Formulation and In-vitro Evaluation of Orodispersible Tablet

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Abstract

The formulation researches are oriented towards increasing safety and efficacy of existing drug molecule through a novel concept of drug delivery, one of these is the orodispersible tablet, so the aim of this research is to mask the bitter taste of the nizatidine and to formulate in vitro evaluation of nizatidine orodispersible tablets.

Complexation of nizatidine with Kyron T134 showed a better way to mask the bitterness taste of the nizatidine. Nizatidine orodispersible tablet were prepared by direct compression method using sodium starch glycolate, croscarmellose sodium, crospovidone as superdisintegrants.

The prepared tablets were evaluated for pre and post compression parameter including Carr's index, angle of repose, Hausner ratio, hardness, friability, wetting time, in vitro disintegration time, and in vitro drug release. The tablets prepared by direct compression method showed an acceptable flow character. All the formulas exhibited a good mechanical strength.

The tablets which prepared by direct compression method showed an acceptable flow character. All the formulas exhibited a good mechanical strength. Crospovidone showed the shortest disintegration time among other superdisintegrants. Moreover the addition of microcrystalline cellulose (Avicel PH102) in a suitable concentration to the formulas containing crospovidone will decrease the disintegration time. The overall results suggested that the prepared formula of nizatidine orodispersible tablet (NF 11) could be promising as a new dosage form for the oral administration.

Key Words: Nizatidine, Crospovidone, Microcrystalline cellulose, direct compression

Introduction

The commonly used formulation pediatrics the liquid dosage form that is safe and easily administered to the children. However, the bitter taste masking represents serious challenge during formulation development of liquids. Other difficulties with liquid dosage forms are bulkiness, reduced stability, and incompatibilities [1].Because the oral dosage form can be self-administered by the patient, they are obviously more profitable to manufacturer than parenteral dosage form that must be administered in most cases by trained personnel, this reflected by the fact that well over 80% of the drugs in the united states that are formulated to produce systemic effect are marketed as oral dosage form [2].

Orodispersible tablets (ODTs [3]

Oral dispersible tablets (ODTs) are the novel dosage form which rapidly disintegrates in the mouth (1-3 min) without chewing upon oral administration and without the need of water, unlike other conventional oral solid dosage form. Oral Dispersible Tablets (ODTs) are also known as "fast dissolve", "rapidly disintegrating", "quick-dissolve", "crunch-melt", "bite-dispersible", "mouth-dissolve", and "orodispersible" tablets[6]. Oral dispersible minitablets (ODMTs) are more suitable for pediatric patients because of their small size, pleasant mouth feel and fast disintegration in mouth.

Main ingredients used in preparation of ODT [4]

Important ingredients that are used in the formulation of ODTs should allow quick release of the drug, resulting in faster dissolution. This includes both the actives and the excipients. Disintegration and solubilzation of a directly compressed tablet depend on single or combined effects of disintegrates, water-soluble excipients and effervescent agents. Excipients balance the properties of the actives in FDTs. This demands thorough understanding of the chemistry of these excipients to prevent interaction with the actives. The choice of the binder is critical in a fast-dissolving formulation for achieving the desired

sensory and melting characteristics, and for the faster release of active ingredients. Commonly available fats such as cocoa butter and hydrogenated vegetable oils can also be use.

Mechanism of Superdisintegrants Superdisintegrants provide quick disintegration due to combined effect of swelling and water absorption by the formulation. Due to swelling of superdisintegrants, the wetted surface of the carrier increases, this promotes the wet ability and dispersibility of the system, thus enhancing the disintegration and dissolution. The optimum concentration of the superdisintegrants can be selected according to critical concentration of disintegrants. Below this concentration, the tablet disintegration time is inversely proportional to the concentration of the superdisintegrants, whereas if concentration of superdisintegrants is above critical concentration, the disintegration time remains almost constant or even increases[5] .

Type of superdisintegrant

Synthetic superdisintegrant

Synthetic superdisintegrants are frequently used in tablet formulations to improve the rate and extent of tablet disintegration thereby increasing the rate of drug dissolution. The most widely used synthetic superdisintegrants are illustrated below [6].

