

# Design and Evaluation of Fast Dissolving Films Containing Nizatidine

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## ABSTRACT

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The present study deals with the formulation of fast dissolving films of nizatidine as a model drug which is used for the treatment of acid-reflux disorders, peptic ulcer disease, and active duodenal ulcer. Rapidly dissolving dosage forms have acquired great importance in pharmaceutical industry because of their unique properties. In the present research work various trials were carried out using maltodextrin and the concentration of excipients were optimized to prepare an ideal film for drug loading. Casting method was used for the preparation of films. The prepared films were evaluated for film thickness, folding endurance, disintegration time, dissolution time and for drug content. The *in vitro* dissolution studies were carried out in three media, distilled water, simulated gastric fluid (pH 1.2) and simulated salivary fluid (pH 6.8). The prepared films were found to be uniform, flexible, more than 90% of the drug was found to be released from the film within 4 min which is a desirable characteristic for fast absorption. FTIR and DSC studies were carried out to study drug excipient interactions. From these studies it is observed that there was no interaction between drug and excipients used and the drug is stable in the formulation. The *in vivo* disintegration time and taste evaluation studies were carried out in human volunteers after taking approval by the ethical committee, IPT, SPMVV (Sri padmavathi mahila Visva Vidyalayam). These results revealed that there was no bitter taste, no irritation and good mouth feel was observed. The *in vivo* disintegration time was in agreement with *in vitro* results. This confirms the successful formulation of nizatidine in the form of fast dissolving films.

**Keywords:** Fast dissolving Films, Nizatidine, Taste masking.

## INTRODUCTION

There are many different forms into which a medicinal agent can be placed for the convenient and efficacious treatment of a disease. Amongst all the routes of administration oral route is most preferred route receiving more attention in the pharmaceutical field because of flexibility in the designing of dosage form than drug delivery design of other routes. The peroral application is an effective and inexpensive way for drugs that can be absorbed in the gastrointestinal tract.<sup>1,2</sup> Mouth dissolving product (tablets and films) may show greater patient acceptability and convenience<sup>3</sup>. They can be taken with ease at any time by the patient without water.<sup>4,5</sup> Rapidly dissolving dosage forms have acquired great importance in the pharmaceutical industry because of their unique properties.<sup>6,7</sup> Rapidly dissolving dosage forms are also called as quick dissolving delivery systems, quick disintegrating, mouth dissolve dosage forms or melt-in-mouth dosage forms.<sup>6,8,9</sup> These dosage forms disintegrate or dissolve in the salivary fluids of the oral cavity within 1 min, releasing the drug and inactive ingredients<sup>11</sup>. This fast dissolving action is primarily due to the large surface area of the film, which wets quickly when exposed to the moist oral environment.<sup>7</sup> Most of the drug is swallowed with the saliva

where subsequent absorption takes place in the gastrointestinal tract.<sup>8,9</sup> Fast dissolving films is a novel approach to get quick onset of action and to get immediate relief of the symptoms. Hence, fast dissolving films are the best formulations as they are soluble in saliva within 1 minute releasing the drug and inactive ingredients. Most of the drug is swallowed with saliva where subsequent absorption takes place in gastrointestinal tract. The objective of the present study was to design and optimize the fast dissolving film of nizatidine by casting method using maltodextrin, glycerin and sorbitol monooleate and saccharin sodium for taste masking of the drug nizatidine and to optimize the concentration of maltodextrin, glycerine and sorbitol monooleate for obtaining a film with satisfactory characteristics. Nizatidine is used for the treatment of acid-reflux disorders (GERD), peptic ulcer disease, active benign gastric ulcer, and active duodenal ulcer<sup>10</sup>. The drug is bitter in taste and having bioavailability more than 70%, The  $C_{max}$  is 700 to 1,800 mcg/L (150 mg dose) and  $T_{max}$  is 0.5 to 3 h. Food increases nizatidine AUC and  $C_{max}$  by approximately 10%. Gastric ulcers and duodenal ulcers are the general symptoms mainly observed in elderly people that cause severe pain because of sour stomach, hence fast relief from the pain is necessary. Moreover in geriatric patients have difficulty of swallowing hence fast dissolving films for Nizatidine were formulated. Drug excipient interaction were studied by using Fourier Transform Infrared Spectroscopy and the physical state of the drug in the formulation was studied by Differential Scanning Colorimetry. The *In vivo* disintegration time and taste

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evaluation were done in human volunteers after taking approval from ethical committee.

