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FORMULATION AND EVALUATION OF MUCOADHESIVE MICROSPHERES OF CIMETIDINE FOR ITS GASTRO RETENTIVE DRUG DELIVERY EFFICACY

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ABSTRACT: The Aim and objective of this work were to build up a gastro retentive drug delivery system. Cimetidine is used as a model drug for making mucoadhesive dosage forms. The formulation can be achieved by using the ionic gelation method. The model drug used in this work plan is categorized in antiulcer treatment. The extended-release mucoadhesive microspheres of the drug provide constant plasma concentration with a less frequent administration and also reduce the side effects to some extent. They provide good administration and enhance patient compliance. The present study aims to develop mucoadhesive microspheres of the model drug by using polymers like Sodium alginate and Carbopol 934 as an excellent mucoadhesive agent that can adhere to the gastrointestinal membrane for sustained drug delivery in the stomach. Calcium chloride was also used for making a solvent system. The preformulation study shows no interaction between drugs and excipients. The prepared microspheres of cimetidine particle size between 167.14-218.23µm. The entrapment efficiency of formulations was found to be 70.06-87.67%. *In-vitro* drug release after 7 h of F6 formulation showed good release was 85.60 %. SEM of prepared microspheres reveals a very smooth surface with a spherical shape. All prepared formulations exhibit good percentage yield and drug release rate. The increased amount of polymer was raised the particle size of microspheres significantly. *In-vitro* drug release studies were used to indicate a controlled and prolonged release of drug in the stomach and intestine. So we can say the formulation F6was a better candidate of all the developed formulations.

INTRODUCTION: The American Society of testing and materials characterize the mucoadhesive medication conveyance frameworks. In this framework, two surfaces are tied by interfacial powers. This can contain valence powers, interlocking activity, and both activity [1].

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These frameworks are utilized for building up the drug for longer duration of time with target site and assimilation of the drug [2]. Microspheres are free-flowing spherical particles be composed of decomposable polymers.

Microsphere assumes a significant job in upgrading the bioavailability of standard medications and beating the symptoms [3, 4]. Cimetidine is histamine (H2 blocker) and treats ulcers, acid-peptic disease, and heartburn. It is also known as an H2-receptor antagonist. This is responsible for inhibiting acid development in the stomach [5]. It squares H2 receptors in parietal cells, which stifles basal and

supper invigorated corrosive emission in a portion subordinate way. Cimetidine also restrains gastric corrosive emission in the stomach invigorated by food, histamine, pentagastrin, caffeine, and insulin [6].

MATERIALS AND METHODS: The Material used to prepare mucoadhesive microspheres are cimetidine drugs obtained from Konark herbal, Himachal Pradesh, sodium alginate, carbopol 934, calcium chloride, and solvents from R.V. Northland Institute Dadri, G.B. Nagar (2019) and Ionic gelation method.

Preformulation Studies:

The Angle of Repose: The prepared cimetidine mucoadhesive microspheres were assessed for the edge of rest by utilizing a fixed pipe stand strategy. The angle of repose spoke to by θ and utilized for computing the stream properties of microspheres granules. Arranged microspheres granules were permitted to stream the pipe hole that remains on a superficial level on a fixed paper. The recipe utilized for computing the edge of rest was given underneath [8].

$$\theta = \tan\text{-}1 \times h / r$$

Where,
Θ = angle of repose
h = height of the pile
r = radius of the pile

Bulk Density (BD): Bulk density is used to measure the uniformity of particles. The bulk density of the given material depended on particle cohesiveness, particle range, particle size, and particle shape. The test material weighed with an accurate amount with the help of balance. Take a dried cylinder apparatus for measuring the bulk density of microspheres.

The material quantity may be modified with the cylinder apparatus volume. The apparent volume of material was measured by using a cylinder and cylinder filled by given material accurately. Filled material settled in the cylinder without any fore carefully. The unsettled volume read and calculated the bulk density of given materials and it was measured by in g/ml. The formula for bulk density was given below [9].

