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Formulation and Evaluation of Mucoadhesive Microspheres of Cimetidine for its Gastro Retentive Drug Delivery Efficacy

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Key words: Cimetidine, microspheres, mucoadhesion, entrapment efficiency, bioavailability, *in-vitro*, gastrointestinal residence time

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Abstract: Cimetidine is histamine (H_2 blocker). It is used in the treatment of ulcer, acid-peptic disease and heartburn. It is also known as an H_2-receptor antagonist who is responsible for inhibiting acid development in the stomach. The Aim and objective of this work was to build up a gastro retentive drug delivery system. The cimetidine used as a model drug for making mucoadhesive dosage form. This formulation can be achieved by using ionic gelation method. The model drug used in this work plan is categorized in the treatment of antiulcer. The extended-release mucoadhesive microspheres of model 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 model drug using Sodium alginate and Carbopol 934 used as an excellent mucoadhesive agent which can adhere on the gastrointestinal membrane for sustained drug delivery in the stomach. The calcium chloride was also used for making solvent system and to evaluate the model drug mucoadhesive microspheres *in-vitro* for their drug release pattern FTIR, SEM and DSC curve. The mucoadhesive microspheres were prepared by ionic gelation method by using polymers like carbopol 934 used as mucoadhesive polymer and sodium alginate as rate controlling polymer. Preformulation study shows no interaction between drug and excipients. The prepared mucoadhesive microspheres of cimetidine shows particle size of between 167.14-218.23 µm. Entrapment efficiency of formulations was found to be 70.06-87.67%. *In-vitro* drug release after 7 h of F6 formulation show good release was 85.60%. The surface morphology using SEM of prepared microspheres reveals very smooth surface with spherical shape. All prepared

formulations exhibits good percentage yield and drug release rate. As the amount of sodium alginates and calcium chloride was increased it reduces percentage drug release. The increased amount of polymer was raised significantly the particle size of microspheres. *In-vitro* drug release studies were used for indicating that there was a controlled and prolong release of drug in the stomach and intestine. So, we can say the formulation F6 was better candidate of all the developed formulations.

INTRODUCTION

The mucoadhesive medication conveyance frameworks are characterized by the American Society of testing and materials. In this framework, two surfaces are tie by interfacial powers. This can contain valence powers, interlocking activity and both activity[1]. These frameworks are utilized for building up the definitions longer the living arrangement time of the details at the objective site and assimilation of the plans. The mucoadhesive medication conveyance framework is additionally used to builds sedate bioavailability[2]. Microspheres are free-flowing spherical particles be composed polymers that are decomposable. Microsphere assumes a significant job to upgrade the bioavailability of standard medications and for beat the symptoms[3, 4]. Cimetidine is histamine (H_2 blocker). It is used in the treatment of ulcer, acid-peptic disease, and heartburn. It is also known as an H_2-receptor antagonist who is responsible for inhibiting acid development in the stomach. It takes a shot at the serious enemy at the site of the H_2 receptor. It squares H_2 receptors in parietal cells which stifles basal and supper invigorated corrosive emission in a portion subordinate way. Cimetidine additionally restrains gastric corrosive emission in the stomach which is invigorated by food, histamine, pentagastrin, caffeine and insulin.

MATERIALS AND METHODS

Materials: The material used for the preparation of mucoadhesive microspheres are cimetidine drug obtained from Konark herbal, himachal Pradesh, sodium alginate, carbopol 934, calcium chloride and solvents from R.V. Northland Institute Dadri, G.B. Nagar.

