Asian Journal of Pharmaceutical and Health Sciences
Journal Homepage : www.ajphs.com

Formulation and Optimization of Hydro Dynamically Balanced Tablet of Ranitidine Hydrochloride

Natasha Sharma*, Dilip Agarwal, Gupta M.K., Mahaveer Pr. Khinchi
Department of Pharmaceutics, Kota College of Pharmacy, Kota Rajasthan-325003

ARTICLE HISTORY

Received : 26-Feb-2011

Accepted : 17-Mar-2011

Available online: 10-May-2011

Keywords:

Ranitidine, Carbopol 934, HPMC, buoyancy

***Corresponding author:**

E-mail : natasha83sharma@gmail.com

ABSTRACT

Hydro dynamically tablet of ranitidine hydrochloride were prepared by wet granulation method. The tablets were formulated and optimized on the basis of *in vitro* drug release studies. Tablet were fabricate using high viscosity grade of polymers HPMC K100M with another gelling properties polymer carbopol 934 and effervescing agent sodium bicarbonate ($NaHCO_3$) in combination with acidulent adipic acid $(CH_2)_4(COOH)_2$. Before development of formulation of ranitidine hydrochloride tablet, the Preformulation study was done successfully. IR spectra studies revealed that the drug and the polymers used were compatible. Various batches were prepared and optimized on the basis of various evaluations parameters. The evaluation parameters like hardness, friability and content weight uniformity were within the limits for various formulated batches. Buoyancy lag time (BLT), Total buoyancy time (TBT) and in vitro drug release study batch F_3 showed satisfactory results.

INTRODUCTION

The hydro dynamically balanced tablet is a part of gastro retentive drug delivery systems can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the gastrointestinal tract. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability[1]. Ranitidine hydrochloride (RHCl) is histamine H_2-receptor antagonist. It is widely prescribed in active duodenal ulcers, gastric ulcers, Zollinger-Ellison syndrome, gastro esophageal reflux disease, and erosive esophagitis [2].

The recommended adult oral dosage of ranitidine is 150 mg twice daily or 300 mg once daily. The effective treatment of erosive esophagitis requires administration of 150 mg of ranitidine 4 times a day. A conventional dose of 150 mg can inhibit gastric acid secretion up to 5 hours but not up to 10 hours. An alternative dose of 300 mg leads to plasma fluctuations; thus a sustained release dosage form of ranitidine hydrochloride is desirable [3].

The short biological half-life of drug (~2.5-3 hours) also favors development of a sustained release formulation. A traditional oral sustained release formulation releases most of the drug at the colon, thus the drug should have absorption window either in the colon or throughout the gastrointestinal tract. [4, 5]. Ranitidine is absorbed only in the initial part of the small intestine and has 50% absolute bioavailability. Moreover, colonic metabolism of ranitidine is partly responsible for the poor bioavailability of ranitidine from the colon. These properties of ranitidine hydrochloride do not favor the traditional approach to sustained release delivery. Hence, clinically acceptable sustained release dosage forms of ranitidine hydrochloride prepared with conventional technology may not be successful [6].

MATERIALS AND METHODS

Materials

Ranitidine was received as a gift sample from Ranbaxy Lab Ltd, Dewas, India. Polymers such as hydroxypropyl methylcellulose K100M and carbopol 934 were received as gift samples from Colorcon Asia Pvt. Ltd., Goa, India. Magnesium stearate, hydrochloric acid, sodium bicarbonate and adipic acid were purchased from S.D. Fine-Chem. Ltd, Ahmadabad, India. Polyvinyl pyrrolidone K-30 (PVP K-30) was procured from Ottokemi, Mumbai, India. Purified talc was purchased from E. Merck (India) Ltd., Mumbai. All other ingredients were of Analytical grade.

METHODS

Spectroscopic Analysis

UV-Spectrum: 100 mg of ranitidine hydrochloride was weight accurately and transferred it to 100 ml volumetric flask. Dissolved it in 0·1 N HCl and make up the volume up to 100 ml. This was considered as stock solutions (1000 mcg/ml). Further dilution were done with this medium and resulting solution were scanned in the range of 400 to 200 nm using 0·1 N HCl as a blank with the help of UV-visible spectrophotometer [7].

