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Formulation and evaluation of fast dissolving Tablets of nizatidine

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A B S T R A C T

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 Nizatidine with acceptable taste and minimum disintegration time. The solid dispersions of drug with Eudragit E100 which has both taste masking and superdisintegrant properties were prepared by solvent evaporation method and spray drying method and characterized by FTIR, SEM and DSC. 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 and 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, Superdisintegrant.

A R T I C L E I N F O

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1. Introduction

Solid dosage forms are popular because of ease of administration, accurate dosage, self medication, pain avoidance and most importantly the patient compliance. The most popular solid dosage forms are being tablets and capsules [1]. A fast-dissolving drug delivery system, in most cases, is a tablet that dissolves or disintrigrants in the oral cavity without the need of water or chewing. Most fast-dissolving delivery system films 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 [2,3].

Pharmaceutical marketing is another reason for the increase in available fast dissolving/disintegrating products [4]. The challenges faced by researchers in the development of FDTs are to produce the tablet with sufficient mechanical strength, which disintegrates rapidly in the mouth. The tablets should have an acceptable taste and leave minimum or no residue in the mouth [5,6]. So in the present research work solid dispersion of Nizatidine is formulated by using Eudragit E100 polymer by two different methods to mask the taste of drug and formulated FDTs of Nizatidine-drug complex using 3 different Superdisintegrants.

2. Experimental

Materials

Nizatidine was obtained from Dr. Reddy Laboratories Private Limited, Hyderabad. Eudragit E100 from Evonik Degussa India Private Limited, Mumbai.Titan Laboratories Ltd. Mumbai. Crosspovidone from International Speciality Product, Hong kong Ltd. Soy polysaccharide was obtained from JRS Pharma, Rosenberg. Croscarmellose Sodium and Microcrytalline Cellulose from the Anglo French Drug Co. Ltd, Bangalore. Mannitol, Talc, Magnesium Stearate from SD Fine chemicals and all the other chemicals used were of analytical grade.

Method

Preparation of Solid Dispersion

Spray Drying:

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, 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.

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%. Formulated solid dispersions were characterized by Infrared spectroscopy, Scanning electron microscopy, Differential scanning calorimetry and Dissolution studies.

Preparation of Nizatidine FDT's

Tablets containing Nizatidine-Eudragit E100 solid dispersions were formulated using various super disintegrants like crospovidone soypolysaccharide (SYP) in concentrations ranging from 6-15% (same for F1-F9 and F10-F18). 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. Formulation table was shown in table 1, 2.

3. Results and Discussion

Evaluation

Nizatidine FDTs were evaluated for pre-compression properties like Determination of density Percentage compressibility or Carr's index, Hausner ratio, Angle of repose.

Post-Compression Parameters [7-15]

Thickness:

Six tablets were randomly selected and the thickness of each was measured by digital

Vernier caliper. Mean and standard deviation were computed and reported.

Hardness:

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

Friability:

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 four minutes. After four minutes the tablets were weighed again. The % friability was then calculated using the formula:

% Friability =Initial weight-final weight/Initial weightX100

Weight variation:

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 limit.

Disintegration test:

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 $37^0C \pm 0.5^0C$ and the time taken for each tablet to disintegrate completely was recorded.

Wetting time:

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.

Drug content uniformity:

Ten tablets were randomly selected and allowed to equilibrate with gastric simulated fluid (without enzyme) overnight and was filtered 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.

In-vitro dissolution study:

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 was maintained at 37^0C. 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 enzyme 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.

Discussion

Drug Excipient Interaction Study

The infrared spectrum of Nizatidine and solid dispersions of Nizatidine with other excipients indicated that there was no chemical interaction found between Nizatidine and other excipients.