## MATERIALS AND METHODS

### General method of preparation of nizatidine fast dissolving film by casting method:

#### Optimization of the Formula:

Various trails were carried out to prepare the placebo films to optimize the concentration of maltodextrin, glycerin and sorbiton monooleate to obtain a film with satisfactory characteristics. The optimized formula for the preparation of films was given in the table 1.

#### Preparation of the Film

The aqueous dispersion was prepared by dissolving polymers, plasticizers and the other components of the placebo formulations in distilled water maintained at 80°C and stirred with a magnetic stirrer. The obtained dispersion was then cooled down to 40°C and the active ingredient was added in the specific proportion. The suspension was stirred for 1 hr. and cooled down to room temperature. The suspension was poured onto the mould and left undisturbed for at least 24 hrs for the formation of films. The mould size was 4 x 4 cm<sup>2</sup> and the mould capacity was 2.5 ml yielding thin flexible rapid dissolving films

#### EVALUATION OF FAST DISSOLVING FILMS:

The prepared films were subjected for *in vitro* evaluation tests like film thickness, folding endurance, disintegration time, dissolution time and for drug content. Film thickness was measured using screw gauge at five different places and the mean was calculated. Folding endurance of patch was determined by repeatedly folding a small strip of film (2 cm x 2 cm) at the same place till number of times the film could be folded at the same place without breaking was recorded as the folding endurance value. The folding endurance values of the prepared films were given in the table 2. Drug content was estimated by dissolving a sample of 2cm<sup>2</sup> is dissolved in 100 ml distilled water, pH 1.2 buffer solution (Gastric pH) and simulated saliva consisting of phosphate buffer (pH 6.8). Then the absorbance of solutions was noted using spectrophotometer at 256 nm. The drug obeyed the beer's law limit in the range of 5 – 35 g / ml. *In vitro* dissolution studies were carried out for the films using U.S.P. dissolution apparatus I (Paddle type)<sup>12</sup>. Disintegration test was carried out by taking six 2 x 2 cm<sup>2</sup> films. These were placed in the disintegration apparatus maintaining the temperature at 37 ± 2°C, and the time taken for disintegration of the films was noted. Although, no official guidance is available for oral fast disintegrating films<sup>13</sup>.

**Table 1: Formula for Preparation of Nizatidine films**

S.No.	Ingredient	Use	Percentage used (% w/w)
1.	Maltodextrin	Polymer and film former	2.05g
2.	Glycerin	Plasticizer	0.32 w/w
3.	Sorbiton mono oleate	Plasticizer	0.05 ml
4.	Nizatidine	API	300 mg
5.	Sodium saccharin	Sweetening agent	270 mg
6.	Pine apple flavour	Flavouring agent	Quantity sufficient

**Table 2: Evaluation Values of the Prepared Films**

S No.	Trails	Folding endurance (Mean ± S.D)	Mean thickness(µm)	% of the drug
1	Trail -1 (placebo)	35±0.05	361±0.01	-
2	Trail -2 (placebo)	32±0.02	365±0.015	-
3	Trail -3 (placebo)	28±0.04	368±0.011	-
4	Trail -4 (placebo)	18±0.02	373±0.015	-
5	Trail -5 (optimized formula)	27±0.06	371±0.02	92.34

**Table 3: Drug Content values for Optimised Formulation of Nizatidine Films**

S.No	Dissolution media	Average drug content in each film(mg)	% of the drug
1.	Distilled water	69.26±1.2	92.34
2.	Simulated salivary buffer (pH6.8)	70.70±0.8	94.26
3.	Simulated gastric buffer (pH 1.2)	70.46±0.6	93.94

#### DRUG EXCIPIENT INTERACTION STUDIES:

Drug excipient interaction studies were studied by using Thermo Electron FTIR spectrometer to confirm possible interaction between the polymer and drug. The film was finely ground with KBr to prepare the pellets under a hydraulic pressure of 600 psi and spectra were scanned in the wavelength range of 400 and 4000 cm<sup>-1</sup>. The physical state of the drug in the formulation was studied by using differential scanning calorimetry using modulated differential scanning calorimeter (Model TAG 1000). The analysis was performed by heating the 2-3mg samples on aluminum crimp pans at a rate of 10°C / min in a nitrogen atmosphere (50 ml, min<sup>-1</sup>).

