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Formulation & Evaluation of Sustained Release Diclofenac Sodium Microspheres

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ABSTRACT

The present work sought to explore the dissolution profile and release kinetics of modified release diclofenac sodium microspheres comprising sodium carboxy methyl cellulose, hydroxy propyl methyl cellulose (HPMC), and polyvinyl pyrrolidine (PVP K30). The impact of these polymers on drug release mechanism was investigated. The Ionic-gelation process was used to create nine formulations with varying quantities of polymers. The FT-IR technique was employed for analysing interactions among polymers and active medicinal molecules. Scanning electron microscopy was utilized to examine the produced microspheres' form and surface morphology. The average particle size was determined using optical microscopy. The produced microspheres ranged from 50-110 µm and were ideal for modified medication delivery. Moisture content, drug entrapment efficiency, and percent yield were measured for the prepared microspheres, and the findings were satisfactory. F3 created with a drug: polymer ratio of 1:3 and 3% sodium alginate in 4% calcium chloride shown up to 99% retarding effects during an invitro drug release testing. Statistical models revealed that the drug release mechanism followed the zero order kinetic model. Finally, it was determined that sodium carboxy methyl cellulose, hydroxy propyl methyl cellulose (HPMC), and polyvinyl pyrrolidine (PVP K30) were acceptable polymers for producing diclofenac sodium microspheres as a modified or sustained release drug delivery method.

Keywords: Diclofenac sodium, Ionic gelation, Sodium CMC, HPMC, PVP K30, Sustained release drug delivery, FT-IR, Scanning Electron Microscopy

1. INTRODUCTION

Conventional drug delivery systems rapidly release medicines but do not maintain therapeutically effective concentrations over extended period of time. To maintain optimal plasma concentrations, these dosage forms must be taken often. Conventional drug delivery systems might generate unwanted side effects by delivering medication to various locations in the body other than the intended site of action. Conventional dosage formulations frequently result in higher medicine concentrations than indicated, causing unpleasant side effects. Newer pharmaceutical delivery systems are intended to overcome difficulties with traditional dosage forms. An effective and nontoxic medication delivery technique should maintain therapeutic plasma concentrations throughout time. To accomplish this, unique and sophisticated processes known as "NOVEL DRUG DELIVERY SYSTEMS" have been created. (1)

New drug delivery strategies, such as sustained/controlled release formulations, have been developed to address limitations in traditional treatment. These solutions

maintain consistent medication plasma levels throughout time, reducing changes in blood levels and minimising negative effects. [2]

Diclofenac sodium (2-[(2,6-dichlorophenyl) amino] benzene acetic acid) is a commonly used (NSAID) nonsteroidal anti-inflammatory medicine used to reduce pain and inflammation with fewer adverse effects, notably in the gastrointestinal tract, as seen with NSAID therapy. Diclofenac sodium is insoluble in water, although it has high permeability and belongs to the biopharmaceutics categorization system (BCS) class II. Diclofenac has narrow "therapeutic window", therefore it can be used to treat the symptoms of osteoarthritis, rheumatoid arthritis, spondylitis, and other acute pain problems.

Diclofenac is entirely absorbed from the GI tract; however it presumably undergoes extensive first-pass metabolism, with only 60% of the medication reaching systemic circulation intact. Absorption is dose proportionate from 25 to 150 mg. T_{max} varies with formulation, with the oral solution approaching peak plasma concentrations in 10-40 minutes, the enteric coated tablet in 1.5-2 hours, and the sustained & extended-release formulations lasting even longer. Food administration has no major impact for AUC; however it delays T_{max} by 2.5-12 hours. Diclofenac is predominantly eliminated by metabolism. The urine eliminates 60-70% of the whole dosage, whereas the faeces remove 30%. The terminal half-life of diclofenac is around 2 hours, while the apparent half-life, which includes all metabolites, is 25.8-33 hours.

Diclofenac has a plasma clearance of 16L/h. Diclofenac is over 99.7% bound to serum proteins, most notably albumin. It also has a low affinity for lipoproteins, with 1.1% bound to HDL, 0.3% to LDL, and 0.15% to VLDL. [3,4,5]

Arthritis is characterised as joint inflammation that causes swelling, redness, and pain. In order to treat arthritis with pills or capsules, the medication has been linked to gastrointestinal issues and requires numerous doses owing to its short half-life. Multiple dosing can cause fluctuations in drug levels and undesirable effects. Additionally, it may not release the medication at the proper rate or volume, thus leading to poor patient compliance and ineffective therapy. Microencapsulation is a widely used technique for sustaining drug release, reducing gastrointestinal irritation, improving dose adherence, and improving compliance in pharmacotherapy for arthritis, inflammation, and pain.

