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Formulation and Optimisation of Mucoadhesive Microsphere of H2 Antagonist Drug

Akshay S. Raut[1]; Dr. Sachin J. Dighade[2]; Esha S. Rithe[3]; Reema R. Mangwani[4]; Ashish L. Pohane[5]; Samiksha S. Bhamburkar[6]

[1;2;3;4;5;6]Institute of Pharmacy and Research Badnera, Amravati.

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Abstract: The administration of pharmaceuticals to patients is the primary focus of a drug delivery system, which aims to maximize therapeutic benefits while reducing hazards. Drugs may be administered in various ways, from the digestive tract to the skin and veins. One novel approach developed to assure sustained, steady medication release is gastro-retentive drug delivery systems (GRDDSs). Mucoadhesive drug delivery devices are a top choice for medications with low oral bioavailability. Nizatidine hydrochloride is an H_2 receptor antagonist, and its incorporation into mucoadhesive microspheres has been a primary focus in recent years. The pharmacological effect of the medicine is improved, and its release is prolonged using this method. This formulation uses sodium alginate dissolved in distilled water, carbopol solution, and Nizatidine in different amounts to accomplish ionotropic gelation. After the mixture is well emulsified, a calcium chloride solution is added. The number of microspheres adhering to tissue was counted at the end of 30 minutes, 1h, and hourly intervals up to 12 hours. Microspheres' potential mucoadhesive characteristics are shown by in vitro adhesion tests after careful preparation. The effectiveness of encapsulation and assessments of pharmaceutical content over predetermined batches (T1-T9) testify to the successful encapsulation of medications inside the delivery system, which serves as validation. To better treat disorders like peptic ulcers, this research highlights the promise of mucoadhesive microspheres as a regulated medication delivery route for Nizatidine.

Keywords: *Nizatidine, Ionotropic Gelation Technique, Microspheres, Sustained Release, Carbopol.*

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I. INTRODUCTION

A drug delivery system is a device that delivers medicine or other therapeutic agents to a patient in a manner that optimizes benefits while reducing hazards. 2012 (Umakanthareddy).

Oral, transdermal, topical, and parenteral modes of administration are all viable options for delivering drugs to the human body. More than half of all pharmaceuticals are administered orally, making it the most common route of administration. The efficiency of this method lies in its seeming ease of implementation.(Umakanthareddy, 2012) Storing dose forms in the stomach is a novel strategy known as gastro-retentive drug delivery systems (GRDDSs). These systems enhance controlled drug release since the pharmaceuticals are gradually released over an extended period. (Garg, 2012) Drugs absorbed in the upper GIT, those less soluble in the stomach, or those destroyed by basic pH, may also benefit from prolonged gastric retention.

The increased surface area of the stomach and better medicine solubility influence the absorption phase of oral pharmaceutical formulations in the small intestine's proximal segment. One technique for changing the gastrointestinal transit of oral pharmaceutical formulations is to create formulations that adhere to the stomach lining since this retains the medicine at the target absorption location for longer. (Jain, 2004) Pharmacological therapy is successful if the medication's target concentration in the blood or tissues is attained and the therapeutic amount of the drug is delivered to the site of action. (Garg, 2012) Microspheres, solid, approximately spherical particles with a pharmaceutical core and polymer outside layers as coating material, are one example of a novel dosage form that has recently gained interest. However, their short duration at the absorption site restricts their potency. (Khobragade, 2012)

The most frequent medication administration method is oral, albeit this method includes drawbacks such as unpredictable drug concentrations. These issues may be avoided with a specified medicine release profile (Rowland, 1972). (Collett, 2002) As regulated pharmaceutical delivery technologies, microspheres and microcapsules are gaining prominence. (Rao, 2005) Gastric retention has been studied to concentrate drug delivery in the stomach. (Zheng, 2006)

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Mucoadhesion, which happens when polymers engage with the intestinal epithelium, allows drugs to be targeted to the intestinal mucosa. (2005) (Burruano) Multifunctional polymers such as efflux pump inhibitors, permeation enhancers, and mucoadhesive polymers are all instances of polymer advancement throughout time. (Vigl, 2009) Chemical modification of the polymer carbopol improved solubility, mucoadhesion, and penetration. This modification is designed to increase the time the medication spends in the digestive system, boosting bioavailability.

Patients with peptic ulcer disease are given the H2 receptor antagonist Nizatidine HCl. It is available in 150mg and 300mg standard tablets for oral use. Its bioavailability is nevertheless hampered by high protein binding and first-pass metabolism. To meet therapeutic aims, the limits of current dosage techniques need the creation of a new drug delivery system. Mucoadhesive drug delivery devices are the preferred mode of administration for drugs with inadequate oral bioavailability. The fact that mucoadhesive microspheres stay at the site of administration or absorption for a longer time increases therapeutic effectiveness. 2004 (Chowdary) Famotidine, a histamine H2 receptor antagonist, treats gastric ulcers, duodenal ulcers, Zollinger-Ellison syndrome, and gastroesophageal reflux disease. (1999, Kathleen) Gastro retentive dosage forms, which have a half-life of roughly 3 hours in healthy people, may improve absorption from the proximal small intestine by holding the medication in the stomach for longer. Local administration to the receptor on the parietal cell wall may increase drug absorption and efficacy in reducing acid secretion. (Lee, 2003) Famotidine may be given more efficiently both systemically and locally using this approach, reducing stomach acid output. Marina and colleagues (2012)Nizatidine HCl is an H2 blocker administered to people suffering from ulcers, GERD, and Zollinger-Ellison syndrome. Nizatidine, available without a prescription, may help prevent and relieve heartburn caused by acid reflux and a sour stomach. (Dave, 2004)

Nizatidine is now available in conventional drug delivery methods and combined with nonsteroidal anti-inflammatory medications. Researchers used solvent evaporation and ethanol co-solvent systems to create Nizatidine hydrochloride microspheres, only one of the numerous continuous drug delivery strategies they investigated. Higher bioavailability is complemented by greater buoyancy in these microspheres with a biphasic controlled release pattern. Other solutions include floating drug concepts, magnetic microspheres, mouth-dissolving tablets, emulsion technology in carbopol microspheres, gastro-retentive bilayer tablets, and spray-drying microspheres containing Amoxicillin and alginate.

The H2 receptor antagonist Nizatidine hydrochloride must be dosed often to maintain therapeutic efficacy. It has a half-life of just 2-3 hours. The longer the drug is in the stomach, the more likely it will have an impact. Mucoadhesion is an excellent method for maintaining the drug where it needs to be for prolonged pharmacological action. Variables such as processing processes and mucoadhesive delivery polymers utilized significantly impact the system's performance.

II. MATERIALS AND METHODS

➢ *Materials*

The Nizatidine was provided by Stride Shasun., India. In Mumbai, India, Loba Chemicals supplied sodium alginate and carpool, while SD Fine Ltd in the same city provided calcium chloride. Other than that, all compounds employed in this investigation were of analytical quality.

➢ *Preparation of Nizatidine Microspheres*

The microspheres were made using the compositions shown in Table 1 using the ionotropic gelation process. In the first step, sodium alginate was dissolved in distilled water using low heat and a magnetic stirrer. Different concentrations of carpool solution were made according to the Taguchi design for the whole solution, then mixed with a weighed quantity of Nizatidine and allowed to emulsify at 500 rpm while being kept at room temperature. After 30 minutes of stirring, the mixtures were sonicated to remove any remaining air bubbles. For 30 minutes, a 10% w/v, 15% w/v, and 20% w/v calcium chloride solution were agitated at 150rpm, 200rpm, and 250rpm, respectively, while the above dispersion was added dropwise using a 24-gauge size needle attached to a 10ml syringe. After that, we used Whatman filter paper to strain the solution and distilled water to rinse the microspheres. Drying the Nizatidine microspheres in a hot-air oven for 2 hours at 60 degrees Celsius.

➢ *Evaluation of Microspheres*

- *Encapsulation Efficiency and Loading Efficiency Study*

Accurately weighed 100 mg of microspheres were crushed in a mortar and added to 100 ml of acid buffer pH 1.2 and 7.4. This mixture was stirred for 24 hours on a magnetic stirrer and filtered through Whatman filter paper no. 42 and analyzed spectrophotometrically at 213 nm.

$$\%\ \text{Encapsulation Efficiency} = \frac{\%\ \text{Encapsulation Efficiency}}{\text{Theoretical drug content}} \times 100 \quad (1)$$

$$\%\ \text{Drug Loading Efficiency} = \frac{\text{Weight of drug in microspheres}}{\text{Weight of drug-loaded microspheres}} \times 100 \quad (2)$$

- *In-vitro Mucoadhesion Study*

The wash-off technique of in vitro adhesion testing was used to measure the mucoadhesive property of microspheres. Goat intestine mucosa, freshly removed, measured 7 by 2 centimeters and was mounted onto glass slides measuring 3 by 1 inch, using cyanoacrylate adhesive. Each tissue specimen was washed in water and then coated with around 50mg of microspheres before the support was suspended from the arm of a USP pill-dissolving test machine. The tissue specimen was immersed in the test fluid (500 ml pH 1.2 phosphate buffer) at 37 degrees Celsius and moved up and down at regular intervals by the disintegration test machine. Microsphere adhesion to tissue was measured after 30 minutes, 1 hour, and every hour up to 12 hours.

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➢ *Differential Scanning Calorimetry (DSC)*

A differential scanning calorimeter was used for the thermal study. The samples were warmed to 200 degrees Celsius in a sealed aluminum pan. The sample was scanned from 40 to 380 degrees Celsius at 10 degrees per minute after being cooled to room temperature. During a given transition (transition energy), the quantity of heat added to the system always equals the amount of heat absorbed or released.

➢ *In vitro Drug Release Study*

The USP type - I rotating basket technique was used for the dissolution investigations, and the simulated stomach fluid pH 1.2 (900 ml) was analyzed in a fully calibrated eight-station dissolution test equipment (37 ± 0.50°C, 50 rpm). Microspheres used in dissolving research typically contain 15mg of medication. The release of the medicine was monitored by taking absorbance readings at 213 nm from aliquots of the sample at regular intervals. Simulated gastric fluid with a pH of 1.2 was heated and replaced with the same amount at regular intervals to keep the sink at a constant temperature and pressure.

The following materials were procured for the formulation and optimization of the mucoadhesive microspheres:

Nizatidine hydrochloride, purchased from Chennai's Burgeon Chemical Ltd., was utilized as the H2 antagonist in the mucoadhesive microsphere formulation. In addition, we selected high-quality sources for our carpool, polyvinyl alcohol (PVA), eudragit RS 100, dichloromethane, acetonitrile (HPLC grade), potassium dihydrogen orthophosphate, sodium hydroxide, liquid paraffin, and hexane. These chemicals and materials were chosen with care to provide a consistent and high-quality composition.