BD = weight of powder blend / Untapped volume of packing

Tapped Density (TD): The tapped density of the material can be done by tapping the material by using a given apparatus. The powder material can be weighed and through into the measuring cylinder for measuring the tapped density. The tapping of material into the cylinder can be done by using a tapping tester by mechanical force. The tapping tester range is about 300 drops/min. This process is done several times and checked the tapped volume after each step of tapping. Measure the tapped density of the given material by using a given formula [10].

TD = weight of powder blend / Untapped volume of packing

FTIR Studies: The transmittance mode of this Fourier Spectroscopy for cimetidine mucoadhesive microspheres was captured by maintaining a room temperature of a spectrophotometer (Perkin Elmer, Japan). The given samples were placed into pestle and mortar after this sample was mixed. The sample was placed with the help of nujol with KBr plates. The KBr plates are used to form a delicate compressed film. The infrared spectrometer was used to obtain the spectra. The wavenumbers of spectra were 4000-400 cm^{-1} [11, 12].

DSC Studies: DSC range 60 with TA60 software, Shimadzu, Japan is used in this study. The aluminum pan is used for measuring DSC at temperatures 25-350 °C. The given sample was carefully heft and heated in aluminum pans. The reference used in this was an empty pan [13].

Preparation of Microspheres: The formulation of mucoadhesive Cimetidine microspheres was prepared by using the ionic gelation method with the help of a magnetic stirrer as apparatus. In this formulation of preparing microspheres of cimetidine, sodium alginate was used as mucoadhesive polymer, and carbopol 934 was used as the rate-controlling polymer. In this study, both polymers of cimetidine were used in varying quantities. In this study, eight formulations were performed **Table 1**. Firstly all the ingredients were weighed with the help of electronic balance and weighed the quantity of sodium alginate added into the distilled water to make a solution with the help of a magnetic stirrer at 500 rpm. The calcium chloride solution was prepared in distilled water. Cimetidine and polymer were added to the sodium alginate solution.

The drug-polymer solution was added with the help of a syringe into the calcium chloride solution, which was stirred at 100 rpm **Fig. 1**. The resultant solution was washed with the help of water and dried at room temperature, and stored [7].

TABLE 1: COMPOSITION OF DIFFERENT MICROSPHERES FORMULATION CODE

Formulation code	Drug (mg)	Carbopol 934 (mg)	Sodium alginate (gm)	Calcium chloride (gm)
F1	100	50	1	2
F2	100	100	1	2
F3	100	200	1	5
F4	100	50	1	5
F5	100	100	2	5
F6	100	200	3	5
F7	100	50	2	7
F8	100	100	2	7