Microspheres are solid, spherical particles that range in size from 1-1000µm. Microspheres are free-flowing powders made from biodegradable proteins or synthetic polymers. Microcapsules include a distinct wall around the entrapped material, whereas micro matrices disperse the substance throughout the matrix. Solid biodegradable microspheres with a drug dispersed or dissolved in the particle matrix can provide controlled drug release. They consist of biodegradable synthetic polymers & modified natural components. [6,7,8,9]

A sustained-release formulation is a dosage form that delivers a medicine at a consistent pace over an established time period. Typically, the medicine is supplied in an initial therapeutic dose, followed by a gradual and consistent release. Advantages of sustained release polymers include increased drug bioavailability, ease of administration, drug stability, reduced gastrointestinal irritation, minimal side effects, and reduced toxicity. However, disadvantages include a high cost, increased risk of drug tolerance and dumping. Some of the sustained release polymers include Sodium Carboxy Methyl Cellulose, HPMC (Hydroxy Propyl Methyl Cellulose), PVA (Polyvinyl alcohol), PVP (Polyvinylpyrrolidone), PEG (Polyethylene glycol), PLA (Polylactic acid), PGA (Polyglycolic acid), etc. [10,11,12]

Diclofenac sodium is an excellent choice for developing the sustained release formulations. Therefore, in the present investigation, an attempt was made to develop and optimize sustained release microspheres of Diclofenac sodium by

ionotropic gelation method using sodium alginate as a gelling agent in combination with hydrophilic polymers like Sodium CMC, HPMC & PVP K30 as drug release modifiers in different compositions to overcome the drug related adverse effects and improve drug bioavailability.

2. MATERIALS & METHODOLOGY

Diclofenac sodium, Sodium alginate, Sodium Carboxy Methyl Cellulose, Hydroxy Propyl Methyl Cellulose, Polyvinyl Pyrrolidine K-30, Calcium chloride

2.1. Calibration of Diclofenac sodium: [13]

Accurately weighed 100 mg of pure Diclofenac sodium was dissolved in 5 ml of ethanol. The mixture was then made up to 100 ml with pH 6.8 Phosphate buffer to obtain the working stock of 1000 µg/ml. From the stock solution, pipetted out 10 ml and made up to 100 ml with buffer to develop a primary dilution of 100 µg/ml. Similarly, pipetted out 10 ml from primary dilution and made up to 100 ml with the same buffer and labelled it as secondary dilution of 10 µg/ml. Also made sample dilutions of 2-10 µg/ml from the secondary dilution (as mentioned in Table 2). Absorbance of the above solutions was measured at 276 nm by using UV visible spectrophotometer against the blank solution prepared in the same manner without adding the drug. A graph of absorbance Vs concentration was plotted.

2.2. Formulation of Microspheres: [14]

Diclofenac sodium microspheres were formulated using an ionotropic gelation process. The current research designed three sets of microspheres by combining sodium alginate with polymers such as Sodium CMC, HPMC, PVP K30 and calcium chloride as counter ions. Table 1 provides the precise makeup of the various formulations.

Table No-1: Formulation of Diclofenac microspheres

Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)
Diclofenac sodium	100	100	100	100	100	100	100	100	100
Sodium alginate	1000	2000	3000	1000	2000	3000	1000	2000	3000
Sodium CMC	100	200	300	-	-	-	-	-	-
HPMC	-	-	-	100	200	300	-	-	-
PVP K30	-	-	-	-	-	-	100	200	300
Calcium chloride	4000	4000	4000	4000	4000	4000	4000	4000	4000
Water	Q. S.	Q. S.	Q. S.	Q. S.	Q. S.	Q. S.	Q. S.	Q. S.	Q. S.

Preparation of Microspheres: [15,16]

Diclofenac microspheres were formulated with the ionotropic gelation process, which involves reacting sodium alginate with polyatomic ions such as calcium to create a hydrogel network of calcium alginate. As of total, 9 formulations of Diclofenac sodium were designed using three different polymers (Sodium CMC, HPMC, PVP K30) and variations in their concentrations. Initially, to create a homogenous mixture, the sodium alginate polymer of 1000 mg, 2000 mg and 3000 mg was dispersed in 100 ml of distilled water and stirred continuously on magnetic stirrer until gel matrix was formed. Then accurately weighed drug and polymer in the ratio 1:1, 1:2 and 1:3 was added to the sodium alginate mixture respectively. Then to create a viscous dispersion, the drug was extensively mixed into the polymer solution using a stirrer. The resultant dispersion was added to an aqueous solution of calcium chloride (4% w/v) using a 26 G hypodermic needle. The addition was done with continuous stirring at 400 rpm for 1 hour. Droplets were cured in a calcium chloride solution for 30 minutes, resulting in standard swollen, spherical microspheres. The solution was filtered and obtained microspheres were washed thoroughly to remove impurities The spheres were allowed to dry completely in the hot air oven. Finally,

the dried microspheres were carefully packed and stored for further use.