1. Sodium Starch Glycolate (Explotab and Primogel)

Sodium Starch Glycolate is the sodium salt of acarboxymethyl ether of starch. These are modified starches made by cross linking of potato starch as it gives the product with the best disintegrating properties. The degree of cross linking and substitution are important factors in determining the effectiveness of these materials as superdisintegrants. The effect of the cross linking is to reduce both the water soluble fraction of the polymer and the viscosity of dispersion in water [7].

2. Cross-linked poly-vinyl Pyrrolidone (Crospovidone)

Unlike other superdisintegrants, which rely principally on swelling for disintegration, crospovidone use a combination of swelling and wicking. Due to its high crosslink density, crospovidone swells rapidly in water without gelling. Crospovidone particles are found to be granular and highly porous which facilitates wicking of liquid into the tablet and particles to generate rapid disintegration. Larger particles provide a faster disintegration than smaller particles. Crospovidone disintegrants are highly compressible materials as result of their unique particle morphology. Crospovidone can also be used as solubility enhancer. It is available in two particle sizes in the form of Polyplasdone XL and Polyplasdone XL-10[8].

3. Croscarmellose sodium (Ac-Di-Sol)

It is an internally cross linked polymer of carboxymethyl cellulose sodium. It has high swelling capacity with minimal gelling resulting in rapid disintegration .Due to fibrous structure, croscarmellose particles also show wicking action .In tablet formulations, croscarmellose sodium may be used in both direct compression and wet-granulation processes. When used in wet-granulation, the croscarmellose sodium should be added in both the wet and dry stages of the process (intra- and extra-granularly) so that the wicking and swelling ability of the disintegrant is best utilized[9].

4. Resins (Ion Exchange Resin)

The INDION 414 and KYRON 314 have been used as a superdisintegrant for ODT. It is chemically cross-linked polyacrylic potassium (Polacrillin potassium), with a functional group of – COO – and the standard ionic form is K+. It has a high water uptake capacity. It is a high purity pharmaceutical grade weak acid cation exchange resin supplied as a dry powder. It is an extremely effective tablet disintegrant which provides the necessary hardness and chemical stability to the tablet. The product swells up to a very great extend when in contact with water or gastrointestinal fluids causing rapid disintegration without the formation of lumps. It is a high molecular weight polymer; therefore it is not absorbed by the human tissues and totally safe for human consumption-HPC (Low substituted hydroxyl-propyl cellulose) insoluble in water rapidly swells in water[10].

Coating Technology for taste masking of bitter drugs

Using of triglycerides for taste masking of bitter drugs. Triglycerides which, when mixed together, melt at body temperature and a polymer, that is insoluble at pH 7.4 and soluble in the stomach (i.e. which dissolves at a pH of 5.5 or lower) are used in this .

Materials and Methods

Materials

Molecular formula: C12H21N5O2S2

Chemical name: 1, 1-Ethenediamine, *N*-[2-[[[2-[(dimethylamino) methyl]-4 thiazolyl] methyl thioethyl] -*N*methyl-2-nitro-. *N*-[2-[[[2-[(Dimethylamino) methyl]-4-thiazolyl] methyl] thio] ethyl]-*N*-methyl-2-nitro-1, 1-ethenediamine

Chemical structure

nizatidine

Figure 1: Chemical structure of Nizatidine

Molecular weight: 331.46

Category: Histamine H2 receptor antagonist which inhibits gastric acid secretion.

Solubility: It is freely soluble in chloroform; soluble in methanol; sparingly soluble in water.

Mechanism of action: Nizatidine inhibit acid production by reversibly competing with histamine for binding to H2receptorsonthebasolateralmembraneofparietalcells [11].

Methods

Characterization of nizatidine

1-Determination of Melting Point

The melting point of NIZ was determined by the capillary method according to BP. A sufficient quantity of NIZ powder was introduced into a capillary tube to give a compact column of 4-6 mm in height. The tube was put in electrical melting point apparatus and the temperature was raised gradually. The melting point recorded was the temperature at which the last solid particle of a compact column of NIZ in a tube passed into the liquid phase [12].

2-Determination of λ max

Nizatidine in 0.1N HCL solution was prepared then scanned by a UV spectrophotometer at wavelengths ranging from 400nm to 200nm, and the λ max for this solution was determined**.**

3-Determination of solubility in acidic media

Solubility of NIZ was determined at pH 0.1NHCL using the shake-flask method by placing excess amounts of drug in 30 ml vials then 20 ml was added to the vial. The vial were sealed well and covered with opaque aluminum foil then incubated together in a shaking water bath at 25˚C for 72hours.Samples were withdrawn then filtered and suitably diluted. The diluted samples, along with an appropriate standard curve, were analyzed by UV spectrophotometer at respective λ max to determine the dissolved quantity of NIZ [13].