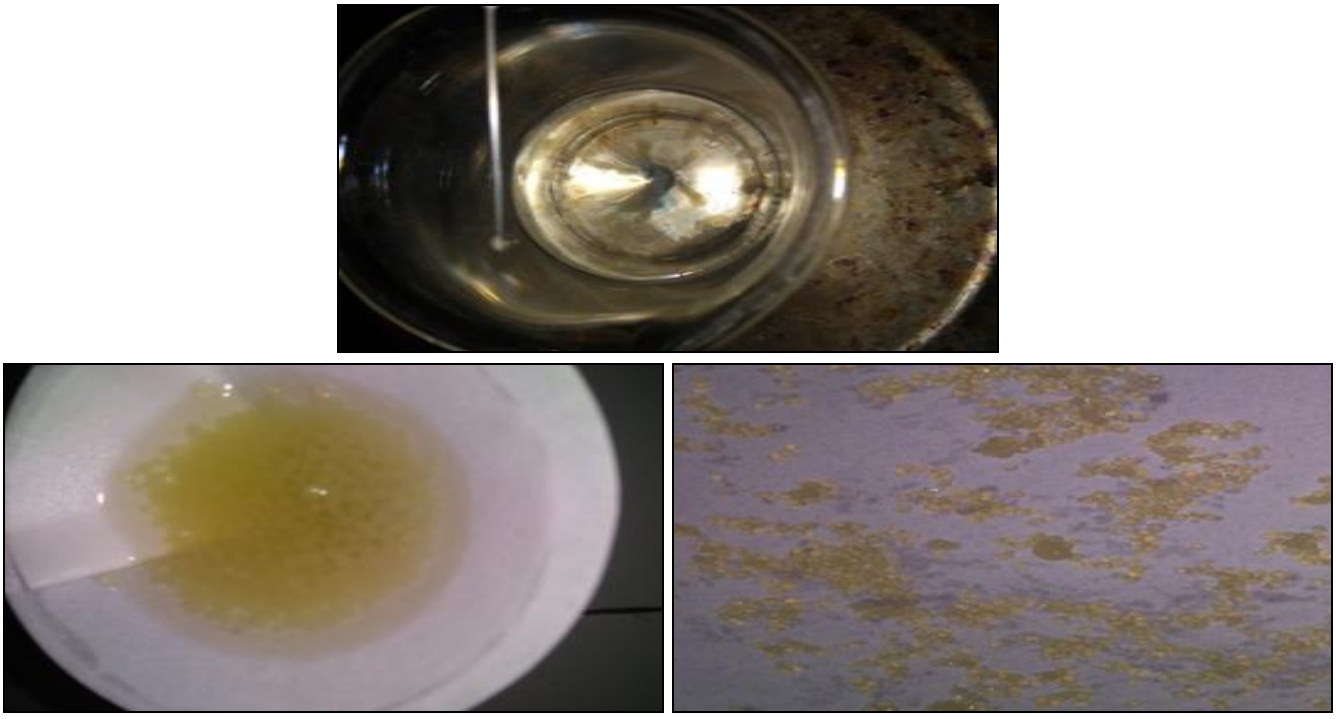

FIG. 1: FORMULATION OF MUCOADHESIVE MICROSPHERES OF CIMETIDINE

Evaluation of Formulated Microspheres:

Particle size Analysis: The method used for determining the particle size was the optical microscopy technique. More than 100 given mucoadhesive microspheres of cimetidine were used to analyze the particle size, and the given microspheres were counted in the microscope [14].

Determination of Microspheres Percentage Yield: The percentage yield of given cimetidine mucoadhesive microspheres of all formulation codes was performed by weighing the microspheres. The % yield defines by the total amount or weight of prepared mucoadhesive microspheres divided by the weight of the drug used in the preparation of mucoadhesive microspheres plus the weight of the polymers and substances used in the formulation and multiplied by a hundred [15].

Swelling Index: The swelling index of cimetidine mucoadhesive spheres was used to measure microspheres' swelling properties. The swelling index of spheres was done by using an accurate amount of microspheres, and intestinal solution with pH range is 7.4 phosphate buffers.

The given microspheres were placed into the solution and kept for some time to get swollen. The extra fluid on the swollen surface of microspheres was discarded with the help of paper and weighed accurately using a weighing balance. The swelling index was measured from the final weight of microspheres minus the initial weight of

microspheres divided by the initial weight of microspheres multiplied by a hundred [16].

Entrapment Efficiency: The entrapment efficiency of cimetidine mucoadhesive microspheres was evaluated by UV Spectrophotometer (UV-1700 Shimazu, Japan) at wavelength 291nm in 0.1N hydrochloric acid. The different dilutions were prepared for all formulations codes. The flask was used for making dilutions, and the solution was stirred on a stirrer for 24 h. The prepared solution was measured for accurate efficiency. The % entrapment efficiency defined by the weight of the actual content of drugs divided by the theoretical content of drugs multiplies by a hundred [17].

Drug Content: The ultraviolet (UV) spectrophotometer (218 nm) was used to analyze the drug content of the given materials. The prepared mucoadhesive cimetidine microspheres were used, and dried microspheres were mashed into the pestle and mortar. In this mashed material, added buffer liquid at pH maintaining l.2 with the temperature at 37 °C, kept for some hours. Filter this prepared solution with the help of filter paper. This prepared transparent liquid was analyzed by UV spectrophotometer [18].

