Research Article

Formulation and evaluation of effervescent granules of Ranitidine Hydrochloride

K. Munirajalakshmi*, P. Keerthana, O. Koushik, G. Himabindhu, T. Usha Kiran Reddy, G. Sindhu

S. V. University College of Pharmaceutical Sciences, S. V. University, Tirupati-517502, A.P, India

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Abstract

Objective: Peptic ulcer causes lesions in the stomach and oesophagus. The present work is aimed to develop the effervescent granules of Ranitidine Hydrochloride to relieve the pain instantly. **Materials and methods**: Effervescent granules were prepared by dry granulation technique using disodium citrate, sodium saccharin, polyvinyl pyrrolidine, glycine, sodium benzoate, sodium bicarbonate. The prepared granules were evaluated for angle of repose, bulk and tapped density, carr's index and hausner's ratio, in-vitro drug release studies and DSC. **Results:** The angle of repose for formulations F1-F6 was obtained in the range of 32.38°±0.34 to 37.65°±0.53 which indicates the passible flow property of the formulation. Bulk density and Tapped density for formulations F1-F6 was obtained in the range of 0.42 ± 0.01 to 0.46 ±0.02 and 0.51±0.02 to 0.58±0.02 respectively. The Carr's Index and Hausners Ratio for the formulations F1-F6 was obtained in a range of 15.85±2.97 to 22.4 ± 2.88 and 1.256±0.05 to 1.196±0.04 which indicates good flow property of the given formulation. Percentage release of the drug for the formulations F1-F6 was obtained in a range of 50% to 91%. **Conclusion:** Among all formulations F4 formulation has highest amount of drug release compared to other formulations. Hence it was considered as promising formulation for further studies. DSC of F4 formulation was found be at 184.5 which indicates that there is no incompatibility between the drug and excipients.

***Keywords**:* Ranitidine Hydrochloride, sodium saccharin, polyvinyl pyrrolidinee

Introduction

Peptic ulcers are sores that develop in the lining of the stomach, lower oesophagus, or small intestine. They're usually formed as a result of inflammation caused by the bacteria H. pylori, as well as from erosion from stomach acids. Peptic ulcers are a fairly common health problem. The main cause of peptic ulcer is the increase acids secretion and disturbance of the normal equilibrium either caused by enhanced diminish or aggression in mucosal resistance (Bolton and Char-les, 2013). Other causes of peptic ulcer are a bacterial infection (H. pylori), long-term uses of NSAIDS such as ibuprofen, naproxen sodium, etc., stress and spicy food habit. Hydrochloric corrosive and pepsin harm the mucous film of the gastrointestinal tract as the outcome both gastric and duodenal ulcers happen. Ulcers, for the most part, extend between 3 mm and a few centimetres in measurement. Duodenal ulcers are more common in adult males. Gastric ulcers happen commonly at old age person and in the middle class of people. Peptic ulceration occurs in those areas where acid secretion is generally more (Chao and Lin, 2012).

H2 receptor blockers, or H2 receptor antagonists (H2RAs), are a class of gastric acid-suppressing agents frequently used in various gastric conditions. H2RAs may also be used off-label for stress ulcer prophylaxis, esophagitis, gastritis, gastrointestinal haemorrhage, or urticarial. H2RAs decrease gastric acid secretion by reversibly binding to histamine H2 receptors located on gastric parietal cells, thereby inhibiting the binding and activity of the endogenous ligand histamine. H2 blockers thus function as competitive antagonists. The increase of H+/K+ ATPase transporters at the plasma membrane allows for the secretion of more acid from parietal cells (Dey and Dey, 2002). Examples are Ranitidine, Nizatidine, Famotidine, Cimetidine.

Proton pump inhibitors are used to:

relieve symptoms of acid reflux, or gastroesophageal reflux disease (GERD). This is a condition in which food or liquid moves up from the stomach to the esophagus (the tube from the mouth to the stomach).

Treat a duodenal or stomach (gastric) ulcer.

Address for Corresponding Author:
Dr. K. Muni Raja Lakshmi,
SVU College of Pharmaceutical Sciences, SV University, Tirupati - 517501, Andhra Pradesh, India
Email: munirajalakshmi005@gmail.com

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Treat damage to the lower Oesophagus caused by acid reflux.

There are many names and brands of PPIs. Most work equally as well. Side effects may vary from drug to drug. Eg: Omeprazole, Esomeprazole, Lansoprazole, Rabeprazole, Pantoprazole, and Dexlansoprazole .

Antacids are the medicines that counter act and neutralizes the acid that is secreted in the stomach to relieve the indigestion and heart burn in the stomach (Dong et al., 2013). Eg: Aluminium hydroxide, Magnesium carbonate, Magnesium hydroxide, Magnesium trisilicate, Calcium carbonate, and Sodium carbonate.

