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# Design, development and evaluation of floating tablet of ranitidine hydrochloride for the treatment of duodenal Ulcer

## Pawan Jalwal and Anil Middha

**Abstract**
The present study involved the preparation of floating tablet of ranitidine. The tablets were prepared with both direct compression and wet granulation methods. It was found that wet granulation method facilitated greater efficiency in controlling ranitidine release. Hence, all further formulations were prepared with wet granulation technique. We prepared 11 batches (R01-R11). (R01) was prepared by direct compression but it was failed because it was not compressed so this batch failed. Ranitidine hydrochloride is also a $H_2$-receptor antagonist. It is degraded in the gastric acid. Floating dosage form is the best alternate to increase the bioavailability. It has a furan ring. It has melting point 69-70 ˚C. The wavelength of ranitidine is at 229 nm and 315 nm (water used as medium).

**Keywords:** Famotidine, Zollinger Ellison syndrome, duodenal ulcer, gastrin, histamine

## Introduction
Ranitidine hydrochloride is also a $H_2$-receptor antagonist. It is degraded in the gastric acid. Floating dosage form is the best alternate to increase the bioavailability. It has a furan ring. It has melting point 69-70 ˚C. The wavelength of ranitidine is at 229 nm and 315 nm (water used as medium). The chemical formula is $C_{13}$ $H_{22}$ $N_4$ $O_3$ S. The molecular weight is 314.
The chemical name of Ranitidine is dimethyl(5-(((2-((e)-1-(metylamino)-2-nitroethenyl)amino)ethyl)sulfanyl)methyl)furan-2-yl) methyl)amino. The structure of Ranitidine is given below

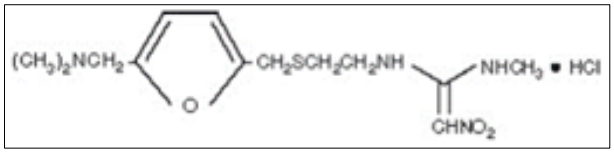


**Fig 1:** Ranitidine Hydrochloride

## Pharmacokinetics

**Table 1:** Pharmacokinetics of Ranitidine Hydrochloride

| **Bioavailability** | **approximately 50% orally** |
|---|---|
| Plasma Half Life | Approximately 2-3 hrs. |
| Plasma Protein Binding | 15- 20% |
| volume of distribution | about 1.4L/Kg |
| protein binding | serum protein binding is 15% |
| Metabolism | It has hepatic metabolism. |
| Elimination | Through urine via active tubular secretion |
| Clearance | It has 29ml/min and 3ml/min/kg in neonatel patients |

## Material and methods
Ranitidine Hydrochloride was received as a gift sample from Belco Pharma, Bahadurgarh, Haryana, India. Guar gum and Pectine were purchased from Thomas baker (chemicals) Pvt. Ltd. Mumbai. Isopropyl Alcohol was purchased from S.D fine chem. Ltd. Mumbai. Magnesium stearate and talc were perchased as a gift from Qualikems Fine Chemicals Pvt. Ltd, Delhi. Lactose was purchased from S.D. fine chem. Ltd. Mumbai. Sodium carbonate and

citric acid were purchased from Merck supplement Pvt. Ltd. Mumbai.

**Experimental methods**

Preparation of tablets containing Ranitidine by direct compression method:

**Table 2:** Formulation of Ranitidine by direct compression

| Ingredients | R01(mg/tab) |
|---|---|
| Drug | 150 |
| Guar Gum | 80 |
| Pectin | - |
| Citric acid | 30 |
| Sodium bicarbonate | 70 |
| Magnesium stearate | 3 |
| Talc | 3 |
| Lactose | 64 |

Preparation of tablets containing Ranitidine by wet granulation method:

**Table 3:** Composition of different formulations of Ranitidine floating tablets

| Ingredients (mg per tablet) | Formulation | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Ranitidine HCl | R02 | R03 | R04 | R05 | R06 | R07 | R08 | R09 | R10 | R11 |
| | 150 | 150 | 150 | 150 | 150 | 150 | 150 | 150 | 150 | 150 |
| Lactose | 144 | 144 | 104 | 104 | 64 | 64 | 104 | 104 | 144 | 144 |
| Sodium bicarbonate | 70 | 70 | 70 | 70 | 70 | 70 | 70 | 70 | 70 | 70 |
| Citric acid | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 |
| Guar gum | 40 | 40 | 40 | 40 | 80 | 80 | 80 | 80 | - | - |
| Pectin | - | - | 40 | 40 | 40 | 40 | - | - | 40 | 40 |
| Magnesium stearate | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Talc | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |

*All the quantities are in mg

Each tablet contains uniform weight of 400 mg and containing Isopropyl alcohol

**Preformulation studies**

**Melting point**

Melting point was noted from the melting point apparatus. The melting point was recorded and was compared with literature value and reported in table 4.