***In-vitro* Dissolution Studies of Microspheres:** The dissolution parameter was used for drug release study with the help of the USP paddle apparatus at a temperature under 37±0.5 ºC. The liquid medium used for the dissolution parameter was 0.1N hydrochloric acid (900ml). Maintain the speed of the paddle apparatus at 100 RPM. Each time interval for 12 h withdraws 5ml of liquid. The liquid medium quantity was maintained by adding 5ml of fresh buffer in every withdrawal step. A given sample's absorbance was measured using UV spectrophotometry at 291nm, and cumulative percentage release was calculated[19].

SEM Studies: The morphological characters of cimetidine microspheres were evaluated along with Scanning electron microscopy. The evaluation of microspheres by SEM required an aluminum counterfoil with adhesive tape. The counterfoil covers with samples were added to the electron microscopy. The used platinum thickness is 10 Å with an argon environment. The gold sputter was used in this test with the high-vacuum evaporator. The given mucoadhesive microspheres sample was scanned and visualized by photomicrographs [20].

Drug Release Mechanism: *In-vitro* drug release data were fitted to Zero-order, First-order[21]. Drug release kinetics was analyzed by plotting cumulative drug release vs. time by fitting to an exponential equation-

$$Mt / Ma = Ktns$$

Where Mt/Ma is the fraction of the drug release by time t, K is the rate constant, and n is the exponent release.

RESULTS AND DISCUSSION: Angle of repose of prepared mucoadhesive microspheres belonging to cimetidine showed excellent results in the formulation of F3 (24.21), F6 (26.11), and F8 (27.18). The best result of bulk density was shown in the formulations of F3 (0.66) and F6 (0.69). The formulation F3 (0.75) and F6 (0.78) was shown the best result for tapped density. The peaks obtained in the FTIR spectra show the absence of drug-excipient interactions. The DSC analysis was applied to determine the interaction between drug and polymers used. There was no interaction between both pure drug cimetidine and prepared formulation **Fig. 2.**

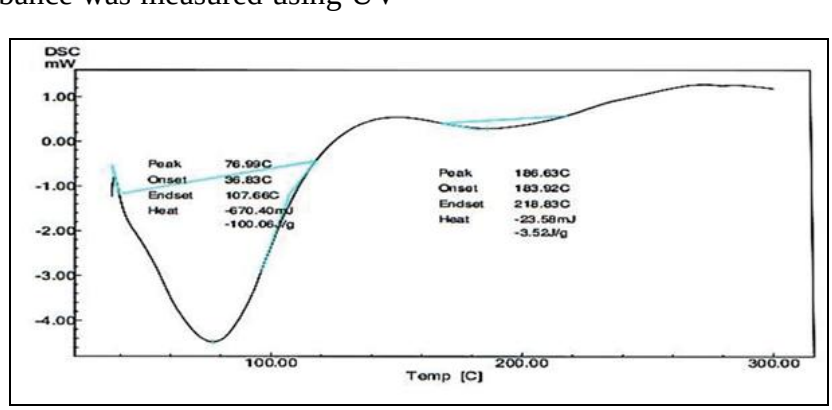

FIG. 2: DSC OF DRUG WITH POLYMERS

In this study F6 showed greater particle size 218.23µm. The best percent yield was given by the F3 formulation, 95.12%. The best swelling index of prepared microspheres was in F3, 85.12. The total amount of drug present in all formulations of mucoadhesive microspheres was calculated by entrapment efficiency. The best entrapment efficiency of microspheres was shown in F3, which is 87.67. The drug content of prepared mucoadhesive microspheres was 16.35-20.12%. The SEM of prepared microspheres reveals a very smooth surface with spherical shape **Fig. 3.**

