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# FORMULATION AND EVALUATION OF SUSTAINED RELEASE FLOATING-MUCOADHESIVE TABLET OF CIMETIDINE HYDROCHLORIDE

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**ABSTRACT**

The purpose of the present study to develop an optimized gastric floating drug delivery system (GFDDS) to prolong the gastric residence time after oral administration, at a particular site and controlling the release of drug especially useful for achieving controlled plasma level as well as improving bioavailability. Cimetidine hydrochloride is a histamine H2-receptor antagonist that inhibits stomach acid production. It is commonly used in treatment of peptic ulcer disease (PUD) and gastro esophageal reflux disease (GERD). Cimetidine is also used alongside fexofenadine and other antihistamines for the treatment of skin conditions such as hives. The proposed work is envisaged to carry out the preformulation, optimization, development of *in-situ* orifice forming floating tablet and evaluation of floating tablet. *Floating mucho adhesive tablet of* cimetidine is the one which suit the concept of better patient compliance, delayed release, more efficacies and enough bioavailability to show required pharmacological action and less gastrointestinal side effects. The sustained realese floating-muchoadhesive tablet system was successfully developed and evaluated.

**Key words:** Preformulation, Muchoadhesive, Gastrointestin.

## INTRODUCTION

Oral route of drug administration is oldest and safest mode of drug administration. The reasons that the oral route achieved such popularity may be in part attributed to its ease of administration belief that by oral administration of the drug is well absorbed. In oral controlled drug delivery the amount of drug release is constantly predetermined and these constant releases of drug provide a constant blood plasma level of drug for a therapeutic response. It decrease the fluctuation of drug plasma conc., it reduce toxicity, provide a sustained effects, reduced the dosing frequency. Apart from other advantage it reduces total amount of drug used, improve patient compliance and reduced patient care time **[**1].

Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects.

## SUSTAINED RELEASE SYSTEM

SR systems are those, which achieves slow release of drug over an extended period of time and in this drug is initially made available to the body in amount to cause the desired pharmacological response.

## EXPERIMENTAL WORK

**Materials:** Cimetidine (drug) was provided by Herb Edge Health Care Pvt. Ltd., Ujjain HPMC, Carbopol, Citric acid, Talc, Magnesium stearate, Aerosil-200 and other chemicals were provided by Sagar Institute of Research Technology & Science-Pharmacy Bhopal

### Dry Granulation

When tablet ingredients are sensitive to moisture or are unable to withstand elevated temperature during drying and when the tablet ingredients have sufficient inherent binding or cohesive properties, slugging may be used to form granules. The active ingredient, diluents and a part of lubricant are blended powdered material contains a considerable amount of air, under pressure this air to expelled and a fairly dense piece is formed. The more time allowed for this air to escape the better the tablet or slug. When slugging is used, large tablets are made as slugs

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because fine powders flow better into large cavities Now these compressed slugs are comminuted through the desirable mesh screen either by hand or for large quantities through the Fitzpatrick or similar comminuting mills after this the granulation is blended gently with lubricants and then compressed to form tablets [1,2].

**Wet Granulation**

The unique portions of wet granulation process involve the wet massing of powders, wet sizing or milling and drying. Wet granulation forms the granules by binding the powders together with an adhesive instead of compaction. The wet granulation technique employs a solution suspension or slurry containing a binder which is usually added to the powder mixture however the binder may be incorporated dry into the powder mix and the liquid may be added by itself. Therefore, when only a small quantity is permissible, the binder is blended in with the dry powders initially; when a large quantity is required the binder is usually dissolved in the liquid. Once the granulating liquid has been added mixing continues until a uniform dispersion is attained and all the binder has been activated, After sufficient blending now the wet mass is made to undergo wet screening by passing through a hammer mill or oscillating granulator equipped with screens having large perforations.

**Direct Granulation**

Implies direct compression consists of compressing tablets directly from powdered material without modifying the physical nature of the material itself. Formerly this method was only applicable to chemicals like potassium salts (Chlorate, Chloride, Bromide, etc) ammonium chloride and methenamine. These materials possess cohesive and flow properties that make direct compression possible.

**RESEARCH ENVISAGED**

**Reason for selection of project**

- A floating drug delivery system is a good approach for Sustain Release formulation of different therapeutic agents.
- Foating-mucoadhesive tablet increases the bioavailability of the drug.