3. EVALUATION & CHARACTERIZATION OF OBTAINED MICROSPHERES:

The developed Diclofenac sodium microspheres were subjected to evaluation tests to determine various parameters like particle size analysis, percentage yield, entrapment efficiency, swelling index, moisture content, in-vitro drug release studies, SEM analysis& FTIR studies.

3.1. Determination of particle size: (14)

Prepared microspheres were measured using optical microscopy and a calibrated stage micrometre. To assess particle size, over 50 microspheres from each formulation were randomly selected and quantified. The stage micrometre was calibrated at 5^{th} division, whereas the eyepiece was calibrated at 45^{th} division using a calibration factor.

$$\text{Calibration factor} = \frac{\text{Divisions of stage micrometre}}{\text{Divisions of optical micrometre}} \text{x} 100$$

3.2. Determination of %Yield: (15)

The formulated microspheres were dried &weighed individually for each trial batch and weights were recorded. From the obtained weight of microspheres, % yield was calculated using the following formula.

$$\text{\% Yield} = \frac{\text{Weight of obtained microspheres}}{\text{Total weight ofdrug \& } polymer\ in\ each\ batch} \text{x } 100$$

3.3. % Drug Entrapment Efficiency (%DEE): (14)

Drug-loaded microspheres (100 mg) were dissolved in 500 ml of pH 6.8 phosphate buffer and sonicated for 10 minutes. The mixture was agitated at 1000 rpm for 4 hours and then filtered using Whatman® filter paper. The UV-VIS spectrophotometer (Shimadzu, Japan) was used to measure drug concentrations in filtrates at 276 nm. The % drug entrapment efficiency of each formulation was calculated using following formula.

$$\text{DEE (\%)} = \frac{\text{Actual drug content}}{\text{Theoritical drug content}} \text{ x } 100$$

3.4. Determination of Swelling Index: (17)

Accurately weighed Diclofenac sodium microspheres (100 mg) were soaked in phosphate buffer pH 6.8 for 24 hrs (as shown in Figure 4). Later the swollen microspheres were filtered and weighed periodically for 2hrs, 4hrs, 6hrs and 24 hrs. Swelling indexes were determined using the formula given below.

$$\text{Swelling index} = \frac{\text{Weight of swollen microspheres} - \text{Dry weight}}{\text{Dry weight}} \text{ x } 100$$

3.5. Determination of Moisture content: (13)

The moisture content of microspheres was assessed to evaluate their hydrophilicity. After weighing the microspheres and noting their initial weight (W1), they were placed in a hot air oven at 105^0C for 2 hours. The ultimate weight (W2) was then recorded. The moisture content was calculated according to the formula given below.

$$\text{Moisture content (\%)} = \frac{\text{Initial weight (W1)} - \text{Final weight (W2)}}{\text{Final weight (W2)}} \text{ x } 100$$

3.6. In-vitro drug release studies: (13,18)

Diclofenac sodium-loaded microspheres were tested for drug release in 6.8 pH phosphate buffer using USP I basket type dissolution apparatus. The baskets were covered with 100-mesh nylon cloth to prevent the escape of the beads. The baskets containing beads were stirred in 900 ml of phosphate buffer dissolution medium at a speed of 50 rpm. Samples were collected for up to 12 continuous hours. To maintain the sink condition, the removed samples were replenished with an equivalent amount of buffer at regular intervals. The absorbance of collected samples was measured using a UV spectrophotometer, and the percentage

cumulative drug release (% CDR) was calculated using the following formula.

$$\% \text{ CDR} = \frac{\text{Amount of drug release}}{\text{Amount of drug loaded}} \times 100$$

3.7. Scanning Electron Microscopy (SEM) analysis: [14]

Scanning electron microscopy was performed to determine the form and surface parameters utilising gold sputtering. Before microscopy, the particles were vacuum dried and coated with gold palladium to a thickness of 0.02 µm. The operational conditions included a 20nm working distance, a zero-degree tilt, and a 15kv accelerating voltage.

3.8. Determination of compatibility: [19]

FTIR (Fourier Transform Infrared) of Diclofenac sodium loaded sodium alginate microspheres was performed. FT-IR analysis was used to study the interaction between drugs and polymers. The IR spectra of pure and drug-loaded microspheres were obtained. The peaks showed N-H, C-H, C-Cl, and O-H stretching. [20,21,22,23]

RESULTS AND DISCUSSION

4.1. Calibration graph

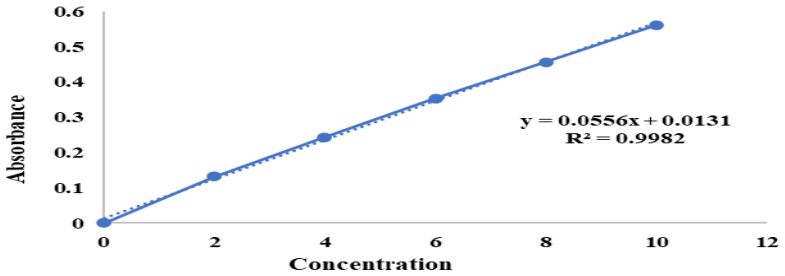
A graph of absorbance Vs concentration was plotted according to Table 2 and was found to be linear over a range of 2-10 µg/ml indicating its compliance with Beer's law (as shown in Figure 1).

