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Preparation and *in vitro* Evaluation of Nizatidine immediate release tablets

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Abstract: The objective of the present work is to prepare and evaluate (*in vitro)* nizatidine immediate release tablets. The developed drug delivery system delivers a programmed dose of drug intended for excessively secreted gastric acid and for promoting healing of duodenal ulcers thereby spontaneously delivering the drug when exposed into GIT for producing an anti-ulcer effect. Accordingly, immediate release drug-containing core tablets of Nizatidine were prepared by wet granulation method. The obtained tablets were evaluated for weight variation, thickness, hardness, drug content, disintegration and *in vitro* dissolution studies. Stability studies of the optimized formulation was carried out as per ICH guidelines at 40 ± 2°C / 75 ±5% RH for one month and it was found to be stable.

Key words: Immediate release tablets, anti-ulcer activity, wet granulation.

INTRODUCTION:

The delivery of drug to a human body can be achieved through several routes like oral, transdermal, topical and parenteral administration. Among this the oral ingestion is the predominant and most preferable route for drug delivery [1]. More than 50% of drug deliveries available in the market are oral drug delivery system. Oral route is the most convenient and extensively used for drug administration [2]. The route has high patient acceptability, primarily due to ease of administration.

Nizatidine, a H2 receptor antagonist, was used as a model drug which is a competitive inhibitor of gastric acid secretion and is used for the treatment of acid-reflux disorders (GERD), peptic ulcer disease, active benign gastric ulcer and active duodenal ulcers. It is having an oral bioavailability of 70% with a very short biological half life of 1-2 hours. It does not have any demonstrable anti-androgenic effects and drug interactions compared to any other class of H2 Receptor Antagonists [3, 4].

It also finds applications in the field of local delivery of drug to the stomach and proximal small intestine and importantly in treating microorganisms (Helicobacter pylori) [5, 6] which colonize the stomach because the major factors governing reduced luminal drug delivery are gastric acidity, gastric emptying and the epithelial mucus layer and therefore it helps to provide better availability of new products with new therapeutic possibilities and increased patient compliance.

MATERIALS AND METHODS:

Materials:

Nizatidine, a water-soluble, H2 receptor antagonist was obtained as a gift sample from Dr. Reddys Laboratories Ltd. Micro crystalline cellulose (Avicel PH 102, used as a diluent), Sodium starch glycolate (SSG, used as a Super disintegrant) were obtained from Sigma Aldrich, USA. All the chemicals and reagents used were of analytical grade.

Methods:

Preparation of Nizatidine Immediate release core tablets:

Accurately weighed amounts of Nizatidine and Avicel PH101 (diluent) were sifted and blended for 30mins. To this varying amount **(**table 1**)** of sifted Sodium starch glycolate (SSG) was added and together blended for 15mins. Granules were prepared either with PVP K-30/HPME E5 [7] aqueous solution which were dried at 40^{o}C for 2hrs, and then sifted through sieve no 22, to get uniform sized granules ready for compression. Sifted talc and magnesium stearate were added to the prepared granules which were then compressed by a 6 mm automatic multi station tablet punching machine.

Physico-chemical characterization:

The prepared tablets were characterisesd for their physical properties, disintegration time and drug dissolution characteristics as discussed below

1. **Flow properties**
   The flow properties of granules were characterized in terms of angle of repose, Compressibility (Carr) index and Hausner's ratio.
   Tan θ = h/r (θ = angle of repose, height of the pile, r=radius of the pile)
   Compressibility Index = {tapped density-bulk density}/tapped density*100
   Hausner ratio = tapped density / bulk density
   Weight variation: 20 tablets were randomly selected from the prepared batches and their average weight was calculated using a digital balance. Individual weight of each tablet was also determined and compared with the average weight.
2. **Hardness:** Erwika hardness tester was used to determine the tablet hardness for all the formulated batches.
3. **Thickness:** Vernier caliper was used to determine the thickness of the prepared tablets. 20 tablets were randomly selected from each trial batch and were measured by placing the tablet between the anvils and sliding knob was rotated until the tablet was ruptured.
4. **Drug content:** 20 tablets were randomly selected from the prepared batch and triturated to get fine powder. 100mg of the powder was taken and dissolved in 100ml of water. Absorbance was noted spectrophotometrically at 315nm. Accordingly drug content was calculated.
5. ***In vitro* Disintegration test:** The various core tablet formulations prepared by wet granulation method are subjected to disintegration studies using 900ml water (as a disintegrating medium) and the time taken for disintegration is noted .
6. ***In vitro* Dissolution test [8, 9]:** I*n vitro* dissolution test was carried out by triplicate method using USP Type II (Paddle type) Apparatus. 900ml of distilled water was used as dissolution medium, and the paddle was rotated at 50rpm for 1 hr at a temperature of 37^{0}C. Sampling was done at regular intervals and was replaced by water afetr each sampling interval. The samples are then analysed spectrophotometrically at 315nm.
7. **Drug-excipient compatibility:**
   Infrared spectroscopy (IR): Shimadzu FTIR 8300 Spectrophotometer was used and the Infrared Spectra was recorded in the region of 4000 to 400 cm^{-1} for pure drug and optimized formulation(S-II).
   Differential scanning calorimetry (DSC): DSC-60 Shimadzu, Japan was used to check the physical, chemical and biological characteristics of drug substance alone and its combination with various formulation excipients used in the final product. The samples (drug and optimized formulation S-II) were placed in a sealed aluminium pans and heated under nitrogen flow (30 ml/min) at a scanning rate of 5 ^{0}C/min from 25 ^{0}C to 250 ^{0}C.
8. **Stability studies:** Accelerated stability studies were conducted for the optimized formulation (S-II) as per ICH guidelines for one month.