**PREFORMULATION STUDIES:**

Preformulation testing is the first step in the rational development of dosage forms of a drug. It can be defined as an investigation of physical and chemical properties of drug substance, alone and when combined with excipients.

**Identification tests**

**IR spectroscopy**

The FT-IR spectrum of the obtained sample of drug was compared with the standard FT-IR spectra of the pure drug. The infrared absorbance spectrum of Cimetidine HCl was recorded over the range of 400 – 4000 $cm^{-1}$ at a resolution of 2 $cm^{-1}$

**Organoleptic properties**

Cimetidine is a white to pale yellow crystalline powder, odorless and bitter in taste.

**Solubility analysis**

Preformulation solubility analysis was done to select a suitable solvent system to dissolve the drug and also to test its solubility in the dissolution medium which was to be used.

**Melting Point determination**

The melting point of Cimetidine HCl was found to be 136-142$^{o}$C. The reported melting point range of the drug is 138$^{o}$C & 284$^{o}$C.

**Partition Coefficient measurement**

The partition coefficient is defined as the ratio of the equilibrium concentrations of a dissolved substance in a two-phase system consisting of two largely immiscible solvents. In the case n-octanol and water:

$$P_{o/w} = c_{n\ octanol} / c_{water}$$

**Preparation of SGF**

Accurate weight 2gm of Sodium Chloride was dissolved in 7ml of conc. Hydrochloric acid & resulting solution is diluted with 1000ml of distilled water & the final pH of solution was adjusted to 1.2.

**Preparation of standard solution of Cimetidine HCl**

Weight of Cimetidine HCl taken = 100mg
Volume made up to 100 ml
Concentration of standard solution = 100µg/ml

**U.V ABSORBANCE**

**CHARACTERIZATION**

Various parameters that need to be evaluated in instant release formulations include disintegration time, content uniformity, hardness, friability, weight variation,dissolution profiles, in case of solid dosage forms.

**Evaluation of tablets**

**General Appearance**

This may include tablet's size, shape, colour, presence or absence of an odour, taste, surface texture, physical flaws and consistency and legibility of any identifying marking.

**Size and Shape**

The size and shape of the tablet can also influence the choice of tablet machine to use.

**Tablet thickness**

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Tablet thickness is an important characteristic in reproducing appearance and also in counting by using filling equipment.

**Tablet hardness**

Hardness of the tablet of each formulation was determined using Monsato Hardness tester. It was measured in kg/cm$^2$.

**Weight variation**

Initially twenty (20) tablets were taken and their weight was determined individually and collectively on a digital weighing balance having sensitivity to the four places after decimal. The average weight of one tablet was determined from the collective weight [3-5].

**Drug content uniformity**

The 20 tablets were powdered and weighed accurately equivalent to 100mg of Cimetidine Hcl. The powder was transferred to 100ml volumetric flask. To this 70ml of water was added, and stirred for 15 min. The volume was made up to 100ml with water and filtered.

