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FORMULATION AND EVALUATION OF NIZATIDINE FAST DISSOLVING TABLETS.

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ABSTRACT

Nizatidine is a H_2 receptor antagonist used to treat gastric and duodenal ulcers and gastroesophogeal reflux disease. Fast dissolving tablets of Nizatidine offer the advantage of convenience of administration during travelling and patient compliance. The present study aims to formulate and evaluate fast dissolving tablets (FDT's) of Nizatidine with acceptable taste and minimum disintegration time. The solid dispersions of drug with Eudragit E100 which has both taste masking and super disintegrant properties were prepared by solvent evaporation method and spray drying method. The drug, polymers and physical mixtures are subjected for compatibility studies using FTIR and DSC studies. Fast dissolving tablets were prepared by direct compression method using prepared solid dispersions and superdisintegrants Crospovidone, Croscarmellose sodium and Soy polysaccharide in various concentrations (6%, 10% and 15%). The tablets were evaluated for hardness, wetting time, friability, disintegration time and in-vitro dissolution. The disintegration time and wetting time of the prepared tablets was found to be in the range 8.40±0.369 to 87.13±0.364sec and 6.79±1.712 to 32.46±2.488 sec. respectively. The dissolution release rates after 10min.were found to be in the range 31.51±0.74 to 68.69±0.65 for all the formulations. The formulation containing solid dispersion of drug prepared by solvent evaporation and 15% polyplasdone was found to give the best results with disintegration time of 8.40±0.369 sec.

KEYWORDS: Nizatidine; Fast dissolving tablets; Eudragit E100; Solvent evaporation; Spray drying; Superdisintegrants.

INTRODUCTION

The enhancement of the solubility and bioavailability of weakly water soluble drugs remains one of the most challenging aspects of drugs development. Weakly water soluble drugs often require high doses in order to reach therapeutic plasma concentration often oral administration. Improvement in the extent and rate of dissolution is highly desirable for such compounds, as this can lead to an increased and more reproducible oral bioavailability and subsequently to clinically relevant dose reduction and more reliable therapy. Numerous works have been carried out in order to modify the dissolution kinetics of poorly soluble drugs to improve their bioavailability. Bioavailability can be defined as rate and extent at which the drug is delivered to the systemic circulation from dosage form and reaches the site of action to produce the desired effect.[1] Hence drugs whose aqueous solubility is less will definitely create bioavailability problem and thereby effecting therapeutic efficiency, once we are able to increase the aqueous solubility of the drug the disintegration and dissolution properties can be easily altered, as a result an increase in bioavailability can be easily achieved.[2]

Methods to increase aqueous solubility of a drug or salt formation, solubilisation, particle size reduction, complexation, solvent evaporation, solid solution and solvent formation.[3] They have been commonly used to increase dissolution rate and there by oral absorption and bioavailability of such drugs, but there are practical limitations to these techniques.[4] Practical methods where by many of the limitations with the bioavailability enhancement of poorly water soluble drugs just mentioned can be overcome by the solid dispersion technique.[5]

Solid dispersion are defined as dispersion of one or more active ingredients in an inert carrier matrix at solid-state prepared by the melting (fusion), solvent or melting- solvent method. Several insoluble drugs have been shown to improve their dissolution character when incorporated into solid dispersion. Solid dispersion technique has been widely employed to improve the dissolution rate, solubility and oral adsorption of poorly water soluble drugs. Experience with solid dispersions over the last 20-30 years indicates that this is a very fruitful approach to improving the solubility, dissolution rates and consequently the bioavailability of poorly soluble drugs.[6] A number of insoluble drugs have shown to improve their dissolution character when converted to solid dispersion. Solid dispersion is used to produce a homogeneous distribution of a small amount of drug in solid state.[7]

The concept of SDs was introduced in 1961 by Sekiguchi and Obi in which the drug is dispersed in inert water soluble carrier at solid state. Solid dispersion technology is a well-known process used to increase the dissolution kinetics and oral absorption of poorly water soluble drugs using water soluble inert carriers. The use of hydrophilic polymers as carriers for the dissolution enhancement of poorly water-soluble drug is increasing. Several water soluble carriers such as mannitol, urea, lactose, citric acid, polyvinyl pyrrolidone (PVP) and polyethylene glycols (PEG) are used as carriers for SDs.