Table No-2: Calibration curve of Diclofenac sodium

S. No	Concentration (µg/ml)	Absorbance (nm)
1	0	0
2	2	0.132 ± 0.011
3	4	0.243 ± 0.021
4	6	0.354 ± 0.01
5	8	0.456 ± 0.033
6	10	0.562 ± 0.018

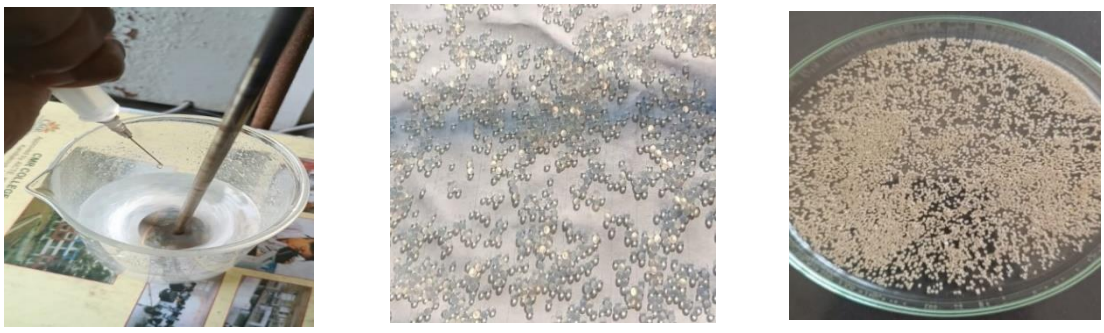
The values are expressed as mean ± SD, (n=3)

Figure 1: Calibration curve of Diclofenac sodium



4.2. Formulation of microspheres

According to Table 1, nine different formulations were developed with varied concentrations of drug polymer ratios using sodium alginate as a gelling agent. The preparation method, filtered microspheres and dried microspheres stages were shown in Figure 2.



(a) (b) (c)

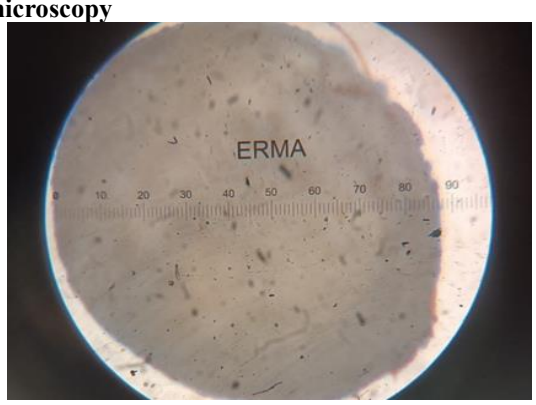
Figure 2: (a) Preparation of microspheres by ionic gelation method. (b) Microspheres after filtration. (c) Microspheres after drying.

4.3. Determination of Particle size

Over 50 microspheres were evaluated for particle size and the results were noted down in the Table 3. The results obtained were in the limit of 54-110 µm (as shown in Figure 3) which is in the range as per the literature reviews. The particle size of each microsphere was calculated using the following formula.

Average particle size = Microsphere diameter x Calibration factor

Figure 3: Particle size determination using optical microscopy



4.4. Determination of % yield

% Yield evaluation of obtained microspheres indicated the yield ranging from 70-96 % and good entrapment efficiency was observed for all the formulations indicating the efficiency of sustained release coated polymers. From the obtained weight of microspheres the percentage yield was calculated and noted in the Table 3.

4.5. % Drug Entrapment Efficiency (%DEE)

After sonication the entrapment efficiency of the weighed microspheres were measured by UV visible spectrophotometer and the values were recorded in Table 3.

4.6. Determination of Moisture content

Minimum moisture content was found in all the formulations which avoids drug degradation therefore enhance drug stability. The moisture content of microspheres was assessed to evaluate their hydrophilicity and noted down in Table 3.

Table No-3: Values of Average particle size, % Yield, % DEE & % Moisture content

Formulation	Average Particle size (µm)	% Yield	% DEE	% Moisture content
F1	54.28 ± 0.52	83.3 ± 0.22	92.7 ± 0.05	5.2 ± 0.254
F2	70.4 ± 0.34	91 ± 0.3	92.8 ± 0.59	6.59 ± 0.55
F3	110.4 ± 0.30	73.5 ± 0.15	93.3 ± 0.56	3.3 ± 0.681
F4	59.3 ± 0.75	85 ± 0.85	94.08 ± 0.31	4 ± 0.264
F5	78.5 ± 0.23	93.4 ± 0.64	90.8 ± 0.87	7.5 ± 0.541
F6	90.5 ± 0.45	75 ± 0.55	95.3 ± 0.54	3.6 ± 0.88
F7	56.5 ± 0.89	87.5 ± 0.32	90.9 ± 0.94	6 ± 0.64
F8	74.6 ± 0.44	96 ± 0.87	90.8 ± 0.88	10 ± 0.24
F9	93.8 ± 0.65	76 ± 0.63	94.8 ± 0.31	3.5 ± 0.689