➢ *Preparation of Mucoadhesive Microspheres*

The solvent evaporation technique produced mucoadhesive microspheres throughout the formulation process. The following measures were taken:

- *Study of Drug-Polymer Compatibility:* To examine any possible interactions, a compatibility study was done between the medicine (Nizatidine hydrochloride) and several polymers (carbopol, polyvinyl alcohol, and Eudragit RS 100).
- *Microsphere Formulation:* Different drug and polymer combinations were created by dissolving the necessary amounts in a suitable solvent (dichloromethane). To obtain a stable emulsion, the fluid was emulsified using a probe homogenizer (Virtis Cyclone IQ, USA).
- *Emulsion Crosslinking:* Under continual stirring, the emulsion was dropwise added to a crosslinking solution containing a crosslinking agent (glutaraldehyde or calcium chloride). Through solvent evaporation and polymer precipitation, this process aided in the production of microspheres.
- *Washing and drying of microspheres:* The microspheres were washed with distilled water to eliminate any remaining solvent and unreacted components. They were then lyophilized using a Labconco Lyophilizer (USA) to produce dry microspheres.

➢ *Characterization of Microspheres*

Microspheres' size, shape, and surface properties were evaluated using a scanning electron microscope for this investigation. UV-Visible Spectrophotometry was used to measure drug loading efficiency, and an in vitro mucoadhesion test was conducted to measure mucoadhesive strength. An HPLC system was used to investigate the kinetics of drug release in vitro.

The drug's thermal characteristics and interactions with polymers were studied using Differential Scanning Calorimetry. Researchers used a probe homogenizer, centrifuge, and lyophilizer to mix the medicine and polymer. Electronic balances, scanning electron microscopy, ultraviolet-visible spectrophotometers, differential scanning calorimeters, high-performance liquid chromatography, and bulk density apparatus were used to make accurate measurements.

III. RESULTS AND DISCUSSION

➢ *Encapsulation Efficiency*

Information is provided for batches designated T1 through T9, namely their encapsulation efficiencies and medication contents. The success of drug encapsulation inside delivery systems may be measured by these characteristics, making them a standard tool in pharmaceutical and drug delivery research.

The proportion of medicine that was effectively encapsulated is measured by the Percent Encapsulation Efficiency metric, whereas the amount of drug that was really present in the formulation is measured by the Percent medicine Content metric. These factors are essential for pharmacokinetic and pharmacodynamic analyses, which are necessary for determining the efficacy of drug delivery systems.

Table 1 Percent encapsulation efficiency and percent drug content of batches T1 to T9

Batch number	% Entrapment efficiency	% Drug content Efficiency
T1	39.85 ± 0.97	25.56 ±0.58
T2	46.69 ±0.82	25.799±0.77
T3	43.13 ±1.21	24.99±0.39
T4	61.63 ±1.15	20.28±0.16
T5	86.18 ±1.34	23.54±0.60
T6	67.94 ±0.98	21.60±0.54
T7	80.05 ±1.31	19.71±0.17

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T8	94.24 ±1.29	21.15±0.23
T9	79.18 ±1.23	21.10±0.36

*Each value represents mean ± standard deviation (n=3)

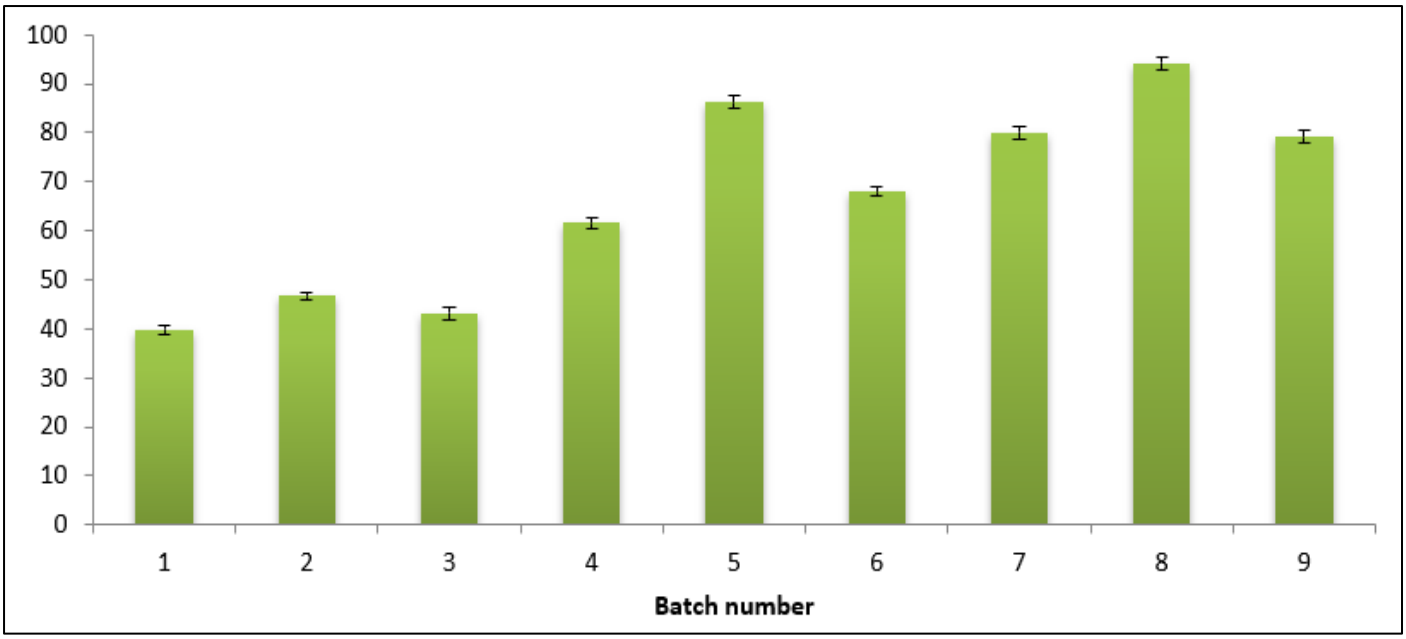

Fig 1 Entrapment Efficiency of Batches T1 to T9

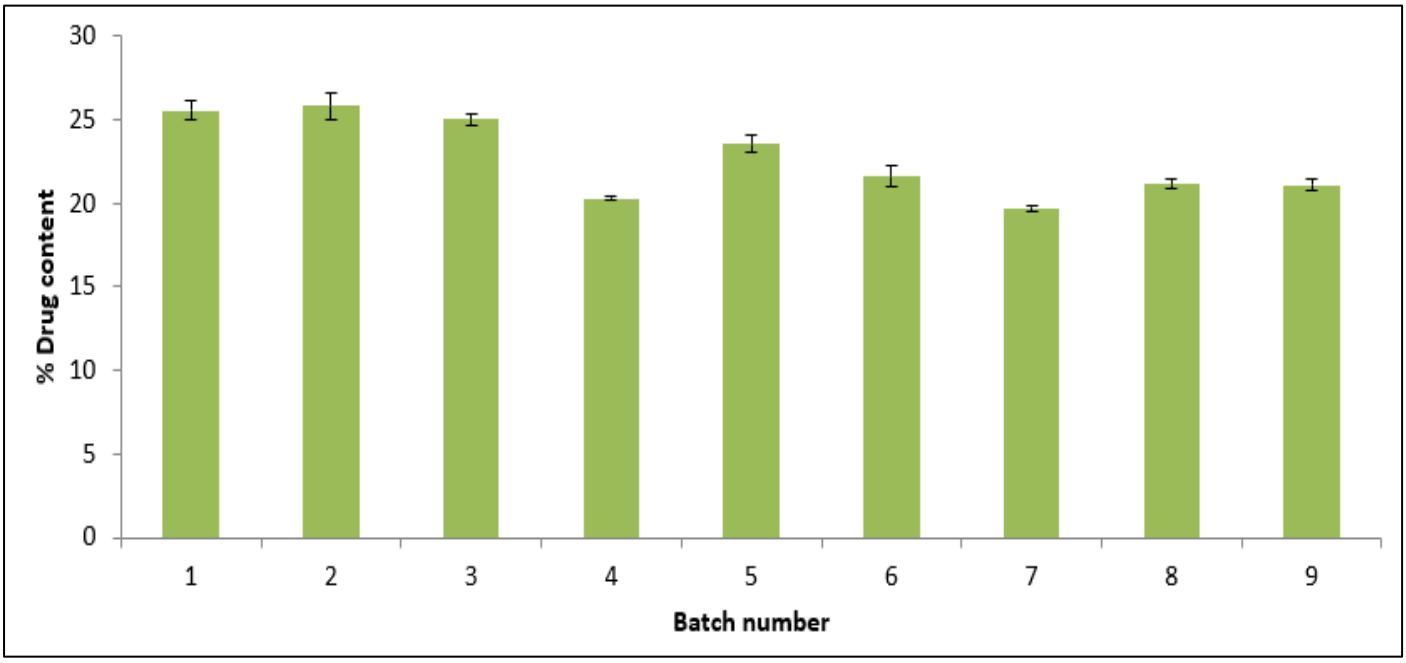

Fig 2 %Drug Content of Batches T1 to T9

Each batch's encapsulation efficiency (35 – 79%) and drug (25 - 21%) content are shown in the data (from T1 to T9). These numbers show how much of the medicine is present and how well it was incorporated into the delivery mechanism. A more excellent drug content and encapsulation efficiency suggest that more of the formulation consists of the active ingredient. T8 has shown the highest Percent Encapsulation Efficiency, 94.24 ± 1.29%, and Percent Drug Content, 21.15 ± 0.23%. It is essential to remember that the ideal ranges for these parameters may vary depending on the medicine and the drug delivery method being researched. The reliability and repeatability of experimental findings may be evaluated using standard deviations (SD), which give information about the variability of the data.

➢ *Percent Mucoadhesion*

Drug delivery systems with higher mucoadhesion percentages are more likely to be retained and have their intended effects at their intended administration locations, as shown by data for batches T1 through T9.