Nizatidine is a poorly water soluble Histamine H_2 receptor antagonist which inhibits gastric acid secretion. Nizatidine is rapidly absorbed after oral administration, with peak serum concentrations within 1 to 3 hours. Nizatidine inhibit acid production by reversibly competing with histamine for binding to H2 receptors on the basolateral membrane of parietal cells. Thus there is need to improve bioavailability of Nizatidine by increasing its aqueous solubility and overcoming the first pass metabolism, if it is to be delivered by oral route. This encouraged to formulate mouth dissolving tablets using solid dispersion of Nizatidine with Eudragit E100 as a carrier by solvent evaporation method, spray drying method which will improve solubility and consequent compliance and convenience.

MATERIALS AND METHODS

Nizatidine (Dr. Reddy's Laboratories Private Limited, Hyderabad), Eudragit E100(Evonik Degussa India Private Limited, Mumbai. Titan Laboratories Ltd. Mumbai), Crospovidone(Polyplasdone XL-10) (International Speciality Product, Hong kong Ltd) ,Soy polysaccharide(Emcosoy) JRS Pharma, Rosenberg (Germany), Croscarmellose Sodium (The Anglo French Drug Co. Ltd, Bangalore), Microcrystalline Cellulose(The Anglo French Drug Co. Ltd, Bangalore) ,Mannitol, Lactose , Magnesium stearate , Ethanol, Methanol ,Petroleum ether (s.d fine chemicals Ltd., Mumbai).

Preparation of solid dispersion

The Drug-Eudragit E100 complexes were prepared by two different methods i.e. Spray Drying Method and Solvent evaporation method.

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 ratio and spray dried using Labultima spray dryer model LU222 and employing following optimized parameters:

Spray concentration: 20%w/v, Inlet temperature: 50^0C, Outlet temperature 40^0C, Inlet temperature: 50^0C, Aspiration speed: 60 Feed rate: 8. The typical recovery of the spray dried product was 80-90% and product was in the form of micromatrix.[8,9]

Solvent evaporation method

Nizatidine was dissolved in a solvent blend of methanol and dichloro methane (1:4) to get a clear solution in a 100ml round bottom flask. The excipient (Eudragit 100) was then added and dispersed. The solvent from the mixture was removed by evaporation at 50ºC under pressure while mixing the contents. The mass obtained was pulverized, mixed and passed through mesh no#6. The dried mass was stored in dessicator until further use.[10]

Compatibility Studies

Infrared spectroscopy

IR spectroscopy[11, 12] is one of the important analytical techniques for characterization of compounds. The IR spectra of pure Nizatidine, Eudragit E100 and Nizatidine-Eudragit E100 physical mixture were subjected to IR studies using potassium bromide. The samples were mixed with dry potassium bromide and this mixture was taken in a diffuse refluctance sampler and IR spectra were recorded and compared.

Differential scanning calorimetry (DSC)

The samples were hermetically sealed in flat bottomed aluminum pans and heated over a temperature range of 0^0C to 250^0C at a rate of 10^0C/min using alumina as a reference standard. Thermograms of Nizatidine, Eudragit E100 and physical mixtures were recorded using a differential scanning calorimetry and were compared.[13, 14]

Formulation of tablets using Nizatidine-Eudragit Solid Dispersion Complex

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. All the ingredients were passed through a screen number 20 prior to mixing. Nizatidine-Eudragit E100 solid dispersion, Mannitol, Microcrystalline cellulose and the superdisintegrants 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. The blend was compressed into tablets using a 14 mm flat punch in a rotary tablet press. The detailed composition of tablet formulations was shown in Table 1.

Evaluation of powder mixed blend

Angle of Repose

Angle of repose is defined as the maximum angle possible between the surface of the pile of the powder and the horizontal plane. The flow characteristics of different granules were studied by measuring the angle of repose employing fixed funnel method. The angle of repose was calculated by using the following formula.[15]

$$\text{Tan}\theta = \frac{\text{Height of the pile}}{\text{radius of the base of the pile}}$$

where θ = tan-1 (h / r) θ = angle of repose.