The values are expressed as mean ± SD, (n=3)

4.7. Determination of Swelling Index :

The swelling index has varied for each formulation at different time intervals based on the sodium alginate concentration and swelling property of different polymers and noted down in Table 4. As per the values obtained, % swelling index was ranging between 10-30% in 24 hrs (as shown in Figure 4 below) and maximum swelling was observed in F7. According to the literature, % swelling index values concludes that higher the swelling property, more the gel matrix formation and slower the drug release due to reduced porosity of the coating polymer. Based on the results obtained, graph was plotted between time and % swelling index (as represented in Figure 5).

Figure 4: Microspheres before swelling and after swelling.

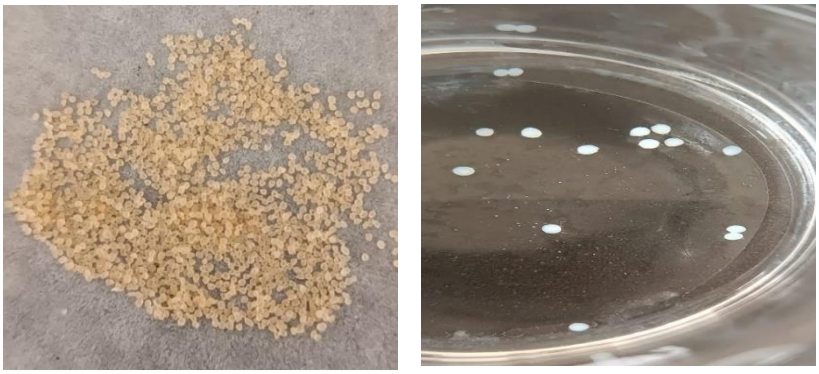


Table No-4: Values of % Swelling Index

S. No	Formulation	% Swelling Index			
		2 hrs	4 hrs	6 hrs	24 hrs
1	F1	1.3 ± 0.12	5.3 ± 0.49	7.3 ± 0.84	10.6 ± 0.82
2	F2	3.3 ± 0.56	8 ± 0.567	12.6 ± 0.86	14.6 ± 0.21
3	F3	2.6 ± 1.46	8.6 ± 0.446	14 ± 0.46	19.3 ± 0.16
4	F4	4 ± 0.467	10 ±0.86	14.6 ± 0.39	20 ± 0.31
5	F5	6 ± 1.34	11.3 ± 1.68	18.6 ± 1.48	26.6 ± 0.98
6	F6	2 ± 1.547	6 ± 1.669	11.3 ± 1.85	17.3 ± 0.49
7	F7	5.3 ± 0.33	12 ± 1.46	17.3 ± 0.76	28 ± 1.671
8	F8	2.6 ± 0.958	8 ± 0.99	16.6 ±1.228	21.3 ± 1.55
9	F9	4 ± 0.547	8.6 ± 1.60	14 ±1.349	18.6 ± 1.64

The values are expressed as mean ± SD, (n=3)