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 which remains on a fixed paper on a superficial level. The recipe utilized for computing the edge of rest was given underneath[5]:

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

Where:
θ = Angle of repose
h = Height of the pile
r = Radius of the pile

Bulk Density (BD): The 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 measured by in g/ml. The formula for bulk density was given below[6]:

$$BD = \frac{\text{Weight of powder blend}}{\text{Untappedvolume of packing}} \quad (2)$$

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 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[7]:

$$TD = \frac{\text{Weight of powder blend}}{\text{Tapped volume of packing}} \quad (3)$$

FTIR studies: 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

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

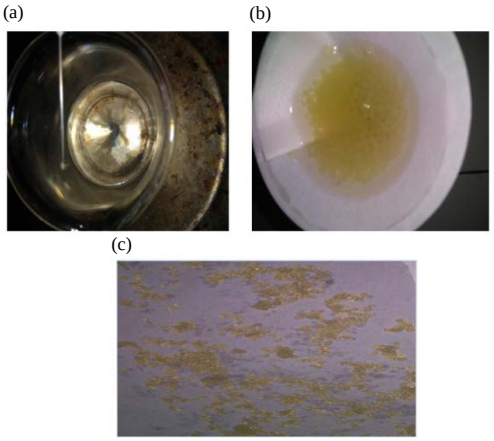

Fig. 1(a-c): Formulation of mucoadhesive microspheres of cimetidine

a delicate compressed film. The infrared spectrometer was used to obtain the spectra. The wavenumbers of spectra were 4000-400 cm^{-1}[8].

DSC studies: In this studies DSC range 60 with TA60 software, Shimadzu, Japan are used. The aluminum pan is used for measuring DSC at temperature 25-350°C. The given sample was carefully heft and heat in aluminum pans. The reference used in this was an empty pan[9].

Preparation of microspheres: The formulation of mucoadhesive cimetidine microspheres was prepared by using the ionic gelation method with the help of magnetic stirrer as apparatus. In this formulation of preparing microspheres of cimetidine sodium alginate was used as mucoadhesive polymer and carbopol 934 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 magnetic stirrer at 500 rpm. The calcium chloride solution was prepared in distilled water. Cimetidine and polymer were added into the sodium alginate solution. The drug-polymer solution 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[10].

Evaluation of formulated microspheres

Particle size analysis: The method used for determining the particle size was optical microscopy technique. More than 100 given mucoadhesive microspheres of cimetidine were used for the analysis of the particle size and the given microspheres were counted in the microscope[11].

Determination of microspheres percentage yield: The percentage yield of given cimetidine mucoadhesive microspheres of all formulation code were 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 hundred[12].

Swelling index: The swelling index of cimetidine mucoadhesive spheres was used for measuring swelling properties of microspheres. 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 for get swollen. The extra fluid on the swollen surface of microspheres was discarded with the help of paper and weighed accurately using weighing balance. The swelling index was measured from the final weight of microspheres minus initial weight of microspheres divided by the initial weight of microspheres multiplied by hundred[13].

Entrapment efficiency: The entrapment efficiency of cimetidine mucoadhesive microspheres was evaluated by UV Spectrophotometer (UV-1700 Shimazu, Japan) at wavelength 291nm in 0.1 N hydrochloric acid. The different dilutions were prepared for all formulations code. The flask was used for making dilutions and the solution was stirred on a stirrer for 24 h. The prepared solution measured for accurate efficiency. The % entrapment efficiency defined by the weight of the actual content of drugs divided by the theoretical content of drugs multiply by a hundred[14].

Drug content: The Ultraviolet (UV) spectrophotometer (218 nm) was used for the analysis of the drug content of the given materials. The prepared mucoadhesive cimetidine microspheres were used and dried microspheres were mash 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[15].

***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±0.5ºC. The liquid medium used for the dissolution parameter was 0.1 N hydrochloric acid (900 mL). Maintain the speed of the paddle apparatus at 100 RPM. Each time interval for 12 h withdraws 5 mL of liquid. The liquid medium quantity was maintained by adding 5 mL of fresh buffer in every step of withdrawal. The absorbance of a given sample was measured by using U.V spectrophotometry at 291 nm and percentage cumulative release was calculated[16].

SEM studies: The morphological characters of cimetidine microspheres were evaluated along Scanning electron microscopy. The evaluation of microspheres by SEM required an aluminum counterfoil with adhesive tape. The counterfoil covers with samples were added into 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[17].