**Kinetic release profile of Cimetidine Floating-mucoadhesive tablet Formulation :**

**Fig 1. I.R Spectrum of Cimetidine & HPMC**

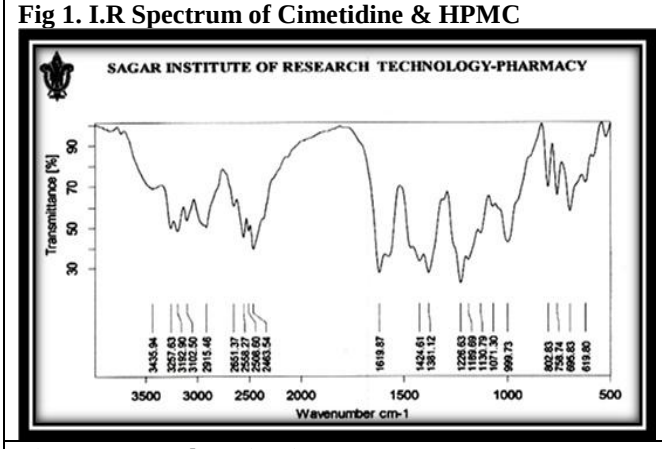


**Fig 2. Calibration Standard curve of Cimetidine HCl**

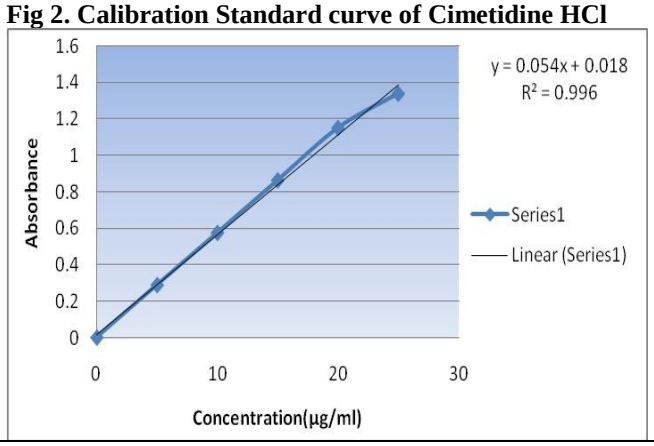


**Fig 3. Zero Order Kinetics**

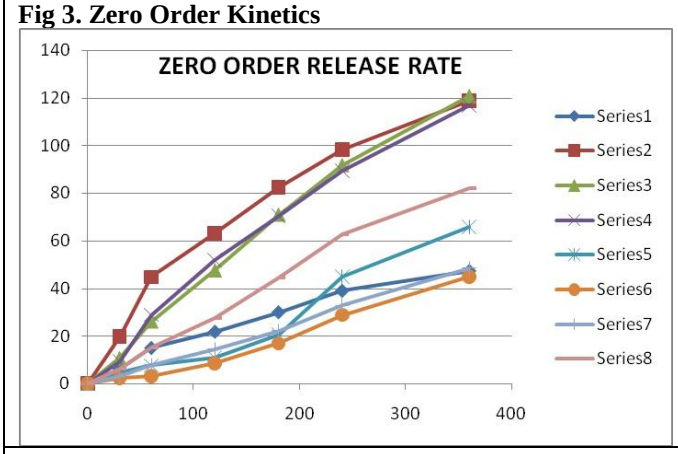


**Fig 4. First Order Kinetics**

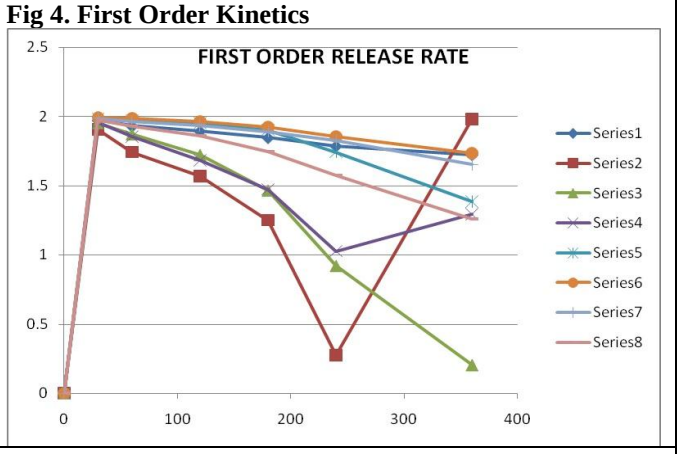


**Fig 5. Higuchi model**

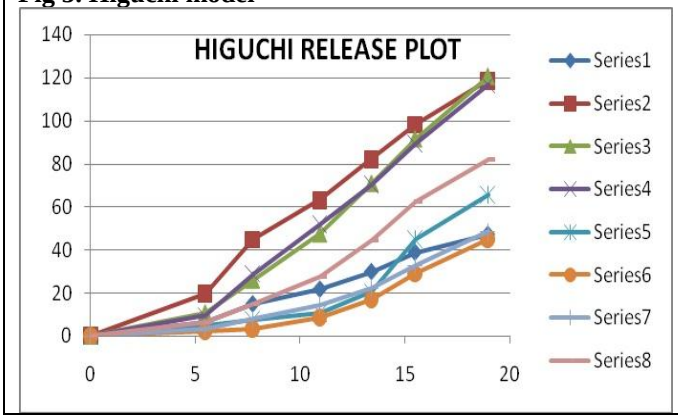


**Fig 6. Calibration Standard curve of Cimetidine HCl**

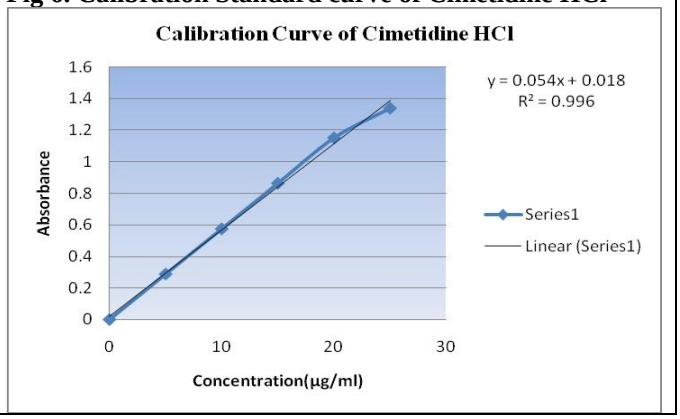

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**Table 1. Composition of floating-mucoadhesive tablet of Cimetidine hcl in different batches (Weight– 300mg)**

| Ingredients | SR-I | SR-II | SR-III | SR-IV | SR-V | SR-VI | SR- VII | SR-VIII |
|---|---|---|---|---|---|---|---|---|
| | mg | mg | Mg | mg | mg | Mg | mg | mg |
| Cimetidine hydrochloride | 150 | 150 | 150 | 150 | 150 | 150 | 150 | 150 |
| HPMC K4M | - | - | - | - | 65 | 30 | 35 | - |
| HPMC K5M | 80 | 70 | - | - | - | - | 30 | 35 |
| HPMC K15M | - | - | - | 60 | - | 30 | 25 | 25 |
| HPMC K100M | - | - | 50 | - | - | - | - | 30 |
| Carbopol 934P | 20 | 30 | 40 | 40 | 25 | 30 | 20 | 20 |
| Sodium bicarbonate | 30 | 30 | 30 | 30 | 30 | 30 | 20 | 20 |
| Citric acid | 10 | 10 | 10 | 10 | 10 | 10 | 8 | 8 |
| Aerosil | - | - | 5 | 3 | 5 | 5 | 3 | 3 |
| Magnesium stearate | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Lactose | 5 | 5 | 10 | 2 | 10 | 10 | 4 | 4 |
| Talc | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |

**Table 2. Various Evaluating Parameter of Batch-I to Batch-VIII batches of Cemetidine Floating-mucoadhesive**

| Batch | Angle of Repose (θ°) | Bulk Density ($g/cm^3$) | Tapped Density ($g/cm^3$) | Compressibility Index | Hausner Ratio |
|---|---|---|---|---|---|
| SR-I | 28±1.5 | 0.385±0.03 | 0.569±0.02 | 31.17±1.56 | 1.37±0.03 |
| SR-II | 28±1.75 | 0.384±0.05 | 0.502±0.03 | 23.21±1.45 | 1.27±0.01 |
| SR-III | 32±1.56 | 0.366±0.06 | 0.506±0.01 | 25.32±1.67 | 1.12±0.01 |
| SR-IV | 30±1.73 | 0.356±0.12 | 0.515±0.02 | 28.32±1.57 | 1.25±0.02 |
| SR-V | 32±1.26 | 0.365±0.11 | 0.509±0.01 | 25.30±1.67 | 1.29±0.01 |
| SR-VI | 28±1.85 | 0.384±0.13 | 0.505±0.01 | 30.17±2.00 | 1.15±0.01 |
| SR- VII | 30±1.34 | 0.365±0.23 | 0.509±0.02 | 27.36±1.59 | 1.21±0.01 |
| SR- VIII | 27±1.23 | 0.38±0.12 | 0.505±0.01 | 28.21±1.56 | 1.16±0.01 |

**Table 4. *In vitro* drug release studies of Cimetidine Floating tablet.**

| Time in min. | Formulation code | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | FT-I | FT-II | FT-III | FT-IV | FT-V | FT-VI | FT-VII | FT-VIII |
| **30** | 6.17±0.8 | 19.73±0.7 | 10.71±0.9 | 9.375±0.5 | 4.68±0.23 | 2.16±0.12 | 3.11±0.38 | 6.11±0.32 |
| **60** | 8.75±0.12 | 25±0.15 | 15.40±0.41 | 19.41±0.23 | 2.88±0.55 | 1.08±0.63 | 4.79±0.47 | 8.91±0.22 |
| **120** | 6.84±0.18 | 18.32±0.24 | 21.42±0.38 | 23.10±0.54 | 3.24±0.11 | 5.4±0.31 | 6.52±0.22 | 12.56±0.48 |
| **180** | 8.16±0.22 | 19.17±0.43 | 23.43±0.17 | 18.41±0.34 | 9.72±0.64 | 8.28±0.36 | 7.89±0.62 | 16.74±0.74 |
| **240** | 8.88±0.28 | 18.89±0.38 | 20.75±0.38 | 19.08±0.54 | 24.48±0.28 | 11.88±0.62 | 10.58±0.72 | 18.23±0.59 |
| **360** | 8.39±0.32 | 20.58±0.51 | 28.99±0.16 | 27.4±76 | 20.88±0.53 | 16.21±0.52 | 15.66±0.88 | 19.36±0.115 |