Bulk Density & Tapped Density

Bulk density and tapped density were measured by using 10 ml of graduated cylinder. The pre weighed sample was placed in a cylinder; its initial volume was recorded (bulk volume) and subjected to tapings for 100 times. Then the final volume (tapped volume) was noted down. Bulk density and tapped density were calculated from the following formula.[15]

$$\text{Bulk Density} = \frac{\text{mass of microparticles}}{\text{bulk volume}}$$

$$\text{TappedDensity} = \frac{\text{mass of microparticles}}{\text{tappedvolume}}$$

Carr's Index

Compressibility index (CI) or Carr's index[15] value of granules was computed according to the following equation: $\text{Carr's Index (\%)} = \frac{\text{Tappeddensity - Bulk density}}{\text{Tappeddensity}} \text{X}\,100$

Hausner's Ratio

Hausner ratio[15] of powder blend was determined by comparing the tapped density to the bulk density using the equation: $\text{Hausner's Ratio} = \frac{\text{Tappeddensity}}{\text{Bulk density}}$

Evaluation of Nizatidine fast dissolving tablets

The prepared fast dissolving tablets were evaluated for hardness, friability, weight variation, thickness, disintegration time and content uniformity, wetting time.[16]

In vitro dissolution test

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. The raw dissolution data was analyzed for calculating the amount of drug released and percentage cumulative drug released at different time intervals. For finding out the mechanism of drug release from FDTs, the dissolution data obtained from the experiments were treated with the different release kinetic and mechanism equations.[17]

RESULT AND DISCUSSION

Nizatidine solid dispersions were successfully prepared by using solvent evaporation and spray drying method.

Compatibility Studies

The IR spectra of pure Nizatidine, Eudragit E100, Nizatidine-Eudragit E100 physical mixture were recorded using FTIR, and are shown in figure 4(a), 4(b), 4(c) and 4(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 confirmed the chemical integrity of drug in Eudragit E100 complex. The FTIR spectra's were shown in Figure 1.

The DSC thermogram of Nizatidine displayed the characteristic peak at 135.91^{0}C compare to its melting point 132^{0}C. Similarly the Eudragit E100 thermogram showed peak at 62.40^{0}C. The physical mixture of the drug and Eudragit E100 showed the DSC thermogram at 132.02^{0}C which reveals that drug is complexed with Eudragit E100. There is a slight shift in melting point because of moisture content. The DSC thermograms were shown in Figure 2.

FDTs containing Nizatidine-Eudragit E100 solid dispersion were prepared using different superdisintegrants such as Crospovidone, Croscarmellose sodium and Soy polysaccharide in various ratios (6-15%) by using direct compression method.

Evaluation of granular properties

The flow properties of the granules (F1-F18) were evaluated by determining the Carr's index, Hausner ratio and angle of repose. Poured density values of different batches were found to range between 0.518 and 0.585 gm/ml^3, whereas tapped density values were found to vary from 0.641 to 0.668gm/ml^3. Carr's index, Hausner ratio and angle of repose were range between 18.24 to 20.30, 1.22 to 1.25, and 21^{o}40' to 29^{o}66' respectively, which indicates that granules prepared exhibit good flow properties. The results of flow properties were shown in Table 2.

Evaluation of Nizatidine Tablets

Tablets (F1-F18) were evaluated for tablet properties like thickness, hardness, friability, disintegration time, weight variation, wetting time and drug content uniformity. The results of these studies were shown in Table 3.