**Table 4:** Theoretical and observed melting point values of Ranitidine

| Experimental value | Literature value |
|---|---|
| 69 ˚C | 69 ˚C - 70 ˚C |

Melting point of Ranitidine was found to be 69 ºC. The practical and the theoretical values match. Therefore we can say that Ranitidine is in pure form.

**Partition coefficient study**

Equal volume of n-octanol and 0.1N HCl were saturated for a period of 24 hrs. 10 mg of Ranitidine was added to the mixture and was agitated for one hour. Acid phase was then diluted suitably and absorbance was taken at $\lambda_{max}$ 229 nm. Partition coefficient was calculated as the ratio of drug concentration in n-octanol to that in HCl. The partition value was calculated and compared with literature value shown in table 5

**Table 5:** Theoretical and observed partition coefficient values of Ranitidine

| Medium | Experimental value | Literature value |
|---|---|---|
| Hydrochloric acid | 0.068 | -1.1 |

Partition coefficient value of Ranitidine was found to be 0.068. The practical and theoretical values match. Therefore we can say that Ranitidine is in pure form.

**Determination of saturation solubility**

The solubility of Ranitidine in media 0.1N HCl is given in table 6.

**Table 6:** Solubility of Ranitidine in 0.1N HCl

| Media | Solubility Drug (mg)/Media(ml) | Category |
|---|---|---|
| Water | 9.9 mg/ml | Very Soluble |
| 0.1 N Hydrochloric acid | 9.8 mg/ml | Soluble |
| Methanol | 9.6 mg/ml | Soluble |
| Ethanol | 9.4 mg/ml | Sparingly Soluble |

Solubility of Ranitidine in water was found to be 9.9 mg/ml, 9.8 mg/ml in 0.1N HCl 9.6 mg/ml in methanol, 9.4 mg/ml in ethanol.

**Preparation of calibration curve**

A solution of Ranitidine (10µg/ml) in 0.1 N HCl, when scanned between 200 to 400 nm exhibits absorption maxima ($\lambda_{max}$) at 229nm. Absorbance of the concentrated solution was taken in duplicate and average absorbance was calculated. Calibration curve in media (0.1 N HCl) was prepared by plotting absorbance with respect to concentration. The Regression coefficient value ($R^2$) was 0.999. This showed a

good linearity. The absorbance values for concentrated solutions in 0.1N HCl is given in Table 7. The calibration plot for 0.1N HCl is given in figure 2.

**Table 7:** Data for Standard calibration curve of Ranitidine in 0.1N HCl:

| Sr. No. | Conc. (µg/ml) | Absorbance (229 nm) |
|---|---|---|
| 1. | 1 | 0.153 |
| 2. | 2 | 0.32 |
| 3. | 3 | 0.48 |
| 4. | 4 | 0.614 |
| 5. | 5 | 0.77 |
| 6. | 6 | 0.936 |

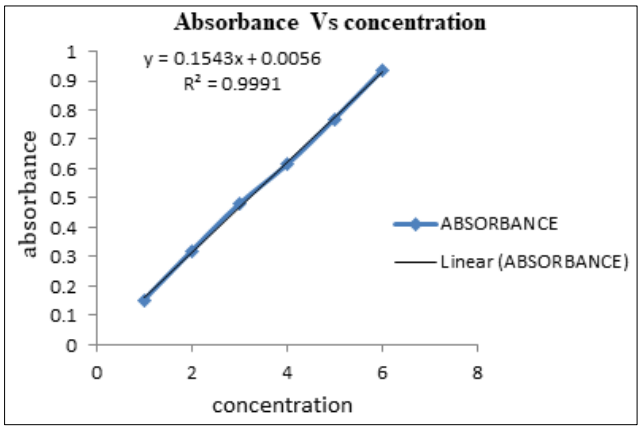


**Fig 2:** Calibration curve of Ranitidine in 0.1N HCl:

**Characterization of granules prepared by selected manufacturing process for all the formulation batches:**
Flow property of all the formulation batches was accessed through the precompression parameter like Tapped density, Bulk density, Angle of repose, Carr's index, Hausner's ratio.

