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Research Article

Formulation and Evaluation of Fast Dissolving Tablets of Nizatidine

SHELKE DATTATRAYA*[1], VILEGAVE KAILASH[2], UMA A. PATIL[3], VILEGAVE PRATIBHA[4]

*[1]Department of Pharmaceutics, Dayanand College of Pharmacy, Latur – 413512. Dist-Latur Maharashtra, India

[2]Department of Pharmaceutics, Shivajirao S. Jondhle College of Pharmacy Asangaon, Tal-Shahapur- 421601

[3]Department of Pharmaceutical Technology, K.L.E. Society's College of Pharmacy Bangalore- 560 010

[4]Dept. of Chemistry, Shivajirao S. Jondhle College of Polytechnic Asangaon. 421601

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ABSTRACT

Recent developments in technology have presented viable dosage alternatives for patients who may have difficulties in swallowing tablets or capsules. Conventional tablets and capsules administered with water may be inconvenient or impractical for other patients. In such conditions there is a requirement of fast disintegrating/dissolving tablets (FDT) which can be administered without water. In the present study an attempt to formulate fast dissolving tablets containing Nizatidine-Eudragit E100 complex using direct compression method. The main objective is prepare the Nizatidine complexes with Eudragit E100 to mask the bitter taste of the drug and to prepare fast dissolving tablets containing these complexes to improve patient compliance. The complexes were prepared by solvent evaporation method and spray drying method and were characterized by IR, SEM and DSC to check for chemical integrity, crystallinity and stability.

FDTs were prepared by direct compression method using various superdisintegrants like crospovidone(CRP), croscarmellose sodium(CSS) and soypolysaccharide (SYP) in varying range (6-15%). The formulated tablets were evaluated for thickness, hardness, friability, weight variation, wetting time, drug content uniformity, disintegration time and *In-vitro* dissolution study. It was concluded that CRP was beneficial in decreasing disintegration time of tablets. Solvent Evaporation technique was found to be more suitable and cost effective than spray drying to prepare solid dispersions of Nizatidine in small scale.

INTRODUCTION

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage forms. The development of pharmaceutical products for oral delivery, irrespective of physical form involves varying extents of optimization of dosage form characteristics within the inherent constraints of GI physiology. Therefore, a fundamental understanding of various disciplines, including GI physiology, pharmacokinetics, pharmacodynamics and formulation design are essential to achieve a systemic approach to the successful development of an oral pharmaceutical dosage form.

Author for Correspondence:
Email: dattashelke2025@gmail.com

The more sophisticated a delivery system, the greater is the complexity of these various disciplines involved in the design and optimization of the system. In any case, the scientific frame work required for the successful development of an oral drug delivery system consists of a basic understanding of the following three aspects:

1. Physicochemical, pharmacokinetic and pharmacodynamic characteristics of the drug
2. The anatomic and physiologic characteristics of the GIT, and
3. Physicochemical characteristics and the drug delivery mode of the dosage form to be designed [1].

Recent developments in technology have presented viable dosage alternatives for patients who may have difficulties in swallowing tablets or capsules. Conventional tablets and capsules administered with water may be inconvenient or

impractical for other patients. In such conditions there is a requirement of fast disintegrating/dissolving tablets which can be administered without water. Such fast dissolving/disintegrating tablets (FDT) disperse rapidly to form a suspension or solution of the drug after mixing with saliva which is easily swallowed by the patients [2].

A fast-dissolving drug delivery system, in most cases, is a tablet that dissolves or disintegrates in the oral cavity without the need of water or chewing. Most fast-dissolving delivery systems must include substances to mask the taste of the active ingredient. This masked active ingredient is then swallowed by the patient's saliva along with the soluble and insoluble excipients [3, 4].

Some FDTs also claim an increased bioavailability compared to traditional tablets because of dispersion in saliva resulting in pregastric absorption. FDTs have started gaining popularity and acceptance as new delivery system, because they are easy to administer and lead to better patient compliance.

A. Ideal characteristics of FDTS: [5]

- They should not require water or other liquid at the time of administration.
- They should easily disintegrate or dissolve in oral cavity.
- They should allow high drug loading.
- They should have pleasant mouth feel.
- They should have negligible or no residue in the oral cavity after administration as whole drug passes to GIT.
- They should show low sensitivity against environmental conditions i.e. moisture, temperature etc.

B. Significance/Advantages of FDTs: [4, 6-8]

- As FDTs are unit solid dosage forms, they provide good stability, accurate dosing, easy manufacturing, small packaging size and easy handling by patients.
- No risk of obstruction of dosage form, which is beneficial for travelling patients who do not have access to water.
- Easy to administer for paediatric, geriatric and institutionalized patients (especially for mentally retarded and psychiatric patients).
- Rapid disintegration of tablet resulting in quick dissolution and rapid absorption, which provides rapid onset of action.
- Excellent mouths feel property produced by use of flavours and sweeteners which has changed the concept of medication as "Bitter pill".
- Increased bioavailability of drugs that are absorbed from mouth, pharynx and oesophagus.
- Reduced dose and increase in bioavailability due to pre-gastric absorption of drugs which avoid hepatic metabolism.

C. Challenges to Develop FDTs: [7, 8]

- Achieve rapid disintegration of tablet.
- Avoid increase in tablet size.
- Possess sufficient mechanical strength.
- Leave minimum or no residue in mouth.
- Protection from moisture.
- Good package design.
- Compatible with taste masking technology.
- Not affected by drug properties.

D. Formulation Aspects in Developing FDTs: [8, 9]

These differ from the conventional tablets in properties such as;

- Mechanical strength of the tablets.
- Taste and mouth feel.
- Swallow ability.
- Rate of drug dissolution in saliva.
- Rate of absorption from the saliva solution.
- Drug and dosage form stability.

E. Drugs Explored for FDTs: [2, 8-9]

The drugs can be considered to be formulated as FDTs are Analgesics, Anaesthetics, Antianginal, Anticonvulsants, Antipyretics, Anti-inflammatory, Antibiotics, Antihistaminic, Antispasmodic, Antiasthmatics, Diuretics, Antiarrhythmic, Antimigraine, Antipsychotics, Antiulceretive, Antivenin Bronchodilator etc.

F. Solid Dispersion:

It is the dispersion of one or more active ingredients in an inert excipient or matrix, where the active ingredients could exist in finely crystalline, solubilised or amorphous states. Good dissolution & bioavailability can be obtained from solid dispersion of pharmaceutically active ingredients. Particle size reduction often leads to improvement in dissolution rate of poorly soluble drugs through increase in effective surface area. Such a molecular mixing results in enhanced drug surface area and consequently enhanced dissolution rate. Solid dispersion can minimize the molecular mobility of drug by increasing its glass transition temperature consequently improving physical stability of drug.

F.1. Classification:

On the basis of fast release mechanisms solid dispersions are classified into following groups:

- Simple eutectic mixtures.
- Solid solutions.
- Glass solutions & glass suspensions.
- Amorphous precipitation of drug in crystalline carrier.
- Compounds or complex formation between drug & carrier.
- Drug and polymer exhibiting immiscibility in fluid state.
- Multicomponent solid dispersion.

F.1.1. Simple eutectic mixtures:
Eutectic mixtures are formed when the drug and polymer are miscible in their molten state, but on cooling, they crystallize as two distinct components with negligible miscibility. These systems are also prepared by fusion method. At the eutectic composition, both drug and carrier exist in finely divided state, which results in higher surface area and enhanced dissolution rate of drug.