#### Measurement of the *in vivo* disintegration time in human volunteers:

Taste acceptability was measured in human volunteers after the informed consent. The volunteers are informed to keep the 2 x 2 cm<sup>2</sup> film in their mouth until it dissolved completely, and then they were asked to spit out the mouth content and to wash their mouth with distilled water. The reports from the

volunteers were collected about taste, dissolution time, mouth feel and irritation. The study was approved by the Ethical committee, IPT(Institute of Pharmaceutical technology) SPMVV.

**RESULTS AND DISCUSSION**

Various trails were carried out to optimize the formula for the preparation of films. From these trails, the films prepared with 82% maltodextrin, 16% of glycerin and 2% sorbiton monooleate were ideal and used for drug loading. The optimized films were evaluated for thickness, folding endurance, drug content and in vitro disintegration time. Further these films were evaluated in healthy human volunteers for acceptability and *In vivo* disintegration time. The film thickness was found in the range of 361±0.01 to 373±0.015µm. The optimized film was found to have 371±0.02µm which was acceptable. The folding endurance value of the prepared films ranged from 18±0.02 to 35±0.05. The optimized film was found to have folding edurance value 28±0.04 which was desirable. The drug content was found to be in the range of 69.26±1.2 mg to 70.46±0.6 mg. The optimized film to have 92.34 % to 94.26 % of the drug which was well with in the limits and acceptable. *In vitro* dissolution studies were carried out in three media, distilled water, simulated gastric fluid (pH 1.2) and simulated salivary fluid (pH 6.8). The drug release in salivary pH 6.8 was found to be

92.17±3.012 slightly higher when compared to drug release at pH 1.2 and in distilled water which is desirable( Figure 6,7&8). *In vitro* disintegration time carried out for the optimised film and it was observed to be 2 min.52 sec±1.2 which was with in the limits and acceptable. The spectral analysis was carried out such as FTIR studies, DSC studies for pure drug, placebo film, and drug loaded nizatidine films and they revealed that the there are no interactions between drug and excipients used and the drug is stable in the formulation. The FTIR spectra (Figure 1&2) of the commercial sample of Nizatidine displayed bands at 3421 cm<sup>-1</sup> due to N-H stretch, at 2951 cm<sup>-1</sup> due to C-H stretching, at 1618 cm<sup>-1</sup> due to C=C stretching conjugated with NO<sub>2</sub>. The spectra also showed bands at 1479 cm<sup>-1</sup> due to C-H deformation in NCH<sub>3</sub>, CH<sub>2</sub> & CH stretch. A band at 1363 cm<sup>-1</sup> and 1314 cm<sup>-1</sup> due to thiazole ring and symmetrical NO<sub>2</sub> hydrogen bonded and conjugated. The FTIR spectrum of film containing nizatidine exhibited characteristic bands consistent with the molecular structure of nizatidine such as bands at 3439.9 cm<sup>-1</sup> due to N-H stretch, at 2925.0 cm<sup>-1</sup> due to C-H stretch, at 1639.4 cm<sup>-1</sup> due to C=C stretch and at 1451.9 cm<sup>-1</sup> due to C-H deformation. Some additional bands are also present in the spectra such as a band