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Table 2 Percent Mucoadhesion of Batches T1 to T9

Batch no	% Mucoadhesion
T1	56.92±1.32
T2	67.28±1.15
T3	62.90±0.78
T4	73.48±0.84
T5	81.50±0.97
T6	77.48±1.04
T7	79.56±1.34
T8	95.68±1.22
T9	92.24±0.98

*Each value represents mean ± standard deviation (n=3)

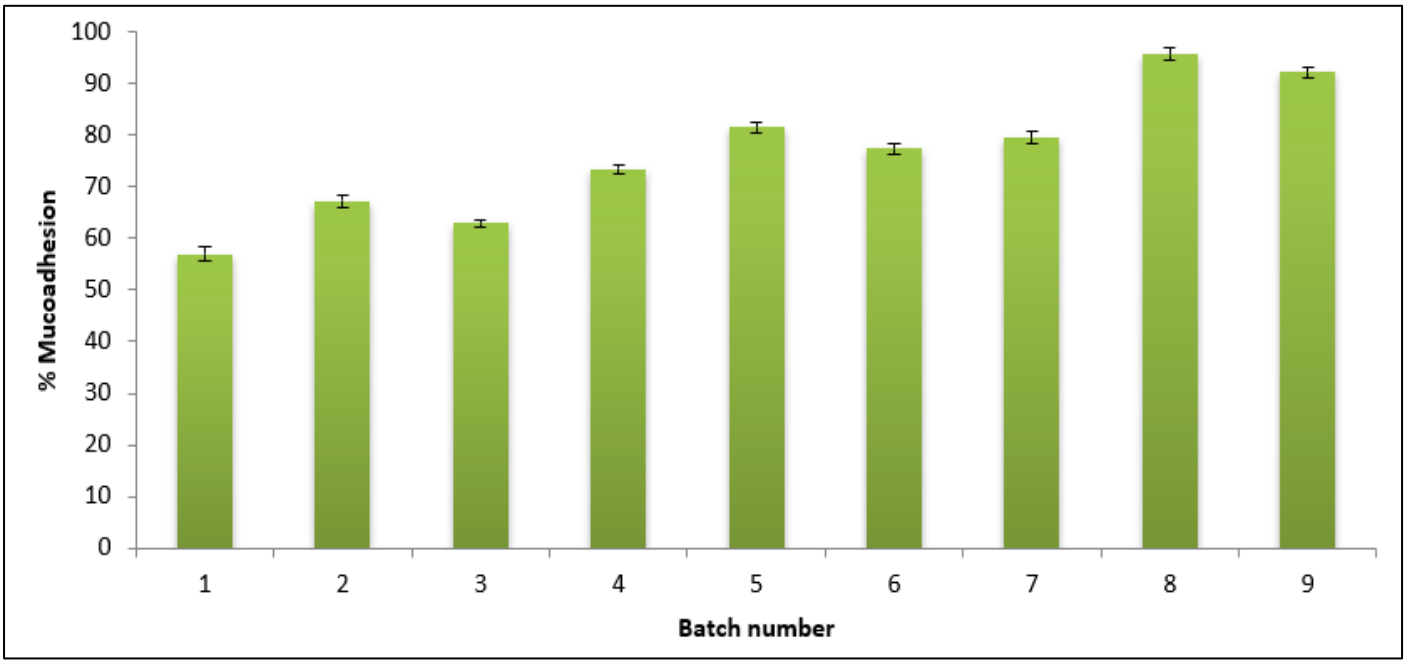

Fig 3 % Mucoadhesion of Batches T1 to T9

Indicating the drug delivery system's ability to adhere to mucosal surfaces, the data shows the mean values and standard deviations of % mucoadhesion for each batch (T1 to T9). Enhanced treatment effectiveness and increased residence time at the site of action are associated with higher mucoadhesion values. The effect of formulation parameters, such as polymer choice or preparation procedures, on the system's mucoadhesive characteristics may be seen in variations in mucoadhesion values across various batches. The repeatability and reliability of the technology are reflected in the standard deviations, which provide insight into the variability of mucoadhesion readings. Strong adhesion to mucosal surfaces is shown by the high mucoadhesion percentages of 95.68 and 92.24 for batches T8 and T9, respectively. These results indicate that batches T8 and T9 of the drug delivery system formulations have achieved outstanding mucoadhesion, leading to more precise drug administration and better clinical outcomes. When determining the relevance of mucoadhesion percentages, it is essential to consider the experimental setting, formulation design, and planned use.

- *Differential Scanning Calorimetry (DSC)*

The drug's thermal characteristics and those of the drug-and-excipients combination are important because they may be used to evaluate the interaction between the various ingredients in a formulation. The melting point of pure Nizatidine (NIZ) is between 128 and 132 degrees Celsius, and its DSC curve exhibited a single strong endothermic peak at 133.81 degrees Celsius, beginning at 130 degrees Celsius and ending at 136 degrees Celsius.

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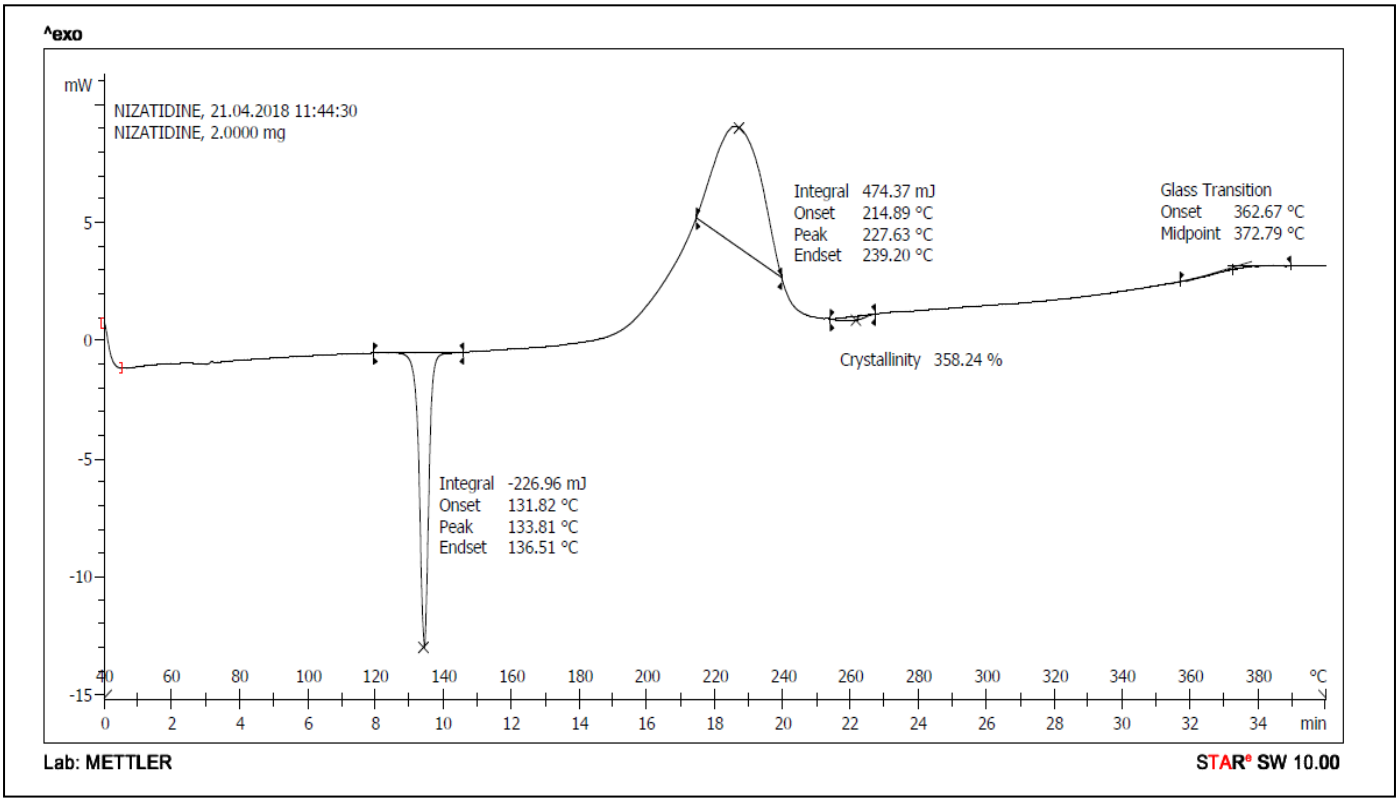

Fig 4 DSC of Nizatidine

Similarly, batch no T8 thermogram showed a peak at 132.42 C. The physical mixture of the drug and batch no T8 showed the DSC thermogram at 134.62 C, which reveals that the drug is complex with batch no T8. There is a slight shift in melting point because of moisture content.

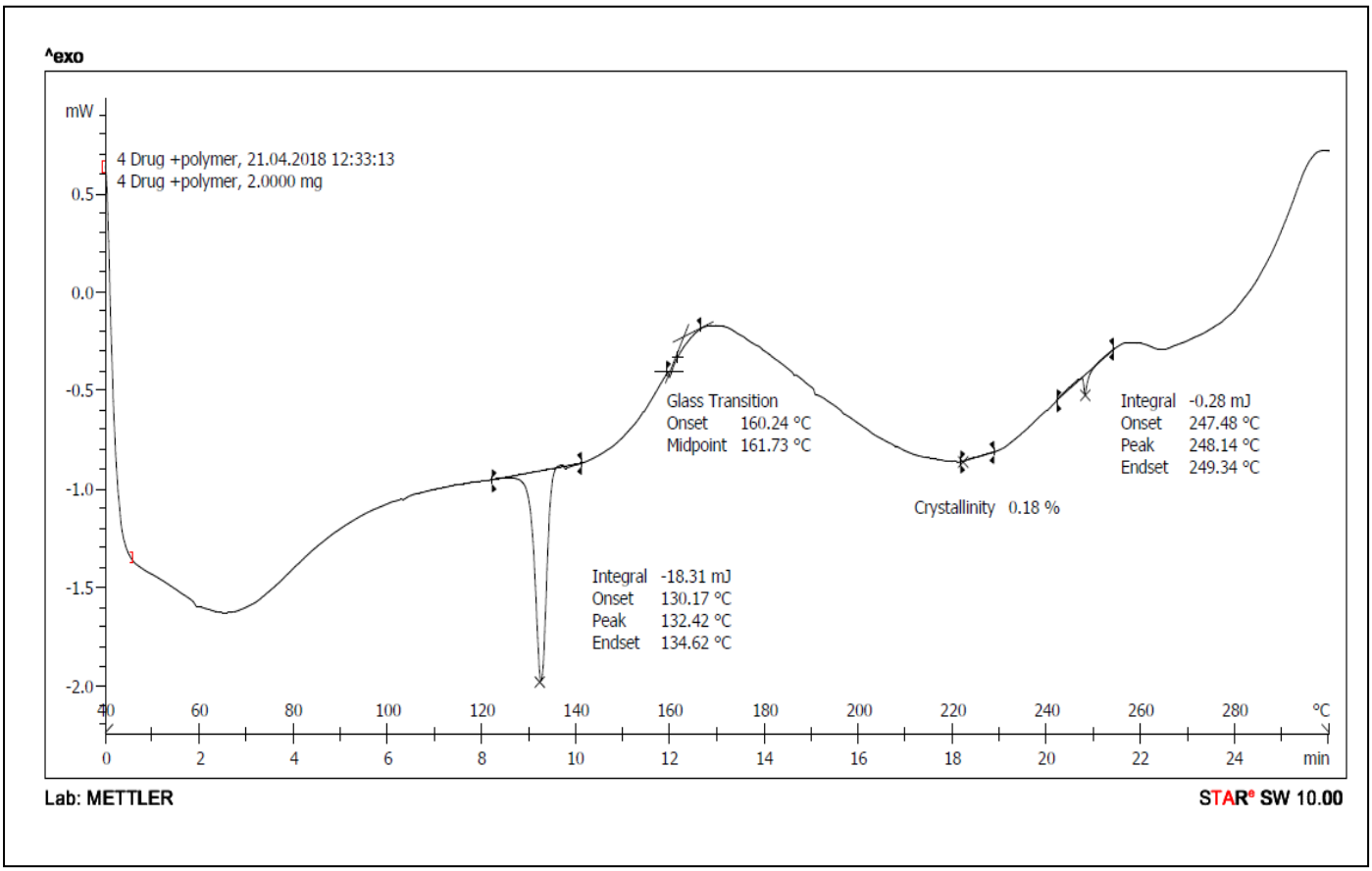

Fig 5 DSC of Batch no T8

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➢ *Morphological Characterization (SEM)*