Characterization of superdisintegrants

1-Determination of compactibility [14]

The compactability of the three superdisintegrants (CP, CC (Aci Di sol) and SSG) was evaluated by comparing the breaking force (hardness) of the pure compacts of them at various compression forces as follows [19].Amounts of 180 mg (using the same die fill) of each superdisintegrant with a small amount of lubricant, were compressed under various compression forces using a single punch tablet machine of a 7.6 mm diameter die. The hardness (determined by Monsanto hardness tester) and the thickness (determined by digital vernier caliper) of the resulting tablets were recorded and compared.

2-Determination of Swelling Indices of the Superdisintegrants

Samples of fixed volume of each superdisintegrant were conveyed to 100 ml graduated cylinders and the initial volume (VI) occupied by the superdisintegrant was recorded. For each cylinder the volume is completed with the specified medium (either 0.1 N HCl, pH 1.2) or (phosphate buffer, pH 6.8) to 100 ml with continuous stirring, and then the cylinders were incubated at 37±0.5˚C for 24 hours. After incubation, the final volume of

the swelled superdisintegrant (VF) was recorded and the swelling indices were calculated using the following equation [15]

$$\textbf{Swelling index} = \frac{Vf - Vi}{Vi} \times 100 \quad \ldots\ldots\ldots\ldots\ldots (1)$$

Formulation of orodispersible tablets:

Formulation of nizatidine with Kyron T 134

Nizatidine resinate was prepared using a batch process. For preliminary study, we optimized the ratio of resin to drug at 1:1. Drug (150 g) Resin (150.0 g) was placed in a glass beaker and then 380 ml of distilled water was added. The mixture was stirred in the water bath at 37 C. Then, the NIZ resinates were separated from the filtrates by filtration, washed several times with distilled water, dried overnight at 50C and kept in air tight container

Formulation of Nizatidine orodispersible tablets:

Different formulas shown in table (1) were prepared with NIZ. The formulas (NF1- NF15) were prepared by direct compression method and as following:

The superdisintegrant (CC, SSG or CP), sweetening agent (Aspartame) and mannitol were triturated together well in a mortar for 5 minutes then conveyed to a mill and milled for 2 min., then through sieve no. 18 then weighed and the amounts of glidants and lubricant were calculated according to the yielded weight of powder. Talc and the lubricant (usually Mg. stearate) were incorporated and mixed for 10 min. The powder were then compressed into a 20 mm diameter tablets using a single punch tablet machine of 20 mm diameter die at different Compression forces (ranging from 37-42 kN) to get the desired hardness.

Table 1: Composition of Nizatidine orodispersible tablet (A)

Formula Ingredient Ingredients (mg/tab.)	**NF1**	**NF2**	**NF3**	**NF4**	**NF5**	**NF6**	**NF7**
Nizatidine / Kyron T 134	300	300	300	300	300	300	300
Crospovidone	25 (5%)	50 (10%)	75 (15%)				
Croscarmellose Sodium				25 (5%)	50 (10%)	75 (15%)	
Sodium Starch Glycolate							25 (5%)
Microcrystalline Cellulose (avicel pH102)							
Crospovidone +cross carmellose sodium							
Aspartame	5	5	5	5	5	5	5
Talc	7	7	7	7	7	7	7
Mg stearate	3	3	3	3	3	3	3
Mannitol up to	500	500	500	500	500	500	500

Table 1: Composition of Nizatidine orodispersible tablet (B)

Formula Ingredient(mg/tab)	NF8	NF9	NF10	NF11	NF12	NF13	NF14	NF15
Nizatidine / Kyron T 134	300	300	300	300	300	300	300	
Crospovidone			75 (15%)	75 (15%)	75 (15%)			
Croscarmellose								
Sodium Starch Glycolate	50 (10%)	75 (15%)						
Microcrystalline Cellulose (avicel pH102)			25 (5%)	50 (10%)	75 (15%)			
Crospovidone +cross carmellose sodium						5 % (2.5%) (2.5%)	10 % 5%) (5%)	
Aspartame	5	5	5	5	5	5	5	
Talc	7	7	7	7	7	7	7	
Mg stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	
Mannitol up to	500	500	500	500	500	500	500	500