FTIR Spectrum

The IR analysis of the sample was carried out for qualitative

compound identification. For this drug are mixed with dried potassium bromide in ratio and placed in cell and scanned at wavelength 4000 cm^{-1} - 600 cm^{-1}.

Solubility Analysis (Different Solvents)

25 mg of drug was suspending in 25 ml of distilled water in 50 ml volumetric flask. This flask was place in a mechanical shaker for 24 hrs. Then filter the dispersion and dilute suitably with distilled water. The filter analyzes spectrophotometer at a wavelength 313 nm and the concentrations of ranitidine in each sample were determined from a previously prepared standard curve [8].

pH Analysis

The pH of a drug measure using calibrated pH-meter. The pH-meter was calibrated before each use with buffered solutions of pH 4, 7 and 10 [9].

Melting Point

Melting point was determined by using melting point apparatus [8].

Partition coefficient

The partition coefficient of Ranitidine hydrochloride was determined in n-octanol: 0.1N hydrochloride acid system. Briefly an excess amount of ranitidine was added in to 50 ml. each of n-octanol and 0.1 N hydrochloride acid. The mixture was shaken for 24 hrs until equilibrium was reached. Phases were separated in separating funnel and the aqueous phase was filtered through 0.45µ membrane filter, suitably and amount of ranitidine solublized in aqueous phase determined by measuring absorbance at 313 nm spectrophotometrically. The partition coefficient of ranitidine was calculated from the ratio between the concentration of ranitidine in organic and aqueous phases using the following equation [9]:

$$K_{o/w} = (C_{oil} / C_{aq.})$$

ASSAY METHOD

Preparation of Perchloric acid (0.01M): To 4.5 ml of perchloric acid was added 150 ml anhydrous glacial acetic acid 25 ml of acetic anhydride, mixed well; added 10.5 ml acetic anhydride and allow the solution cool for 30 min; finally diluted to 500ml with glacial acetic acid cool and anhydrous glacial acetic acid to produce the 1000 ml. Allow the preparation solution to stand for1 day. This perchloric acid (0.1 M) was diluted to 0.01 M with glacial acetic acid and standardized with the pure potassium hydrogen phthalate and crystal violet indicator.

Crystal violet indicator: Crystal Violet Indicator: Prepared by dissolving 0.1 g of dye in 100 ml glacial acetic acid.

Perchloric Acid-Crystal Violet Mixture (1.5mM $HclO_4$-0.25mM Crystal Violet) : Prepared by mixing15 ml of 0.01 M perchloric acid and 10 ml of 1000 µg ml-1 crystal violet solutions and diluting to 100 ml with glacial acetic acid in a drug calibrated flask.

Standard Drug Solution: A stock standard solution containing 2 mg/ml RNH was prepared by dissolving 500 mg of pure drug in glacial acetic acid and diluting to the mark in a 250 ml calibrated flask. This solution (2 mg/ml) was used for titrimetric work, and for spectrophotometrically work, the same was diluted appropriately with glacial acetic acid to get 100 g/ml working concentration.

General Procedures

Visual Titration (Method A): A 10 ml aliquot of the drug solution containing 1-15 mg of RNH was pipette out into a clean and dry 100 ml titration flask, 2 drops of crystal violet indicator was added and titrated with standard 0.01 M perchloric acid to an emerald green end point. The amount of the drug in the measured aliquot was calculated from:

Amount (mg) = VMR

Where: V = volume of perchloric acid required, ml

M= relative molecular mass of drug,

R = molarity of perchloric acid.

Spectrophotometric Estimation

Different aliquots (1.0–7.0) of standard 100 mcg/ml drug solution were accurately transferred in to a series of 10 ml calibrated flasks. An exactly measured volume of (2 ml) perchloric acid-crystal violet mixture was added to each flask, and the volume was diluted to the mark with glacial acetic acid, and mixed well. Absorbance was measured at 570 nm against a reagent blank. The increasing absorbance values at 570 nm were plotted against the concentration of the drug to obtain the calibration graph. The concentration of the unknown was read from the calibration graph [11].