Fig. 1: FTIR Spectrum of Pure Nizatidine

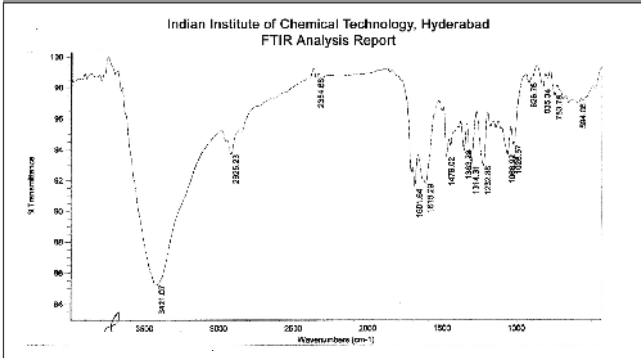


Fig. 2 : FTIR Spectrum of Nizatidine Loaded Film

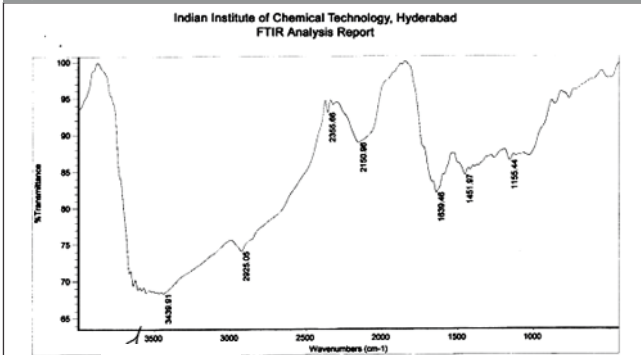


Fig. 3: DSC Thermogram of Pure Nizatidine

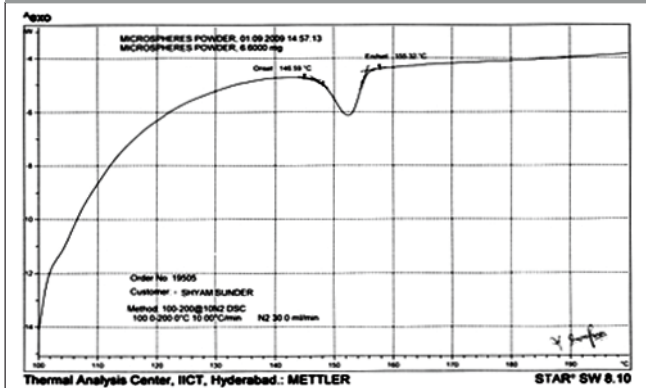
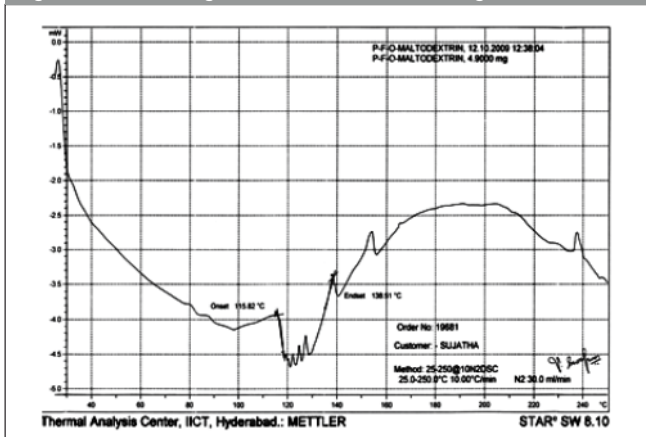


Fig. 4 : DSC Thermogram of Blank Fast Dissolving Film



at  $2150.9\text{ cm}^{-1}$  indicating the characteristics of the film material. Therefore, the presence of characteristic absorption bands of nizatidine and the film containing nizatidine suggest that the drug does not undergo any significant interaction with the film material. The DSC thermogram of the commercial sample of the nizatidine exhibited a sharp endotherm with an onset of melting at  $146.59^{\circ}\text{C}$  and the melting was completed at  $155.32^{\circ}\text{C}$ . The thermogram of the nizatidine loaded film exhibited endotherm melting at onset temperature of  $111.77^{\circ}\text{C}$  and endset temperature of  $137.69^{\circ}\text{C}$ . The melting behaviour of film containing nizatidine is slightly lower than the placebo film and the nature of the endotherm resembles that of the drug. The DSC thermograms of the commercial sample, placebo film and drug loaded film (Figure 3-5) indicate that the thermogram of the film loaded with nizatidine retained the properties of the drug as well as film material indicating that the drug did not interact with the excipients used in the film. Measurement of the *In vivo* disintegration time and taste