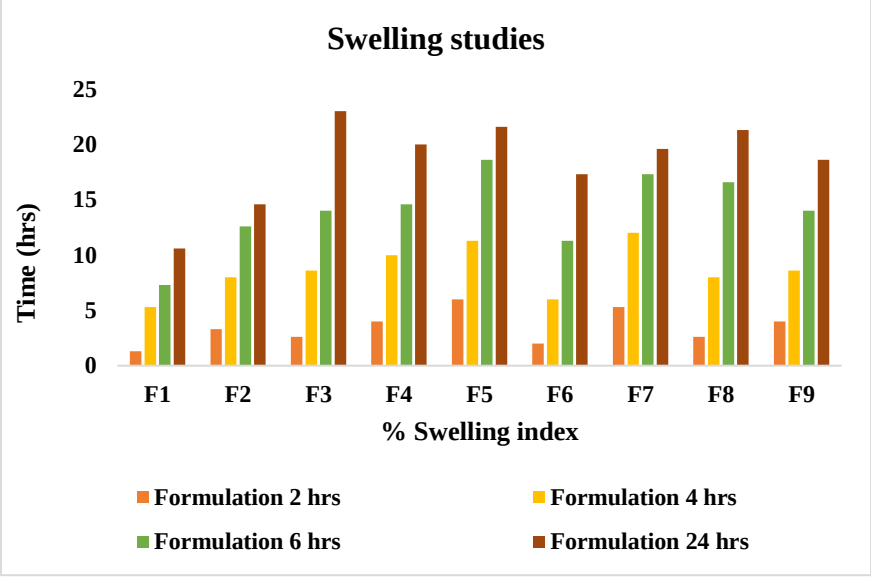
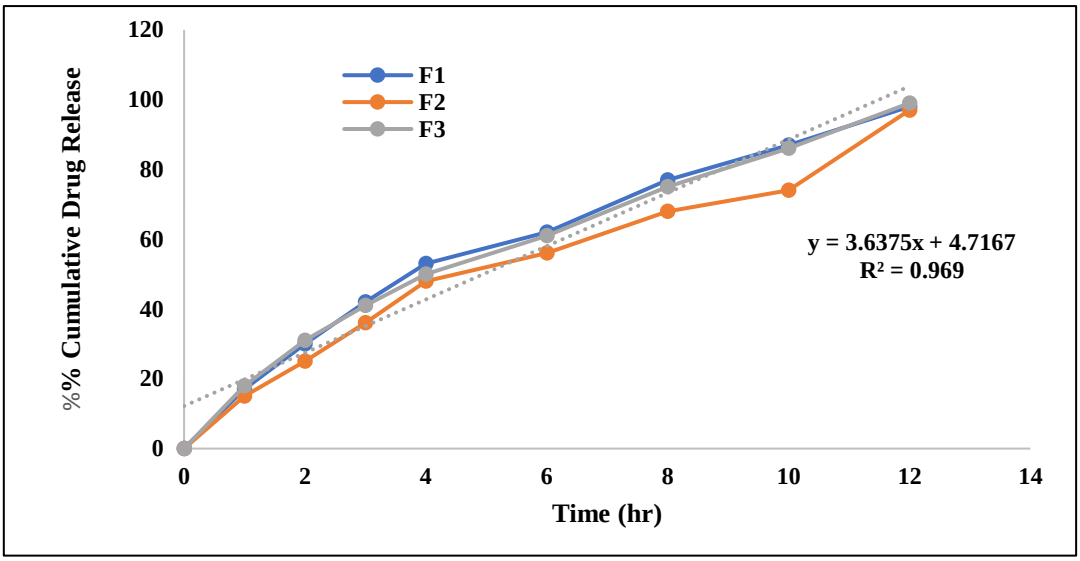


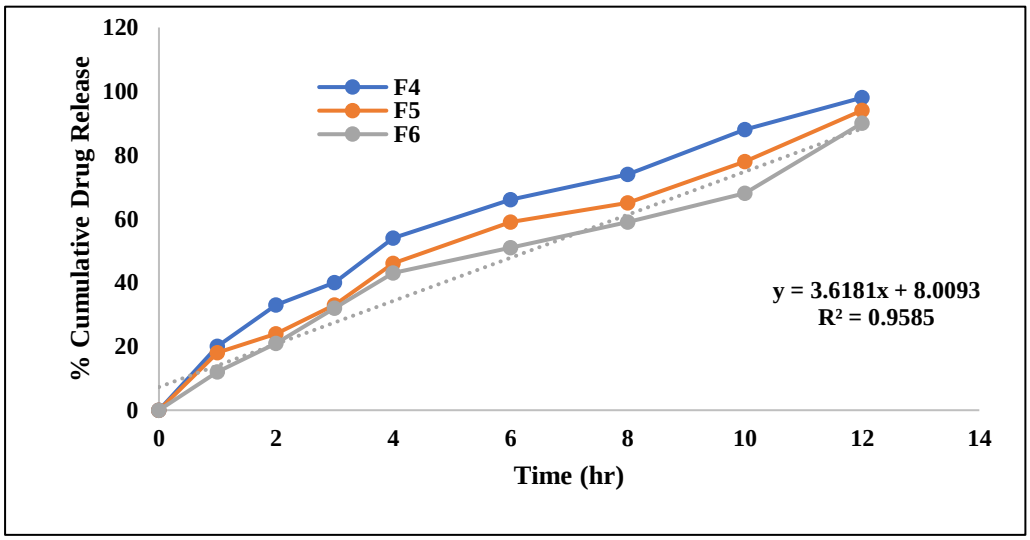
Figure 5: % Swelling index graphical representation