Determination of compactability

The compaction profiles of the three superdisintegrants, Figure (2), showed that CP produces the hardest tablets under lower compression forces followed by croscarmellose sodium and finally SSG. Also the results of thickness measurement under the same compression force (38 KN) showed that CP produced the thinnest tablets and this reveal that CP exhibits better compressibility than croscarmellose sodium and SSG .In manufacturing of ODTs, it is desirable to have tablets with acceptable hardness (3 kg/cm2) at a given compression force to produce robust tablets that avoid the need to use specialized packaging while maximizing production speed. Thus, a more compactable disintegrant will produce stronger, less-friable tablets.

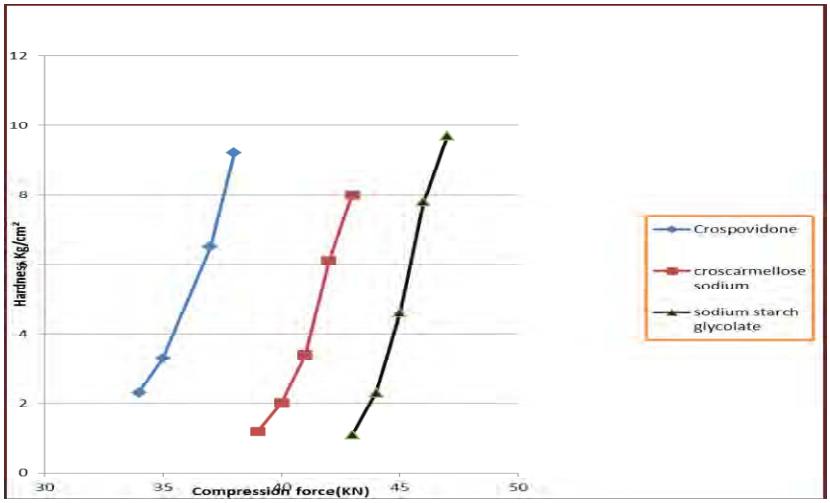

Figure 2: Compaction profiles of pure compacts of crospovidone, CCS and Sodium starch glycolate

Effect of combination of CP with other superdisintegrant

NF13, NF14 and NF15 were prepared to investigate the influence of substitution half concentration of CP (w/w) with CCS (the result reveals that this substitution led to increase in the angle of repose when CCS was used (NF11) as well as addition of CCS improves it, also there is a very little change regarding the Carr's index, so it appear that CCS decreases the flowability of precompression powder while SSG improves it. This could be attributed to the fact that both CP and SSG are free flowing powder and so mixing them together improves the flow property of the whole blend, where this doesn't occur with CCS.

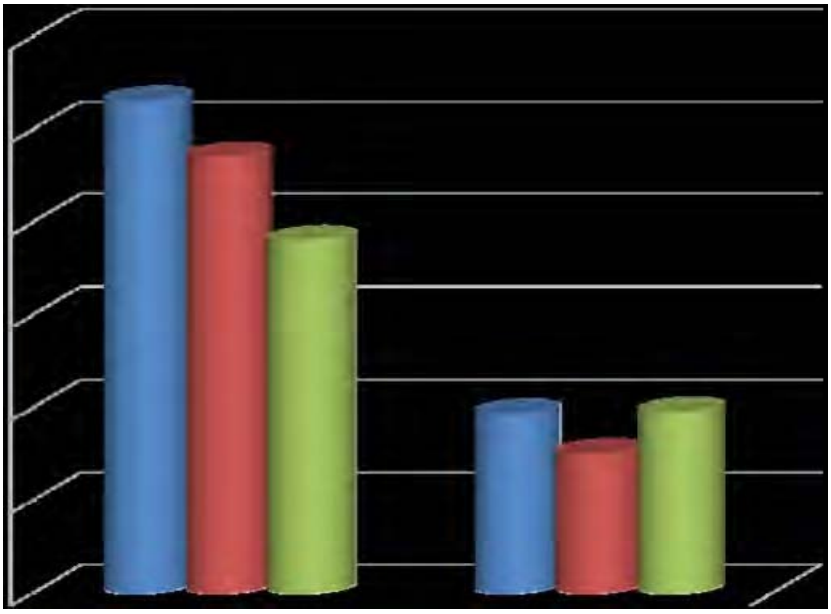

Figure 3: Wetting time and *in-vitro* disintegration time for the prepared NIZ ODTs of different formulas (mean ±SD, n=3).