Fig. 5 : DSC Thermogram of Nizatidine Loaded Fast Dissolving Film

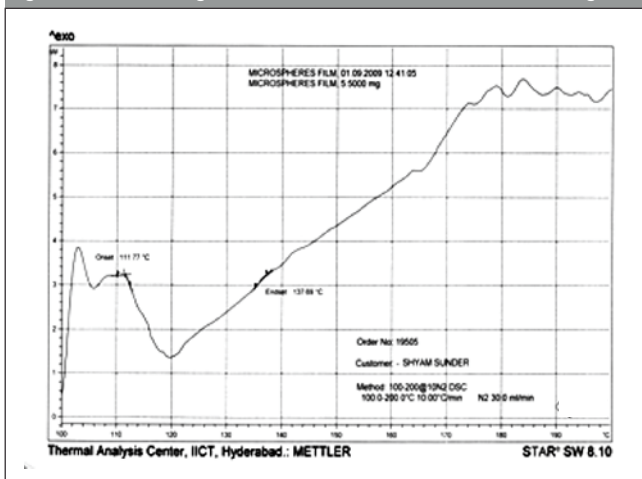


Fig. 6: Drug Release Profiles of Nizatidine Films in pH 6.8

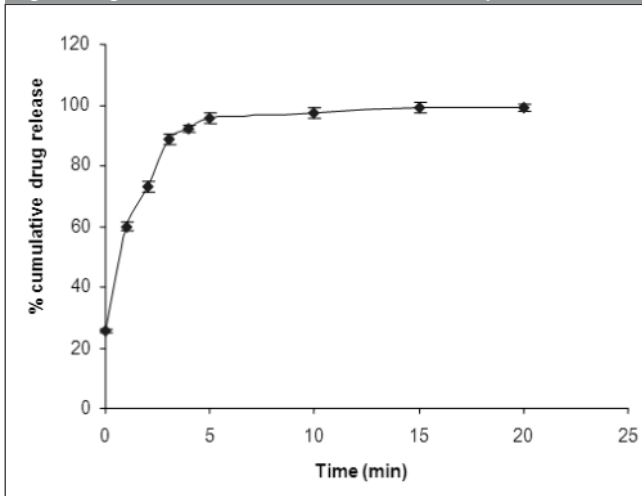


Fig. 7: Drug Release profiles of Nizatidine Films in pH 1.2

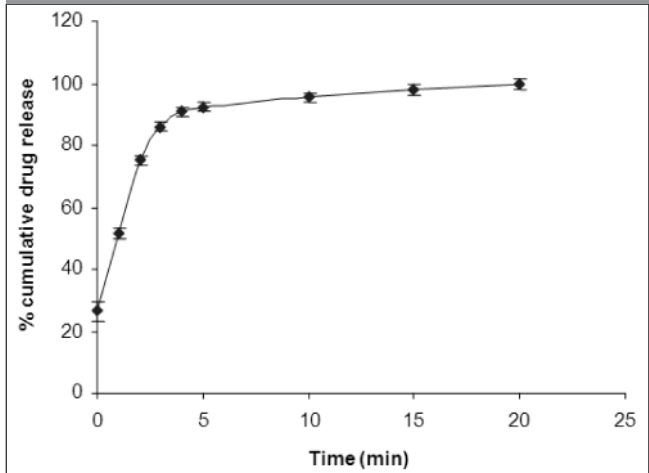
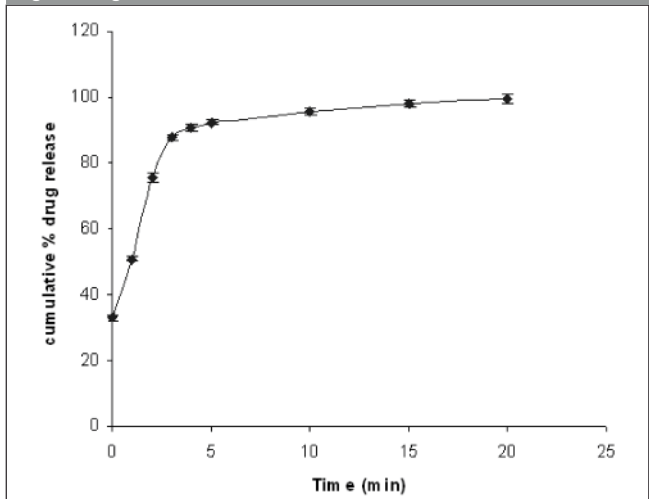