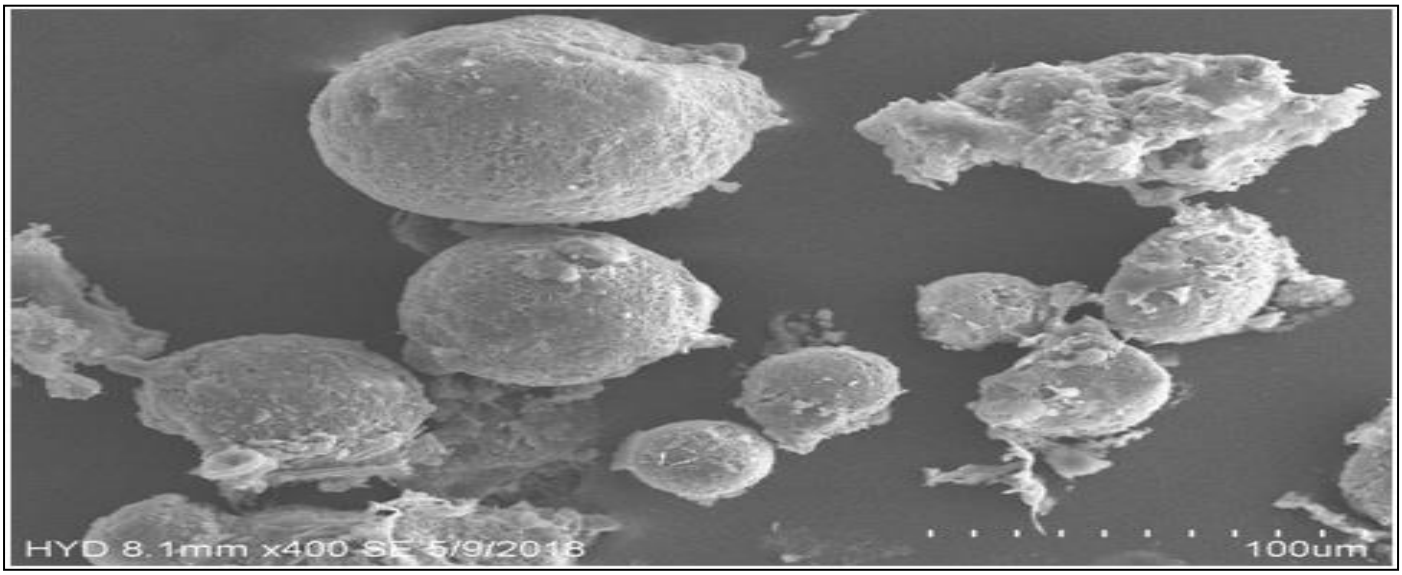

Fig 6 SEM of Batch no T8

According to the particle size analysis data, the generated microspheres had an average particle size of 256.2 µm. With an increase in polymer content, larger particles were produced. SEM examination of Batch T8 indicates an average particle size of 600.2 nm and a PDI of 0.944. Particles with a width of 41.55 nm and a specific size of 256.2 nm predominate. With a width of 41.55 nm, the spread is narrow compared to the average. This might be because the matrix density of the microspheres rose as the polymer concentration increased, which in turn could have led to an increase in the particle size of the microspheres. According to the data above, particle size is positively influenced by polymer concentration and negatively by stirring speed. It is recommended to use a lower polymer level to create microspheres with a smaller particle size. From the scanning electron micrograph of the final, optimized formulation (Fig. 6), it was clear that the microspheres had a round shape.

➢ *In-vitro Drug Release Study*

According to the statistics, the rate of drug release from each batch changes with time, with no medication being released from Batch T8 at 0 hours and 33.76 percent being released at 1 hour. A higher fraction of the medicine is released at later points in time. This trend holds for all batches tested (T1 through T9), suggesting that only minor adjustments to the drug's composition or delivery method are at play here. The drug release rate, release profile, and overall performance may all be evaluated by in-vitro drug release experiments, making them essential for understanding drug formulation behavior over time. This data is crucial for achieving therapeutic objectives via the delivery mechanism, improving drug formulations, and establishing safe and effective dosage schedules. The most successful formulations for attaining the desired medication release pattern may be identified by comparing the drug release profiles of various batches.

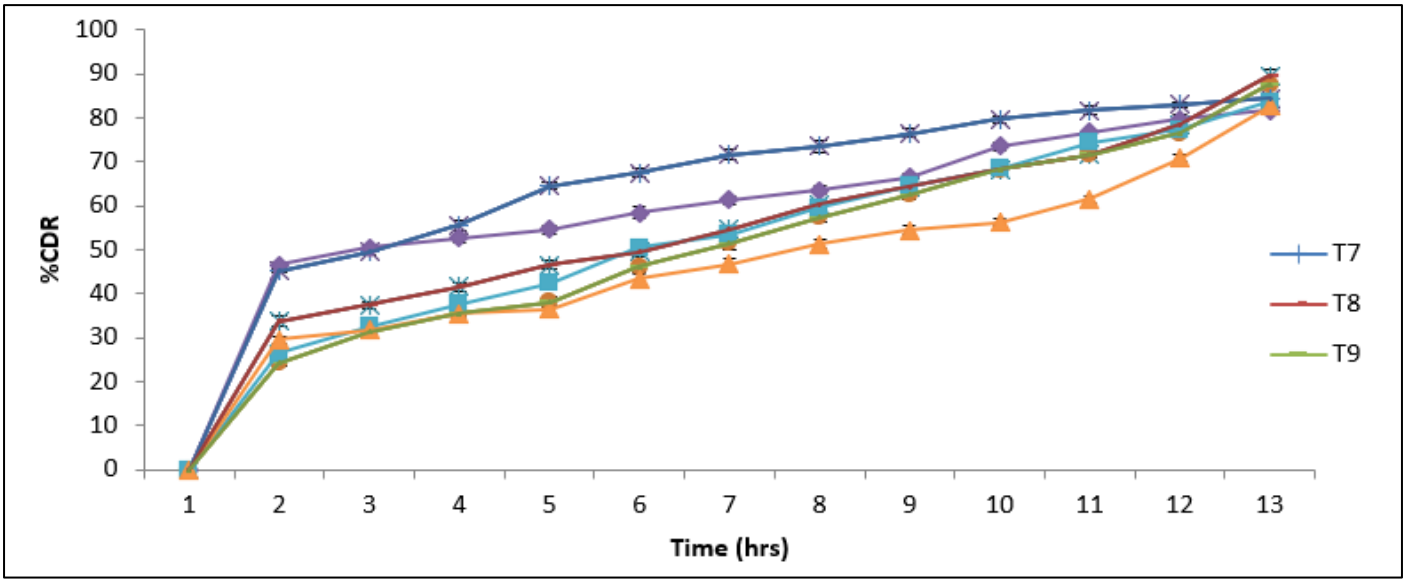

Fig 7 The Percentage Cumulative Drug release of Formulation Batch T7-Batch T9

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➢ *Stability Study*

Table 3 % Mucoadhesion of Batch no. 8, which kept under Stability Study

Sr. no.	0 Month	1st Month	2nd Month	3rd Month
1	93.33%	92.33%	92.00%	91.77%

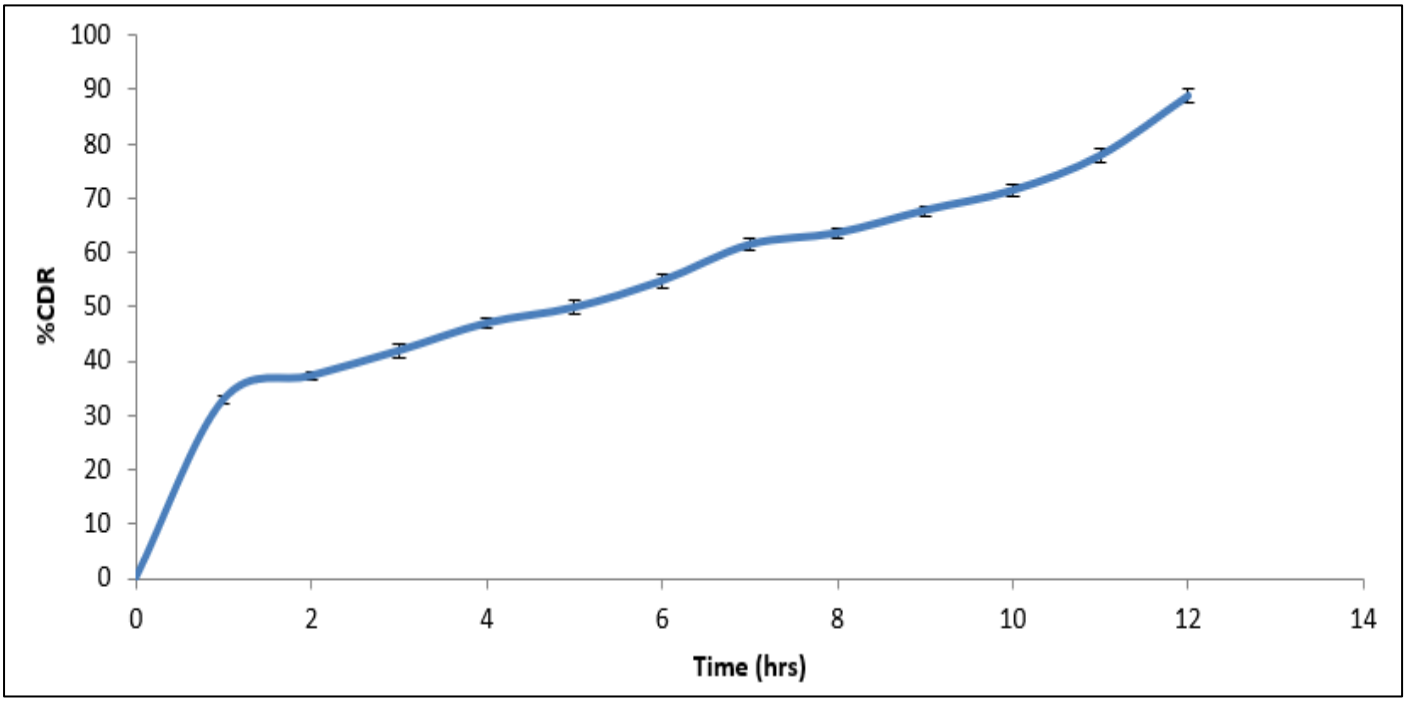

Fig 8 In- vitro Drug release of Optimized Batch T8 kept under Stability Study for Zero Months