F.1.2. Solid solutions:
Solid solution is a solid dispersion that is miscible in its fluid as well as solid state. A crystalline solid solution may result when a crystalline drug is trapped within a crystalline polymeric carrier. Poorly soluble drugs have been incorporated in carrier molecules using crystal inclusion and crystal doping techniques. Amorphous solid solutions (also termed as amorphous molecular dispersion) have shown to enhance the dissolution rate of poorly soluble drugs. As the drug is molecularly dispersed in the carrier matrix, its effective surface area is significantly higher and hence the dissolution rate is increased. Solid solutions have also improved physical stability of amorphous drugs by inhibiting drug crystallization by minimizing molecular mobility.

F.1.3. Glass solutions & suspensions:
A glass solution is a homogenous, glassy system in which a solute is usually obtained by abrupt quenching of the melt. Many compounds like sucrose, glucose, ethanol, 3-methyl hexane etc. have the ability to form glasses readily upon cooling from liquid state. Glass formation is due to strong hydrogen bonding (in polyhydroxy molecule such as sugars), which prevents crystallization. Glass formation can occur for the pure substances itself or in presence of other components. The strength of chemical binding in a glass solution is much less compared to that in a solid solution. Hence dissolution rate of drugs in the glass solution is faster than in solid solution.

F.1.4. Amorphous solid dispersion:
If the drug-polymer fluid mixture is cooled at a rate that does not allow for drug crystallization, then drug is kinetically trapped in its amorphous or a solidified-liquid state.

F.1.5. Compounds or complex formation between drug & carrier:
Dissolution and absorption of a drug will increase from a complex between the drug & an inert soluble carrier. Complexation also implies that dissolution could be retarded, as observed with PVP - Hexaresorcinol & PEG 4000 - Phenobarbital. However formation of a soluble complex with a low association constant result in increased rates of dissolution & absorption.

F.1.6. Drug and polymer exhibiting immiscibility in fluid state:
If the drug and polymers are immiscible in their fluid state, it is likely that they would not exhibit miscibility on solidification of the fluid mixture. Such systems may be regarded as similar to their corresponding physical mixtures, although any enhancement in dissolution performance compared to physical mixture may be owing to modification in morphology of drug and/or polymer due to physical transformation (i.e. solid to liquid state and back), intimate drug-polymer mixing and/or enhanced surface area. Formation of crystalline or amorphous solid dispersions can be influenced by the rate of solidification of mixture and the rate of crystallization of drug, polymer or both.

F.1.7. Drug and polymer exhibiting miscibility in fluid state:
If the drug and polymers are miscible in their fluid state, then the mixture may or may not undergo phase separation during solidification, thereby influencing the structure of solid dispersion.

F.1.8. Multicomponent Solid Dispersion:
Ternary agents have been added to solid dispersion of two components either to enhance drug dissolution rate or to overcome manufacturing or stability issues. Surfactants are added to solid dispersions to improve the dissolution rate of poorly water soluble drugs

F.2. Manufacturing of Solid Dispersion:
When selecting a suitable technique, the following factors have to be considered;

- Physicochemical properties of raw materials.
- Ease of manufacturing, scale-up and theassociated cost.
- Reproducibility of drug product attributes.
- Intellectual property and freedom to operate.

F.3. Methods of preparation:
Solid dispersions can be prepared by the following methods;

a) Melting method.
b) **Solvent evaporation method:** This method is used in the preparation of solid solutions or mixed crystals of organic or inorganic compounds. They are prepared by dissolving a physical mixture of two solid components in a common solvent followed by evaporation of the solvent.

Advantages:
- Thermal decomposition of drugs or carriers can be prevented because of low temperature required for the evaporation of organic solvents.
- Time saving.
- Drug loss is less compared to other methods.

Disadvantages:
- High cost of preparation.
- Difficulty in complete removal of solvents.
- Difficulty in producing crystal forms.

c) Melting solvent method.
d) Hot melt extrusion technique.
e) Dropping method.
f) Spray drying.
g) Supercritical fluid technology.

Objective
Nizatidine is a H_2 receptor antagonist used to treat gastric and duodenal ulcers, gastroesophogeal reflux disease and other gastrointestinal disorders. It acts by inhibiting release of acid and pepsin into stomach. The aim of this work was to prepare fast dissolving tablets of Nizatidine to improve patient compliance.

Specific objective of the research is as follows,
- Formulation of solid dispersion of Nizatidine by using Eudragit E100 polymer to mask the taste of drug.
- Evaluation and characterization of the prepared dispersion.
- Formulation of fast dissolving tablets of Nizatidine-drug complex using Superdisintegrants.
- Evaluation of the prepared FDTs for dissolution, disintegration, wetting time, hardness, etc.

MATERIALS AND METHODS

A. UV spectrophotometric method for Nizatidine: [10]

1. UV scanning:
Nizatidine is reported to exhibit λ_{max} at 314nm.
Procedure: 100 mg of Nizatidine was accurately weighed and dissolved in 10ml of gastric simulated fluid (without enzyme) and the volume was made up to 100 ml with same to get a stock solution of 1 mg/ml. Further, an aliquot was pipette out and diluted suitably to get the concentration in the Beer's range and was scanned in the wavelength region of 250-350 nm to record the wavelength of maximum absorption (λ_{max}).

Preparation of standard stock solution: Since the dissolution media for Nizatidine tablets is reported to be gastric simulated fluid, calibration curve was constructed in gastric simulated fluid. 100 mg of Nizatidine was accurately weighed and dissolved in small quantity of gastric simulated fluid. The volume was made up to 100 ml with gastric simulated fluid to get a stock solution of 1 mg/ml.

Preparation of working standard solution: Working standard solutions having concentrations 5 to 20 µg/ml were prepared by appropriately diluting the stock solution. The absorbance of the working standard solution was recorded and a graph of concentration of the solution was plotted against absorbance using Microsoft Excel software®

B. Drug excipient interaction study (Compatibility study): [11, 12]
The infrared spectra of Nizatidine, Eudragit E100 and Nizatidine along with various tablet excipients were recorded using a FTIR spectrophotometer. The IR spectra's of solid dispersions were compared with that of Nizatidine to check for any possible drug-excipient interaction.

C. Preparation of Solid Dispersion:
The Nizatidine-Eudragit E100 complexes were prepared by two different methods.
1. Spray Drying Method.
2. Solvent evaporation method.

1. Spray Drying Method:
Solid dispersion of Nizatidine with Eudragit E100 was prepared by spray drying technique. Nizatidine and Eudragit E100 were dissolved in ethanol in 1:4 ratios and spray dried using Labultima spray dryer model LU222 Advanced

and employing following optimized parameters: Spray concentration: 20%w/v. Inlet temperature: 50^{0}C. Outlet temperature: 40°C. Aspiration speed: 60. Feed rate: 8.

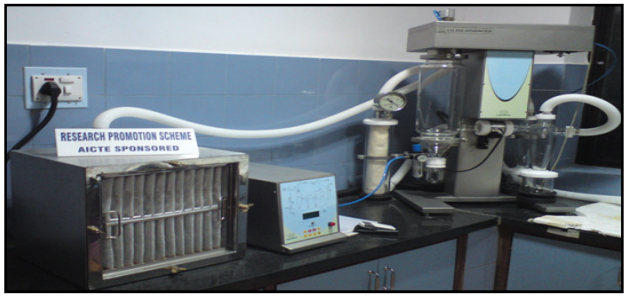

Figure 2: Spray Dryer (Labultima LU222 Advanced).