In-Vitro Dissolution Studies

The release profile of the prepared NIZ ODTs (NF10, NF11, NF12, NF14, NF 15 and (Tazac conventional tablet) was tested using 0.1N HCl which represents the media of stomach where the dissolution of the prepared NIZ ODTs occurs. The prepared NIZ ODTs disintegrate rapidly in the mouth. By swallowing the disintegrated orodispersible tablets, the dissolution process completes in the stomach. Therefore, 0.1N HCl was used to study the dissolution and release profile of the NIZ ODTs.The time required for 80% of the drug to be released (t80%) from the tablet and percent drug dissolved in 2 minutes (D2 min) were considered for the comparison of the dissolution results in 0.1N HCl. The results showed that the selected formula (NF11) has the highest D2 min (91.4%) and the lowest t80% (min) (1.73 minutes) indicating that NF11 gave fastest dissolution rate compared to other formulas (NF10, NF12, NF14 and NF 15) and (the conventional NIZ tablets (Tazac). The results are shown in figures (4).There is a significant difference ($p<0.05$) in the release profiles between formulas containing the MCC PH102 (i.e. NF10, NF11and NF12) and those that do not containing it (i.e. 14, 15) in which the t80% for NF11 (the selected best formula) is about 3-folds less than those for NF15.

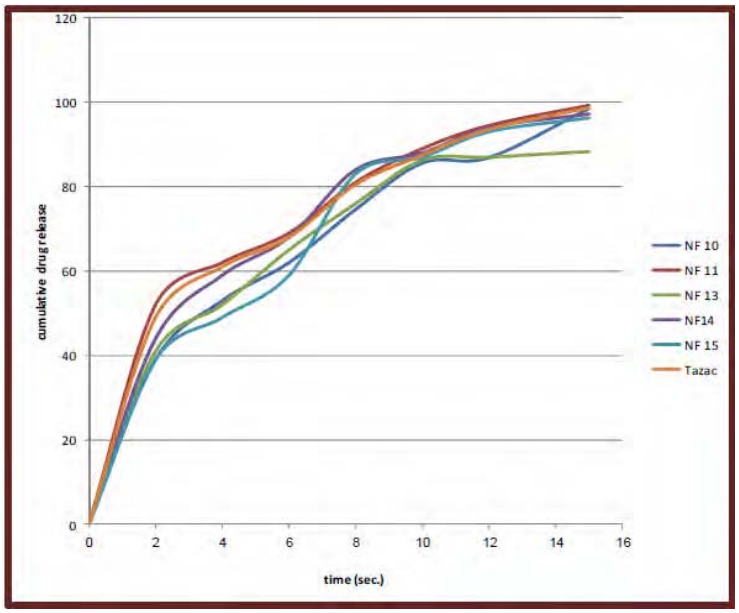

Figure 4: Nizatidine ODTs release profiles for (NF10, NF 11, NF 12, NF 14, NF15and Tazac) and for a commercial conventional tablet in 0.1N HCL buffer, PH=1.2 at 37 °C ± 0.5 °C and 50 r.p.m.

Drug – Excipients compatibility Studies

The FTIR spectra for the pure NIZ powder (Figure 5) showed the characteristic absorption bands of NIZ pure drug at 740 cm-1 for C=C bending of aromatic ring and 702,691 and 964 cm-1 for C-H bending of aromatic ring. There is a distinct peak in the region 3000-2850 cm-1 for C-H aliphatic, 1350-1000 cm-1 For C-N amine and 31500-3100 for 2 amine and 15000 cm and 1350 for drug complex. The results showed that these bands don't change in the FTIR spectra of the selected formula NF11 of the prepared ODTs of NIZ. These results indicated that no interaction of the drug occurred with the component of the formula.