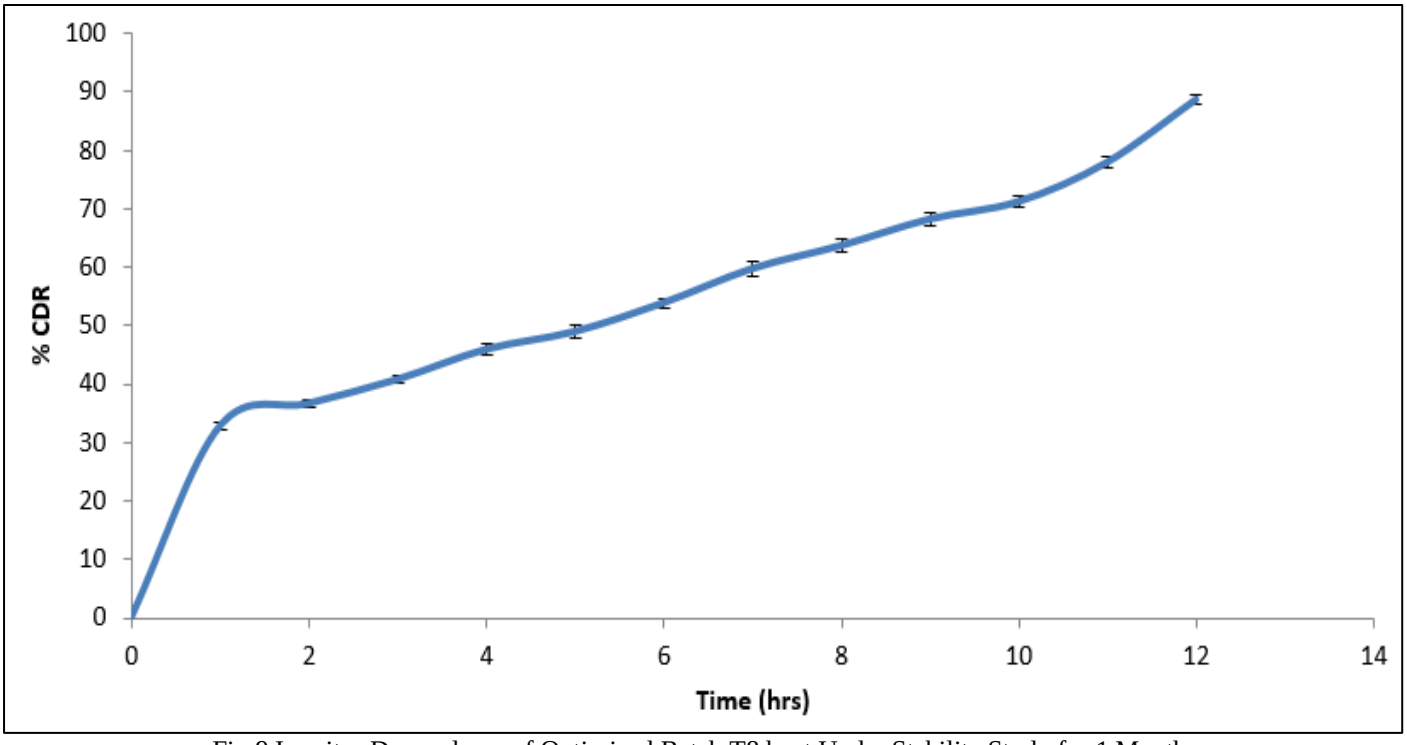

Fig 9 In- vitro Drug release of Optimized Batch T8 kept Under Stability Study for 1 Month

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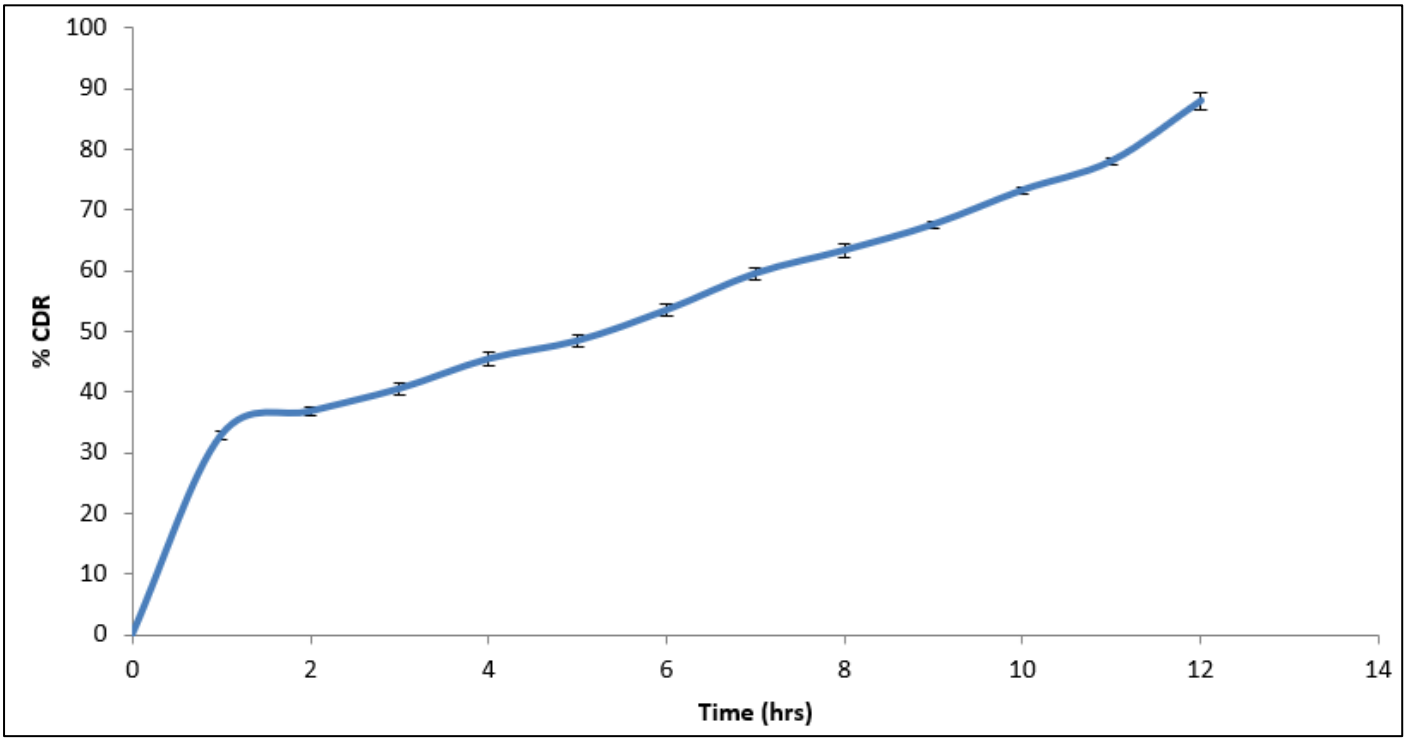

Fig 10 In- vitro Drug release of Optimized Batch T8 kept Under Stability Study for 2 Months

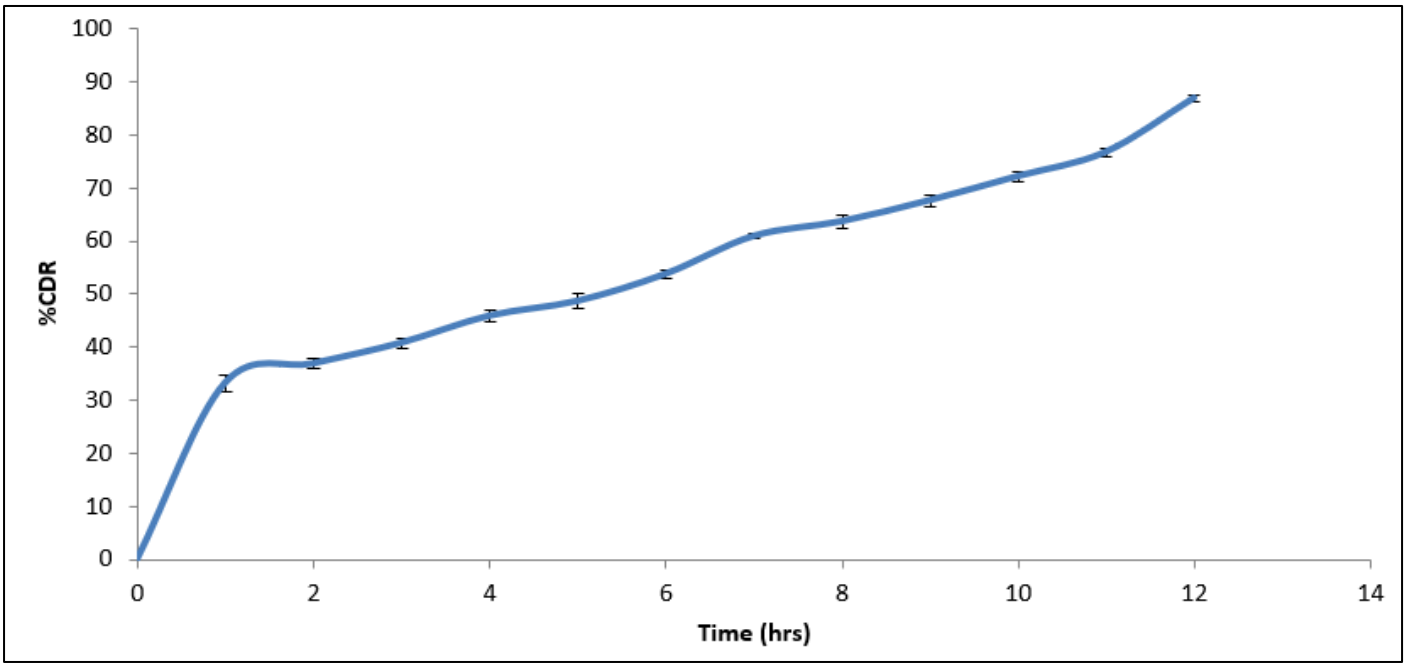

Fig 11 In- vitro Drug release of Optimized Batch T8 kept Under Stability Study for 3 Months

A stability study of optimized formulation Batch 8 was carried out by storing the microspheres (wrapping in aluminum foil) at 40±2º C and 75±5% relative humidity for 3 months. At an interval of 1 month, the microspheres were visually examined for any physical changes, *in-vitro* mucoadhesion, and *in-vitro* release data.

The results demonstrate that after three months, the mucoadhesion of Batch No. 8 had dropped to 91.77 percent. As a result, the formulation's adhesion to mucosal membranes may alter over time. If mucoadhesion is vital for therapeutic efficacy, stability tests are essential to ensure the formulation retains its effectiveness and consistency during the planned shelf life. These findings help determine whether the formulation is stable enough for long-term usage and storage.

