

A Review on Pharmacodynamic and Pharmacokinetic Properties and Physicochemical Characteristics of Ranitidine Tablets

Tambe Sagar Sanjay¹, Gulave Karishma Rajendra², Kale Vaishnavi Anil³

P. G. Student, Department of Pharmaceutics, Amrutvahini College of Pharmacy, Sangamner, Maharashtra, India¹

Associate Professor, Department of Pharmaceutical Chemistry, Pratibhatai Pawar College of Pharmacy, Wadala Mahadev, Maharashtra, India²

Associate Professor, Department of Pharmaceutical Chemistry Pratibhatai Pawar College of Pharmacy, Wadala Mahadev, Maharashtra, India³

ABSTRACT: Ranitidine is a histamine H₂-receptor antagonist with a well-established high degree of efficacy in treating and preventing gastrointestinal lesions aggravated by gastric acid secretion. In healing of peptic ulceration, ranitidine is comparable or superior to other H₂-antagonist drugs. The tablets were evaluated for post-compression features including weight variation, hardness, friability, drug content, dissolution time, carbon dioxide content, effervescence time, pH, content uniformity and water content. Ranitidine is clearly comparable or superior to most other antiulcer agents in the treatment and prevention of a variety of gastrointestinal disorder associated with gastric acid secretion. With its favourable efficacy and tolerability profiles ranitidine must be considered a first line agent when suppression of gastric acid secretion is indicated.

KEYWORDS: Ranitidine hydrochloride (HCl), sustained release, solubility, stability of formulation.

I. INTRODUCTION

Ranitidine hydrochloride (HCl) tablets are easily administered in the elderly and children sometimes they are beneficial in the the all aged humans [1].

Ranitidine, a histamine H₂-receptor antagonist, is now well established as a potent inhibitor of gastric acid secretion effective in the treatment and prophylaxis of gastrointestinal lesions aggravated by gastric acid secretion [5]. The tablets were evaluated for the post compression features like they contained the weight variation, hardness, friability, drug content, dissolution time, carbon dioxide content, ph, content of uniformity and water content [1]. Therapeutic trials involving several thousands of patients with peptic ulcer disease confirm that ranitidine 300mg daily administered orally in single or divided doses is at least as effective as cimetidine 800 to 1000mg daily in increasing the rate of healing of duodenal and gastric ulcers. Similar dosages of ranitidine have been shown to relieve the symptoms of reflux oesophagitis and heal or prevent gastrointestinal damage caused by ulcerogenic drugs. Ranitidine 150mg orally at night maintains ulcer healing in the long term. Ranitidine has also demonstrated good results in the treatment of Zollinger-Ellison syndrome and in the prevention of aspiration pneumonitis when given prior to surgery and to pregnant women at full term [5]. Ranitidine hydrochloride (HCl) to achieve prolong gastric retention, enhance drug bioavailability and to sustained the release of Ranitidine HCl in the stomach, by using different types of the polymer [2]. The mean plasma level profiles of ranitidine hydrochloride, obtained following administration of both floating and conventional type of tablet formulation [6]. It may also have a place in the management of acute upper gastrointestinal bleeding and in the prevention of stress ulcers in the intensive care setting, although these areas require further investigation. Ranitidine has been used safely in obstetric patients during labour, in children, the elderly, and in patients with renal impairment when given in appropriate dosages [5]. Ranitidine hydrochloride is a histamine H₂-receptor antagonist. It is widely prescribed in active duodenal ulcers, gastric ulcers, Zollinger-Ellison syndrome, gastroesophageal reflux disease, and erosive esophagitis. The prepared formulations were evaluated for the physical characteristics like thickness, hardness, friability, weight uniformity [3]. The drug is very well tolerated and is only infrequently associated with serious adverse reactions or clinically significant drug interactions [9].

Even at high dosages, ranitidine appears devoid of antiandrogenic effects. Ranitidine is clearly comparable or superior to most other antiulcer agents in the treatment and prevention of variety of gastrointestinal disorders associated with gastric acid secretion. With its favourable efficacy and tolerability profiles, ranitidine must be considered a first-line

agent when suppression of gastric acid secretion is indicated [5]. Ranitidine is effective in preventing or treating gastrointestinal damage caused by non-steroidal anti-inflammatory drugs (NSAIDs), reducing bleeding, gastric mucosal and duodenal damage in patients with rheumatic disease and with peptic ulcer, often despite continuation of NSAID treatment. One study tested the ability of ranitidine to prevent gastrointestinal damage in patients receiving cytostatic drugs and prednisone for lymphoproliferative disease, with promising results in a small number of patients [5]. 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. Ranitidine is absorbed only in the initial part of the small intestine and has 50% absolute bioavailability.^{3,4} Moreover, colonic metabolism of ranitidine is partly responsible for the poor bioavailability of ranitidine from the colon [4]. Ranitidine, a histamine H₂-receptor antagonist, is a competitive inhibitor of histamine, blocking histamine's action on specific H₂ receptors in gastric parietal cells (9). As a result, ranitidine is a potent inhibitor of basal gastric acid secretion [10].