Compatibility Study (Drug-Excipients Interaction Study)

Excipients are integral components of almost all pharmaceutical dosage forms. The successful formulation of a stable and effective solid dosage form depends on the careful selection of the excipient which is added to facilitate administration, promote the consistent release and bioavailability of the drug and protect it from degradation [8, 9].

Compatibility Studies

They provide framework for the drug in combination with the excipients in the fabrication of the dosage form and establish that active drug has not undergone degradation. This can be confirmed by carrying out infrared light absorption scanning spectroscopy.

FTIR Studies

FTIR was carried out to assess the interaction between the drug and the excipients to understand the physical and chemical interaction that could occur in the drug and excipients. It is one of the most powerful analytical techniques for chemical identification of drug.

Method: The pure drug and its formulation were subjected to IR studies. In the present study, the pure drug, Ranitidine and a mixture of it with the excipients in equal ratio were mixed separately and stored them at 40-50ºC and were scanned over a wave number range of 4000-400 cm^{-1}, and confirmed by TLC after storage under accelerated conditions of temperature and humidity.

Preparation Of Ranitidine Hydro Dynamically Balanced Tablet

Hydro dynamically balanced tablets containing Ranitidine Hydrochloride were prepared by wet granulation process using 2% PVP K-30 in Isopropyl alcohol using varying concentrations of different grades of polymers with Carbopol 934, sodium bicarbonate and adipic acid. Composition of trial, optimized batches are given inTable No.1.

Table No.1: Formulation code of various batch of hydro dynamically balance tablet of Ranitidine hydrochloride

Ingredients*	Formulation batches						
	F_1	F_2	F_3	F_4	F_5	F_6	F_7
Ranitidine HCl	316	316	316	316	316	316	316
HPMC K100	90	85	80	75	70	65	60
Carbopol 934	10	15	20	25	30	35	40
$NaHCO_3$	50	50	50	50	50	50	50
Adipic acid	10	10	10	10	10	10	10
PVP K-30 (w/v)	2%	2%	2%	2%	2%	2%	2%
Magnesium Stearate	1%	1%	1%	1%	1%	1%	1%
Talc	1%	1%	1%	1%	1%	1%	1%

*Formulation F1 to F10 using the HPMC and Carbopol Ratio 4:1.
*All the ingredients are in milligrams per tablet

Polymers and effervescent mixtures were blended in pastel mortar 2% PVP-K30 solution in isopropyl alcohol was used as binder to form a moist mass. Granules were obtained by passing through the sieve no 12 the granules were dried at 45 ºC for 1 hour in oven dried granules were again passed through the sieve no. 22 and granules obtained was compressed in a tablet by using single punch hand operating tablet compression machine [10,11].

Evaluation of Hydro dynamically Balanced Tablet

Physical Parameters: The tablets were evaluated for shape, hardness (Monsanto hardness tester), thickness using calibrated varniear caliper, friability using Roche friabilator and weight variation test [12].

Assay of prepared tablets: Twenty tablet of each formulation were crushed to powder in pestle and motor and power equivalent to 100 mg of drug was added in 100 ml of 0.1 NHCL (pH 1.2). The resulting solution called the stock solution and filters the resulting solution through 0.45 µm membrane, diluted suitably and analyzed for drug content spectrophotometrically at 315 nm using 0.1 N hydrochloric acid as blank [13].

Buoyancy tests: Buoyancy capacity of tablets was determine by using USP (TYPE time between introduction of dosage form and its buoyancy on the simulated gastric fluid and the time during which the dosage form remain buoyant were measured. The time taken for dosage form to emerge on surface of medium called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of time by which dosage form remain buoyant is called Total Buoyancy Time (TBT) or Total Floating Time (TFT) [14].

