed upon tapping. Taped density floating microspheres are determined by dividing the mass of the microspheres by their volume following tapping.

$$\text{Tapped density} = \text{Mass of microparticle s/ Volume of microparticle s after tapping}$$

Carr's Compressibility index: Using the formula, Carr's Compressibility index was calculated.

$$\text{Carr's index}(\%) = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Hausner's ratio: It is important tool for determination of flow property. It was calculated by the bulk density and tapped density of powder.

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

v) In-Vitro Dissolution Study: According to USPXXIV, the rotating basket method was used to release the drug from the microsphere. From one to twelve hours, the in-vitro release profile was investigated in phosphate buffer pH 7.4. The basket was filled with microparticles corresponding to 100 mg of medication, and the medium was rotated at 750 rpm while being held at 37°C. Every hour, an aliquot of 10 ml was taken out and replaced with the same volume of new media. A UV spectrophotometer was used to measure the absorbance at 360 nm in order to calculate the medication concentration that was released at different times. (22, 23)

3. RESULTS AND DISCUSSION

3.1 Infra-Red Spectral Analysis: Tolmetin's pure IR spectra were obtained and recorded. Figure 1 displays the sample drug's FTIR spectrum, while Table 3.4 provides an interpretation of tolmetin.

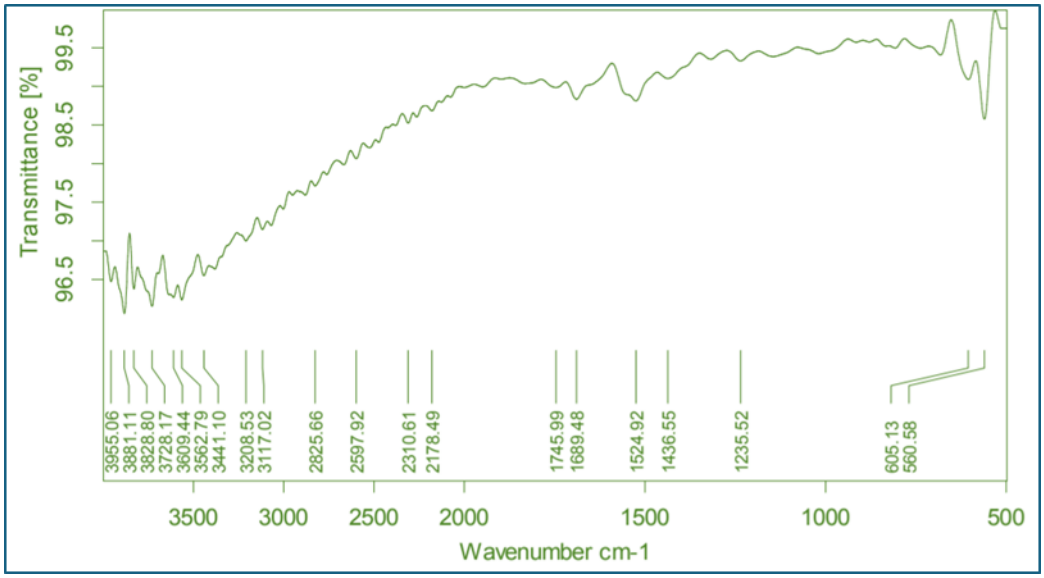

Figure 1: IR Spectra of Tolmetin

Table 2: IR Spectrum Interpretation of Tolmetin

S. No.	Frequency (cm^{-1})	Assignments
1	3562.79 3441.10, 3208.53	N-H stretching (primary amine)
2	2825.66	CH_2 symmetric stretching
3	2597.92	$(CH_3)_2N$ absorption
4	2310.61, 2178.49	C-H stretching
5	1745.99, 1689.48	N-H deformation
6	1524.92, 1436.35.69	N–H bending strongly coupled with C–N stretching (amide II band)
7	1235.52	Ring vibration modes of C–O–C and C–O–H bonds
8	605.13, 560.58	N-H out of plane bending

3.2 Preparation of calibration curves: Calibration curve of tolmetin revealed that the graph obeyed Beers Lambert Law in the concentration range (2-14 µg/ml); Regression equation was found to be: y = 0.0112x - 0.7014 and high coefficient correlation of 0.9708 was also observed. Figure 2 showed a graph between the mean concentrations (µg/ml) versus mean absorbance (nm) of different concentration of tolmetin in phosphate buffer pH 7.4.