- *Characterization of drug, polymer, excipient and physical mixture using Fourier transfer infrared spectroscopy*

The infrared spectrum was obtained with an FT-IR spectrophotometer in the 4000 to 500 cm^{-1} range using the potassium bromide method. : FT-IR

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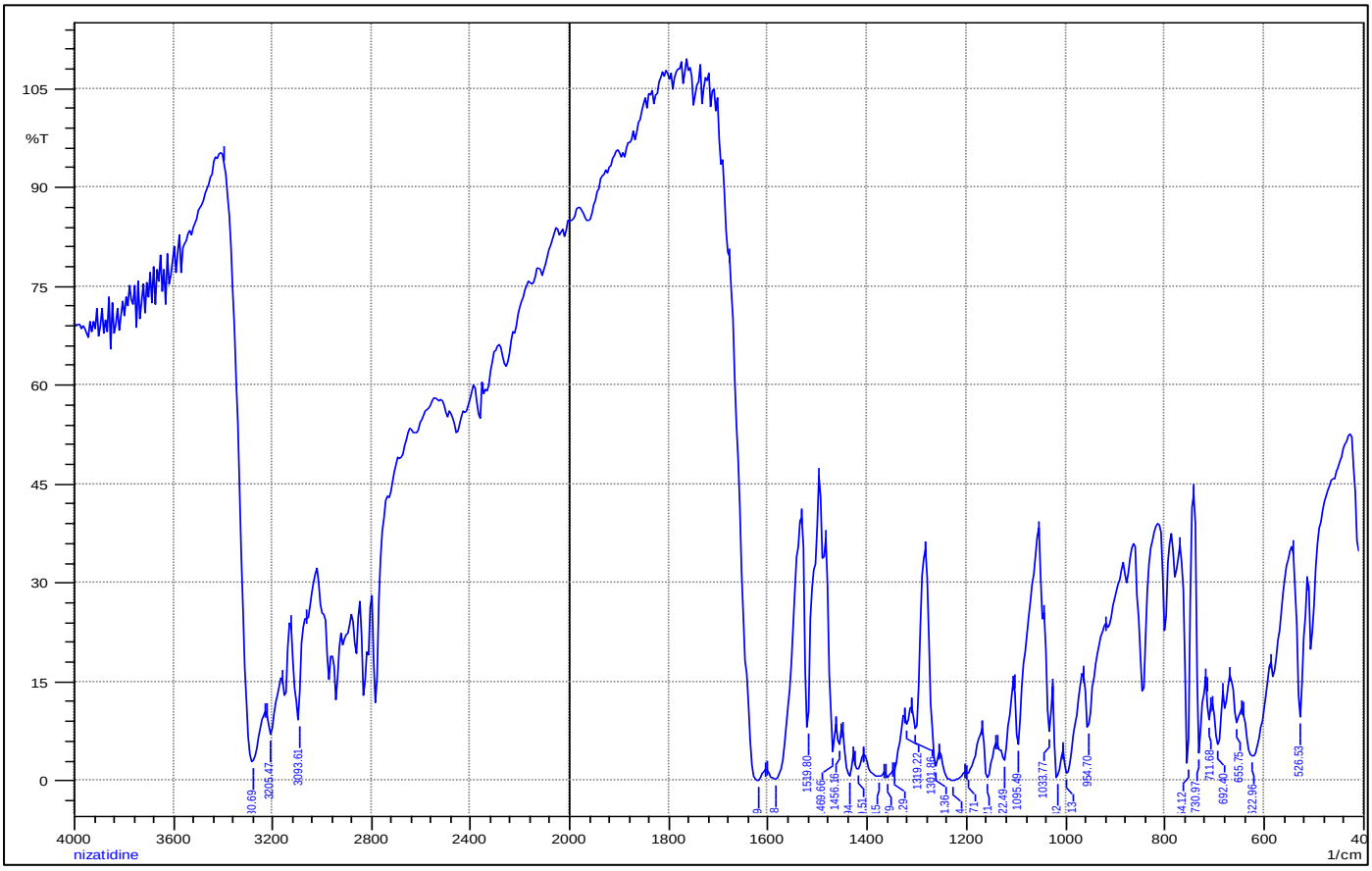

Fig 12 Spectra of Nizatidine

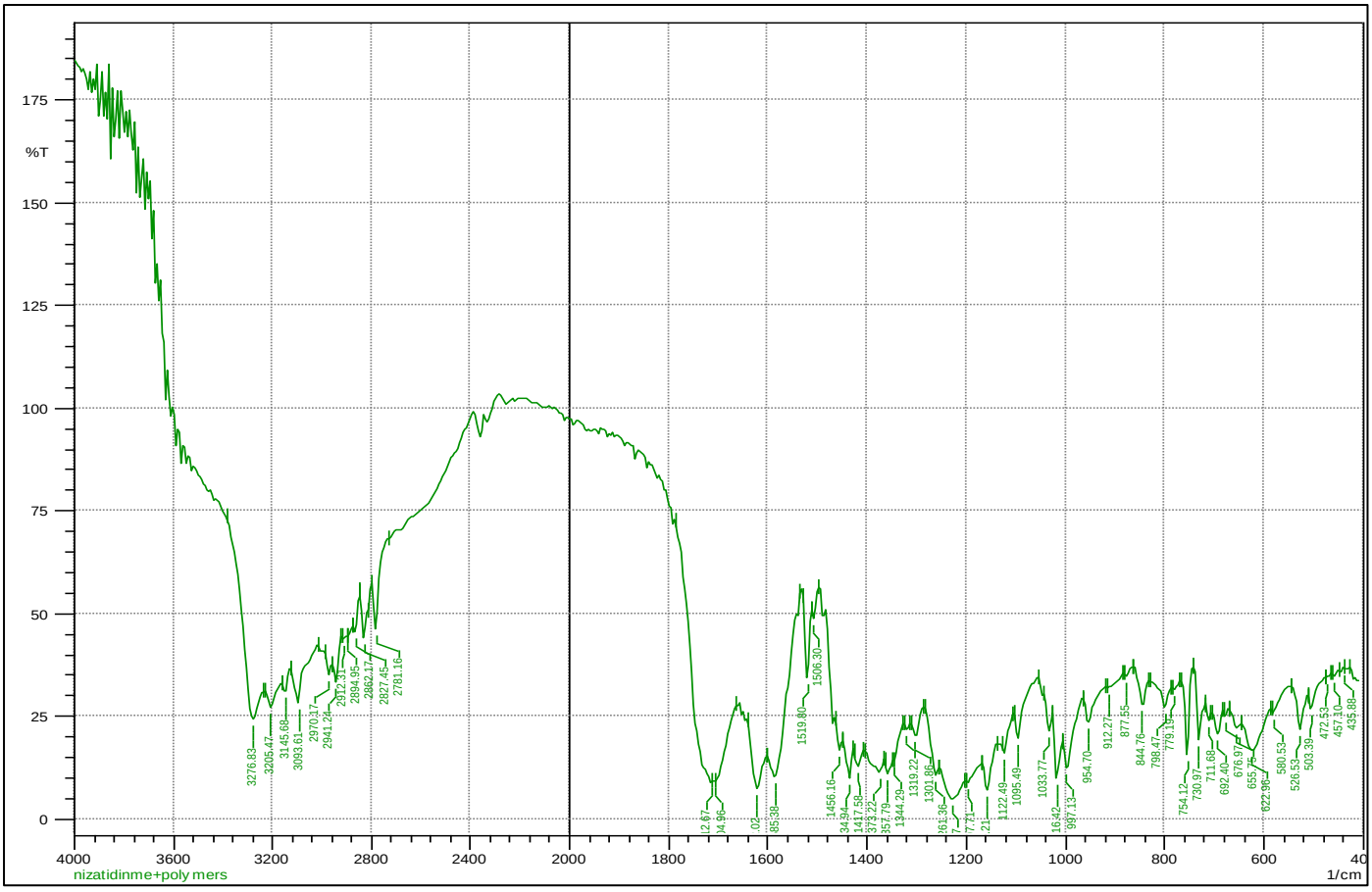

Fig 13 FT-IR spectra of Nizatidine + polymer physical mixture

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The medication, polymer, excipient, and physical combination were analyzed using Fourier transform infrared spectroscopy (FTIR), and the spectrum produced was in the range of 4000 to 500 cm-1 using the potassium bromide (KBr) technique.

The FTIR spectra of pure Nizatidine and carbopol were acquired to describe these precursors further. To ensure that the medication and polymer in the formulation had not interacted due to the manufacturing conditions, an FTIR spectroscopy investigation was conducted. According to these findings, no drug-excipient interactions occurred. Drug, polymer, and formulation FTIR spectra are shown in Fig. 12. Nizatidine's FTIR spectrum displays several bands at around 3540, 3410, and 3300 cm-1, all of which have been attributed to stretching vibrations of OH groups and symmetric stretching peaks of NH. Additionally, the substance's chemical structure assigns the bands about 3075 and 2987 cm1 to the CH furan. The asymmetric vibrations of CO cause the peak at 1150 cm-1 in the FTIR spectra of carbopol. The ring's COH, COC, and CH2OH are attributed to the peaks about 1080-1025 cm-1. Carbopol's saccharide structure wags, which explains the peak of about 890 cm-1. The wave number was tweaked ever-so-slightly, and it caused a shift in the peaks. The formulation's FTIR spectra also found the drug's signature peaks.

IV. CONCLUSION

Using ionotropic gelation procedures, the researchers created mucoadhesive microspheres filled with the H2 antagonist medication Nizatidine. The microspheres have an excellent mucoadhesive profile and encapsulation effectiveness, and they release their contents slowly and steadily over 12 hours. This success is consistent with zero-order and Hixon Crowell models, exemplifying fickian diffusion processes. The research findings have wider application, providing a more efficient treatment strategy for the management of peptic ulcers. The pharmacological effect of H2 antagonist medications like Nizatidine may be improved with the help of mucoadhesive microspheres, which are part of controlled drug delivery systems. Improved drug delivery solutions and therapeutic results may be possible with further investigation and improvement of these microsphere compositions.