The typical recovery of the spray dried product was 80-90% and product was in the form of micro matrix.

2. Solvent evaporation method:

In this method solid dispersion of Nizatidine was prepared by solvent evaporation method. The physical mixture of Nizatidine and Eudragit E100 in the ratio 1:4 was dissolved in sufficient quantity of ethanol in a beaker and the solution was kept overnight in a Petridish for solvent evaporation. The obtained product was scrapped and powdered. The percentage yield was found to be 85%.

D. Characterization of Nizatidine-Eudragit E100 solid dispersions:

The drug-Eudragit E100 solid dispersions prepared were characterized by:

[1] Infrared spectroscopy.
[2] Scanning electron microscopy.
[3] Differential scanning calorimetry.
[4] Dissolution studies.

1. Infrared spectroscopy: [11, 12]

IR spectroscopy is one of the important analytical techniques for characterization of compounds. The IR spectra of pure Nizatidine, Eudragit E100 and Nizatidine-Eudragit E100 solid dispersions were subjected to IR studies using potassium bromide. The samples were mixed with dry potassium bromide and this mixture was taken in a diffuse reflectance sampler and IR spectra were recorded and compared.

2. Scanning electron microscopy (SEM):

SEM is used to assess the microscopic aspects of the drug, the complexing agent, and the complexes formed. This method also helps to assess the existence of a single component in the preparations obtained.

3. Differential scanning calorimetry(DSC): [13, 14]

The samples were hermetically sealed in flat bottomed aluminum pans and heated over a temperature range of 0^{0}C to 250^{0}C at a rate of 10^{0}C/min using alumina as a reference standard. Thermograms of Nizatidine, Eudragit E100 and complex were recorded using a differential scanning calorimeter and were compared.

4. Dissolution studies: [15, 16]

In-vitro dissolution study of the complexes prepared was performed using USP (Type-II) apparatus at a speed of 50 rpm. Dissolution study was carried out using 900 ml gastric simulated fluid as dissolution medium maintained at a temperature of 37°C ± 5ºC. At appropriate intervals, 1 ml of the solution was taken and dissolution medium was replaced by 1 ml of fresh dissolution fluid to maintain constant volume. The samples were then analyzed at 314 nm by UV/visible spectrophotometer using gastric simulated fluid as blank. The mean of three determinations was used to calculate the drug release from each of the solid dispersion.

E. Formulation of FDTs containing Nizatidine-Eudragit e100 solid dispersions:

Tablets containing Nizatidine-Eudragit E100 solid dispersions were formulated using various superdisintegrants like crospovidone(CRP), croscarmellose sodium(CSS) and soypolysaccharide(SYP) in concentrations ranging from 6-15%. The tablets were prepared by direct compression method.

Procedure:

[1] The tablets were prepared by direct compression method.
[2] All the ingredients were passed through a screen number 20 prior to mixing.
[3] Nizatidine-Eudragit E100 solid dispersion, Mannitol, MCC and the superdisintegrant were properly mixed for 30 min in a suitable container to obtain a uniform blend. The blend was further lubricated with magnesium stearate for 5 minutes.
[4] The blend was compressed into tablets with an average weight of 500 mg using a 14 mm flat punch in a rotary tablet press.

Table 1 (a): Formulation of FDTs containing Nizatidine-Eudragit e100 solid dispersions

Sl. No.	Ingredients	Formulations (Quantity per tablet)											
		1		2		3		10		11		12	
		mg	%	mg	%	mg	%	mg	%	mg	%	mg	%
1	Nizatidine-Eudragit E100 Complex*	375	75	375	75	375	75	375	75	375	75	375	75
2	Mannitol	45	9	45	9	30	6	45	9	45	9	30	6
3	Microcrystalline Cellulose	45	9	25	5	15	3	45	9	25	5	15	3
4	Crospovidone	30	6	50	10	75	15	30	6	50	10	75	15
5	Magnesium stearate	5	1	5	1	5	1	5	1	5	1	5	1

* Spray dried complex in ratio 1:4 contain 75mg of Nizatidine and 300mg of Eudragit E100

Table 1(b): Formulation of FDTs containing Nizatidine-Eudragit e100 solid dispersions

Sl. No.	Ingredients	Formulations (Quantity per tablet)											
		4		5		6		13		14		15	
		mg	%	mg	%	mg	%	mg	%	mg	%	mg	%
1	Nizatidine-Eudragit E100 Complex*	375	75	375	75	375	75	375	75	375	75	375	75
2	Mannitol	45	9	45	9	30	6	45	9	45	9	30	6
3	Microcrystalline Cellulose	45	9	25	5	15	3	45	9	25	5	15	3
4	Croscarmellose sodium	30	6	50	10	75	15	30	6	50	10	75	15
5	Magnesium stearate	5	1	5	1	5	1	5	1	5	1	5	1

* Spray dried complex in ratio 1:4 contain 75mg of Nizatidine and 300mg of Eudragit E100

Table 1(c): Formulation of FDTs containing Nizatidine-Eudragit e100 solid dispersions

Sl. No.	Ingredients	Formulations (Quantity per tablet)											
		7		8		9		16		17		18	
		mg	%	mg	%	mg	%	mg	%	mg	%	mg	%
1	Nizatidine-Eudragit E100 Complex*	375	75	375	75	375	75	375	75	375	75	375	75
2	Mannitol	45	9	45	9	30	6	45	9	45	9	30	6
3	Microcrystalline Cellulose	45	9	25	5	15	3	45	9	25	5	15	3
4	Soy polysaccharide	30	6	50	10	75	15	30	6	50	10	75	15
5	Magnesium stearate	5	1	5	1	5	1	5	1	5	1	5	1

* Spray dried complex in ratio 1:4 contain 75mg of Nizatidine and 300mg of Eudragit E100

F. evaluation:

I. Granular properties:

1. Determination of density.
2. Percentage compressibility or Carr's index.
3. Hausner ratio.
4. Angle of repose.

1. Determination of density:[17,18]

A simple test was used to evaluate the flow ability of a powder by comparing the poured density (ρ_{Bmin}) and tapped density (ρ_{Bmax}) of a powder and the rate at which it packs down. Tapped density was determined by taking 20 g of the granules in 50 ml measuring cylinder and tapping it to a constant volume in a bulk density apparatus.

2. Percentage compressibility or Carr's index: [17, 18]

Based on the poured density and tapped density, the % compressibility of the granules was computed using the Carr's index:

$$Carr's\ index\ (\%) = \frac{Tapped\ density - poured\ density}{Tapped\ density} \times 100 \quad \ldots Eq\ (1)$$

Table 2: Carr's Index as an indication of powder flow

CARR'S INDEX (%)	TYPE OF FLOW
5-15	Excellent
12-16	Good
18-21	Fair to passable*
23-35	Poor
33-38	Very poor
>40	Extremely poor

*May be improved by glidant.