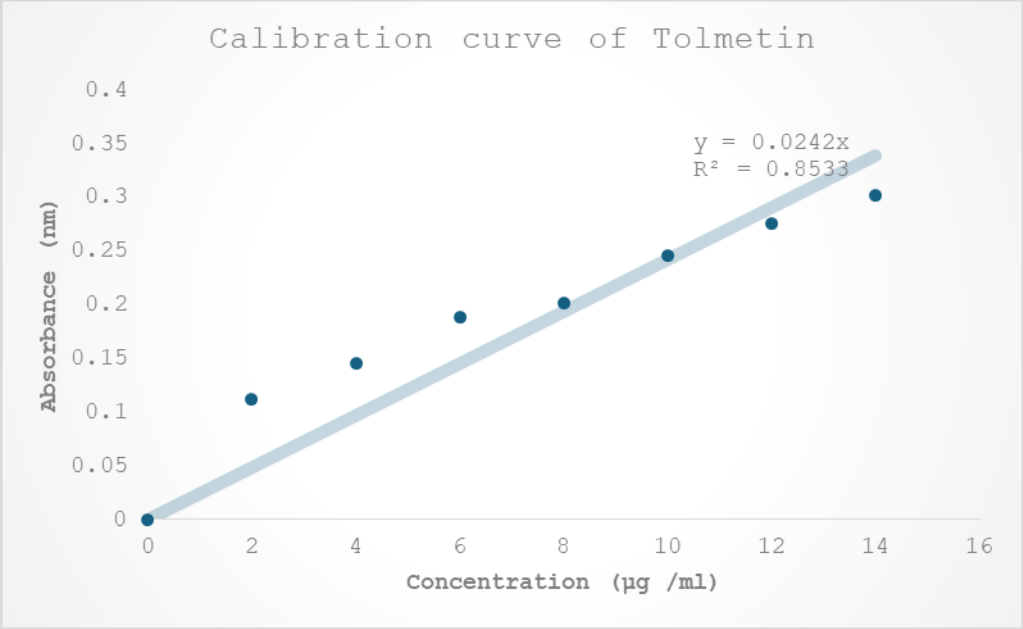

Figure 2: Calibration curve

3.3 Characterization And Evaluation Of Microspheres

i) Percentage Yield: Some formulations have poor percentage yields, which could be the result of lost microspheres after washing. Every formulation has a different percentage yield, with the exception of MF1–MF9, which are displayed in Figure and have the greatest percentage yield of 98%.

ii) Particle size Here, thedrug topolymer ratio was varied while the polymer concentration was kept constant. This increased viscosity affected the size concentration by influencing the correlation in the phase(dispersed) and medium (dispersion). Consequently, the mean particle size increased as a result of the increased relative viscosity. The drug-loaded batches have particle sizes ranging from 190 to 494µm.

iii) Swelling Index (%): All MF1 through MF9 formulations have swelling indices that vary from 156 to 198%.