Tablet thickness was found to range from 4.10±0.03 to 4.12±0.07 mm. Tablets of all the batches were found out to exhibit sufficient hardness, which ranged from 3.10±0.23 to 4.00±0.13 Kg/cm^2. Wetting time of the tablet was found to be in the range of 6.79±1.712 sec. to 32.46±2.488 sec. Friability, weight variation test and percentage drug content uniformity met the specification given in the literature. Disintegration time of these formulations was found to be in the range 8.40±0.369 to 87.13±0.364sec. Increase in the concentration of Crospovidone was found to be beneficial in reducing the disintegration time. Least disintegration time of 8.40±0.369 sec. was obtained with 15% CRP in tablets prepared using Nizatidine-Eudragit E100 complex prepared by solvent evaporation method. The probable reason for delayed disintegration time of tablet with SYP and CCS might be due to slow water uptake and more gelling tendency compared to CRP Similar results was reported in a previous work[18]. Increase in the concentration of superdisintegrants from 6% to 15%, decreases the disintegration time of the tablets. Among the three superdisintegrants used, rapid disintegration was seen in formulation containing Crospovidone. This may be due to rapid uptake of water from the medium resulting in swelling and bursting. These results clearly indicate that rapidly dissolving tablets of Nizatidine-Eudragit E100 complex can be prepared by direct compression method by incorporation of Crospovidone as a superdisintegrants. The data for effect of Crospovidone on disintegration time of formulations is shown in Table 4 and graph is shown in Figure 3.

Percentage cumulative drug release after 10min for the formulations containing

Nizatidine-Eudragit E100 complexes prepared by solvent Evaporation Method (F1, F2, F3) was found to be in the range 62.56±0.34 to 68.69±0.65 as compared to tablets containing Nizatidine-Eudragit E100 complexes prepared by spray drying method (F10, F11, F12) which exhibited % CDR in the range of 51.51±0.74 to 67.47±1.11. The dissolution profiles are shown in Figure 4 and 5. As the tablets prepared by using solid dispersion obtained from solvent evaporation method showed lesser DT compared to that prepared by using spray dried solid dispersion. Dissolution efficiency of Nizatidine tablets was achieved better by using solid dispersion of drug with Eudragit E100 by solvent evaporation method than spray drying method, thus FDTs of Nizatidine with improved taste. This is because of the burst effect of tablet. The data treatment of release profile was done Korsmeyer peppas model. The diffusion data of most forms are fitted well into Peppas release kinetics and first order release kinetics which indicates that release is due to the swelling nature of CRP. This is because of the burst effect of tablet. The data treatment of release profile was done Korsmeyer peppas model. The release kinetics data is shown in Table 5.

Table 1: Composition of Nizatidine Tablet formulations

Ingredients	Formulation Code																	
	Solvent Evaporation SD									Spray Dried SD								
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16	F17	F18
Nizatidine-Eudragit E100 Complex	375	375	375	375	375	375	375	375	375	375	375	375	375	375	375	375	375	375
Mannitol	45	45	30	45	45	30	45	45	30	45	45	30	45	45	30	45	45	30
Microcrystalline Celluose	45	25	15	45	25	15	45	25	15	45	25	15	45	25	15	45	25	15
Crospovidone	30	50	75	---	---	---	---	---	---	30	50	75	---	---	---	---	---	---
Croscarmellose sodium	---	---	---	30	50	75	---	---	---	---	---	---	30	50	75	---	---	---
Soy polysaccharide	---	---	---	---	---	---	30	50	75	---	---	---	---	---	---	30	50	75
Magnesium stearate	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5

Table 2: Flow properties of Granules

Formulation	Poured Density (gm/ml^3)	Tapped density (gm/ml^3)	Carr's index (%)	Hausner ratio (%)	Angle of Repose (degree)
F1	0.539	0.668	19.3	1.24	25^o16
F2	0.585	0.675	13.33	1.22	$23^o 54'$
F3	0.537	0.662	18.88	1.23	$24^o 70'$
F4	0.541	0.668	19.01	1.24	$26^o 59'$
F5	0.539	0.663	18.70	1.23	$24^o 89'$
F6	0.521	0.645	19.22	1.24	$22^o 65'$
F7	0.537	0.660	18.63	1.23	$23^o 73'$
F8	0.518	0.645	19.69	1.24	$28^o 20'$
F9	0.535	0.660	18.94	1.23	$28^o39'$
F10	0.532	0.663	19.76	1.25	$27^o31'$
F11	0.530	0.653	18.84	1.23	$26^o28'$
F12	0.542	0.675	19.70	1.24	$29^o66'$
F13	0.538	0.658	18.24	1.22	$27^o48'$
F14	0.525	0.651	19.35	1.24	$21^o40'$
F15	0.523	0.652	19.78	1.25	$24^o12'$
F16	0.522	0.655	20.30	1.25	$25^o35'$
F17	0.518	0.641	19.19	1.24	$27^o08'$
F18	0.533	0.668	20.21	1.25	$28^o33'$