**Table 8:** Micromeritic properties of formulations (Powder blend)

| Batches | Bulk density (g/ml) | Tapped density (g/ml) | Compressibility index (%) | Hausner's ratio | Angle of repose ($^0$) |
|---|---|---|---|---|---|
| **R01** | 0.696 | 0.791 | 12.01(good) | 1.13(good) | 35.801(fair) |
| **R02** | 0.545 | 0.654 | 16.66(fair) | 1.2(fair) | 28.636(excellent) |
| **R03** | 0.575 | 0.645 | 10.853(good) | 1.12(good) | 40.917(passable) |
| **R04** | 0.531 | 0.635 | 16.378(fair) | 1.19(fair) | 35.809fair) |
| **R05** | 0.545 | 0.645 | 16.667(fair) | 1.2(fair) | 26.031(excellent) |
| **R06** | 0.587 | 0.703 | 16.501(fair) | 1.19(fair) | 27.271(excellent) |
| **R07** | 0.552 | 0.663 | 16.742(fair) | 1.20(fair) | 28.636(excellent) |
| **R08** | 0.502 | 0.620 | 19.032(fair) | 1.23(fair) | 35.801(fair) |
| **R09** | 0.565 | 0.659 | 13.525(good) | 1.16(good) | 31.821(good) |
| **R10** | 0.459 | 0.632 | 27.373(poor) | 1.37(poor) | 30.145(good) |
| **R11** | 0.550 | 0.775 | 29.032(poor) | 1.40(poor) | 33.694(good) |

From the result it was concluded that the powder blend had good flow properties and these can be used for tablet manufacture.

**Evaluation of floating tablet of Ranitidine**
Hardness, Thickness, diameter, Average weight was performed for all the batches (R01to R11) and the data are presented in table 9.

**Table 9:** Evaluation of floating tablet of Ranitidine

| Formulation | Thickness (mm) | Weight (mg) | Hardness (kg/cm$^3$) | Floating Lag Time (min) | Floating duration (hrs) |
|---|---|---|---|---|---|
| R01 | 2.32 | 302.5 | - | - | 12 |
| R02 | 3.04 | 403.4 | 3.6 | 1:49 | 12 |
| R03 | 3.03 | 401.2 | 3.4 | 1:48 | 12 |
| R04 | 3.05 | 401.2 | 4.2 | 2:00 | 12 |
| R05 | 3.06 | 402.2 | 4.3 | 2:00 | 12 |
| R06 | 3.08 | 402.3 | 4.3 | 1:09 | 12 |
| R07 | 3.03 | 401.5 | 4.4 | 1:08 | 12 |
| R08 | 3.04 | 400.3 | 3.4 | 3:00 | 12 |
| R09 | 3.05 | 401.3 | 3.5 | 2:50 | 12 |
| R10 | 3.02 | 399.6 | 2.2 | 3:48 | 12 |
| R11 | 3.03 | 400.1 | 2.1 | 3:55 | 12 |

The result showed that thickness, weight and hardness, floating lag time and floating duration were within pharmacopoeial limits. So they pass the above tests.

Fig. 3 a) after 1:9 min.


Fig. 3 b) after 10 hrs.

**Fig 3:** Ranitidine tablet floats in 0.1 N HCl (100ml)

Friability was performed for all the batches (R01 to R11) and the data are presented in table 10.

**Table 10:** Friability of matrix tablets of Ranitidine

| Formulation | Friability (%) |
|---|---|
| R01 | - |
| R02 | 0.288 |
| R03 | 0.289 |
| R04 | 0.332 |
| R05 | 0.329 |
| R06 | 0.491 |
| R07 | 0.405 |
| R08 | 0.346 |
| R09 | 0.344 |
| R10 | 0.267 |
| R11 | 0.265 |

Friability was found to give satisfactory result for all trials.

## Drug Content Uniformity

**Table 11:** Drug Content in the floating tablets of Ranitidine

| Formulation Code | Drug Content (%) |
|---|---|
| R01 | - |
| R02 | 90 |
| R03 | 90.4 |
| R04 | 94 |
| R05 | 92.5 |
| R06 | 98 |
| R07 | 97 |
| R08 | 95 |
| R09 | 96.3 |
| R10 | 95.5 |
| R11 | 94 |

The drug content uniformity of all the formulation was found to be in the range of 90 % to 98% which showed that there was uniform distribution of the drug throughout the batch.