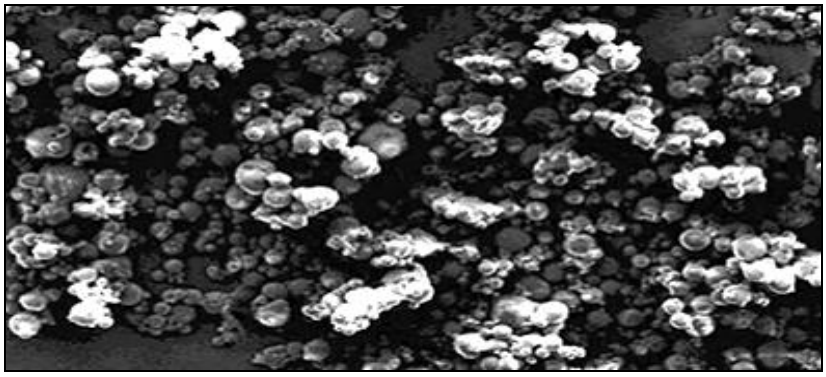

FIG. 3: SEM OF MICROSPHERES (F6)

***In-vitro* Dissolution Studies of Microspheres:** F6 show a good release rate as correlated to other formulations (85.60% drug release rate) **Table 2**. Other formulations release profile was F1=60.02%, F2=80.20%, F3=65.37%, F4=78.18%, F5=69.58%, F6=85.60%, F7=72.10%, F8=65.37%. This *in-vitro* study shows that an increased amount of polymer added to the formulations can reduce the release rate. The release rate profiles of cimetidine are shown in **Fig. 4.**

TABLE 2: THE % CUMULATIVE DRUG RELEASED (F1-F8)

Time (h)	1	2	3	4	5	6	7
F1	34.89	39.98	45.98	56.90	65.34	75.24	81.35
F2	33.21	40.75	56.13	65.62	76.42	75.74	80.20
F3	40.12	42.34	50.13	57.86	59.99	63.09	65.37
F4	37.80	47.32	53.83	71.81	73.10	72.78	78.18
F5	38.90	43.67	49.09	52.89	59.99	63.12	69.58
F6	33.95	42.38	55.15	63.32	72.18	81.95	85.60
F7	23.43	40.09	54.76	63.89	69.10	71.09	72.10
F8	33.87	46.89	49.88	50.32	57.90	62.56	65.37

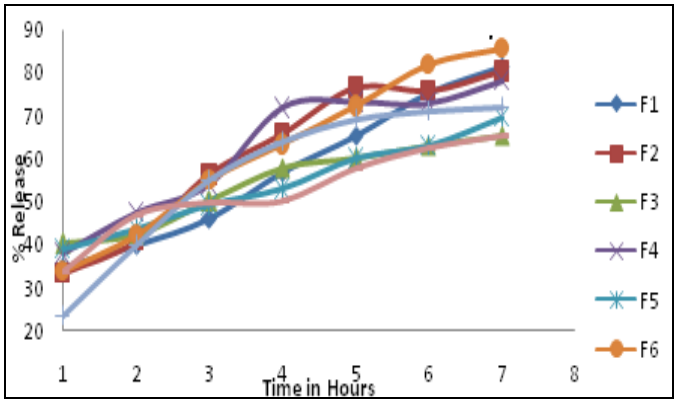

FIG. 4: *IN-VITRO* DISSOLUTION GRAPH

Plotting of Release Data in Various Models: The drug release mechanism of the *in-vitro* drug release study was used in various kinetic equations like zero-order (% release vs. t), first-order (log% release vs. t).

Zero-order Plot: A curve was plotted against time versus % cumulative drug release.

The R^2 was 0.973, shown in **Fig. 5.**

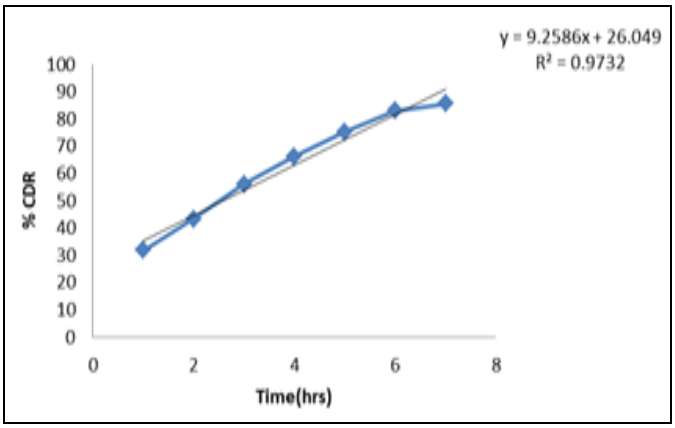

FIG. 5: ZERO-ORDER PLOT

First-order Plot: A curve was plotted against time versus % cumulative drug release. They can measure the remaining drug. The R^2 was 0.927, shown in **Fig. 6.**