**Table 5. Calibration curve of Cimetidine HCl**

| S. No. | Conc.(µg/ml) | Absorbance (at 313nm) | | | |
|---|---|---|---|---|---|
| | | I | II | III | Average |
| 1 | 5 | 0.288 | 0.289 | 0.287 | 0.288 |
| 2 | 10 | 0.577 | 0.575 | 0.575 | 0.575 |
| 3 | 15 | 0.865 | 0.865 | 0.863 | 0.864 |
| 4 | 20 | 1.152 | 1.152 | 1.153 | 1.152 |
| 5 | 25 | 1.342 | 1.338 | 1.340 | 1.340 |

**Table 6. Various Evaluating Parameter of Batch-I to Batch-VIII batches of Cimetidine Floating-mucoadhesive**

| Batch | Angle of Repose (θ°) | Bulk Density ($g/cm^3$) | Tapped Density ($g/cm^3$) | Compressibility Index | Hausner Ratio |
|---|---|---|---|---|---|
| SR-I | 28±1.5 | 0.385±0.03 | 0.569±0.02 | 31.17±1.56 | 1.37±0.03 |
| SR-II | 28±1.75 | 0.384±0.05 | 0.502±0.03 | 23.21±1.45 | 1.27±0.01 |

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| | | | | | |
|---|---|---|---|---|---|
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| SR-VI | 28±1.85 | 0.384±0.13 | 0.505±0.01 | 30.17±2.00 | 1.15±0.01 |
| SR- VII | 30±1.34 | 0.365±0.23 | 0.509±0.02 | 27.36±1.59 | 1.21±0.01 |
| SR- VIII | 27±1.23 | 0.38±0.12 | 0.505±0.01 | 28.21±1.56 | 1.16±0.01 |

**Table 7. Evaluation Parameter of floating-muucoadhesive tablets**

| Batch Code | Hardness ($kg/cm^2$) N=5 | Thickness (mm) N=10 | Friability (%) | Weight variation N=10 | %Drug content |
|---|---|---|---|---|---|
| | | | | | Ranitidine Hydrochloride |
| SR-I | 3.5 ± 0.12 | 4.0 ± 0.17 | 0.218±0.7 | 5.8± 1.05 | 91± 1.2 |
| SR-II | 4 ± 0.56 | 4.0 ± 0.15 | 0.225±0.16 | 5.1± 1.18 | 96 ± 1.1 |
| SR-III | 4 ± 0.31 | 4.0 ± 0.21 | 0.221±0.22 | 5.3± 1.21 | 94 ± 1.4 |
| SR-IV | 3 ± 0.17 | 4.0 ± 0.19 | 0.233±0.19 | 6.2± 1.07 | 95±0.96 |
| SR-V | 3.9 ± 0.24 | 4.0 ± 0.14 | 0.199±0.34 | 4.6± 1.14 | 95 ± 0.8 |
| SR-VI | 3.5 ± 0.35 | 4.0± 0.15 | 0.282±0.57 | 5.1± 0.98 | 97 ± 1.1 |
| SR-VII | 3.9±0.21 | 3.1±0.12 | 0.232±0.37 | 4.5±0.58 | 96±0.91 |
| SR-VIII | 4.1±0.25 | 3.5±0.11 | 0.242±0.47 | 4.9±0.45 | 97±0.58 |