3. Hausner ratio: [17, 18]

Hausner ratio was calculated using the formula:

$$Hausner\ ratio = \frac{Poured\ density}{Tapped\ density} \quad \ldots Eq\ (2)$$

Table 3: Hausner ratio as an indication of powder flow

HAUSNER RATIO	TYPE OF FLOW
Less than 1.25	Good flow
Greater than 1.25	Poor flow
Between 1.25-1.5	Addition of glidant normally improves the flow

4. Angle of repose: [17, 18]

Angle of repose of the granules was determined by height and cone method.

A funnel was fixed to a desired height and granules were filled in it. They were allowed to flow down on a graph paper fixed on a horizontal surface. The angle of repose was calculated using the formula:

$$Tan\ \theta = \frac{2\ h}{D} \quad \ldots Eq\ (3)$$

Where h and D are height and diameter of the pile respectively

Table 4: Angle of repose as an indication of powder flow properties

ANGLE OF REPOSE (DEGREES)	TYPE OF FLOW
< 20	Excellent
20-30	Good
30-34	Passable*
> 40	Very poor

*May be improved by glidant.

II. Tablet properties:

The prepared tablets were evaluated for,

1. Thickness.
2. Hardness.
3. Friability.
4. Weight variation.
5. Disintegration test.
6. Wetting time.
7. Drug content.
8. *In-vitro* dissolution studies.

1. Thickness: [18]

Six tablets were randomly selected and the thickness of each was measured by digital Vernier caliper. Mean and standard deviation were computed and reported.

2. Hardness: [18]

The hardness of ten tablets was measured using Monsanto Hardness tester. Mean and standard deviation were computed and reported. It is expressed in kg/cm^2.

3. Friability: [18]

The friability of the tablets was determined using Roche friabilator. Ten tablets were initially weighed and transferred into the friabilator. The friabilator was operated at 25 rpm for 4 min. After 4 min the tablets were weighed again. The % friability was then calculated using the formula:

$$\%\ Friability = \frac{Initial\ weight - final\ weight}{initial\ weight} \times 100 \quad \ldots Eq\ (4)$$

4. Weight variation: [18]
Twenty tablets were individually weighed and average weight was calculated. The individual weight was compared to the average weight. The tablets pass the test if not more than two tablets are outside the percentage limit and if no tablet differs by more than two times the percentage the percentage limit. The weight variation tolerance for uncoated tablets is as follows:

Table 5: Values of weight variation and comments

Average weight of tablets (mg)	Maximum percentage difference allowed
130 or less	10
130-324	7.5
More than 324	5

5. Disintegration test:[18]
The disintegration test was carried out using USP Disintegration Test Apparatus type-II. Six tablets were placed individually in each tube of disintegration test apparatus and discs were placed over each tablet. Distilled water was used as the medium maintained at 37°C ± 0.5°C and the time taken for each tablet to disintegrate completely was recorded.

6. Wetting time: [18]
Wetting time of dosage form is related with the contact angle. Wetting time of the FDTs is another important parameter, which needs to be assessed to give an insight into the disintegration properties of the tablet. Lower wetting time implies a quicker disintegration of the tablet. The wetting time of the tablets was measured using a simple procedure. Five circular tissue papers of 10 cm diameter were placed in a petridish with a 10 cm diameter. Ten milliliters of water-soluble dye solution was added to Petri dish. A tablet was carefully placed on the surface of the tissue paper. The time required.

7. Drug content uniformity: [18]
Ten tablets were randomly selected and allowed to equilibrate with gastric simulated fluid (without enzyme) overnight and the solution was filtered (0.22µ, Millipore) after 24 hours. Suitable dilutions were made with the same to get the concentration in Beer's range. Absorbance of the solution was noted at 314 nm using gastric simulated fluid as blank and drug content per tablet was calculated.

8. *In-vitro* dissolution study: [16, 18]
Dissolution study was carried out using USP XXII dissolution test apparatus type II. The dissolution medium used was 900 ml of gastric simulated fluid (without enzyme) which was maintained at 37°C. The paddle speed was kept at 50 rpm throughout the study. Two ml of samples was withdrawn at every 10 minutes interval and diluted to 10 ml then 1 ml of fresh dissolution media maintained at the same temperature was replaced. The samples were analyzed spectrophotometrically at 314nm using gastric simulated fluid (without enzyme) as blank.

RESULT AND DISCUSSION

1. UV scanning: When Nizatidine was scanned in the wavelength region of 250- 350 nm, peak was observed at 314 nm.

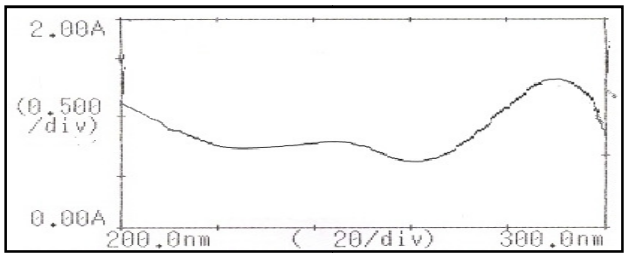

Figure 3: UV Spectrum of Nizatidine in gastric simulated fluid.

2. Calibration curve of Nizatidine:
The calibration curve for Nizatidine in gastric simulated fluid was found to be linear with R^2 value 0.99

Table 6: Data for calibration curve of Nizatidine in Gastric simulated fluid.

Concentration in µg/ml	Absorbance at 314 nm*	Standard deviation
0	0	0
5	0.25	0.003
10	0.493	0.002
15	0.75	0.007
20	0.98	0.013
25	1.244	0.011
30	1.464	0.009

*Average of three reading

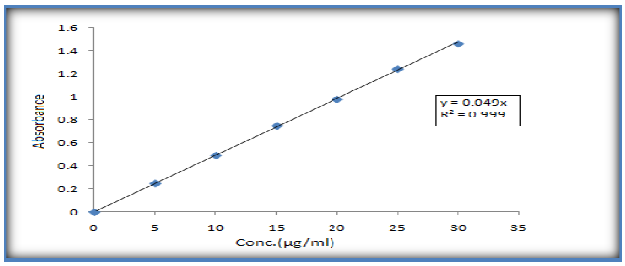

Figure 4: Calibration curve of Nizatidine

B. Drug excipient interaction study:

The infrared spectra of Nizatidine, solid dispersion of Nizatidine-Eudragit E100 and other excipients were recorded using a FTIR spectrophotometer to check for possible drug-excipients interaction. Distinct peak in the region 3000-2850cm^{-1} for C-H aliphatic, 1350-1000cm^{-1} for C-N amine and 3500-3100cm^{-1} for 2^0 amine and 1550 cm-1 and 1350 cm^{-1} for the Nitro group of the physical mixture was identical to that of pure drug which confirm the compatibility of the drug and excipient.

C. Characterization of Nizatidine-Eudragit E100 Complexes:

1. Infrared spectroscopy:

The IR spectra of pure Nizatidine, Eudragit E100, Nizatidine-Eudragit E100 complex prepared by solvent evaporation method (1:4 M ratio) and spray drying method(1:4 M ratio) were recorded using FTIR, and are shown in figure 6(a), 6(b), 6(c) and 6(d) respectively. Distinct peak in the region 3000-2850cm^{-1} for C-H aliphatic, 1350-1000cm^{-1} for C-N amine and 3500-3100cm^{-1} for 2^0 amine and 1550 cm-1 and 1350 cm^{-1} for the Nitro group of the drug complexes was identical to that of pure drug which confirm the compatibility of the drug and polymer.