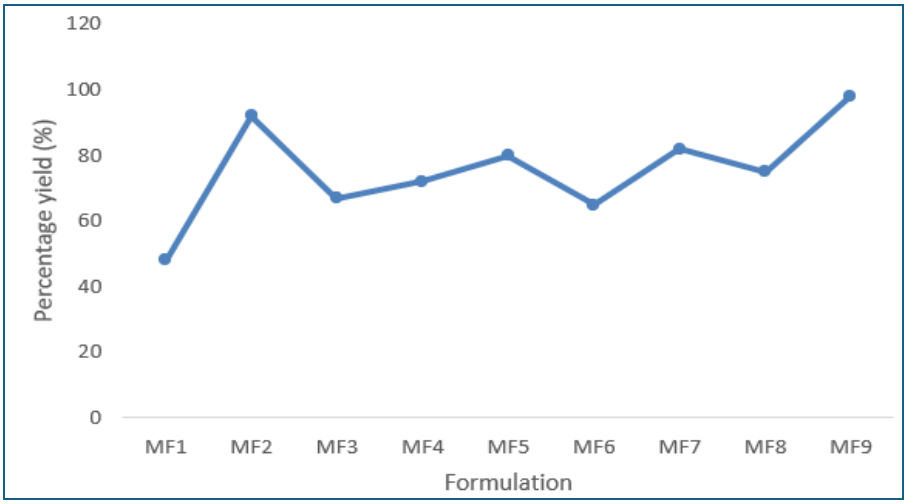

Figure 3: Percentage yield of prepared microspheres

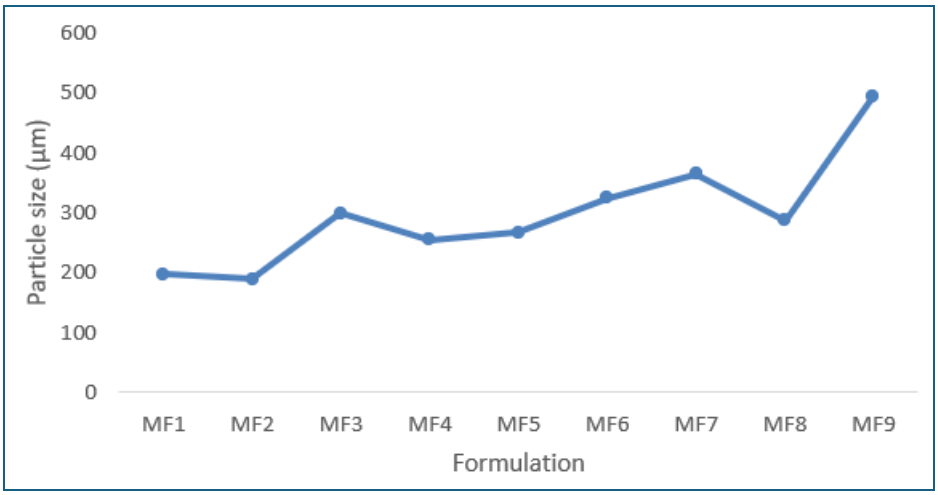

Figure 4: Particle size of microsphere formulation

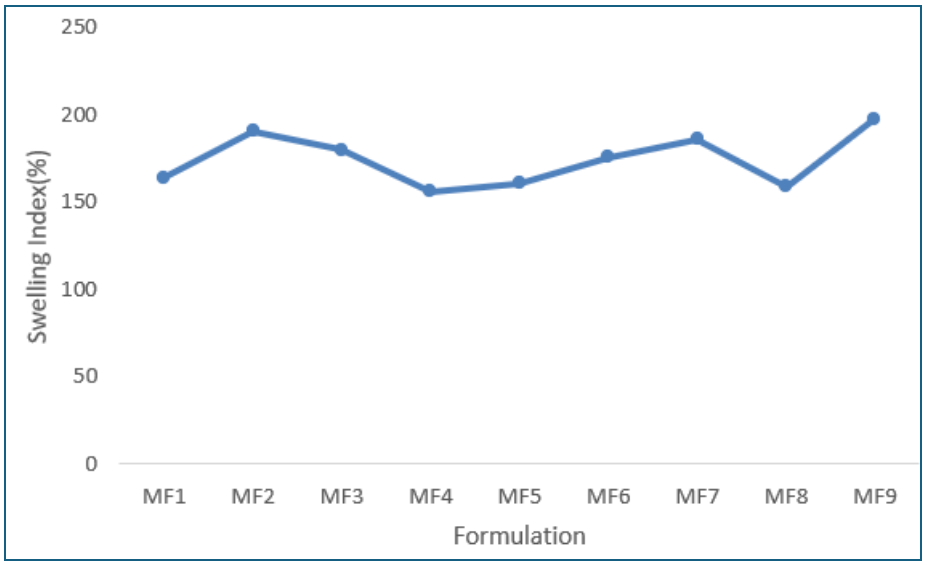

Figure 5: Swelling index of formulation

iv) Drug Content (%): Drug-loaded batch loading efficiency ranged from 80% to 96%. Table 3.9 and Figure 6 displays the drug loading efficiency of each formulation and shows that MF9 had the highest drug loading, at 96%.