Characterization of Nizatidine-Eudragit E100 complex:

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 recor ed 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 20 amine and 1550 cm^{-1} and 1350 cm1 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. Results are shown in fig no 1-5. It was observed from the SEM photograph that Nizatidine was crystalline and cylindrical in shape. The inclusion complexes of Nizatidine-Eudragit E100 prepared by solvent evaporation method showed the complex structure indicating that the drug is complexed uniformly with Eudragit E100 and the inclusion complex prepared by that of Spray drying method showed the spherical Eudragit E100 particles having crystalline drug particles firmly adhered on it which confirms the uniformity of the complex with drug. Results are shown in fig no- 6-9.

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/ml3, whereas tapped density values were found to vary from 0.641 to 0.668gm/ml3. Carr's index, Hausner ratio and angle of repose were range between 18.24 to 20.30, 1.22 to 1.25, and $21^o40'$ to $29^o66'$ respectively, which indicates that granules prepared exhibit good flow properties. Results are shown in table no 3,4.

Evaluation of Tablet Properties:

Tablets (F1-F18) were evaluated for tablet properties like thickness, hardness, friability, disintegration time, weight variation, wetting time and drug content uniformity. 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±0.13Kg/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 were reported in a previous work. 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 superdisintegrant. Results are shown in table no 5,6. 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. 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 and 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 can be prepared by more economical method which is also suitable for small scale production. Results are shown in table no 7,8 and fig no 10,11. 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. Results are shown in table. 9, 10.

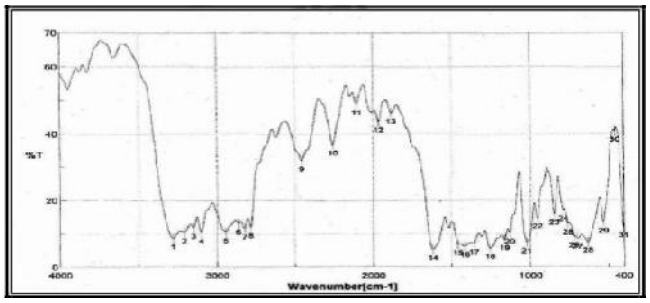

Figure1: IR Spectra of Nizatidine

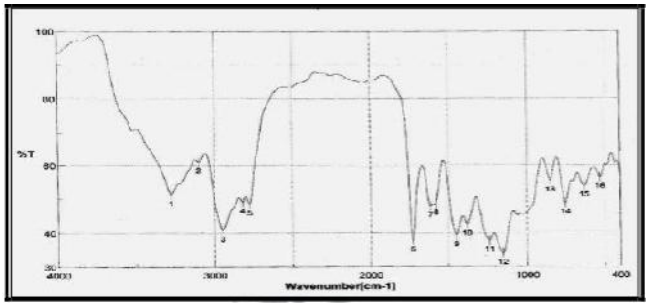

Figure 2: IR Spectra of Nizatidine with tablet excipients.

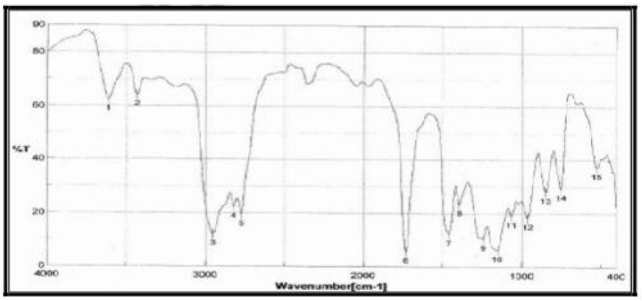

Figure 3: IR Spectra of Eudragit E100

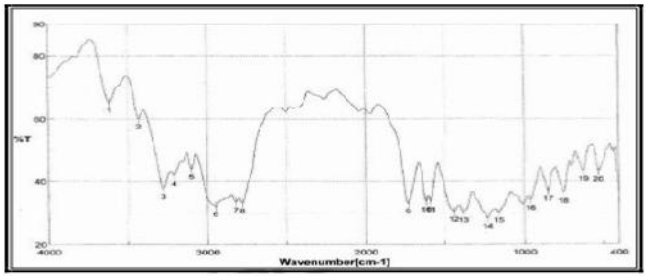

Figure 4: IR Spectra of Nizatidine-Eudragit E100 Solid dispersion evaporation method