Table 3: Evaluation details of Tablet properties

Formula Code	Friability (%)	Thickness (mm)	Hardness (Kg/cm^2)	Wetting time	Drug content uniformity ± SD	Disintegration time (sec)
F1	0.44	4.10±0.07	3.17±0.30	12.88±2.045	74.50±0.008	15.40±0.46
F2	0.63	4.11±0.05	3.12±0.34	10.55±1.002	74.38±0.015	12.27±0.78
F3	0.75	4.11±0.07	3.53±0.25	6.79±1.712	74.60±0.007	8.40±0.36
F4	0.32	4.10±0.03	3.14±0.20	13.69±0.560	75.00±0.041	17.52±0.46
F5	0.42	4.10±0.06	3.23±0.15	11.17±0.850	74.80±0.006	13.85±0.81
F6	0.54	4.10±0.04	3.36±0.12	22.66±0.995	74.93±0.020	10.91±0.67
F7	0.73	4.11±0.07	3.23±0.27	21.42±1.100	74.63±0.014	29.66±0.12
F8	0.66	4.11±0.06	3.26±0.19	22.28±1.564	75.05±0.005	25.96±0.014
F9	0.51	4.11±0.08	3.45±0.22	21.87±1.014	75.20±0.011	23.67±0.16
F10	0.83	4.12±0.04	3.13±0.29	27.74±1.001	76.00±0.008	75.32±0.25
F11	0.48	4.12±0.05	3.10±0.23	29.88±2.045	74.59±0.009	53.12±0.21
F12	0.72	4.11±0.03	3.58±0.25	30.55±1.563	75.03±0.023	37.76±0.18
F13	0.62	4.12±0.04	3.11±0.26	32.23±1.462	75.00±0.014	85.35±0.95
F14	0.83	4.11±0.05	3.21±0.18	29.12±1.025	52.05±0.025	61.46±0.48
F15	0.6	4.12±0.01	4.00±0.13	27.84±1.456	48.30±0.012	42.25±0.14
F16	0.4	4.12±0.02	3.14±0.17	32.46±2.488	50.02±0.004	87.13±0.36
F17	0.5	4.11±0.06	3.67±0.14	30.00±1.123	49.00±0.035	65.40±0.46
F18	0.3	4.12±0.07	3.76±0.24	29.36±1.745	48.85±0.023	44.37±0.78

Table 4: Effect of Crospovidone on disintegration time of formulations

Formulation	% 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

Table 5: Release Kinetics of Nizatidine formulations

Formulation Code	Correlation Coefficient Values (R^2)				N value
	Zero Order	First Order	Higuchi Model	Peppas Model	
F 1	0.8169	-0.9782	0.9559	0.9681	0.3427
F 2	0.7940	-0.9439	0.9438	0.9579	0.3265
F 3	0.7532	-0.9288	0.9214	0.9353	0.2951
F 10	0.7571	-0.9314	0.9235	0.9358	0.3006
F 11	0.7707	-0.9603	0.9315	0.9434	0.3093
F 12	0.8135	-0.9603	0.9441	0.9439	0.4183