Reduction of gastric acidity by the inhibition of secretion or neutralization is the therapeutic principle most widely used in peptic ulcer disease. From a pathophysiological standpoint, this does not appear logical, because in a majority of patients gastric acid secretion is not increased. In addition, there is some concern about the consequences of a reduction in gastric acidity, especially in the long term. And finally, all available inhibitors of gastric acid secretion have a systemic action and may thus cause systemic side effects. Carbenoxolone, sucralfate, and tri-potassium di-citrate bismuthate have been shown to accelerate healing of ulcers without appreciable acid inhibition (Eduardo et al., 2014).

Effervescent preparations are designed to be dissolved or dispersed in water before administration. The tablet is promptly broken apart by internal release of CO_2 in water and the CO_2 reaction is created by an interaction of tartaric acid and citric acid with alkali metal carbonates or bicarbonates in the presence of the water. Effervescent tablets are uncoated tablets that usually consist of acids and bicarbonates or carbonates. Some products are useful for pharmaceuticals that damage the stomach or those which are susceptible to stomach pH (Franz et al., 2014).

Another advantage relating to effervescent tablet is that when they are taken by the patient, exactly the taken amount enters the stomach. In fact, the CO_2 produced in an effervescence reaction increases the penetration of active substances into the paracellular pathway and consequently their absorption (Gupta et al., 2019).

These products contain active ingredients, mixtures of acids/acid salts (citric, tartaric and malic acids or any other suitable acid or acid anhydride), and bicarbonate or carbonate salts (sodium, potassium or any other carbonate or bicarbonate relating to alkali metals) and they all release CO_2 when mixed with water (Harshmohan, 2009; Kempenich and Sirinek, 2018).

The aim of this study was to design, prepare and physiochemically evaluate effervescent tablets of ranitidine HCl. Ranitidine effervescent tablets are of a faster action onset and a more effective treatment for gastrointestinal diseases. Ranitidine of 300 mg effervescent tablets aren't available. The advantages of formulations prepared in this study are their equal properties with other effervescent tablets i.e., suitable flavour and weight. Since the weight of effervescent tablets in this study are about half that of other effervescent tablets, so they are economical for pharmaceutical industries. Effervescent tablets are more suitable for the children due to their better flavour and acceptability. Patients' compliance to the drug can be increased due to the appearance of this product during effervescence, convenience of usage and use of attracting colours and flavours in these products.

Materials and methods

Materials

Ranitidine hydrochloride was purchased from Veerendra Surgicals Pvt. Ltd, Di sodium citrate, Sodium saccharin, Polyvinyl pyrrolidine was purchased from Sr scientific pvt.Ltd, Tirupathi. Glycine, Sodium benzoate, Sodium bicarbonate was purchased from Hi media.

Formulation of effervescent granules

Six formulations F1 to F6 were prepared by dry granulation method and the composition was given in the Table 1.

Table 1. Composition of Ranitidine Hydrochloride effervescent granules

Formulation	Ranitidine hydrochlorid e	Di sodium citrate	Sodium saccharin	Poly vinyl pyrrolidine	Glycine	Sodium benzoate	Sodium bi carbonate
F1	20 mg	100 mg	30 mg	20 mg	QS	4.2mg	200mg
F2	20mg	200 mg	30mg	25mg	QS	4.2 mg	200mg
F3	20mg	200 mg	30mg	30mg	QS	4.2mg	200mg
F4	20mg	400 mg	30mg	35mg	QS	4.2mg	200mg
F5	20mg	500 mg	30mg	40mg	QS	4.2mg	200mg
F6	20mg	600 mg	30mg	45mg	QS	4.2mg	200 mg

Accurately weigh the ranitidine along with the disodium citrate and sodium bi carbonate. Then add poly vinyl pyrrolidine sodium saccharin. Now blend all the powders to form a even mixture then sieve the powder through sieve no 60 Now add the sodium benzoate again mix the powder and transfer to a hot porcelain dish. To this mixture add glycine and the mixture is heated on a boiling water bath without stirring or pressing the powder. Then sieve the resultant mixture through sieve no. 44. Dry the resultant granules obtained at 4^0C. Use the sieve number 14 pass the dried granules and retained over sieve no 85/60 and collect the retained granules over the sieve number 85/60.The final product obtained was dried and stored in desiccator (Kumar et al., 2018).

Characterization of effervescent granules

Angle of Repose

Under the static balance, the angle between the slope of a powder pile and the horizontal plane is Angle of Repose. It is measured when the powders fall to a surface via gravity and form a cone. It indicates the flowability of the powders. The smaller the Angle of Repose is, the better the flowability of the powders (Lagas et al., 2010).