Fig. 8: Drug Release Profiles of Nizatidine Film in Distilled Water



evaluation was carried out in ten healthy human volunteers (Approved by EC of IPT, SPMVV, TPT). The mean disintegration time was  $2.385 \pm 0.652$  minutes which was well in agreement with *In vitro* disintegration time. Further the volunteers have reported that the films are having good mouth feel, no bitter taste and no irritation. These observations clearly demonstrate the successful formulation of fast dissolving film of nizatidine which were having good film characteristics and acceptability by the human volunteers.

### CONCLUSION

Fast dissolving films prepared in the study exhibited good film characteristic features as indicated by thickness measured, folding endurance etc. The prepared films were found to be uniform, flexible, more than 90 % of the drug was released from the film with in 4 min which is desirable for fast absorption. Further *in vitro* and *In vivo* disintegration time were 2 Min 52 Sec. The bitter taste of the drug nizatidine was

successfully masked by using saccharin sodium 270 mg. In vivo evaluation of the film in human healthy volunteers revealed that was no bitter taste, no irritation and good mouth feel was observed. This further confirms successful formulation of nizatidine in the form of fast dissolving films.

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#### REFERENCES

1. S.P. Vyas., Roop K.Khar., controlled oral, administration, In., controlled Drug Delivery concepts and Advances, 1<sup>st</sup> edition, vallabh Prakasham Publications, Delhi, 2002.
2. Loyd V. Allen., Nicholas G. Popavich., Howard C. Ansel., Dosage form design biopharmaceutical and pharmacokinetic considerations, In; Ansel's pharmaceutical Dosage Forms and Drug Delivery systems, 8<sup>th</sup> edition, BI publications, 2006.
3. Renuka sharma, R.K. Parikh, M.C. Gohel and M.M.Soniwala.(2007) Development of taste masked film of Valdecocix for oral use. Indian J. Pharm.Sci., 69(2):320-323.
4. Seager, H. Drug delivery products and zydus fast dissolving dosage forms J. Pharm. Pharmacol. 1998, 50,375.
5. Mashru, R.C., Sutarya, V.B., Sankalia, M.G. and Parikh P.P., Development and evaluation of fast-dissolving film of salbutamol sulphate. Drug Develop. Ind. Pharm., 2005, 31, 25.
6. A.C. Liang and L.H. Chen, "Fast Dissolving Intraoral Drug Delivery Systems," *Exp. Opin. Ther. Patents* **11** (6), 2001, 981–986
7. S. Borsadia, D. O'Halloran, and J.L. Osborne, "Quick Dissolving Films: A Novel Approach to Drug Delivery," *Drug Del. Technol.*, **3** (3), 2003, 84–90
8. J. Klanke, "Dissolution Testing of Orally Disintegrating Tablets," *Dissol. Technol.*, **10** (2), 2003, 6–8.
9. S.R. Parakh and A.V. Gothoskar, "A Review of Mouth Dissolving Tablet Technologies," *Pharm. Technol.*, **27** (11), 2003, 92–100.
10. Chen X, Ji ZL, Chen YZ: TTD: Therapeutic Target Database. *Nucleic Acids Res.* 2002 Jan 1;30(1):412-5.
11. Renuka Mishra, Avani Amin, Formulation Development of Taste-Masked Rapidly Dissolving film of Cetirizine Hydrochloride. *Pharmaceutical Technology*. 2009; volume 33, Issue,2, pp. 48-56.
12. Mashru R.C, Sutariya BC, Parikh PP. Development and evaluation of fast dissolving films of salbutamol sulphate. *Drug Dev Ind Pharm.* 2005 ;31: 25-34.
13. Bhupinder Bhyan , Sarita Jangra, Mandeep Kaur, Harmanpreet Singh: Orally Fast Dissolving Films: Innovations in Formulation and Technology. *Int. JPharm. Sci. Rev. & Res.* 2011; 9, 2-9.

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