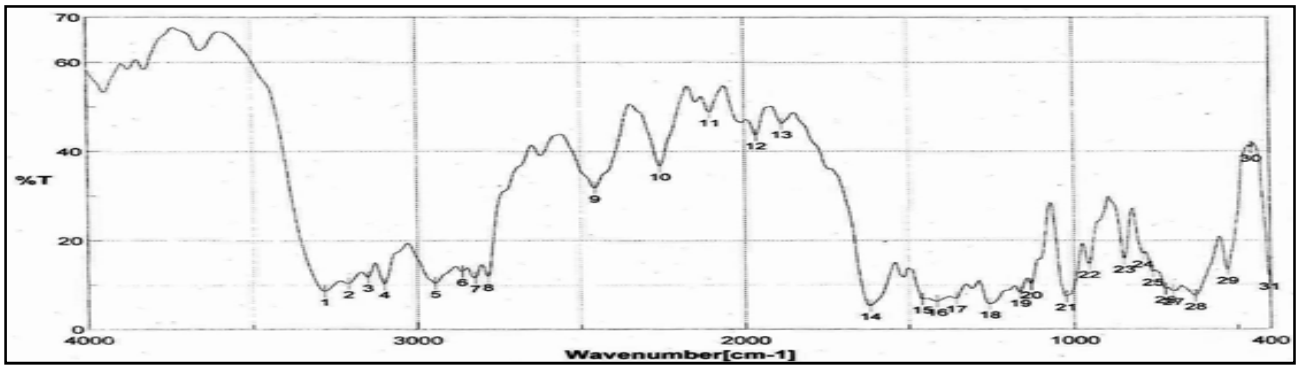

Figure 5(a): IR Spectra of Nizatidine

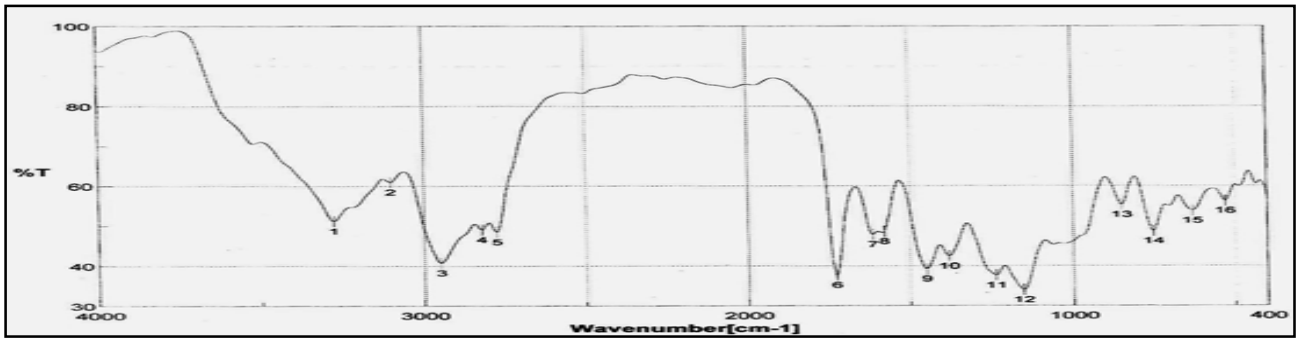

Figure 5(b): IR Spectra of Nizatidine with tablet excipients.

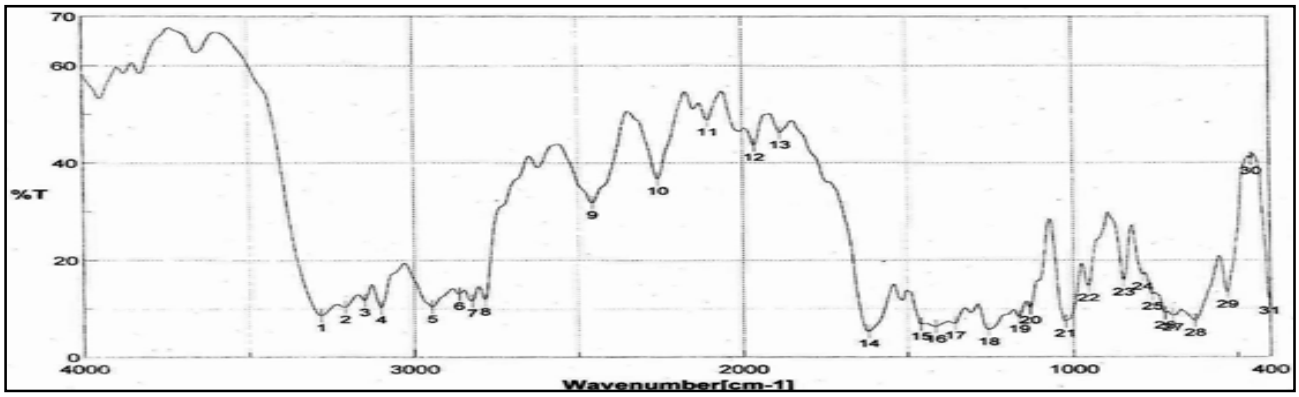

Figure 6(a): IR Spectra of Nizatidine

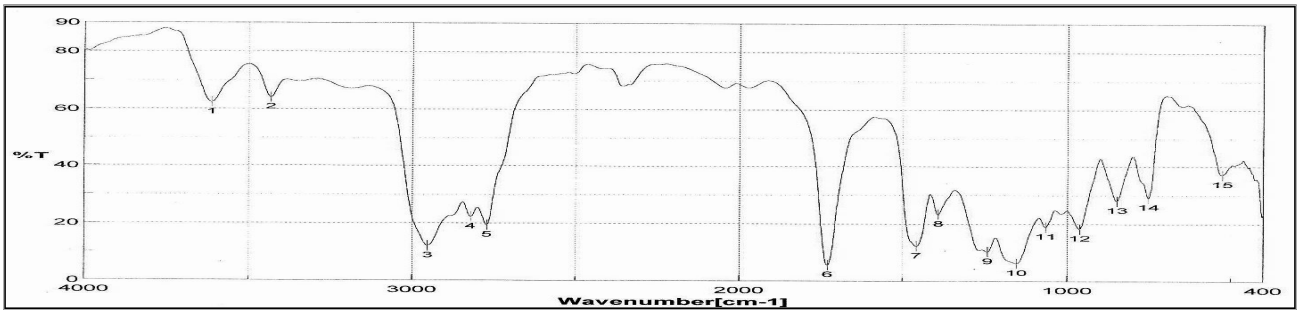

Figure 6(b): IR Spectra of Eudragit E100

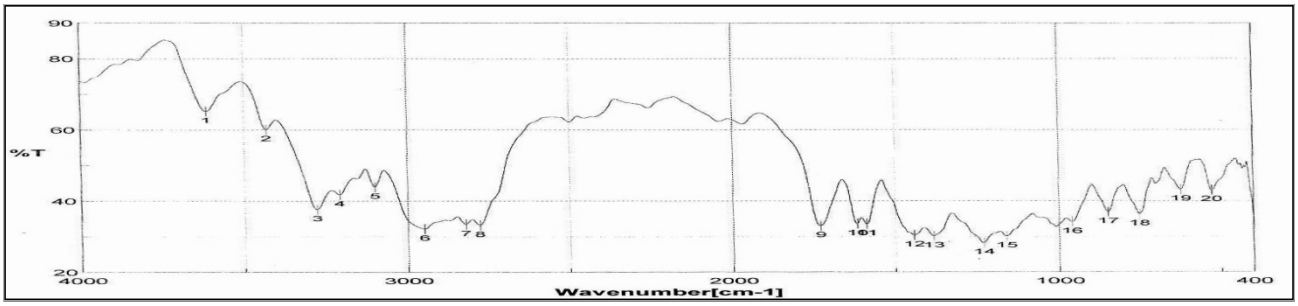

Figure 6(c): IR Spectra of Nizatidine-Eudragit E100 Solid dispersion(Solvent evaporation method)