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TABLES AND FIGURES

Table 4 Batches given by Taguchi Design

Batch Number	Weight of Drug (mg)	Sodium alginate (mg)	Carbopol (mg)	$CaCl_2$ solution (% w/v)	Speed (RPM)
T1	300	400	200	10	150
T2	300	400	200	15	200
T3	300	400	200	20	250
T4	300	400	300	10	200
T5	300	400	300	15	250
T6	300	400	300	20	150
T7	300	400	400	10	250
T8	300	400	400	15	150
T9	300	400	400	20	200

Table 5 Compositions of batches according to Box Behnken design

Batch Number	Weight of Drug (mg)	Sodium alginate (mg)	Carbopol (mg)	$CaCl_2$ solution (% w/v)	Speed (RPM)
B1	300	400	300	15	250
B2	300	400	300	20	150
B3	300	400	200	15	200
B4	300	400	300	20	200
B5	300	400	300	15	250
B6	300	400	300	10	200
B7	300	400	200	15	200
B8	300	400	200	20	250
B9	300	400	400	20	200
B10	300	400	300	20	250
B11	300	400	300	15	200
B12	300	400	400	15	150
B13	300	400	400	10	250
B14	300	400	400	15	150
B15	300	400	200	10	150

Table 6 Percent encapsulation efficiency and percent drug content of batches B1 to B15

Batch number	% Entrapment efficiency	% Drug content
B1	86.18±0.89	23.54±1.02
B2	67.94±0.97	21.62±1.23
B3	46.69±1.2	25.79±1.39
B4	65.82±1.25	20.42±0.82
B5	84.18±1.047	22.38±0.91
B6	61.63±0.64	20.28±0.96
B7	44.73±0.89	23.28±0.83
B8	41.17±0.47	24.99±0.77
B9	79.18±1.25	21.10±1.02
B10	65.14±1.34	20.6±1.33
B11	87.22±1.22	24.58±0.97
B12	94.25±1.04	21.62±0.99
B13	80.06±0.98	19.71±1.21
B14	87.42±0.97	22.42±1.25
B15	39.85±0.84	25.56±1.33

*Each value represents mean ± standard deviation (n=3)

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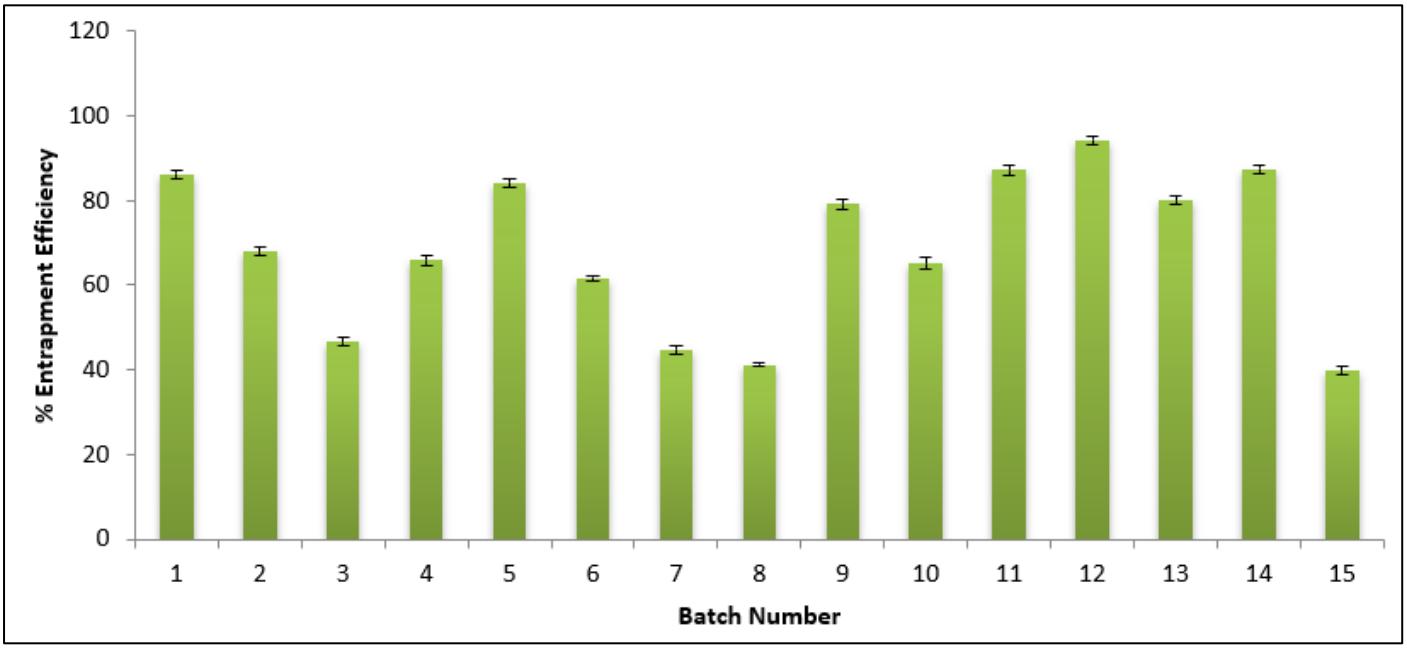

Fig 14 Entrapment efficiency of Batches Batch B1 to B15

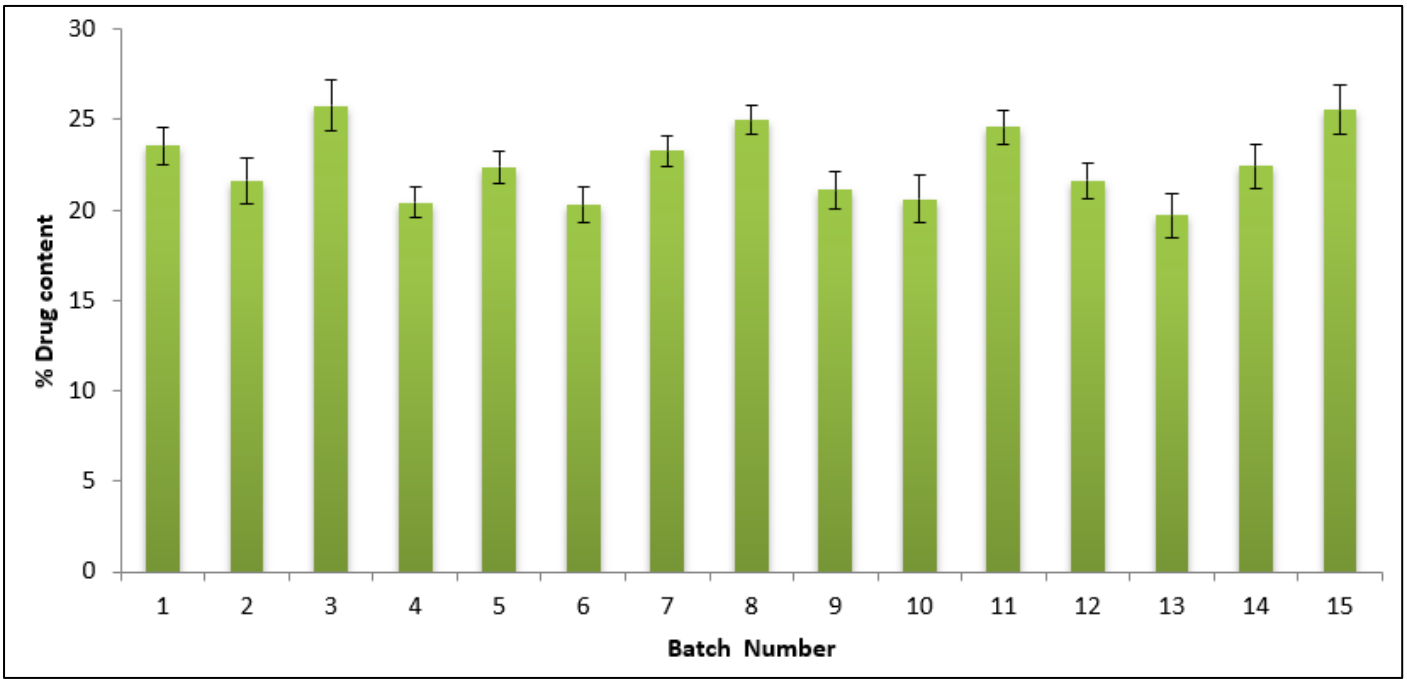

Fig 15 % Drug content of batches B1 to B15

➢ *Mucoadhesion*

Table 7 Percent Mucoadhesion of Formulations B1-B15

Batch no	% Mucoadhesion
B1	81.50±1.01
B2	77.48±0.89
B3	67.68±0.94
B4	75.78±1.04
B5	79.66±1.23
B6	73.48±0.93
B7	67.28±1.34
B8	95.68±0.64
B9	92.24±0.94
B10	74.28±1.02

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B11	79.10±1.17
B12	95.68±1.22
B13	79.40±0.83
B14	92.88±0.93
B15	56.92±1.32

*Each value represents mean ± standard deviation (n=3)

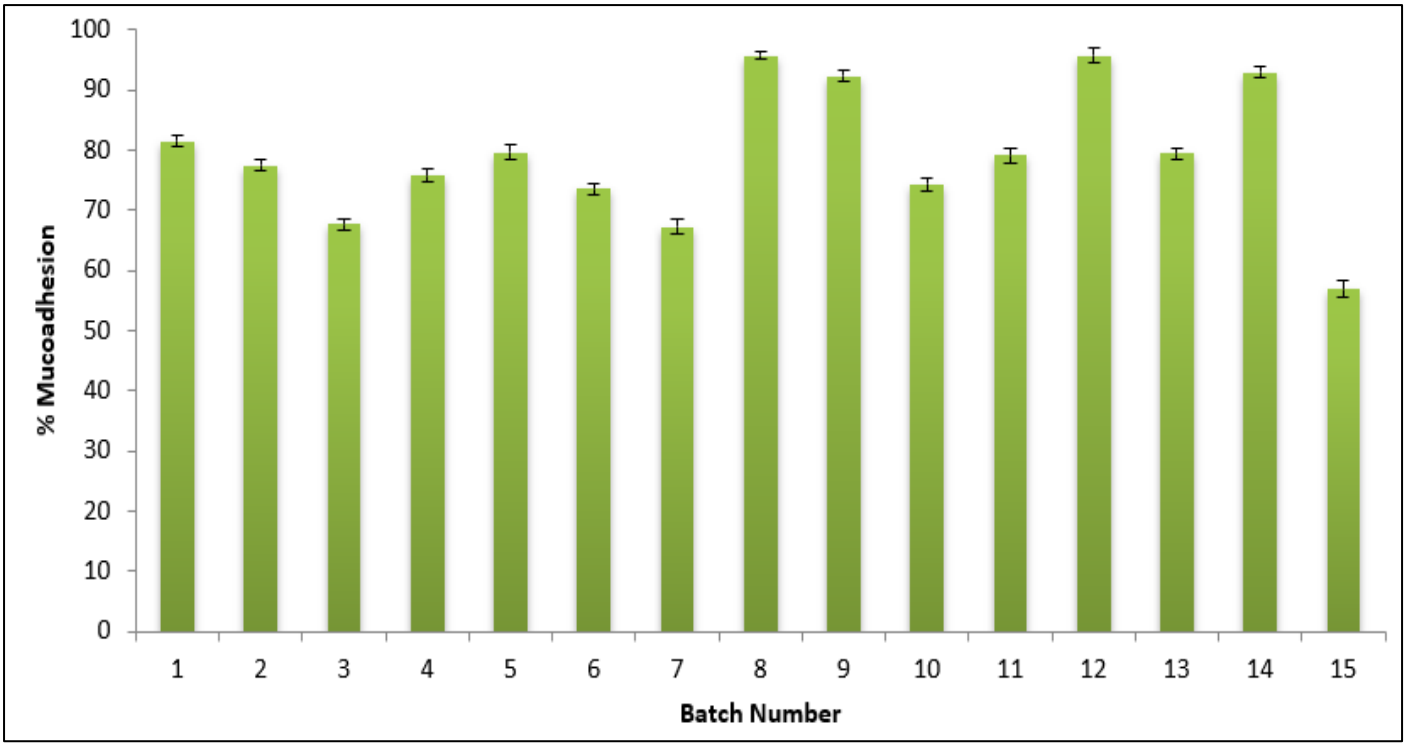

Fig 16 % Mucoadhesion of batches B1-B15

Table 8 Particle size analysis of Batch 8

Batch number	Z-Average (d.µm)	Polydispersity index	Size (d. µm)	% Intensity	Width (d. µm)
T8	600.2	0.944	256.2	100	41.55