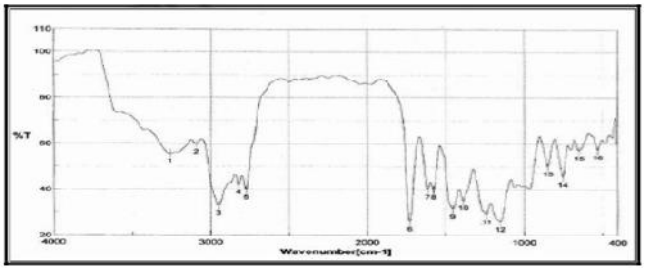

Figure 5: IR Spectra of Nizatidine-Eudragit E100 Solid dispersion (Spray Drying Method)

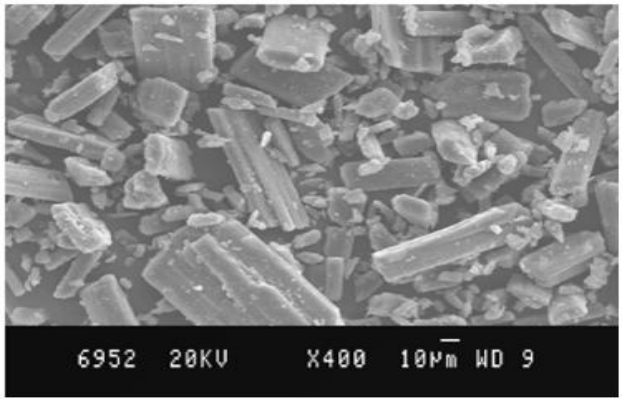

Figure 6: SEM of Nizatidine

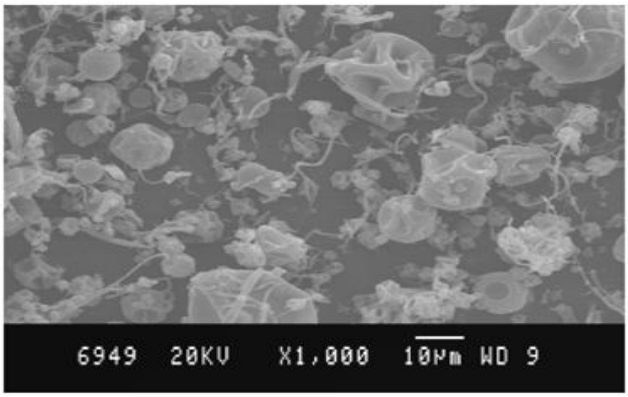

Figure 7: SEM of Eudragit E100

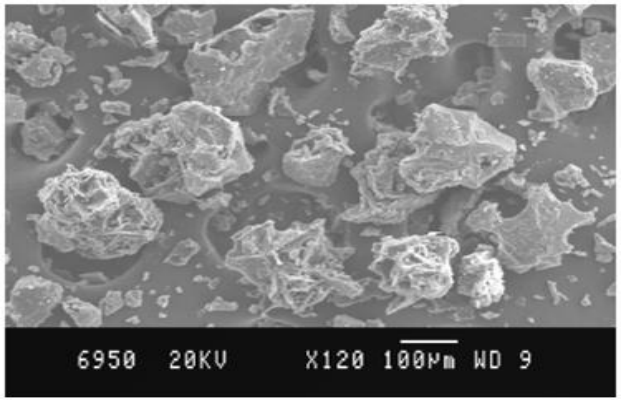

Figure 8: SEM of Nizatidine-Eudragit E100 Solid dispersion (Solvent Evaporation method)