The granules of prepared ranitidine hydrochloride effervescent granules were poured from a funnel and the height of the pile (h) and radius of the pile (r) are measured. From this, the angle of repose, i.e., the angle between the height if the pile and the radius of the pile are calculated with the help of the below formula.

$\text{Tan}\,\Theta = h/r$

$\Theta = \tan^{-1}(h/r)$

Here, h= height of the powder pile

r = radius of the powder pile

Bulk density

The bulk density is obtained by dividing the bulk mass with the volume in cm3. The sample of the substance of 50 cm^3 which is already passed into the sieve no. 20 was carefully taken into a 100ml graduate cylinder. The cylinder was dopped at 2-second intervals 3 times on a hard wooden plank from a height of 1 inch from the wooden plank (Malfertheiner et al., 2009). The bulk density of the formulation can be obtained by dividing the weight of the sample in grams to the final volume obtained in cm3 in the container after 3 consecutive tapping. It is calculated by using equation below

$Df = M/Vp$

Tapped density

Tapped density test is a popular method – thanks to its simplicity and convenience – when it comes to understanding powder flow properties. There has been harmonization and standardization of the test recommended by the European Pharmacopoeia (EP) and the United States Pharmacopoeia (USP), and thus of apparatus and procedure in order to attain reliable and essential results (Malfertheiner et al., 2009).

Table 2. Various evaluation parametere of Ranitidine Hydrochloride effervescent granules

S. No	Bulk density	Tapped Density	Angle of Repose	Carr's Index	Hausner's ratio
1	0.43±0.01	0.51±0.02	34.88 °±1.31	20.97±2.32	1.188±0.02
2	0.46±0.02	0.55±0.02	37.48 °±0.85	16.36±2.97	1.196±0.04
3	0.43±0.01	0.54±0.01	36.57 °±0.44	20.37±2.92	1.256±0.05
4	0.42±0.01	0.53±0.01	32.38 °± 0.34	15.85±1.52	1.262±0.05
5	0.42±0.03	0.53±0.01	35.43°±0.49	20.75±4.03	1.262±0.06
6	0.45±0.01	0.58±0.02	37.65°±0.53	22.40±2.88	1.289±0.05

Table 3. Percentage drug release of Ranitidine Hydrochloride effervescent granules

Time (sec)	f1	f2	f3	f4	f5	f6
0	0	0	0	0	0	0
5	30	50	41	60	35	24
10	45	60	45	75	42	28
15	55	67	58	77	44	30
30	67	78	61	80	55	35
45	70	80	62	85	60	40
60	78	82	66	90	65	46
120	80	84	75	91	76	50

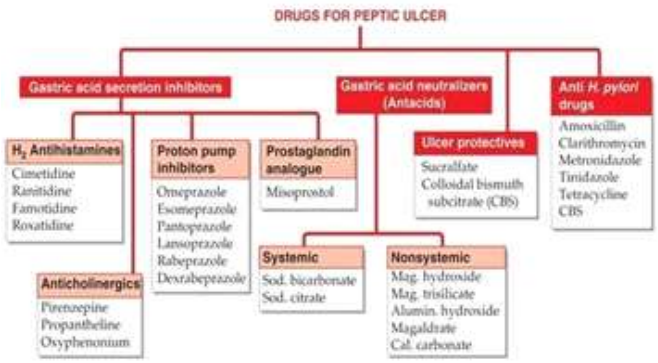

Figure 1. Drugs used for the treatment of peptic ulcer

Do= M/Vp

Carr's compressibility index and Hausner ratio

The compressibility index and the Hausner ratio were determined by measuring both the bulk volume and the tapped volume of powder. The compressibility index and Hausner ratio indicate the ease with which a material can be induced to flow and may be calculated using measured values for bulk density (ρ_{bulk}) and tapped density (ρ_{tapped}) as follows (Sandhir and Gill, 2019).

$$\text{Compressibility Index} = 100 \times \left(\frac{\rho_{tapped} - \rho_{bulk}}{\rho_{tapped}}\right)$$

$$\text{Hausner Ratio} = \left(\frac{\rho\ \text{tapped}}{\rho\ \text{bulk}}\right)$$

Dissolution studies

Dissolution is the process in which a substance forms a solution. Dissolution testing measures the extent and rate of solution formation from a dosage form, such as tablet, capsule, ointment, etc. The dissolution of a drug is important for its bioavailability and therapeutic effectiveness. Dissolution and drug release are terms used interchangeably (Shah et al., 2014). A dissolution test uses an apparatus with specific test conditions in combination with acceptance criteria to evaluate the performance of the product. Dissolution includes 4 standardized apparatus: basket, paddle, reciprocating cylinder, and flow-through cell. Where specified in a monograph, USP dissolution tests are legal requirements. USP training and service are designed to help you meet regulatory compliance requirements while strengthening your quality standards. The tablets were weighed and dissolved in a dissolution medium, (0.1 N Hydrochloric acid) at a temperature of 37 ± 0.5°C the time of dissolution was noted and then the test samples are collected and observed under Ultra violet -Visible spectroscopy on regular intervals (Shanani, 2019).