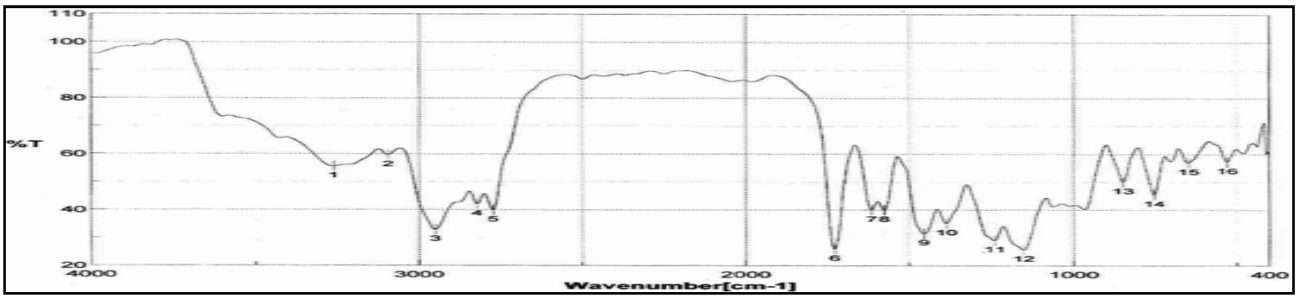

Figure 6(d): IR Spectra of Nizatidine-Eudragit E100 Solid dispersion (Spray drying method)

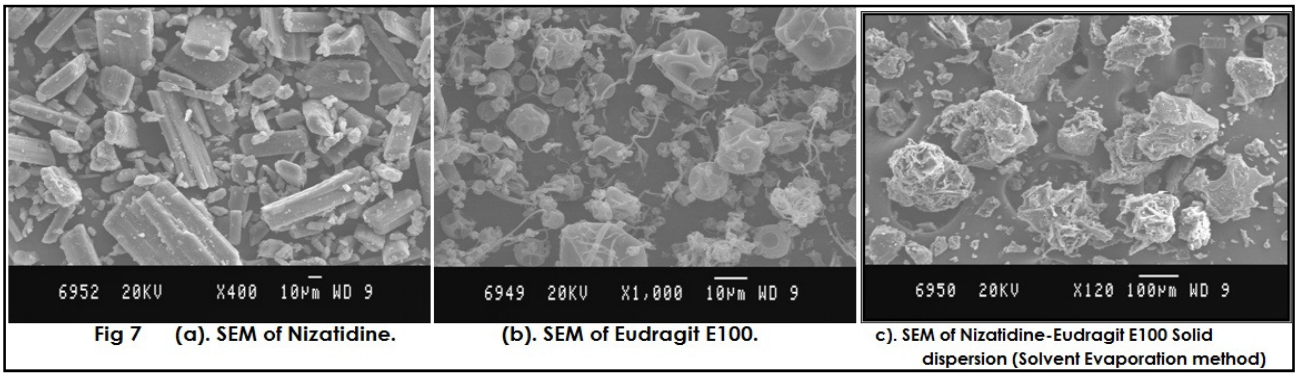

Figure 7: Scanning electron microscopy (SEM)

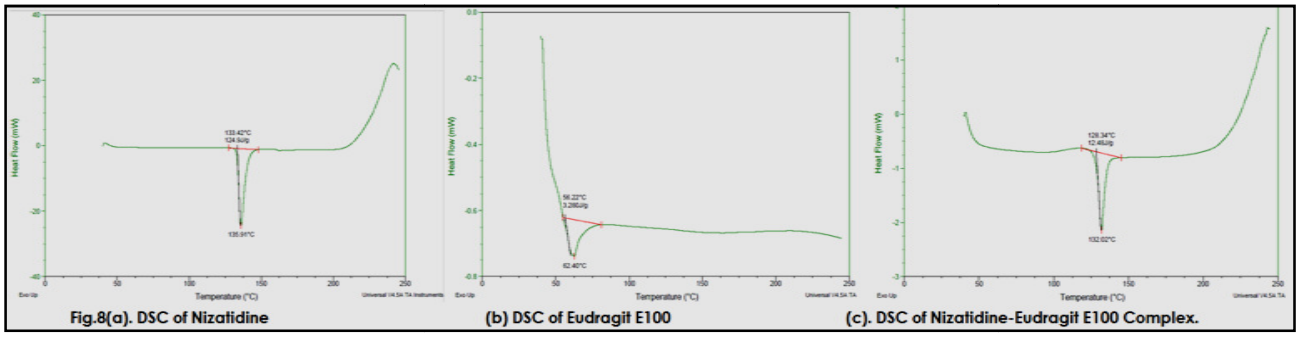

Figure 8: Differential scanning calorimetry (DSC)

Table 7(a): Results of granular properties of formulations (F1-F18).

Formulation	Poured Density* (gm/ml³)	Tapped density* (gm/ml³)	Carr's index (%)	Hausner ratio (%)
F1	0.539	0.668	19.3	1.24
F2	0.585	0.675	13.33	1.22
F3	0.537	0.662	18.88	1.23
F4	0.541	0.668	19.01	1.24
F5	0.539	0.663	18.70	1.23
F6	0.521	0.645	19.22	1.24
F7	0.537	0.660	18.63	1.23
F8	0.518	0.645	19.69	1.24
F9	0.535	0.660	18.94	1.23
F10	0.532	0.663	19.76	1.25
F11	0.530	0.653	18.84	1.23
F12	0.542	0.675	19.70	1.24
F13	0.538	0.658	18.24	1.22
F14	0.525	0.651	19.35	1.24
F15	0.523	0.652	19.78	1.25
F16	0.522	0.655	20.30	1.25
F17	0.518	0.641	19.19	1.24
F18	0.533	0.668	20.21	1.25

* The values represents mean, n = 3

Table 8(a): Results of tablet properties of formulations (F1-F18)

Formulation	Thickness[A] (mm)	Hardness[B] Kg/cm²)	Friability (%)	Disintegration time[C] (sec)
F1	4.10±0.07	3.17±0.30	0.44	15.40±0.469
F2	4.11±0.05	3.12±0.34	0.63	12.27±0.782
F3	4.11±0.07	3.53±0.25	0.75	8.40±0.369
F4	4.10±0.03	3.14±0.20	0.32	17.52±0.469
F5	4.10±0.06	3.23±0.15	0.42	13.85±0.813
F6	4.10±0.04	3.36±0.12	0.54	10.91±0.671
F7	4.11±0.07	3.23±0.27	0.73	29.66±0.125
F8	4.11±0.06	3.26±0.19	0.66	25.96±0.0145
F9	4.11±0.08	3.45±0.22	0.51	23.67±0.160
F10	4.12±0.04	3.13±0.29	0.83	75.32±0.258
F11	4.12±0.05	3.10±0.23	0.48	53.12±0.215
F12	4.11±0.03	3.58±0.25	0.72	37.76±0.189
F13	4.12±0.04	3.11±0.26	0.62	85.35±0.956
F14	4.11±0.05	3.21±0.18	0.83	61.46±0.483
F15	4.12±0.01	4.00±0.13	0.6	42.25±0.146
F16	4.12±0.02	3.14±0.17	0.4	87.13±0.364
F17	4.11±0.06	3.67±0.14	0.5	65.40±0.469
F18	4.12±0.07	3.76±0.24	0.3	44.37±0.782

A-Average of 6 readings ± SD, B- Average of 10 readings ± SD, C- Average of 6 readings ± SD.