Table 9 In-vitro Drug Release Study

Time in Hrs	T1	T2	T3	T4	T5	T6	T7	T8	T9
0	0	0	0	0	0	0	0	0	0
1	23.50±0.22	42.67±0.39	24.75±0.15	46.52±0.53	26.40±0.36	29.6±0.38	45.16±0.41	33.76±0.10	24.20±0.16
2	25.58±0.16	45.43±0.17	33.74±0.02	50.41±0.31	32.61±0.12	31.64±0.05	49.45±0.40	37.51±0.36	31.30±0.13
3	28.52±0.40	50.38±0.21	36.74±0.19	52.68±0.40	37.60±0.11	35.51±0.29	55.61±0.12	41.63±0.17	35.55±0.27
4	31.62±0.45	53.50±0.30	42.65±0.20	54.77±0.13	42.44±0.37	36.39±0.17	64.49±0.44	46.58±0.21	37.98±0.62
5	34.32±0.13	58.40±0.01	48.68±0.27	58.41±0.26	50.48±0.10	43.37±0.13	67.42±0.43	49.45±0.29	46.05±0.49
6	38.39±0.03	61.55±0.34	53.31±0.11	61.24±0.42	53.36±0.33	46.63±0.29	71.67±0.24	54.51±0.29	51.44±0.21
7	42.57±0.20	66.23±0.10	58.24±0.17	63.49±0.38	59.46±0.36	51.30±0.15	73.48±0.28	60.39±0.22	57.44±0.21
8	44.49±0.42	68.44±1.69	63.99±2.57	66.53±0.41	64.45±0.31	54.48±0.08	76.42±0.21	64.35±0.21	62.46±0.11
9	49.47±0.41	72.43±0.33	66.85±0.14	73.54±0.37	68.49±0.08	56.24±0.56	79.70±0.09	68.28±0.45	68.17±0.63
10	53.64±0.33	74.10±0.76	70.44±0.19	76.61±0.20	74.37±0.17	61.50±0.38	81.71±0.15	71.6±0.30	71.63±0.51
11	58.68±0.39	77.23±0.23	73.38±0.13	79.73±0.50	77.39±0.28	70.78±0.84	83.03±0.73	78.58±0.18	76.45±0.31
12	69.33±0.48	78.46±0.28	76.24±0.26	81.73±0.17	83.59±0.28	82.59±0.59	84.35±0.19	89.59±0.19	87.63±0.25

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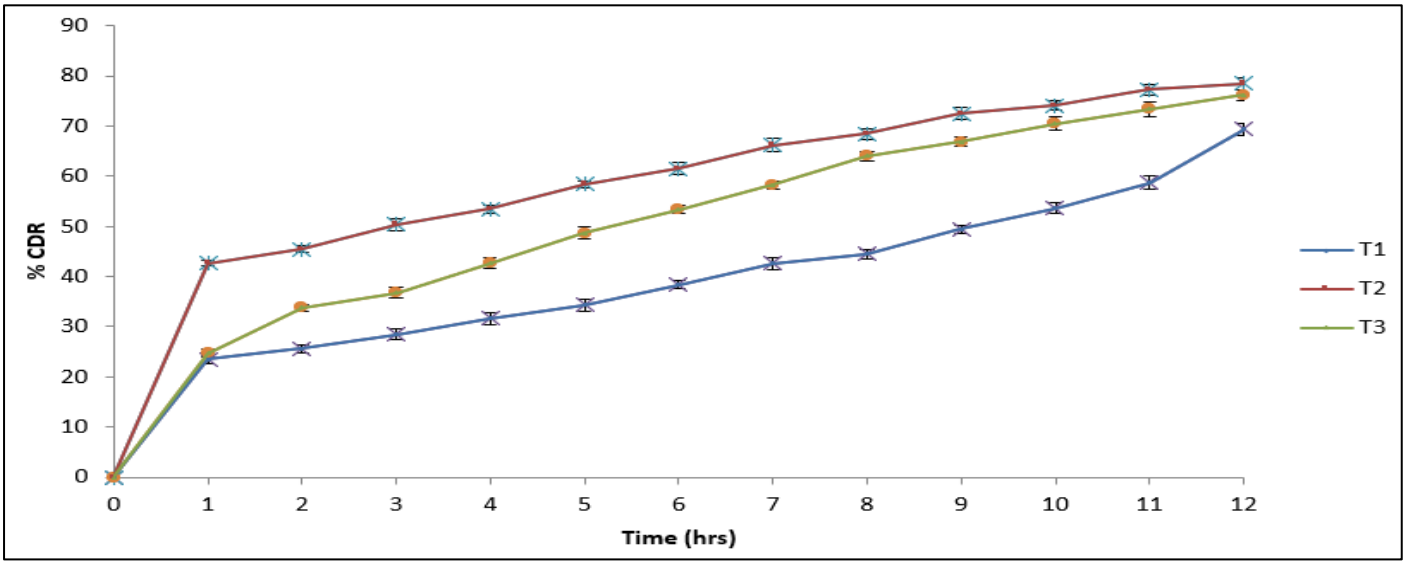

Fig 17 The percentage cumulative drug release of formulation Batch T1 to T3

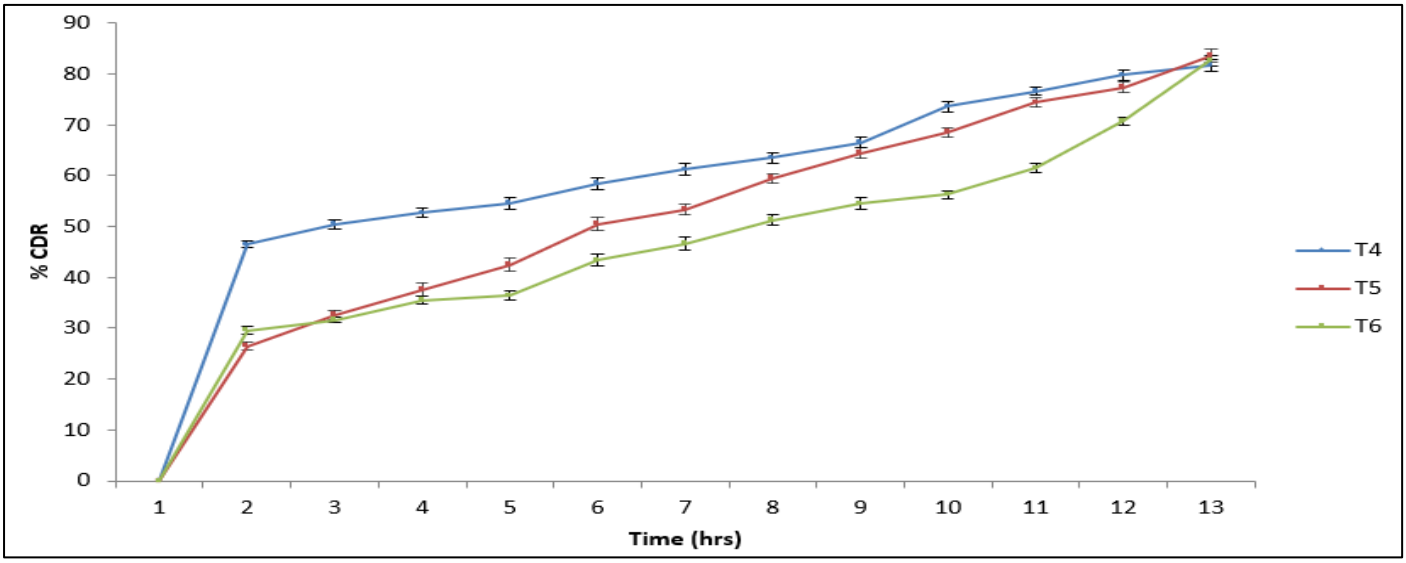

Fig 18 The percentage cumulative drug release of formulation Batch T4 to T6

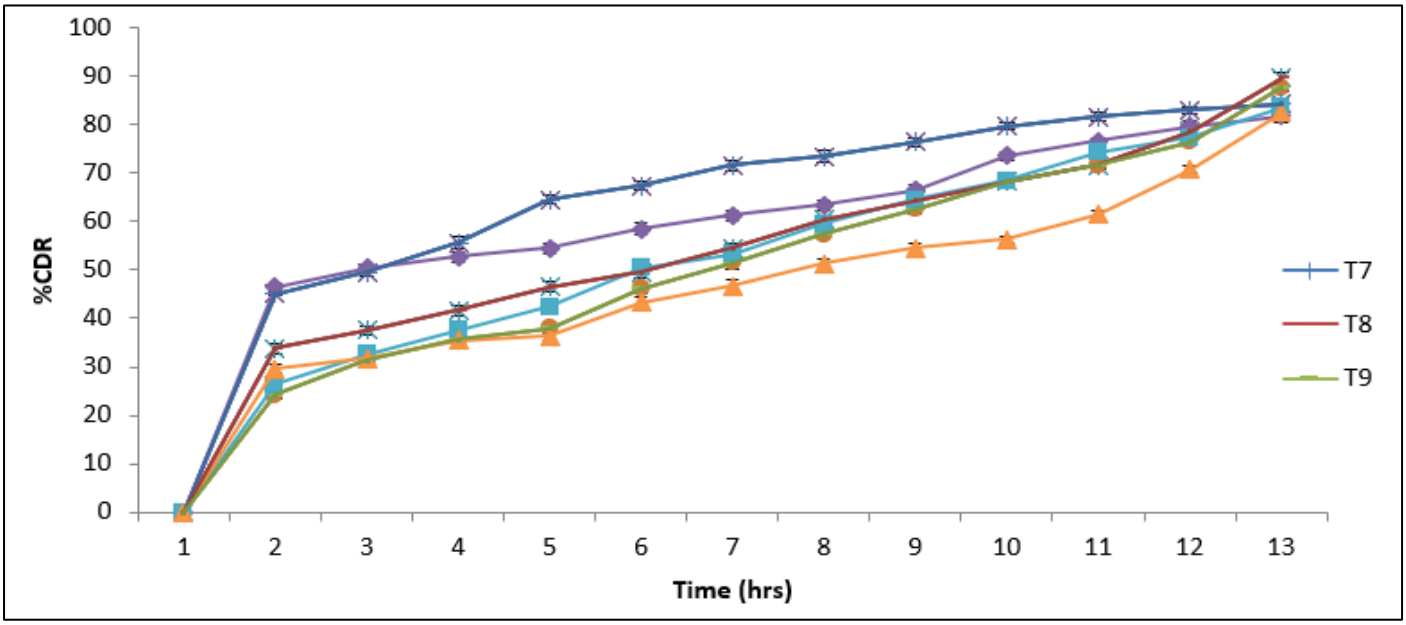

Fig 19 The percentage cumulative drug release of formulation Batch T7-Batch T9