Differential scanning calorimetry (DSC)

The DSC measurements were performed using 3 mg samples placed in sealed aluminum pans, before heating under nitrogen flow (20 ml/min) at heating rate 10˚C/min, over the temperature range of 35˚C to 300˚C. An empty aluminum pan was used as a reference. DSC of the pure ranitidine hydrochloride, lipids (Sharma and Bhatt, 2014) (hydrogenated castor oil or glyceryl bezenate)

Results and discussion

Angle of repose

The angle of repose for formulations F1-F6 was obtained in the range of 32.38 °± 0.34 to 37.65°±0.53 which indicates the passible flow property of the formulation

Bulk density and tapped density

Bulk density and Tapped density for formulations F1-F6 was obtained in the range of 0.42 ± 0.01 to 0.46 ±0.02 and 0.51 ±0.02 to 0.58 ±0.02 respectively.

Carr's Index and Hausners Ratio

The Carr's Index and Hausners Ratio for the formulations F1-F6 was obtained in a range of 15.85±2.97 to 22.4 ± 2.88 and 1.256 ±0.05 to 1.196 ±0.04 which indicates good flow property of the given formulation. These parameters data was given in the Table 2.

Dissolution studies

Percentage release of the drug for the formulations F1-F6 was obtained in a range of 50% to 91% which is given in the Table 3 and Fig 2. Among all formulations F4 formulation has highest amount of drug release compared to other formulations. Hence it was considered as promising formulation for further studies.

DSC

From the Fig 3, it was evident that the DSC of F4 formulation was found be 184.5 which indicates that there is no incompatibility between the drug and excipients.

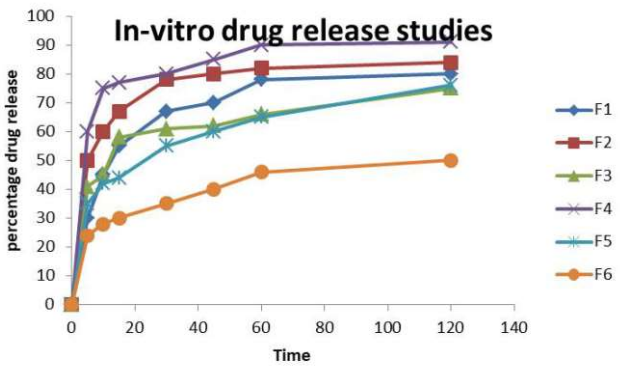

Figure 2. In-vitro drug release of Ranitidine Hydrochloride Effervescent granules F1-F6

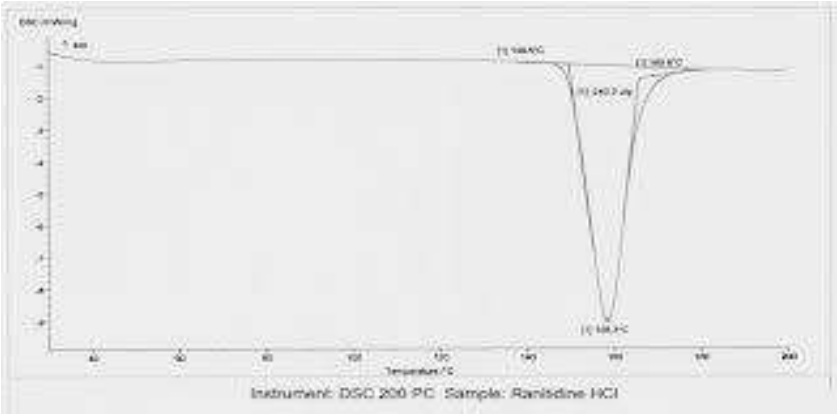

Figure 3. DSC of Ranitidine Hydrochloride Effervescent granules F4

Conclusion

Ranitidine Hydrochloride was prepared as effervescent granules using Ranitidine Hydrochloride, disodium citrate, sodium saccharin, polyvinyl pyrrolidine, glycine, sodium benzoate, sodium bicarbonate. It was found that the prepared effervescent granules had good floe properties. The In-vitro drug release studies reveals that the F4 formulation has 91% of drug release compared to other formulations. DSC shows that the prepared formulation had no incompatability between the drug and excipients.

Conflicts of Interest

No funding was received for this research work

Ethical consent

No animals and humans was used in the present research work

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