Table 8(b): Results of tablet properties of formulations (F1-F18)

Formulation	Wt. variation	Wetting time* (sec)	Drug content uniformity*
F1	PASS	12.88±2.045	74.50±0.008
F2	PASS	10.55±1.002	74.38±0.015
F3	PASS	6.79±1.712	74.60±0.007
F4	PASS	13.69±0.560	75.00±0.041
F5	PASS	11.17±0.850	74.80±0.006
F6	PASS	22.66±0.995	74.93±0.020
F7	PASS	21.42±1.100	74.63±0.014
F8	PASS	22.28±1.564	75.05±0.005
F9	PASS	21.87±1.014	75.20±0.011
F10	PASS	27.74±1.001	76.00±0.008
F11	PASS	29.88±2.045	74.59±0.009
F12	PASS	30.55±1.563	75.03±0.023
F13	PASS	32.23±1.462	75.00±0.014
F14	PASS	29.12±1.025	52.05±0.025
F15	PASS	27.84±1.456	48.30±0.012
F16	PASS	32.46±2.488	50.02±0.004
F17	PASS	30.00±1.123	49.00±0.035
F18	PASS	29.36±1.745	48.85±0.023

* The values represents mean±SD, n = 3

Table 12(a): *In-vitro* dissolution data of F1, F2 and F3.

Time (min)	% CDR*		
	F1	**F2**	**F3**
0	0.00±0.00	0.00±0.00	0.00±0.00
5	42.12±0.75	43.59±0.86	47.73±1.21
10	62.56±0.34	63.3±0.32	68.69±0.65
15	69.98±0.54	71.95±1.6	79.07±0.87
20	76.19±1.21	78.16±0.65	88.22±.53
25	84.860.45	87.32±1.97	92.98±0.23
30	91.57±0.46	87.32±1.1	97.496±1.53
45	95.84±0.67	94.87±0.98	98.1±1.5
60	97.42±0.65	96.2±0.75	98.42±1.53

* The values represents mean±SD, n = 3

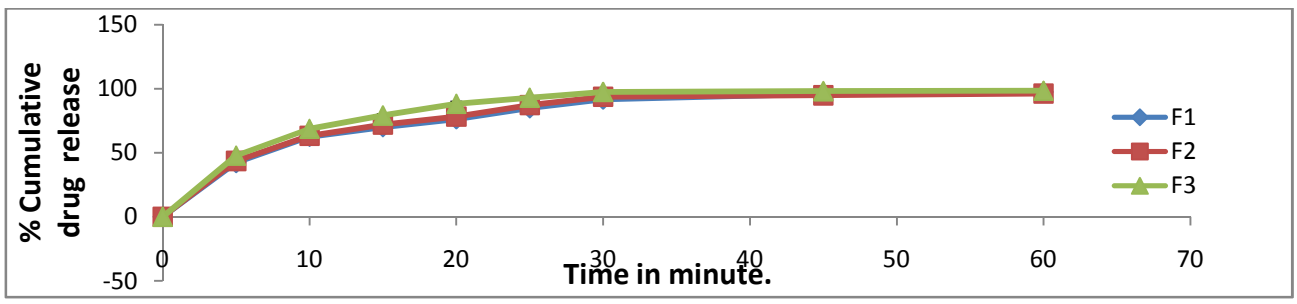

Figure 12(a): *In-vitro* dissolution profile of F1, F2 and F3.

Table 12(b): *In-vitro* dissolution data of F10, F11 and F12.

Time (min)	% CDR*		
	F10	F11	F12
0	0.00±0.00	0.00±0.00	0.00±0.00
5	46.53±0.85	45.3±0.45	39.18±1.32
10	67.47±1.11	66.24±0.9	51.51±0.74
15	78.09±0.98	78.08±1.56	66.290.94
20	87.24±0.89	84.77±0.94	83.531.98
25	91.51±1.49	89.29±0.84	95.54±0.64
30	96.02±0.98	94.04±0.92	97.51±1.39
45	96.6±1.4	96.36±1.46	97.52±0.33
60	97.71±1.23	97.93±0.65	98.66±0.42

* The values represents mean ±SD, n = 3

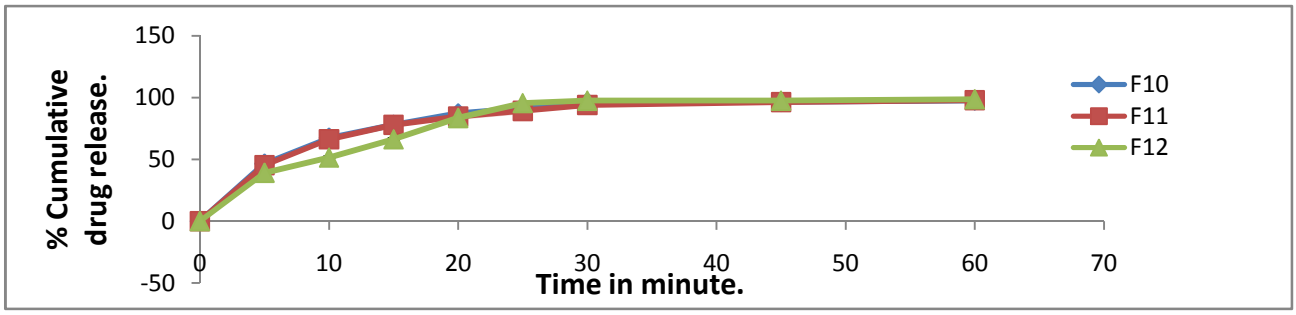

Figure 12(b): *In-vitro* dissolution profiles of F10, F11 and F12.

Table 13(a): Dissolution treatment of data with zero and first order kinetics

Formulation	Zero order		First order	
	R	Slope	R	Slope
F1	0.8169	1.3074	-0.9782	-0.0223
F2	0.7940	1.2720	-0.9439	-0.0198
F3	0.7532	1.2539	-0.9288	-0.0242
F10	0.7571	1.2468	-0.9314	-0.0217
F11	0.7707	1.2579	-0.9603	-0.0221
F12	0.8135	1.4289	-0.9162	-0.0279

Table 13(b). Dissolution treatment of data with Higuchi's matrix and Korsmeyer peppas kinetics

Formulation	Matrix		Korsmeyer Peppas			
	R	Slope	R	Slope	n	k
F1	0.9559	12.6617	0.9681	0.3427	0.3427	26.2901
F2	0.9438	12.5128	0.9579	0.3265	0.3265	28.062
F3	0.9214	12.6938	0.9353	0.2951	0.2951	33.0700
F10	0.9235	12.5855	0.9358	0.3006	0.3006	32.0285
F11	0.9315	12.5811	0.9434	0.3093	0.3093	30.7284
F12	0.9441	13.7236	0.9439	0.4183	0.4183	20.9142

D. Granular Properties:

Poured density, tapped density, Carr's index, Hausner ratio and angle of repose of formulation F1 to F18 are shown in Table 7(a) and Table 7(b).