In vitro Drug Release Studies: Drug release was studied using six station dissolution apparatus USP, XXII (paddle method) in 900 ml 0.1 N hydrochloric acid at 37± °C and 50 rpm, the difference being that although stirring was carried out using paddle shaft, the tablet were kept in to sinker (USP basket closed at both extremes) prior to their exposure into dissolution medium and the sinker was then placed horizontally at bottom. Moreover the paddle height was adjusted at 3.5 cm form the hemispherical bottom to avoid friction between the paddle shaft and sinker, which else may lead to erratic result. This ensured a complete exposure of tablet to the dissolution medium throughout the study. The study was performed in triplicate for a period of 24 hours. Five ml aliquots of sample were withdrawn at regular intervals and equal volume of pre-warmed (37±1°C) fresh dissolution medium was replaced. The samples withdrawn were filtered using 0.45 µm membranes, suitably diluted with 0.1 N hydrochloric acid and analyzed for drug content release using UV-VIS spectrophotometer at 315 nm [15- 17].

RESULT AND DISCUSSION

Spectroscopic Analysis

UV-Spectrum:

I. The ultraviolet absorption of 10 µg/ml in distilled water in the range 200-400 nm exhibit maxima at 313·5 & 228 nm.

II. The ultraviolet absorption of 10 µg/ml in 0·1 N HCL (pH 1·2) in the range 200-400 nm exhibit maxima at 315 & 228 nm.

Infrared Spectroscopy:

The IR analysis of Ranitidine Hydrochloride I.P. in fig. 1 was carried out for qualitative compound identification. All the peaks values were found to be near the standard values to confirm the purity of the drug molecules.

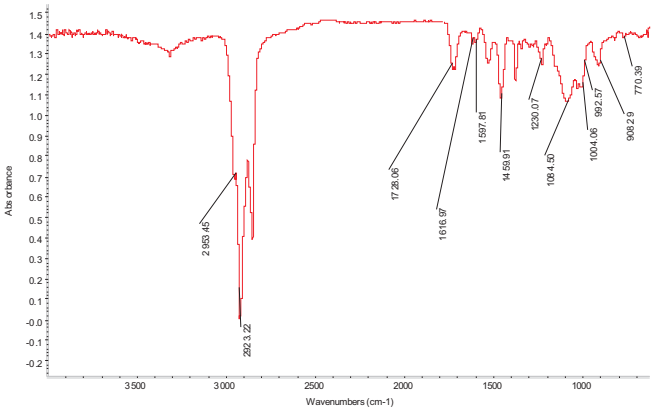

Fig. 1: FTIR Spectrum of Ranitidine hydrochloride (drug)

Solubility Analysis (Different Solvents)

I The solubility of Ranitidine Hydrochloride in water was found to be 447 mg/ml,which is near to the reported value.

II. The solubility of ranitidine hydrochloride in pH 1.2 was found to be 465 mg/ml, which is near to the reported value.

pH determination: The pH of the 1% solution of drug in distilled water found to be 5·2.

Melting Point: The melting point of the drug was found between the ranges of 125 to 134 ºC.

Partition coefficient: The Log P value was found to be 1.03 ± 0.11 in Octanol: 0.1 N HCL pH 1.2 solvent systems.

Table No. 2: Various Precompression Parameters

Batches	Bulk density	Tapped Density	Compressibility (%)	Remarks	Angle of Repose	Remarks
F_1	0.317	0.414	17.64	Good	31°.43′	Possible flow
F_2	0.323	0.386	13.28	Good	33°.70′	Good flow
F_3	0.340	0.431	8.21	Good	32°.15′	Possible flow
F_4	0.330	0.409	14.11	Excellent	33°.07′	Possible flow
F_5	0.366	0.466	17.42	Excellent	34°.77′	Possible flow
F_6	0.344	0.411	11.74	Good	30°.96′	Good Flow
F_7	0.360	0.426	16.12	Excellent	35°.36′	Possible flow

Table No. 3: Various Post Compression Evaluation Parameters

Batches	Hardness ($kg.cm^2$)	Friability (%)	% Drug Content	Weight variation	Buoyancy Lag Time (sec.)	Total Buoyancy Time (Hrs.)
F_1	5 ± 0.5	0.96	97.78	480.65 ±1.29	250S	>12 hrs
F_2	6 ± 0.7	0.77	97.15	485.50 ±1.74	300S	>12 hrs
F_3	6.5 ± 0.4	0.93	98.42	481.55 ±1.18	230S	>12 hrs
F_4	6 ± 0.5	0.84	94.63	484.05 ±1.37	245S	12 hrs
F_5	5.5 ± 0.6	0.79	96.58	485.65 ±1.49	180S	11hrs
F_6	6 ± 0.4	0.86	97.18	483.49±1.49	140S	8 hrs
F_7	5 ± 0.5	0.85	98.13	485. 50±1.70	145S	7 hrs