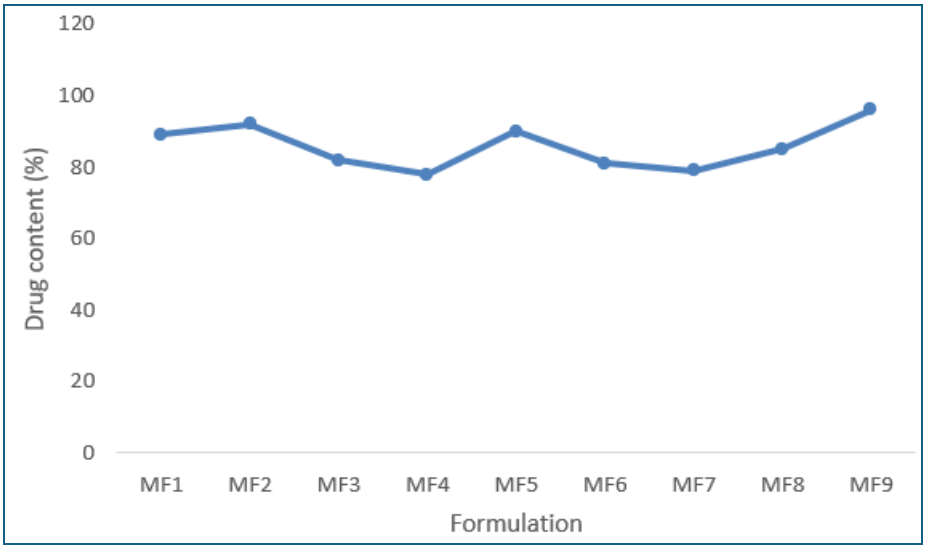

Figure 6: Microsphere's drug content %

v) Drug Entrapment: When the correct ratio increased, the microspheres showed an increase in drug entrapment up to a certain concentration. After that, there was a decline in drug entrapment because to the polymer's saturation capacity. Drug-loaded batch entrapment efficiencies vary from 45 to 95. Table 3.10 and figure 3.10 displayed the results. 95% of the maximum amount of medication entrapped in the MF9 formulation.