II. PHARMACODYNAMIC PROPERTIES

In vitro studies have shown that ranitidine specifically antagonises histamine H₂ receptors, receptors which appear to mediate a final common pathway in the release of gastric acid. In normal volunteers and patients with peptic ulcer disease, ranitidine 150mg daily or 300mg daily in 1 or 2 divided doses decreases the number of low intragastric pH-metre readings per 24 hours and decreases 24-hour integrated hydrogen ion activity predominantly through suppression of nocturnal acid secretion [5]. Ranitidine HCl has a bitter taste and a sulphur-like smell, using sweeteners and flavouring agents is necessary. We used different sweeteners at different levels of the formulation of the tablets [1]. Ranitidine HCl has a bitter taste and sulphur-like odour. Various taste masking techniques such as addition of sweeteners and flavours, filling in capsules, coating with water insoluble polymers or lipids, adsorption to ion-exchange resin, complexing with cyclodextrin, have been employed for masking its bitter taste in order to increase patient compliance [7]. Administration of ranitidine and subsequent inhibition of stomach acid production would improve the relative bioavailability of the formulation [10]. Ranitidine suppresses basal acid output and experimentally stimulated acid secretion but usual therapeutic dosages do not consistently suppress normal meal-stimulated acid secretion. Ranitidine also suppresses pepsin output which, in conjunction with decreased gastric acidity, results in decreased pepsin activity. The pattern of acid and pepsin inhibition achieved during ranitidine treatment of peptic ulcer disease appears not to facilitate microbial colonisation of the stomach, although colonisation may occur during the sustained achlorhydria produced by high-dose intravenous regimens in the critically ill [5]. These properties of Ranitidine HCl do not favour the traditional approach to sustained release delivery of formulation [4]. Cholinomimetic effects have been ascribed to ranitidine *in vitro* and *in vivo* in animals but evidence of clinically significant cholinomimetic effects in humans is lacking. Mixed results have been reported regarding ranitidine-induced changes in gastric motility; the underlying mechanisms and clinical significance of these motility-modifying effects are unclear [5]. The ranitidine formulation enhanced the pharmacokinetic profile and increased bioavailability of the drug formulation and that will increase the stability and the efficacy of the tablet formulation [2].

Some studies suggest that ranitidine treatment is associated with an increase in serum gastrin concentration and/or an increase in meal-stimulated gastrin release. Elevated serum gastrin concentrations return to pre-treatment levels once ranitidine is discontinued. Ranitidine, in therapeutic dosages, does not induce clinically significant changes in serum prolactin, cortisol or thyroid-stimulating hormone, and has no apparent antiandrogen activity. Because ranitidine possesses a furan rather than an imidazole nucleus, it binds only weakly to cytochrome P450 and, in consequence, has minimal effects on drug metabolism by the liver [5]. Gastric acid secretion induced by a variety of physiological and experimental stimuli. The physiological effects of profound histamine H₂-receptor blockade is generally confined to the gastrointestinal system. At therapeutic dosages, ranitidine has not been associated with clinically significant effects other than gastric output suppression [5].

III. PHARMACOKINETIC PROPERTIES

Following oral administration, peak plasma ranitidine concentrations are reached within 1 to 3 hours and are not influenced by food. A single 150mg oral dose of ranitidine produces a peak plasma concentration [5]. This ranitidine tablets were prepared by the direct compression and fusion methods. They were exposed to all the physicochemical test and the evaluation of the tablets [1]. Ranitidine HCL has short biological half-life of drug (~2.5-3 hours) and absorption window only in the initial part of the small intestine with 50% absolute bioavailability, thus why there is a strong need for development of their oral sustained release formulation [2]. Ranitidine is an oral drug that is widely used as an effective H₂ antagonist and blocks the production of acid by acid-producing cells in the stomach. It is commonly used in treatment of peptic ulcer disease and gastroesophageal reflux disease, which are prevalent nowadays in all ages especially elderlies [7]. Ranitidine hydrochloride is a histamine H₂-receptor antagonist. It is widely prescribed in active

duodenal ulcers, gastric ulcers, Zollinger-Ellison syndrome, gastroesophageal reflux disease, and erosive esophagitis [8].