4.8. In-vitro drug release studies

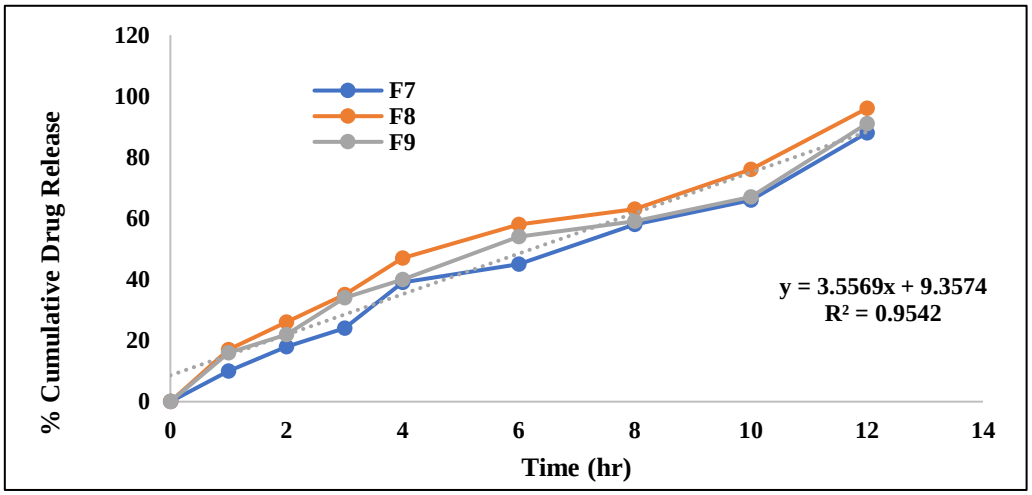
According to the results observed, a time vs % CDR graphs were plotted for all formulations as shown in Figure 6. The drug release pattern was controlled and prolonged up to 12 hrs based on the composition of sodium alginate and drug : polymer ratio.F3 formulation has showed sustained drug release of 99% drug release up to 12 hrs. Therefore the amount of drug release is inversely proportional to the concentration of sodium alginate and directly proportional to polymer ratio.



(a)



(b)



(c)

Figure 6: (a) In-vitro drug release of F1-F3, (b) In-vitro drug release of F4-F5, (c) In-vitro drug release of F6-F9.

4.9. Scanning Electron Microscopy (SEM) analysis

Microspheres prepared were spherical and have rough surfaces (as shown in Figure 7). The drug release showed slow and constant rate of release for 12 hrs due to favourable surface morphology.

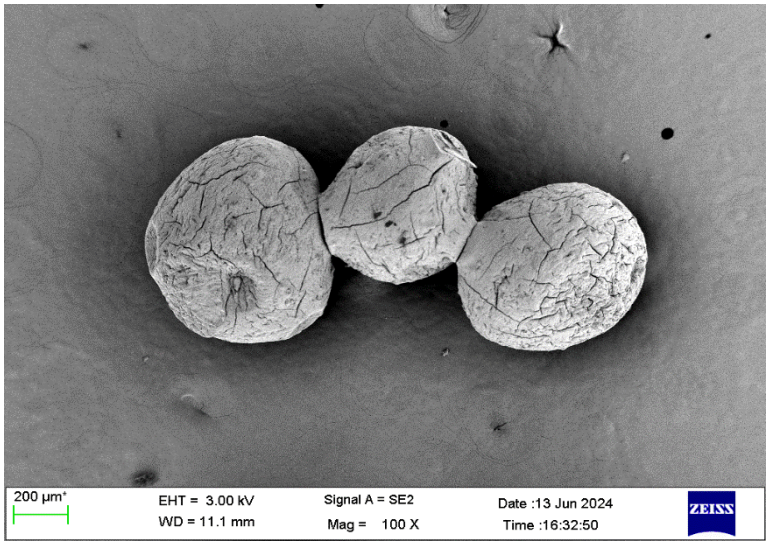
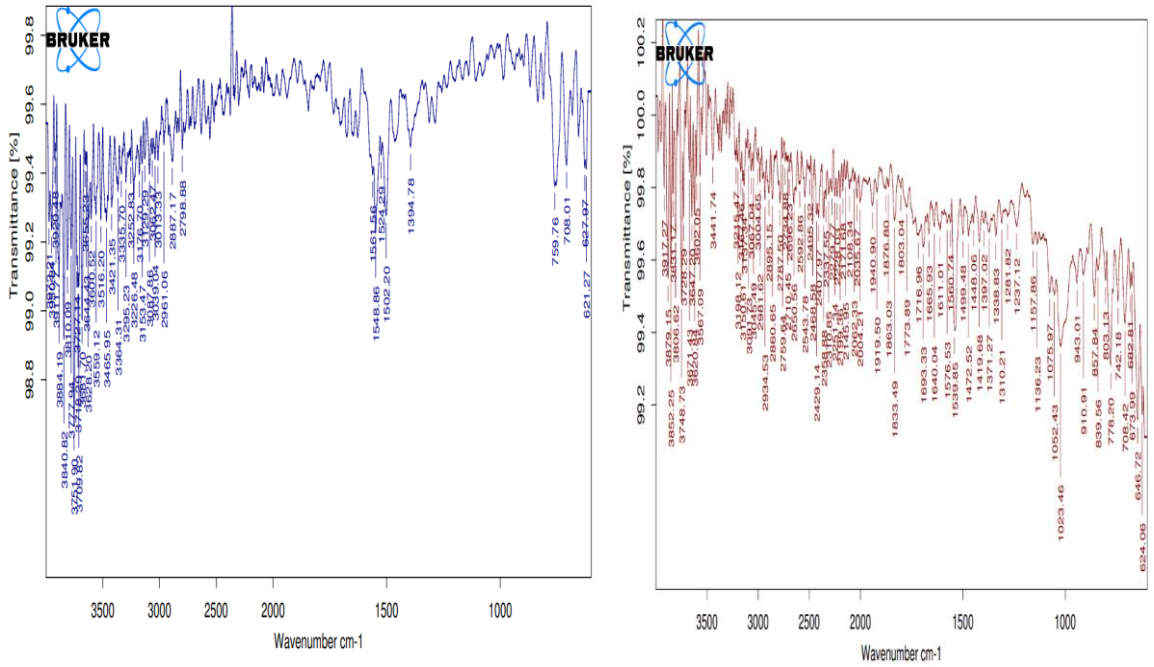