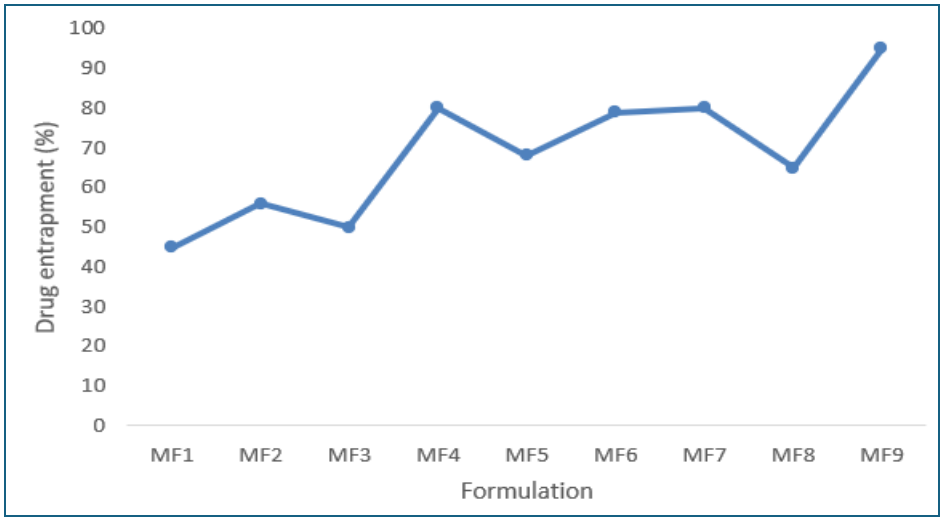

Figure 7: Drug entrapment (%) of formulations

vi) Buoyancy Studies: The values in this study vary from 80.45 to 97.58.

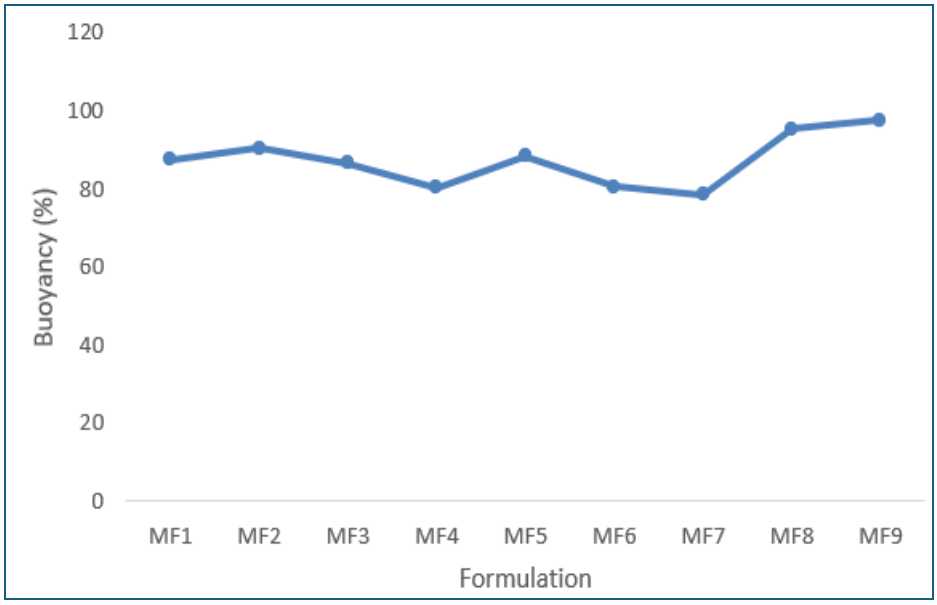

Figure 8: In-vitro Buoyancy studies of formulations

vii) Flow Property:

Angle of repose: Table 3 displays the results. The angle of repose value for all formulations ranged from 22.21±0.11 to 25.90±0.12, indicating the created microsphere's free flow character.

Bulk density and Tapped density: Bulk density readings less than "1.2 gm/cm^3 are said to suggest good glow, whereas values more than 1.5 gm/cm^3 are said to indicate poor flow characteristic and Table 3 shows that the bulk density values are less than 1.2 gm/cm^3, which indicates that the microspheres have favourable flow properties".

Compressibility index: All of the formulations had Carr's indices less than 20, ranging from 8.87±1.13 to 15.68±2.12, indicating satisfactory compressibility and flow characteristics.

Hausner's ratio: The range of Hausner's ratio indicated that all of the preparations had good flow qualities, ranging from 1.104±0.06 to 1.119±0.05. The enhanced flow characteristics imply that handling the microspheres during processing won't be difficult. Table 3.12 displayed the findings.