Table 7(b): Results of granular properties of formulations (F1-F18).

Sl. No.	Formulation	Angle of repose* (degree)
1.	F1	25° 16'
2.	F2	23° 54'
3.	F3	24° 70'
4.	F4	26° 59'
5.	F5	24° 89'
6.	F6	22° 65'
7.	F7	23° 73'
8.	F8	28° 20'
9.	F9	28°39'
10.	F10	27°31'
11.	F11	26°28'
12.	F12	29°66'
13.	F13	27°48'
14.	F14	21°40'
15.	F15	24°12'
16.	F16	25°35'
17.	F17	27°08'
18.	F18	28°33'

*The values represents mean, n=3

Table 9(a): Effects of 15 % Superdisintegrant on Disintegration time (F3, F6 and F9).

Formulation	Superdisintegrant & its concentration	Disintegration time*(SEC)
F3	15% CRP	8.40±0.369
F6	15% CCS	10.91±0.671
F9	15% SYP	23.67±0.160

E. Tablet properties:

The values of thickness, hardness, friability, disintegration time, weight variation and drug content uniformity of all the formulations are shown in Table 8(a) and Table 8(b).

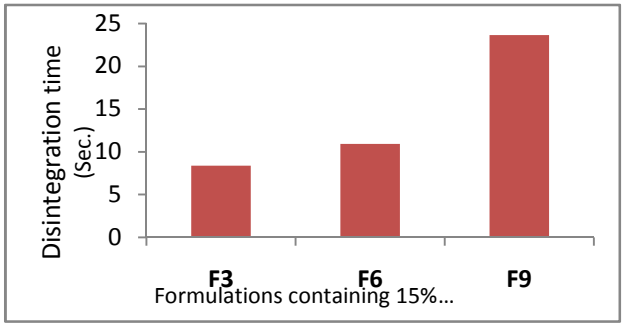

Figure 9(a): Comparative graph showing effects of 15% Superdisintegrants on disintegration time (F3, F6 and F9).

Table 9(b): Effects of 15% Superdisintegrants on Disintegration time (F12, F15 and F18).

Formulation	Superdisintegrant & its concentration	Disintegration time* (sec)
F12	15% CRP	37.76±0.189
F15	15% CCS	42.25±0.146
F18	15% SYP	44.37±0.782

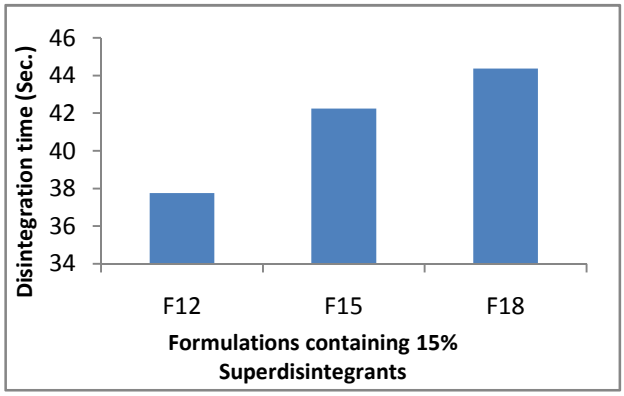

Figure 9(b): Comparative graph showing effects of 15% Superdisintegrants on disintegration time (F12, F15 and F18).

Table 10: Effects of Crospovidone on disintegration time of formulations (F1, F2, F3, F10, F11 and F12)

Sl. No	% CRP	Disintegration time*(sec)
F1	6	15.40±0.469
F2	10	12.27±0.782
F3	15	8.40±0.369
F10	6	75.32±0.258
F11	10	53.12±0.215
F12	15	37.76±0.189

* The values represents mean ±SD, n = 3

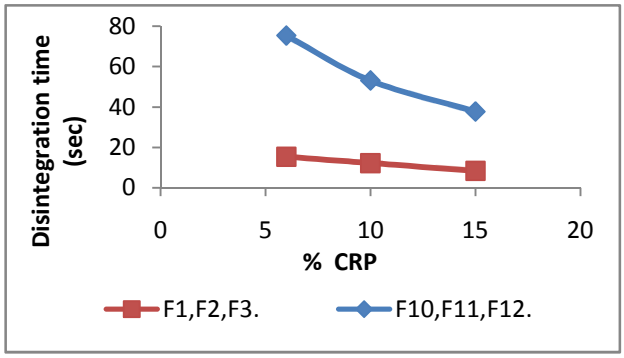

Figure 10: Graph showing effect of CRP on disintegration time (F1, F2, F3, F10, F11 and F12).

Table 11: Comparison of effect of 15% Crospovidone on Disintegration time (F3 and F18)

Formulation	Superdisintegrant & its concentration	Disintegration time* (sec)
F3	15% CRP	8.40±0.369
F12	15% CRP	37.76±0.189

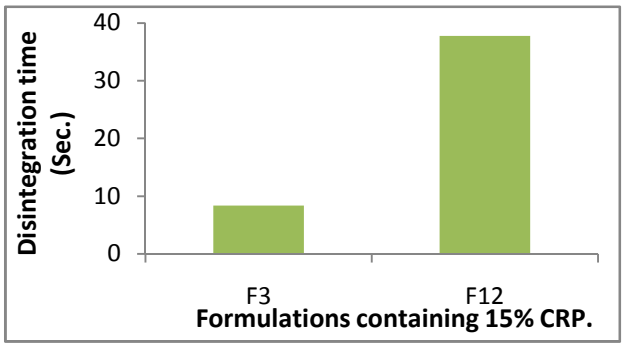

Figure 11: Graph showing effects of 15% Crospovidone on disintegration time (F3 and F12).

9. *In-vitro* dissolution study:

In-vitro dissolution data of the tablet formulations (F1, F2, F3 and F10, F11, F12) are shown in table 10(a) and 10(b). *In-vitro* dissolution profiles are represented in fig 10 (a) and 10 (b) respectively.

CONCLUSION

Nizatidine is a H_2 receptor antagonist used to treat gastric and duodenal ulcers and gastroesophogeal reflux disease. Nizatidine was complexed with Eudragit E100 to mask the bitter taste of the drug. The complexes were prepared by solvent evaporation and spray drying technique and were characterized by IR, SEM and DSC.The complexes (1:4) so prepared were further used in the preparation of fast dissolving tablets. Tablets were prepared by direct compression method using three different superdisintegrants. Desired results (less than 10sec) were achieved with the formulations containing the Nizatidine-Eudragit E100 complex which was prepared by solvent evaporation method and containing 15% CRP.It can thus be concluded that FDTs containing Nizatidine-Eudragit E100 complex with less disintegration time can be prepared by direct compression method using CRP in concentration of 15%.

Formulations needs to be further evaluated for physical and chemical stability under accelerated conditions and on storage at room temperature. However stability studies could not be performed in the present work due to time constraints.

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