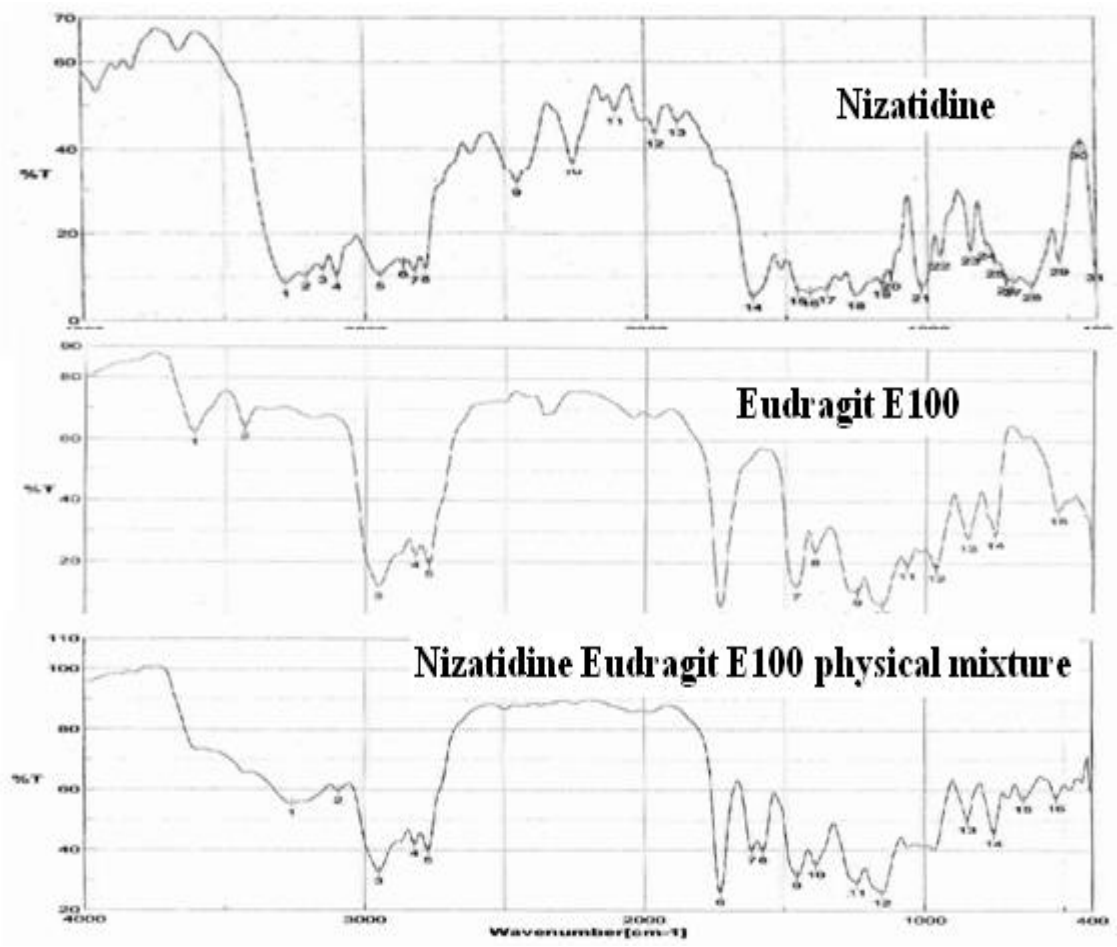

Figure 1: FTIR Spectra of Drug, polymer and physical mixture

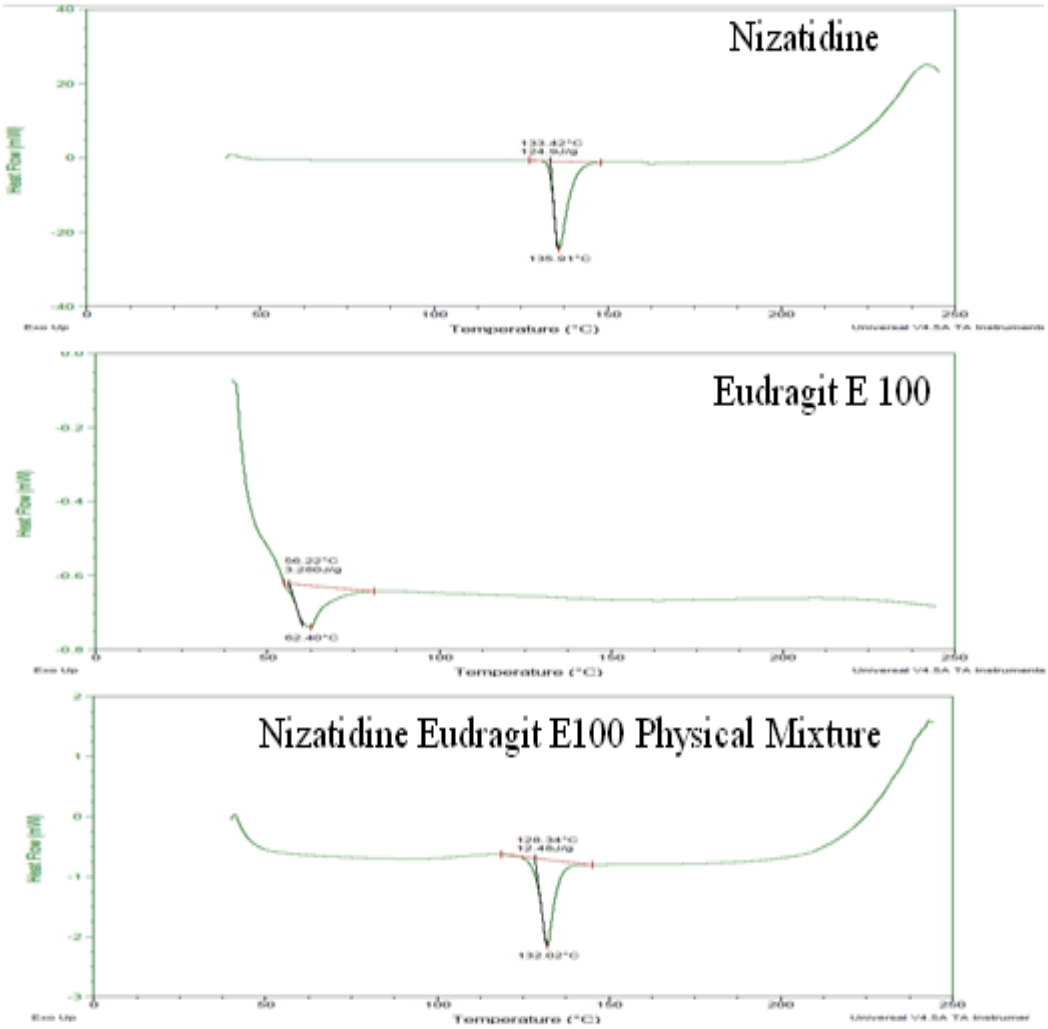

Figure 2: DSC thermograms of drug, polymer and physical mixture

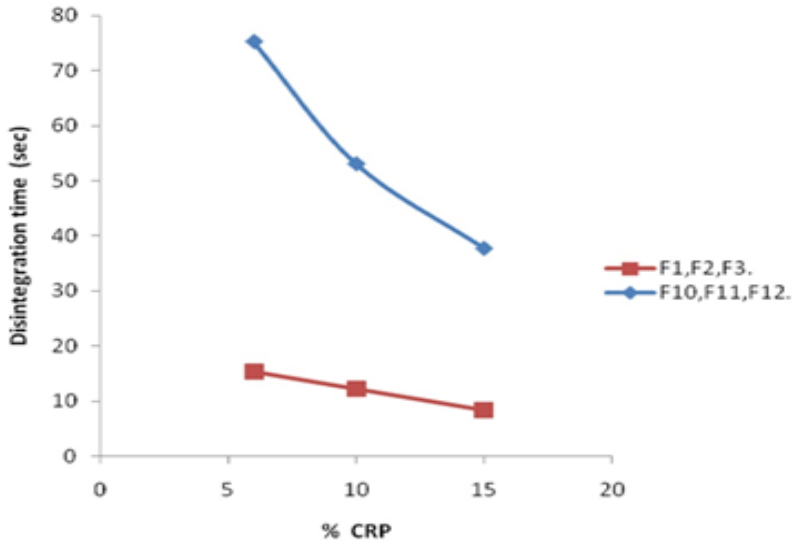

Figure 3: Graph showing effect of CRP on disintegration time

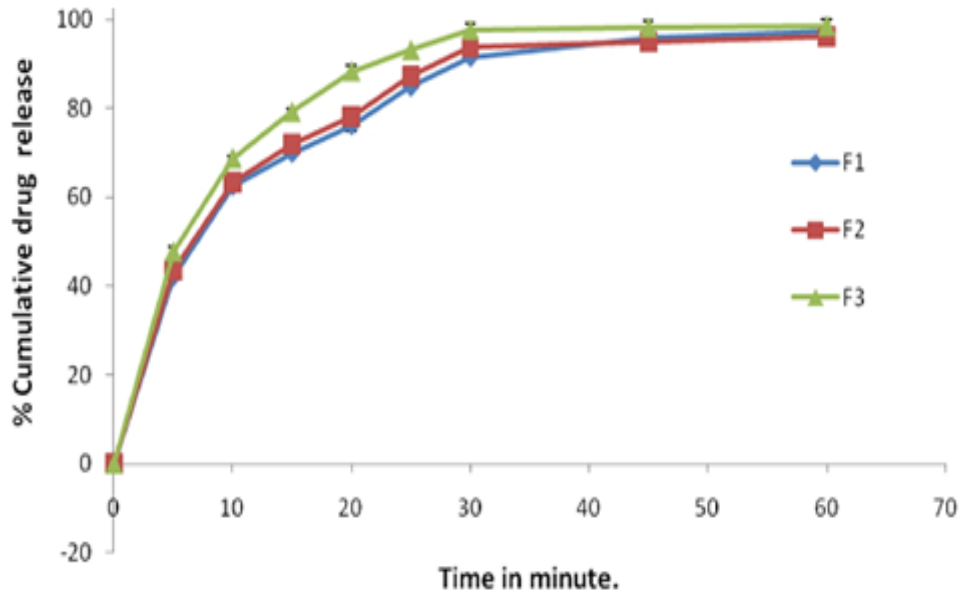

Figure 4: In-vitro dissolution profile of F1, F2and F3.