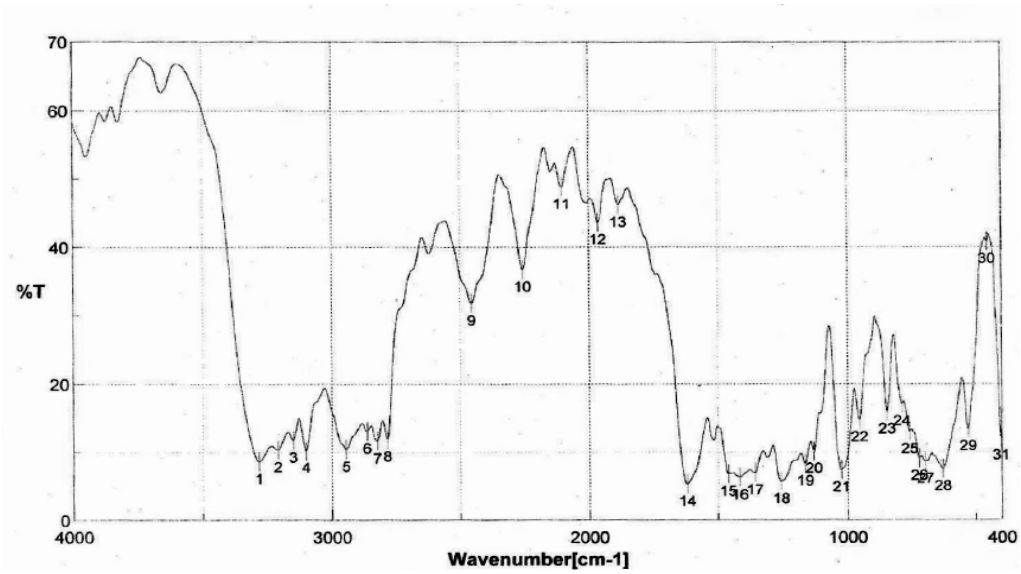

Figure 5: FT-IR spectra for pure NIZ without excipient

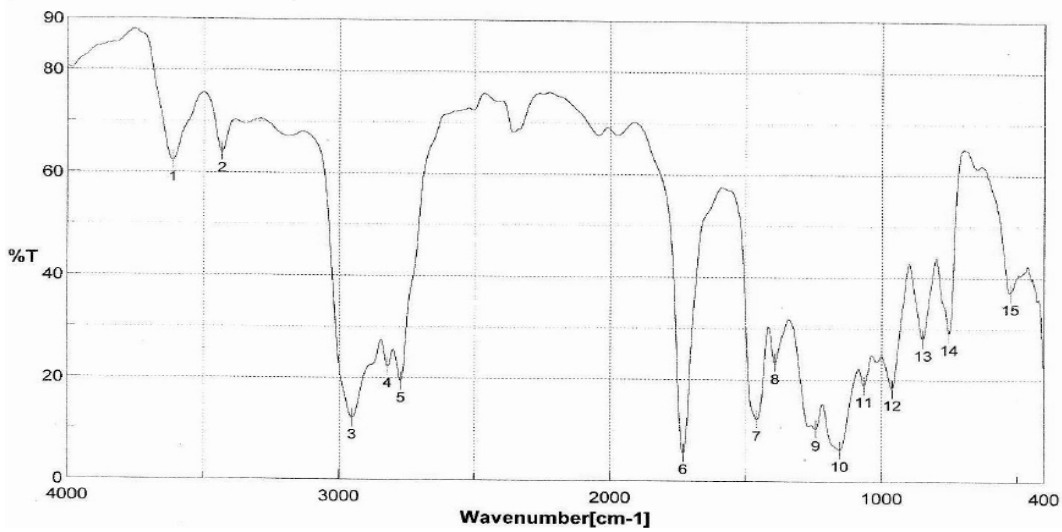

Figure 6: FT-IR spectra for NIZ with kyron T134 and other excipient

Conclusion

Based on the results of this study, we conclude that:

Crospovidone (CP) was the best superdisintegrant used in which the direct compression method is suitable for the preparation of Nizatidine ODTs.So the additions of MCC (avicel pH102) improve the ability of superdisintegrant.While the mixing of two types of superdisintegrant has a valuable effect on the disintegration time.

The drug-excipient compatibility study showed no interaction of the drug occurred with the components of the best formula, and the accelerated stability study at 40 ± 2 °C/75 ± 5 % RH of this formula showed no significant changes ($p<0.05$) in tablet properties. The stability studies showed that he expiration date was 5 years.

The overall results of this study indicate the possibility of utilizing the selected best formula (NF11) in the preparation of nizatidine ODTs as a new dosage form for the oral administration.

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