Table 3: Flow property of formulation MF1-MF9

For. Code	Angle of repose	Hausner ratio	Tapped density	Bulk Density	Carr's Index
MF1	25°.90 ± 0.12	1.112 ± 0.05	0.83± 0.02	0.44± 0.03	8.87 ± 1.13
MF2	25°.12 ± 0.12	1.124± 0.05	0.81± 0.02	0.67 ± 0.01	12.56 ± 2.19
MF3	25°.67 ± 0.13	1.117± 0.04	0.75± 0.02	0.48 ± 0.02	10.62 ± 1.17
MF4	24°.78 ± 0.12	1.121 ± 0.04	0.76± 0.03	0.56 ± 0.01	9.87 ± 2.10
MF5	22°.21 ± 0.11	1.121± 0.03	0.75± 0.03	0.61 ± 0.02	10.44 ± 2.60
MF6	23°.87 ± 0.10	1.104 ± 0.06	0.91± 0.02	0.53± 0.02	15.32 ± 3.18
MF7	23°.56 ± 0.12	1.116 ± 0.05	0.83± 0.03	0.86±0.03	11.29 ± 2.43
MF8	24°.32 ± 0.11	1.118± 0.04	0.74± 0.03	0.72± 0.02	9.69 ± 1.56
MF9	24°.64± 0.11	1.119± 0.05	0.81± 0.02	0.71± 0.01	15.68 ± 2.12

viii) In-vitro drug release study: Tolmetin floating microspheres were the subject of in-vitro drug release investigations in a dissolving test equipment with a pH of 1.2 for 12 hours. The medication release percentage at the end of the 12-hour period is displayed by MF1–MF9. It was discovered that MF9 was the optimum formulation since it releases tolmetin 90% continuously and sustainably over a long period of time (after 12 hours).

It was noted that the percentage of tolmetin released decreased as HPMC concentration increased. An increase in the concentration of ethyl-cellulose causes the polymer matrix inside the microspheres to become denser, lengthening the diffusional channel. This might lessen the drug's total release from the polymer matrix. Additionally, at lower polymer concentrations, smaller microspheres are generated with a higher surface area exposed to the dissolving solvent. A graph is produced with % and time in hours.