Drug release mechanism: *In-vitro* drug release data was fitted to zero-order, first-order. Drug release kinetic was analyzed by plotting cumulative drug release vs. time by fitting to an exponential equation:

$$Mt/Ma = Ktns \quad (4)$$

Where:

Mt/Ma = The fraction of the drug release by time t

K = The rate constant and n is the exponent release

RESULTS AND DISCUSSION

Angle of repose of prepared mucoadhesive microspheres belonging to cimetidine showed excellent result in formulation of F3 (24.21), F6 (26.11) and F8 (27.18). The best result of bulk density was showed in the formulations of F3 (0.66) and F6 (0.69). The formulation F3 (0.75) and F6 (0.78) was showed the best result for tapped density. The peaks obtained in the FTIR spectra shows the absence of drug-excipient interactions. Figure 2 indicates the FTIR spectra of cimetidine with polymers.

The DSC analysis was applied for the determination of interaction between drug and polymers used. Therewas no interaction between both pure drug cimetidine and prepared formulation (Fig. 3).

In this study, F6 showed greater particle size 218.23 µm. The best percent yield was given by the F3 formulation 95.12%. The best swelling index of prepared microspheres was in F3 that is 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 that is 87.67.

The drug content of prepared mucoadhesive microspheres was found to be 16.35-20.12%. The SEM of prepared microspheres reveals very smooth surface with spherical shape (Fig. 4).

***In vitro* dissolution studies of microspheres:** F6 show 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 =

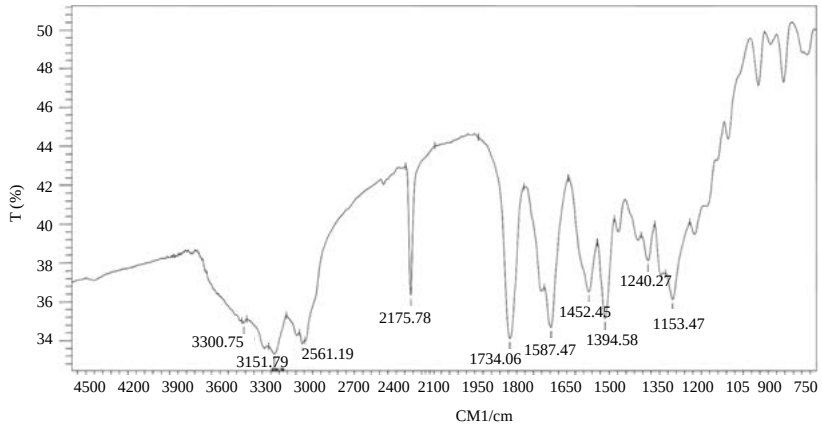

Fig. 2: FT-IR spectrum of model drug with polymers

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

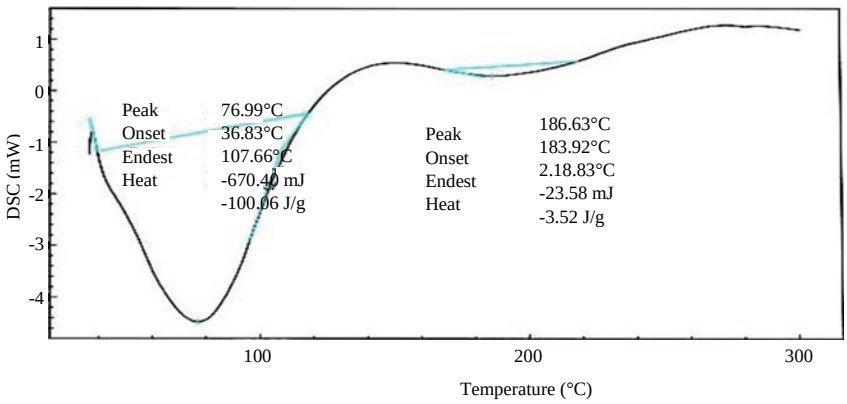

Fig. 3: DSC of drug with polymers

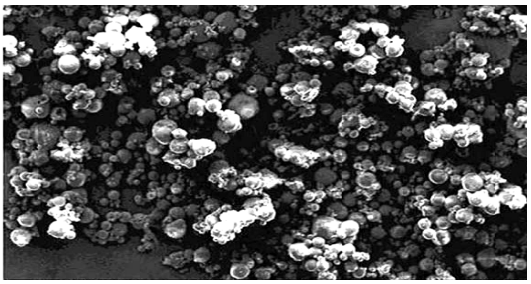

Fig. 4: SEM of microspheres (F6)