Table 1: Composition of Nizatidine core tablets (NZ XI – NZ XIV)

Ingredients (%)	Amount of raw materials/tablet			
	S-I	S-II	S-III	S-IV
Nizatidine	50	50	50	50
Avicel PH 101	43	43	43	43
Sodium Starch Glycolate	2	2	3	3
PVP K-30	-	3	2	-
HPMC E5	3	-	-	2
Talc	1	1	1	1
Magnesium Stearate	1	1	1	1

Table 2: Flow properties of all prepared formulations

Flow properties	S-I	S-II	S-III	S-IV
Angle of Repose (θ)	36.27	26.54	32.24	30.56
Bulk density (gm/cm^2)	0.642	0.576	0.597	0.581
Tapped density (gm/cm^2)	0.769	0.625	0.694	0.674
Compressibility Index	16.51	7.84	13.97	13.79
Hausner Ratio	1.19	1.085	1.16	1.16

Table 3: Disintegration values of all the optimized formulations

Formulation	Time(minutes)
S-I	3.24
S-II	2.46
S-III	2.57
S-IV	3.01

Fig.1: *In vitro* release profile of different formulations (S-I to S-IV)

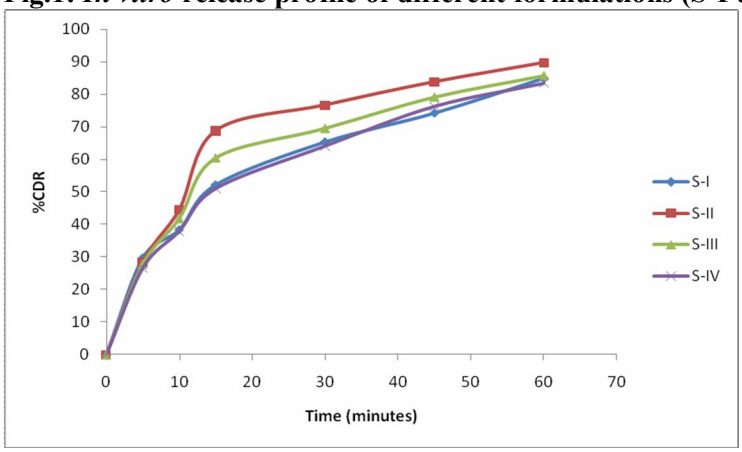


Fig.2. IR studies of the pure drug (S-I) and optimized formulation (S-II)