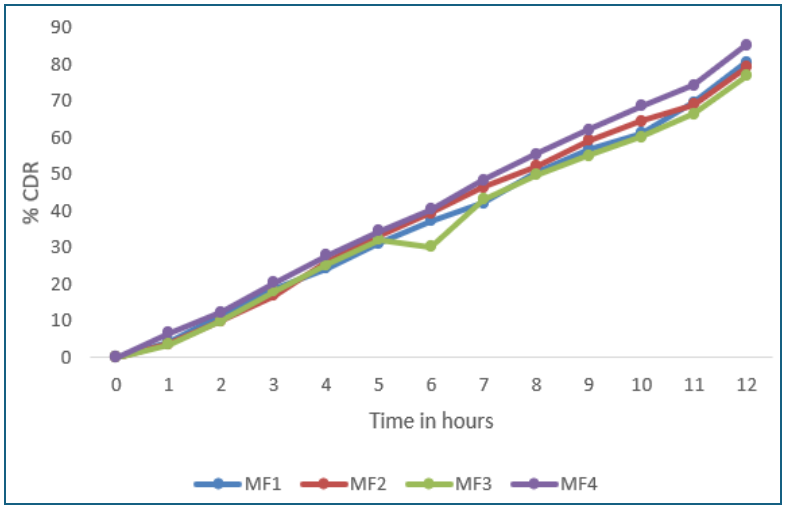

Figure 9: Drug release profile of formulation MF1-MF4

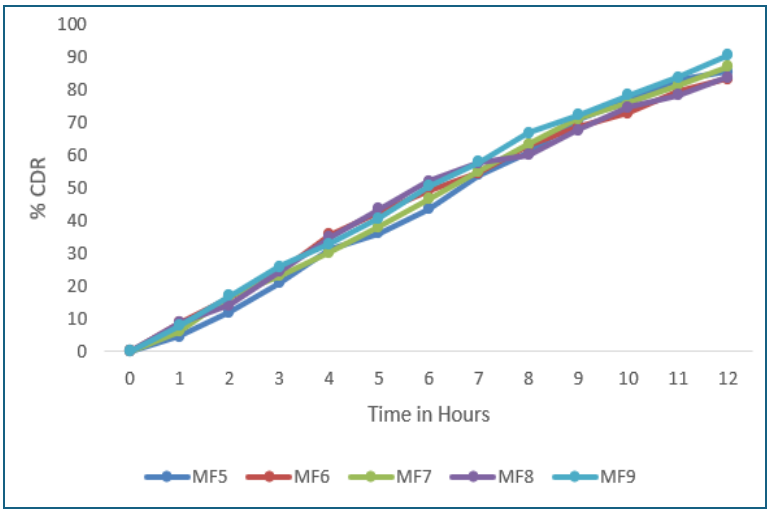

Figure 10: Drug release profile of MF5-MF9 formulation

ix) Kinetic modeling of selected batch MF9: Release constant to release batch MF9 data for different kinetic models. As can be observed, the first order model has the highest R^2 (0.9955), making it the best fit for the release kinetics and providing proof of the drug's continuous release.