**Table 8. *In vitro* drug release studies of Cimetidine Floating tablet.**

| Time in min. | Formulation code | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | FT-I | FT-II | FT-III | FT-IV | FT-V | FT-VI | FT-VII | FT-VIII |
| **30** | 6.17±0.8 | 19.73±0.7 | 10.71±0.9 | 9.375±0.5 | 4.68±0.23 | 2.16±0.12 | 3.11±0.38 | 6.11±0.32 |
| **60** | 8.75±0.12 | 25±0.15 | 15.40±0.41 | 19.41±0.23 | 2.88±0.55 | 1.08±0.63 | 4.79±0.47 | 8.91±0.22 |
| **120** | 6.84±0.18 | 18.32±0.24 | 21.42±0.38 | 23.10±0.54 | 3.24±0.11 | 5.4±0.31 | 6.52±0.22 | 12.56±0.48 |
| **180** | 8.16±0.22 | 19.17±0.43 | 23.43±0.17 | 18.41±0.34 | 9.72±0.64 | 8.28±0.36 | 7.89±0.62 | 16.74±0.74 |
| **240** | 8.88±0.28 | 18.89±0.38 | 20.75±0.38 | 19.08±0.54 | 24.48±0.28 | 11.88±0.62 | 10.58±0.72 | 18.23±0.59 |
| **360** | 8.39±0.32 | 20.58±0.51 | 28.99±0.16 | 27.4±76 | 20.88±0.53 | 16.21±0.52 | 15.66±0.88 | 19.36±0.115 |

## RESULT & DISSUSION

Cimetidine is a histamine H2-receptor antagonist. It is widely prescribed in gastric ulcers, duodenal ulcers, Zollinger-Ellison syndrome and gastroesophageal reflux disease. Cimetidine had maximum solubility in acidic pH. cimetidine has some adverse effect such as diarrhoea, dizziness, headache and anorexia. Prolonged gastric retention improves bioavailability, reduces drug waste and improves solubility for drugs that are less soluble in high pH environment. Effervescence production, decrease the several local GIT side effect, such as gastric irritation, nausea and gastritis.

Formulation development & evaluation parameters have been performed in satisfactory data.. Title of this study will be done for prolonged the bioavailability of the dosage form.

### Cimetidine

Appearance and colour: Cimetidine is a white to pale yellow crystalline powder

Odour: Odourless.

**T**aste: Bitter.

**Solubility analysis:** Soluble in water insoluble in organic solvent.

### Identification of Drug by FT-IR Spectroscopy

IR spectroscopy: - The FT-IR data suggesting a correlation between the pure and the sample drug which will indicates purity of the sample. It will also identify by the characteristic peak of Cimetidine Hydrochloride.

### Evaluation of Floating Tablets

### Evaluation Parameters of the blend

The values of pre-compression parameters evaluated for batches SR-I to SR-VIII was tabulated. and they were within the limits. The value of angle of repose for both batches varies between the range 24°17' to 28°15', and the value of compressibility index varies between the range of 17.60 to 20.95 and 25.32 to31.77 also the value of bulk density, tapped density, hasuner's ratio of SR-I to SR-VIII varies between the range 0.356 to 0.385, 0.506 to 0.569, and 1.15 to 1.37.

## CONCLUSION

**T**his study discusses the preparation of floating tablets of Cimetidine. The effervescent-based floating drug delivery was a promising approach to achieve *in vitro* buoyancy. The addition of gel-forming polymer HPMC K4

M, HPMC K15 M, HPMC K5, HPMC K100, carbopol 934P and gas-generating agent sodium bicarbonate was essential to achieve *in vitro* buoyancy. Addition of citric acid, to achieve buoyancy under the elevated pH of the stomach, caused an enhancement in drug release.Polymer swelling is crucial in determining the drug release rate and is also important for flotation.

Sustained release, Sustained action, prolonged action, Controlled release, Extended release action, Timed release, Depot, and Repository dosage forms are terms used to identify drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. In the case of injectable dosage forms, this period may vary from day to months. In the case of orally administered forms, however, this period is measured in hours and critically depends on the residence time of the dosage form in the GI tract.

The present study was to develop floating-mucoadhesive tablet of Cimetidine HCL in order to achieve an extended retention in the intestine, which may result in enhanced absorption and thereby improved bioavailability.

Floating-mucoadhesive tablets of Ranitidine were obtained with modified wet granulation techniques with substantial result in floating and drug release study. Thus the prepared floating –mucoadhesive formulations may prove to be potential candidate for multiple unit delivery, may result in new therapeutic possibilities with substantial benefit to the patient.

It is a new drug delivery system to maximize effectiveness and compliance. Cimetidine HCL is use for gastric problems. The advantage of floating drug delivery system is to extend the release of drug, increases gastric retention time and enhances bioavailability by superior technology of floatation and adhesion to achieve gastric retention.

**ACKNOWLEDGEMENT**: None

**CONFLICT OF INTEREST:**
The authors declare that they have no conflict of interest.

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