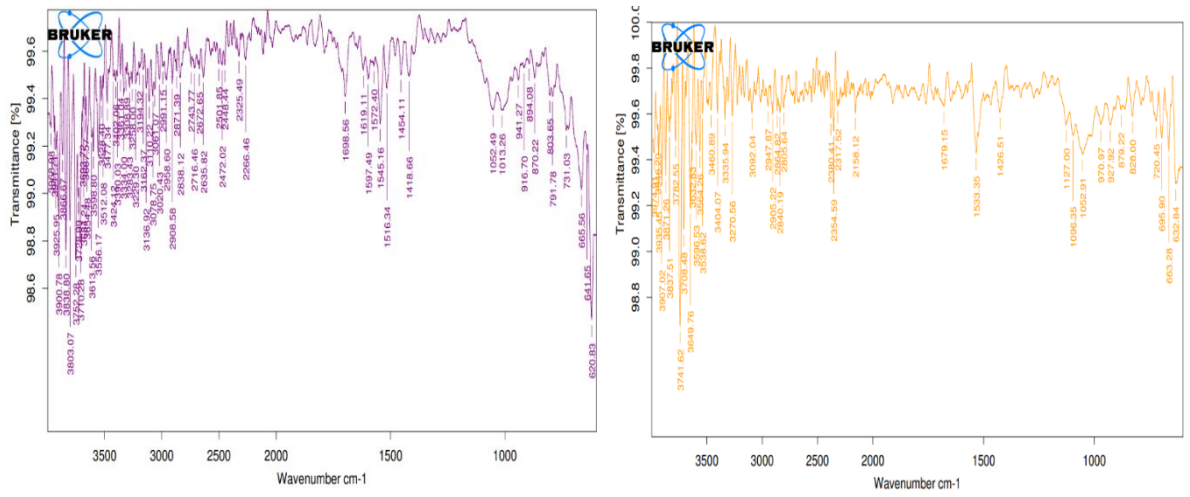
Figure 7: Visual obtained in SEM analysis

4.10. Determination of compatibility

The principle peaks validated the structure of diclofenac sodium. Microspheres loaded with diclofenac sodium exhibited the same structure. The diclofenac sodium-loaded microspheres showed no significant changes in characteristic peaks, indicating medication stability across all formulations. The results obtained did not show any significant incompatibilities among drug and polymer combinations. The graphs generated were shown in Figure 8.



(a) (b)



(c) (d)

Figure 8: FTIR studies of (a) pure drug, (b) drug + Sodium CMC, (c) drug + HPMC & (d) drug + PVP K30

CONCLUSION

An attempt was undertaken to formulate sustained-release microspheres of Diclofenac Sodium. These microspheres are used for treating rheumatoid arthritis. The Ionotropic gelation technique was used to create microspheres with Sodium CMC, HPMC & PVP K30 polymers as retarding polymers. Parameters such as percentage yield, particle size, entrapment efficiency, moisture content and swelling index were evaluated. The morphology of microspheres was examined using SEM. FTIR studies were also performed to determine the compatibility among drug and polymer combinations.

High % yield and entrapment efficiency were achieved with sodium alginate microspheres. Polymer type, concentration, stirring speed, and polymer combination all had an impact on particle size, entrapment efficiency, and manufacturing yield.

As the polymer to drug ratio increased, the amount of drug released has dropped. Increased polymer matrix density leads to slower rates. The pattern of drug release is regulated by the swelling control mechanism. In-vitro drug release studies were performed in phosphate buffer and the optimized formulation F3 showed maximum drug release of 99% sustained up to 12 hrs. Order of kinetics was determined for the optimized formulation and the rate of drug release was fitted with Zero order kinetic model with a regression coefficient of 0.97. From the above studies it was concluded that microspheres formulated with Sodium CMC along with 3% Sodium alginate was found to be the best formulation with 99% drug release in 12 hrs along with other considerable evaluation parameters. Additional research on Na alginate and sustained release polymers with varied calcium chloride concentrations is needed to produce a more effective dosage form with sustained and controlled drug release characteristics.

Declaration by Authors

Ethical Approval: Approved

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Conflict of Interest: The authors declare no conflict of interest.

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