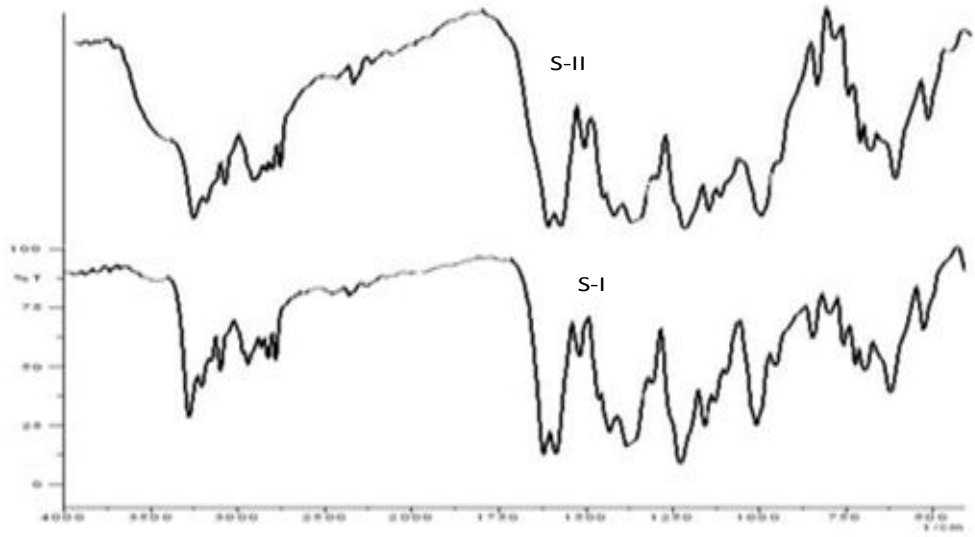
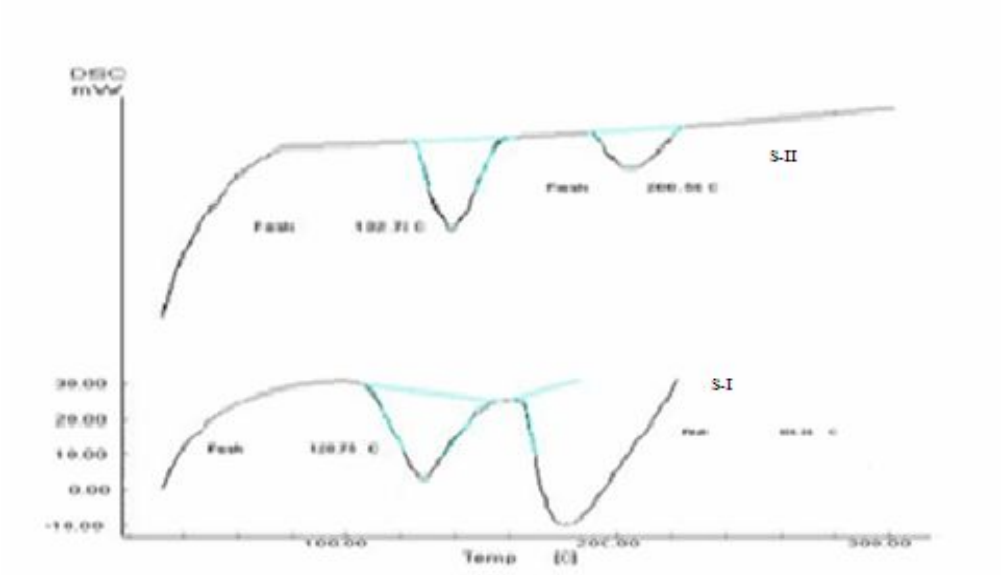


Fig.3. DSC studies of the pure drug (S-I) and optimized formulation (S-II)



RESULTS AND DISCUSSIONS:

Flow properties: Results of test for physico-chemical characterization was optimum and was shown in **table 2.**From the flow property observations, it was concluded that the optimized formulation S-II, had a very good flow properties in comparison with other formulations.

Weight variation, Hardness and Thickness: Weight variation of all the formulated batches shown to be within the limits i.e., 150±1.5 mg. Thickness of tablets found to be 2.6±0.2mm, having a hardness of 4.25±0.25 kg/cm^2.

Drug content: The drug content was found to be uniform for all the prepared formulations (mean drug content=98.1±0.4 %).

***In vitro* Disintegration test:** From the *in vitro* disintegration test (table 3), it was concluded that the S-II batch was choosen to be the best optimised formulation as it was disintegrated in a very quick time compared to other formulations.

***In vitro* Dissolution test:** Drug release profile of all prepared immediate release tablets was shown in **fig.1**.Based on the dissolution data of all the prepared immediate release core tablets, the S-II batch showing 89.71 % drug release in 60 minutes was choosen to be the best optimised formulation.

Drug-excipient compatibility:

Infrared spectroscopy (IR): IR spectra of pure drug Nizatidine and optimized formulation (S-II) are shown in following **fig.2.** Major peaks were observed at1227, 1436, 1586cm^{-1} with pure drug and with optimized formulation (S-II). No significant changes in peaks of optimized formulation was observed when compared to pure drug (Nizatidine), indicating absence of any interaction.

Differential scanning calorimetry(DSC):

The pure drug (S-I) and the optimized Formulation (S-II) was subjected to the compatibility studies, using Differential Scanning Calorimetry (DSC) which is shown below in **fig.3.**

The thermograms of mixtures showed no appreciable change in the melting endotherms of the optimized formulation (S-II) as compared to that of the pure drug (130-134^{0}C) indicating absence of any interaction.

Stability studies: Formulations found to be stable for one month when tested for its *in vitro* dissolution studies (89.71% release at the end of 60 minutes), which were evident of stability of the product.

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