Therapeutic Trials:

Markedly between individuals, averages about 50%. The apparent volume of distribution in normal types of the adults is up to approximately 1.4L/Kg. comparison of ranitidine pharmacokinetic following intravenous and oral administration suggests significant hepatic biotransformation following oral absorption [5]. Thus, 30% of an administered oral dose of ranitidine is excreted unchanged in the urine versus intravenous dose. The normal elimination half-life of ranitidine is 2 to 3 hours, but it is prolonged to 4 to 9 hours in patients with severe renal disease. Ranitidine is approximately 15% protein bound and, while it is removed by dialysis, the percentage of total dose recovered in dialysate is small and dosage supplementation is not recommended. Although the degree of acid inhibition required for ulcer healing is unknown, dose response studies have found that experimentally stimulated acid secretion is decreased [5]. Ranitidine hydrochloride to achieve prolong gastric retention, enhance drug bioavailability and to sustained the release of ranitidine hydrochloride in the stomach, by using types of polymers [3].

The pharmacokinetics of ranitidine have been studied following both oral and intravenous administration of the drug to healthy volunteers and to patients with gastrointestinal disease. In most respects, the pharmacokinetics of ranitidine are additional experience with ranitidine in patients with chronic renal failure and in patients with chronic liver disease has accumulated. There remains a need to clarify the dose-response relationship of ranitidine to gastric acid control and to ulcer healing [5].

The 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 HCl is desirable [2].

The ranitidine Hcl tablets are inhibiting 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 HCl is desirable [4].

- ❖ **Absorption:** After oral administration, absorption of ranitidine is rapid with a mean lag time of 15 minutes and peak plasma concentrations are attained within 1 to 3 hours. Following a single oral dose of ranitidine 150mg, the mean peak plasma concentration and mean area under the concentration-time curve. In healthy volunteers' Considerable variation in ranitidine plasma concentrations between individuals administer the same total dose has been noted. Some studies have demonstrated a second peak in the plasma concentration/time curves following different type ingestion. likely bile or hepatic parenchymal tissues, and is returned to the gut as the gall bladder empties. Transfer of some ranitidine from the systemic circulation into bile with subsequent recycling through the gut may occur regardless of the original route of administration [5].
- ❖ **Distribution:** The apparent volume of distribution of ranitidine is larger than actual body water, indicative of some binding to tissues distribution of ranitidine into all tissues except the central nervous system. studied the penetration of ranitidine into the cerebrospinal fluid (CSF). Plasma protein binding of ranitidine in. normal subjects is around 15% [5].
- ❖ **Elimination:** The forms of ranitidine which are excreted in the urine are unchanged drug, ranitidine-V-oxide, dimethyl ranitidine and ranitidine-S-oxide. The role of the liver in ranitidine disposition has not been fully elucidated. An affinity of ranitidine or its metabolites for bile is supported by the scheme of discontinuous reabsorption. A relatively longer half-life of elimination has been found in both normal subjects and duodenal ulcer patients given oral ranitidine compared with intravenous drug [5].

IV. ADVERSE EFFECTS

- Ranitidine is well tolerated, producing some adverse effects such as headache, diarrhoea and constipation in less than 5% of patients.
- The frequency and effects are similar to those seen in patients receiving placebo.
- Serious and treatment limiting effect for body.
- Adverse effects occur rarely, with elderly and consciously ill patients being more susceptible, or appear to be idiosyncratic.
- Hepatotoxicity, with raised hepatic enzyme.
- levels and biopsy-proven hepatocellular changes, has been seen rarely.
- Haematological changes, such as thrombocytopenia, agranulocytosis and general myelosuppression, have been reported.