Assay Methods (Tritrimetry)

I. Standardization of 0.01 M perchloric acid with potassium hydrogen phthalate: The molarity of 0.01 M Perchloric acid was found to be 0.007 M.

II. Calibration curve of Ranitidine hydrochloride in glacial acetic acid at 570 nm.

The percentage purity of drug was found 95% by titrietic analysis and spectrophotometrically analysis.

Compatibility Studies

There is no interactions was find out with compatability study of drug and various polymers by FTIR and TLC analysis.

Evaluations of Prepared Tablet

Pre compression parameters

The prepared granules were evaluated by various pre compression parameters bulk density, tapped density, compressibility index and angel of repose. Result was given in Table No.2.

Physical Parameters: ***Shape of Tablets:*** Microscopic examination of tablets from each formulation batch showed circular shape with no cracks. ***Tablet Dimensions*****:** Tablets mean thickness were almost uniform in all the formulations and were found to be in the range 0.5 – 0.6 mm. ***Hardness:*** The hardness of

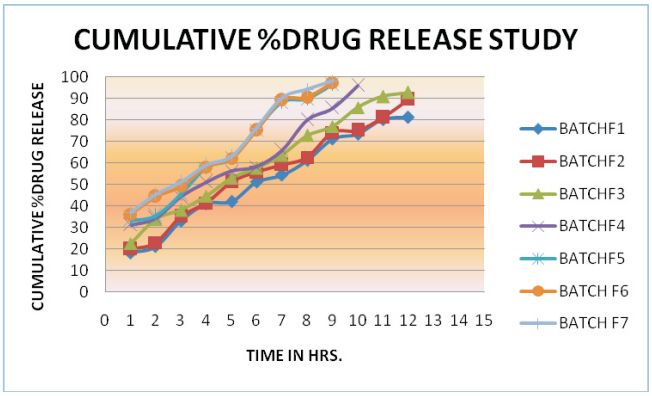

Fig. 2: In-Vitro drug release profile of Ranitidine from batch F1 to F7

the tablets was determined using Monsanto hardness tester. It is expressed in range of 5 – 6.5 kg/cm^2. ***Friability test:*** The test was found with in a limit. % friability of all tablets was found less than 1 %. ***Weight variation:*** All the tablets passed weight variation test as the % weight variation was within the pharmacopoeia limits of 5% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values.

Assay of Tablets: The percentage of drug content was found to be 97.4 % to 99.5 % of ranitidine, which was with in acceptable limit.

Buoyancy/Floating Behavior of tablet: For determination of buoyancy properties immerse the tablets of various batches (F1 to F7) in 0.1N HCl solution pH (1.2) at 37^{0}C, the tablets buoyant, and remained buoyant without disintegration. The results were given in Table No.3.

In vitro Drug Release Studies

The data of *in vitro* release of ranitidine from different formulations combinations were shown in fig no. 2, the release rates of the formulations were compares and it was found that batch F3 gives a desired drug release in specified time period. In the formulations F1, F2, F3, F4, F5, to F7 various grade HPMC k 100 were employed with carbopol 934 in combinations with ratio of 4:1. A desired release rate was observed with F3 batch HPMC K-100 (high viscosity grades polymers) with carbopol (4:1) in formulations given in fig. no 2. Drug release was 92.78 % at the end of 12 h. This slow release could be attributed to the formation of a thick gel structure that delays drug release from the tablets matrix.