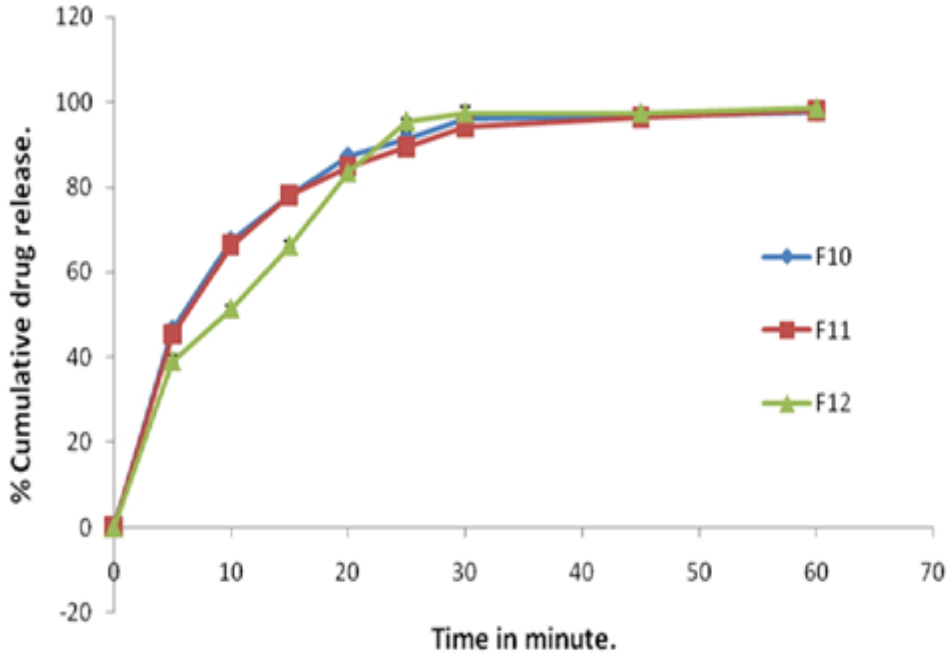

Figure 5: In-vitro dissolution profiles of F10, F11 and F12.

CONCLUSION

Nizatidine is a H_2 receptor antagonist used to treat gastric and duodenal ulcers and gastroesophogeal reflux disease. The Complexes of Nizatidine-Eudragit E100 (1:4) were prepared by two different methods i.e. solvent evaporation method and spray drying method. The pure drug, polymer and physical mixtures are subjected to compatibility studies

and these studies revealed that there is no interaction between the drug and polymers. 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 FDT with less disintegration time can be prepared by direct compression method using CRP in concentration of 15% and Nizatidine-Eudragit E100 complex (1:4).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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