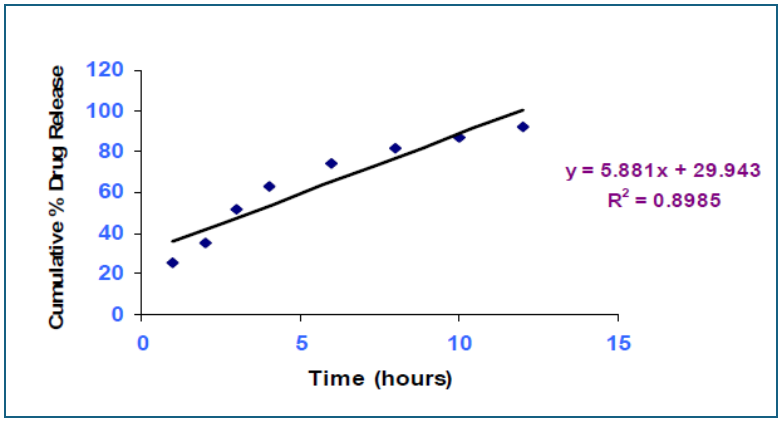

Figure 11: Zero order kinetic

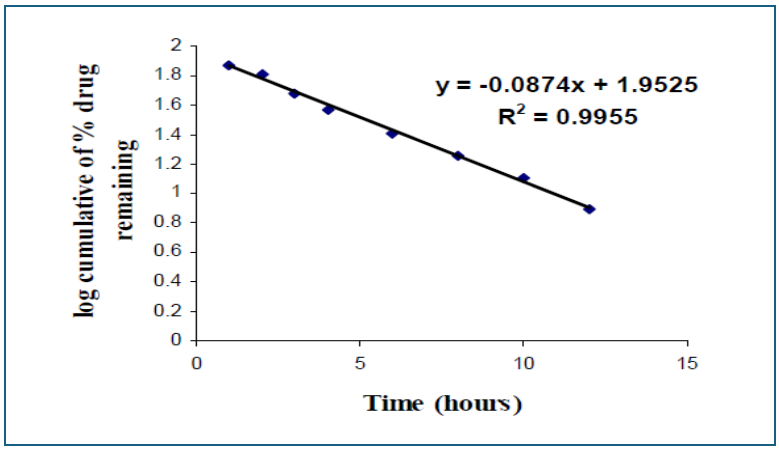

Figure 12: First order kinetic

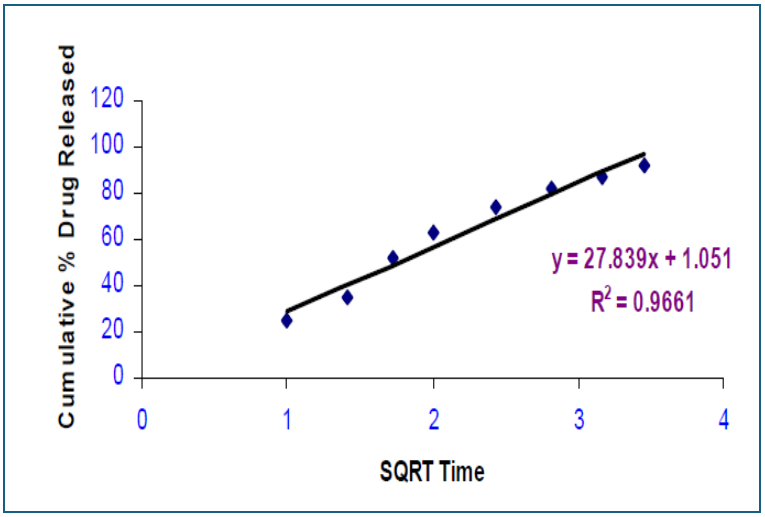

Figure 13: Higuchi graph

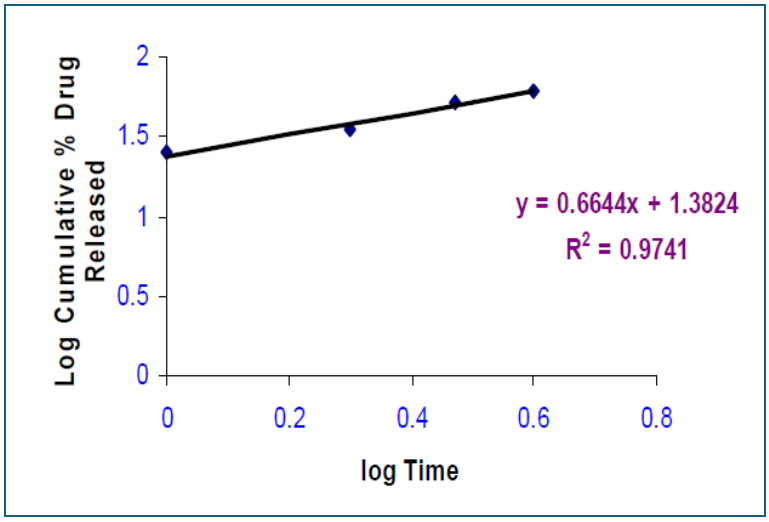

Figure 14: Korsmeyer-Peppas graph

CONCLUSION:

Solvent diffusion-evaporation was used in this investigation to create the floating microsphere of tolmetin. HPMC K4M and ethyl cellulose as a polymer were successfully used to prepare the tolmetin floating microsphere. The floating microsphere's percentage yield of over 70% suggests that the encapsulation method was successful. As the amount of polymer in each preparation was raised, the percentage yield was progressively increased. In every instance, the entrapment effectiveness was commendable. More than 70% of the in vitro tests demonstrated the expected formulations' good outcome. As the amount of polymer in each preparation was raised, the percent buoyancy rose in a sensitive manner. Out of all the formulations, formulation MF9's in-vitro release was determined to be the best since it releases tolmetin 90.32% consistently over an extended length of time (after 12 hours). Microspheres' average particle size fell within the acceptable range. The more polymer there was, the bigger the particle size. Every prepared microsphere had a respectable micromeritics characteristic. MF9 demonstrated good drug content, entrapment efficiency, and cumulative drug release over 80%, indicating that this formulation was the best available. Finally, it was determined that the tolmetin microspheres that were prepared may prove to be a promising candidate for long-term, safe, and effective drug administration that can lower the dosage rate.

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