- Central nervous system adverse effects of mental confusion, severe headache, hallucinations and mania have also occurred in small numbers of patients.
- Various types of idiosyncratic reactions have been reported in individuals, including fever, rashes,
 - bradycardia, heart block, gouty arthritis attacks, erosive duodenitis and gynaecomastia.
- Ranitidine is generally very well endured, with minor side effects such as headache, dizziness
 - and rash occurring but usually not limiting.
- The methods of reporting adverse effects in clinical trials may vary, with some trials reporting all adverse events.
- Reports of serious and treatment-limiting adverse effects are Hepatotoxicity has been reported as occurring in less than ranitidine-treated patients.
- Tests and biopsy-proven hepatocellular abnormalities
- Although liver enzyme levels in these patients rose after ranitidine treatment began and returned to normal when ranitidine was discontinued,

V. IMMUNOLOGICAL EFFECTS

- 1) Histamine is believed to participate in immune modulation by suppressing lymphocyte proliferation in response to mitogen stimulation and by stimulating T cells to release a suppressive factor.
- 2) While some *in vitro* studies suggest that ranitidine, in concentrations approximating therapeutic plasma levels, promotes interleukin-2 production and affects lymphocyte proliferation and T cell responsiveness other investigators have observed no such effects.
- 3) No change in absolute lymphocyte count or lymphocyte response to mitogen stimulation was detected in blood sampled from 15 duodenal ulcer patients.
- 4) Immune modulation uncertain, and evidence for a clinically significant effect on immune function in patients treated with ranitidine for peptic ulcer disease is lacking.
- 5) Cutaneous reactions are primarily histamine H₁-receptor mediated suppressed the cutaneous Reaction.
- 6) Interpretation of an immediate type reaction to a skin test.

VI. CONCLUSION

The ranitidine formulation enhanced the pharmacokinetic profile and increased bioavailability of the drug formulation and that will increase the stability and the efficacy of the tablet formulation. Ranitidine hydrochloride (HCl) tablets are specifically used in treatment of gastric and the duodenal ulcers. There is in the at each stage of formulation were utilized and the best formulation of the tablets are formed. The formulations were selected with the best solubility, stability and pH.

REFERENCES

- [1] Abolfazl Aslami, Hajar Jahangiri, "Formulation, Characterization And Physicochemical Evaluation Of Ranitidine Effervescent Tablets", Advanced Pharmaceutical Bulletin, Vol.3, Issue 2, pp. 315-322, 2013.
- [2] A. K. Dave, V. Saklle, Sachin Jain, and A. Pawar, Formulation Of Ranitidine Hydrochloride Gastro Retentive Floating Tablet By Using Different Ratio Of Polymers, ISSN:0975-8232, Vol. 1, Issue 9, pp. 156-159, 2010.
- [3] Radhika D. Ingale, Vinod M. Thakare, Bharat W. Tekade and Vijay R. Patil, Development And Evaluation Of Ranitidine Hydrochloride Floating Tablet, E-ISSN:0975-8232; P-ISSN: 2320-5148, Vol. 5, Issue 1, pp. 269-274, 2014.
- [4] Brijesh S. Dave, Avani F. Amin, and Madhabai M. Patel, Gastroretentive Drug Delivery System Of Ranitidine Hydrochloride: Formulation And In Vitro Evaluation, Vol. 5, Issue 2, pp. 1-6, 2004.
- [5] Susan M. Grant, Heather D. Langtry and Rex N. Brogden, Ranitidine An Updated Review Of Its Pharmacodynamic And Pharmacokinetic Properties And Therapeutic Use In Peptic Ulcer Disease And Other Allied Diseases, pp. 801-870, 1989.
- [6] M. A. Hassan, Design And Evaluation Of A Floating Ranitidine Tablet As A Drug Delivery System For Oral Application, Vol. 17, Issue 2, pp. 125-128, 2007.
- [7] Zahra Hesari, Akram Shafiee, Shirin Hooshfar, Naser Mobarra and Seyed Alireza Mortazavi, Formulation And Taste Masking Of Ranitidine Orally Disintegrating Tablet, Vol. 15, Issue 4, pp. 677-686, 2016.
- [8] Jain S. Srinath M.S., Narendra C. Reddy S.N., Sindhu A., Development Of A Floating Doage Form Of Ranitidine Hydrochloride By Statistical Optimization Technique, Vol. 2, Issue 4, pp. 342-349.
- [9] R. M. Khoury, P. O. Katz, R. Hammod and D.O. Castell, Bedtime Ranitidine Does Not Eliminate The Need For A Second Daily Dose Of Omeprazole To Suppress Nocturnal Gastric pH, Vol. 13, pp. 675-678, 1998.
- [10] Catherine A. Knupp, Frank M. Graziano Russell M. Dixon, and Rashmi H. Barbhaiya, Pharmacokinetic-Interaction Study Of Didanosine And Ranitidine In Patients Seropositive For Human Immunodeficiency Virus, Vol. 36, Issue 10, pp. 2075-2079, 1992.