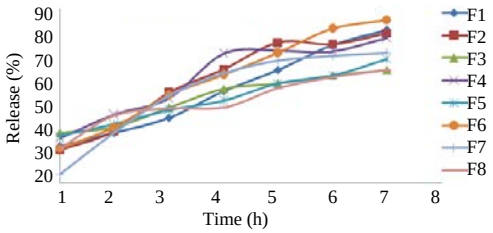

Fig. 5: *In-vitro* dissolution graph

72.10%, F8 = 65.37%. This *in vitro* study show that an increase amount of polymer added in to the formulations can reduces the release rate. The release rate profiles of cimetidine are shown in Fig. 5.

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. 6.

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. 7.

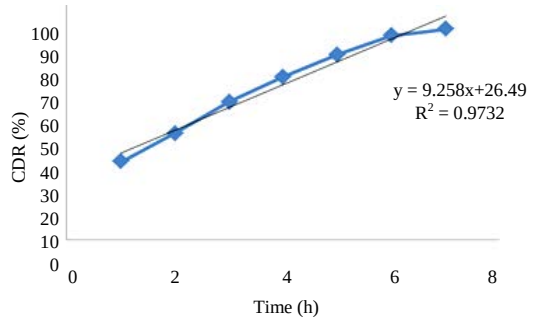

Fig. 6: Zero order plot

Comparison of release rate study with marketed formulation: The comparison of release rate study with marketed product is by dissolution studies were performed for marketed microspheres of cimetidine using

Table 3: Comparative study of marketed 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

Table 4: Stability studies for the model drug floating tablets

	Observation		
Test	Initial	After 15 days	After 1 month
Color	White	No change	No change
Cumulative % drug released after 7 h	85.60	84.31	83.50

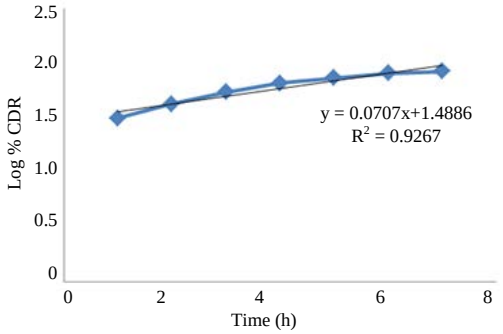

Fig. 7: First order plot

the same dissolution procedure. The comparison profile of marketed microspheres and selected formulation F6 are shown in Table 3.

Stability study: Stability studies for the model drug cimetidine microspheres which are shown in 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 which were 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.

CONCLUSION

Mucoadhesive microspheres of model drug (Cimetidne) were prepared with proper aim and objective of dosage forms to increases or build up a gastro retentive drug delivery system in order to increase its absorption and its bioavailability and to enhanced the drug release in stomach and intestine. The mucoadhesive microspheres shows lower side effects with increased patient compliance. For developing formulations two polymers was 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. Ionic gelation method was used for making muoadhesive microspheres. The method was easy, simple and reproducible for formulating microspheres. The method shows good FT-IR, DSC and SEM profile. All prepared formulations, exhibits good percentage yield and drug release rate. As the amount of sodium alginates and calcium chloride was increased percentage drug release decreased. The increased amount of polymer was raised significant lengthen the particle size of microspheres. In-vitro drug release studies were used for indicating that there was a controlled and prolongs 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 good result as compared to other formulations. F6 showed good SEM and DSC profile.

RECOMMENDATIONS

The present research work can be utilized further by:

- Scale up
- *In-vivo* evaluation

For exploration of the applications of GRDDS, using the cimetidine as model drug.

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