CONCLUSION

In the light of this research work, it may be concluded that hydro dynamically balanced tablet of ranitidine was made by wet granulation method by using various other additives and the Preformulation study was done successfully. Adipic acid was not showing any incompatibility. The tablet showed acceptable weight variation, hardness and drug content. Buoyancy lags time, total buoyancy time showed satisfactory results. In the formulations F1, F2, F3, F4, F5, to F7 high viscosity grade polymer HPMC K 100 M were employed with carbopol 934 in the ratio of 4:1. A desired release rate was observed with batch F3 up to 12 h in comparison to other batches.

ACKNOWLEDGMENTS

Authors wish to acknowledge Ranbaxy Lab Ltd. Dewas, India for providing gift sample of ranitidine and HPMC K100 and Carbopol respectively.

REFERENCES

1. Rocca DJG, Omidian H, Shah K. Progresses in Gastro retentive Drug Delivery systems, Business Briefing. Pharmatech. 2003; (10):152-156.

2. Martindale, The Extra Pharmacopoeia, 30 Ed., The pharmaceutical press, London 1993, p. 770.

3. Dave BS, Amin AF, Patel MM. Gastroretentive Drug Delivery System of Ranitidine Hydrochloride: Formulation and In Vitro Evaluation. AAPS Pharm.Sci.Tech. 2004; 5(2): 34.

4. Punitha K, Khadhir S, ravichandiran ntragastric Floating Drug Delivery System of Ranitidine Hydrochloride: Formulation and Evaluation. Int.J.Pharmacy Pharm.Sci., 2010;2 (4):

5. Joel G Hardman, Lee limbird. Goodman and Gilman's. The Pharmacological Basis of Therapeutics., 10 Ed, New York: McGraw-Hill Company's Inc; 2001, p1102.

6. Lace LF, Basit AW., Colonic Metabolism of Ranitidine: Implication of its Delivery and Absorption, Int. J. Pharm., 2001; 227(1-2):157-65.

7. Indian Pharmacopoeia, Published by the Controller of Publication, Govt. of India; Ministry of Health and Family Welfare, New Delhi. Vol. II, 1996; p. 813.

8. Aulton ME, Pharmaceutics: The Science of Dosage Form Design, Churchill Livingstone, Edinburgh, 2nd Ed., 2002; pp. 109-110.

9. Rowe RC. The adehesion of film coating to tablet surface- the effect of some direct compression Excipients and lubricants. J.Pharmacol.1977; 29: 723-726.

10. Anderson NR, Banker GS, Peck GE. Quantitative evaluation of pharmaceutical effervescent systems II: Design and testing apparatus, Journal of Pharmaceutical Science. 1982; 711: 3-6.

11. Davis SS, Stock well A.F.1986. The effect of density on the gastric emptying of single and multiple- unit dosages form. Pharm.Res. 1986;(4):208-213.

12. Lachman L, Lieberman A, Herbert K, Joseph L. Tablet, The theory and practice of industrial pharmacy; Varghese Publishing House, Mumbai 3rd Ed., 1987; pp. 299-302.

13. Ishikawa T, Watanabe Y, Takayama K, Endo H, Matsumoto M. Effect of Effect of Hydroxy Propyl Methyl Cellulose (HPMC) on the release profiles and bioavaibility of a [poorly water-soluble drug from tablets prepared using macrogol and HPMC. Int.J.Pharm. 2000;20;202(1-2):173-178.

14. Chien YW., Mirchandani HL; Daggy BP, Lins, Lis, "Effect of HPMC and Carbopol on the release and Floating Properties of gastric floating Drug Delivery System Using Factorial Design. Int. J. Pharm. 2003.6; 253 (1-2):13-22.

15. Xu Xiaoqiang, Sun Minjie, Zhi Feng, Hu Yiqiao. Floating matrix dosage form for phenoporlamine hydrochloride based on gas forming agent: In vitro and in vivo evaluation in healthy volunteers. Int. J. Pharm.2006;310: 139–145.

16. Sastry SV, Reddy IK, Khan MA. Atenolol gastrointestinal therapeutic system: optimization of formulation variables using response surface methodology. J. Control.Rele. 1997; 45: 121-130.

17. Mathiowitz E. Encyclopedia of controlled drug delivery. In: Takada K, Yoshikawa H. Oral controlled drug delivery. New York: John Wiley and Sons, Inc.; 1999.pp. 729-736.