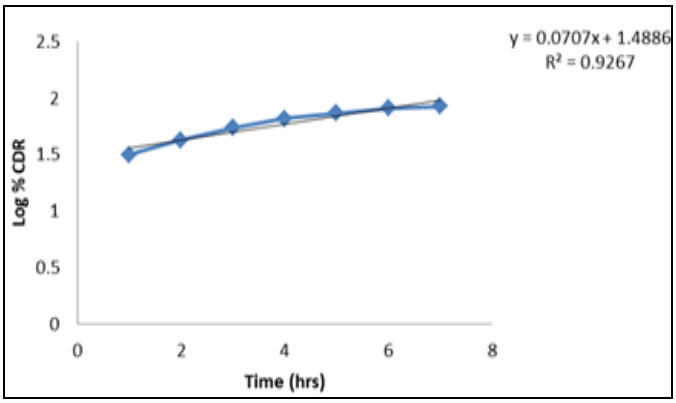

FIG. 6: FIRST ORDER PLOT

Comparison of Release Rate Study with Marketed Formulation: The release rate study with the marketed product is by dissolution studies was performed for marketed microspheres of cimetidine using the same dissolution procedure. The comparison profile of marketed microspheres and selected formulation F6 are shown in **Table 3.**

TABLE 3: COMPARATIVE STUDY OF MARKETDED FORMULATION WITH THE OPTIMIZED FORMULATION

Time (h)	1	2	3	4	5	6	7
% Cumulative drug release of mkt. Preparation	80.11	88.75	93.54	94.10	96.91	96.58	97.80
% Cumulative drug release of optimized formulation	33.93	42.38	55.15	63.32	72.18	81.95	85.60

Stability Study: Stability studies for the Model drug cimetidine microspheres shown in the table did not show any significant change in color, microspheres texture, and drug content after one month **Table 4**. The above results showed that almost all the formulations were stable, tested by UV analysis. There is no change in appearance, drug content, and dissolution results were observed after storage of formulation at 40 °C/75% R.H. for one month. Hence the optimized batch was found stable.

TABLE 4: STABILITY STUDIES OF PREPARED MICROSPHERES

Test	Observation		
	Initial	After 15 days	After one month
Colour	White	No change	No change
Cumulative % drug released after 7 h	85.60	84.31	83.50

CONCLUSION: Mucoadhesive microspheres of the model drug (Cimetidine) were prepared with the proper aim and objective of dosage forms to increase or build up a gastro retentive drug delivery system to increase its absorption bioavailability and to enhance the drug release in the stomach and intestine. The mucoadhesive microsphere shows lower side effects with increased patient compliance. For developing formulations, two polymers were used Carbopol 934 and Sodium alginate, an excellent mucoadhesive agent. This can give good adhering power to prolong drug releases in the stomach. They can be used for distinct concentrations. Calcium chloride powder is also used. The ionic gelation method was used for making mucoadhesive microspheres. The method was easy, simple, and reproducible for formulating microspheres. The method shows good FT-IR, DSC, and SEM profiles. All prepared formulations exhibit good percentage yield and drug release rate. As the amount of sodium alginates and calcium chloride was increased, the percentage of drug release decreased. The increased amount of polymer was raised significantly to lengthen the particle size of microspheres. *In-vitro* drug release studies were used to indicate a controlled and prolonged release of drug in the stomach and intestine. The drug release data study was fitted in

zero, first order. Percent drug release of formulation F6 shows a good result as compared to other formulations. F6 showed a good SEM and DSC profile.

Future Scopes of Work: The present research work can be utilized further by Scale-up and *In-vivo* evaluation, For an exploration of the applications of GRDDS, using the cimetidine as a model drug.

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