## Effects of different of polymers on formulation

Formulation batches were prepared using different polymers alone and lactose as diluents and release profile was given in table 12

**Table 12:** Release profiles of formulation using different polymers

| Time (hrs.) | Cumulative % Drug Release | |
|---|---|---|
| | R03 | R10 |
| 1 | 27.64 | 20.4 |
| 2 | 30.22 | 30.41 |
| 3 | 50.6 | 41.92 |
| 4 | 57.62 | 50.62 |
| 5 | 63.54 | 58.54 |
| 6 | 72.42 | 66.42 |
| 7 | 78.54 | 72.64 |
| 8 | 85.26 | 80.44 |
| 9 | 91.20 | 90.35 |
| 10 | 94.65 | 97.8 |
| 11 | 96.89 | 100 |
| 12 | 98.79 | |

Formulations with different polymers resulted in different release profiles. Guar Gum show slower release profile as compared to pectin because guar gum act as a binder.

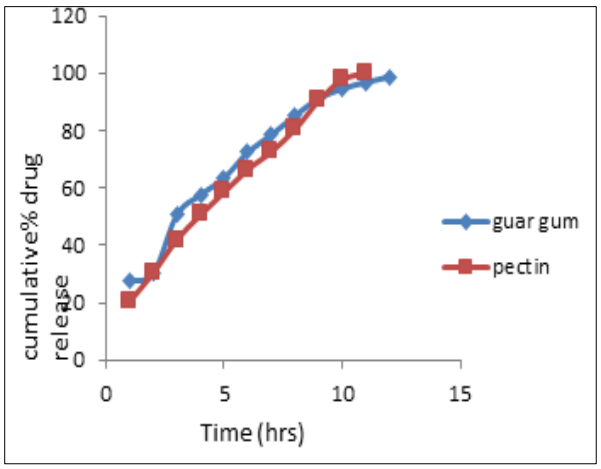


**Fig 4:** Dissolution profile of formulation with different polymers

**Optimization of batches using different concentration of polymers:** Formulation batches were prepared using different concentration of polymers in the formula and their release rates were compared.

## Summary

The present study involved the preparation of floating tablet of ranitidine. The tablets were prepared with both direct compression and wet granulation methods. It was found that

wet granulation method facilitated greater efficiency in controlling ranitidine release. Hence, all further formulations were prepared with wet granulation technique. We prepared 11 batches (R01-R11). (R01) was prepared by direct compression but it was failed because it was not compressed so this batch failed. Then we prepared batches (R02-R11) by wet granulation and studied their release kinetic. The formulations were studied for their floating behaviour using simulated gastric fluid; the floating lag time and duration of floating were noted for each formulation. The tablets were also studied for drug release for 12 h using 0.1N HCl as dissolution media. The release kinetics of the final batch (R06) and batch (R07) was carried out and it was found batch followed zero order kinetic model and less floating lag time.

**Conclusion**

The physical compatibility study at 40ºC/ 75% RH showed that Ranitidine and excipients used found to be physically compatible. FTIR spectra data showed that Ranitidine and excipients used found to be compatible. Melting point of Ranitidine was found to be 69°C. Formulation was prepared with two processes i.e. direct compression and wet granulation; it was found that wet granulation method facilitated greater efficiency in controlling Ranitidine release. Characterization of granules prepared by selected manufacturing processes like bulk density, tapped density, Carr's index, Hausner's ratio, Angle of repose was done and found to have good flow and compressibility. The tablets prepared were found to be within the limits with respect to hardness, average weight, %friability, thickness, swelling index and in vitro dissolution study. *In vitro* dissolution studies of the best formulation (R06) and (R07) showed complete release of drug in 12 hrs. The fine particle grades are more compressible than the standard premium grades, resulting in harder tablets. Increasing tablet hardness provided a much great control over dissolution rate. Guar gum is the best polymer as compared to pectin because when we increase the concentration of guar gum the release was decrease and there was an increase in time of release of drug but when we increase the concentration of pectin the release was increase. The concentration of polymer is the determining factor in controlling the release of Ranitidine. Under the study of kinetic models, five models have been studied namely Zero Order, First Order, Higuchi, Hixon-Crowell, Korsmeyer-Peppas model. It was found that the drug release followed zero order kinetic (having maximum $R^2$ value of 0.998.

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