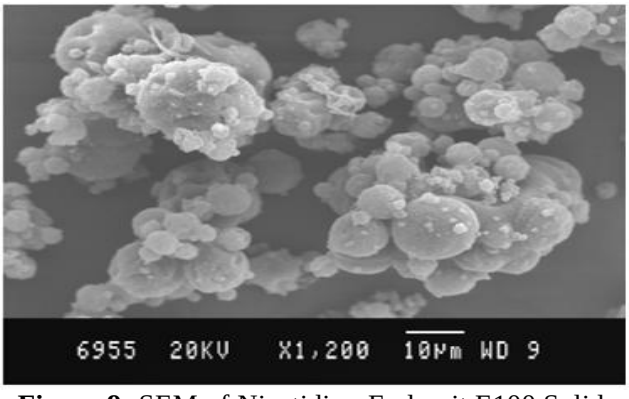

Figure 9: SEM of Nizatidine-Eudragit E100 Solid dispersion (Spray drying method).

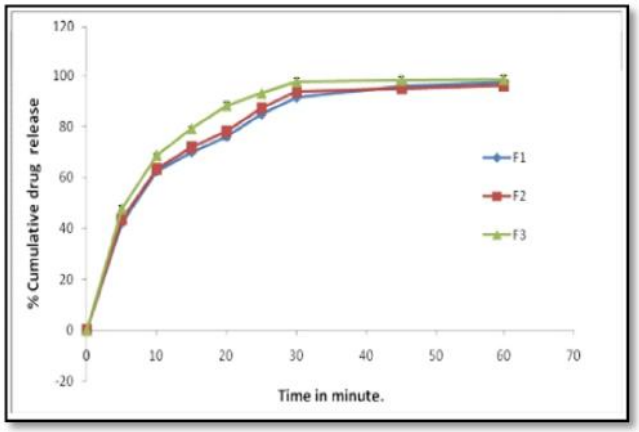

Figure 10: *In-vitro* dissolution profile of F1, F2and F3

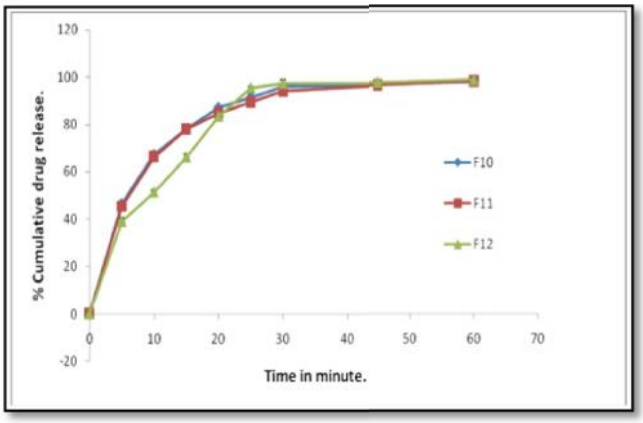

Figure 11: In-vitro dissolution profiles of F10, F11 and F12.

Table 1: Formulation using solid dispersion prepared by Solvent Evaporation Technique

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Nizatidine-Eudragit E100 Complex	375	375	375	375	375	375	375	375	375
Mannitol	45	45	30	45	45	30	45	45	30
Microcrystalline Celluose	45	25	15				45	25	15
Crosscarmellose Sodium				45	25	15			
Soy polysaccharide							30	50	75
Crospovidone	30	50	75	30	50	75			
Magnesium stearate	5	5	5	5	5	5	5	5	5

Table 2: Formulation using solid dispersion prepared by Spray Dried Technique

Ingredients	F10	F11	F12	F13	F14	F15	F16	F17	F18
Nizatidine-Eudragit E100 Complex	375	375	375	375	375	375	375	375	375
Mannitol	45	45	30	45	45	30	45	45	30
Microcrystalline Celluose	45	25	15				45	25	15
Crosscarmellose Sodium				45	25	15			
Soy polysaccharide							30	50	75
Crospovidone	30	50	75	30	50	75			
Magnesium stearate	5	5	5	5	5	5	5	5	5

Table 3: Results of granular properties

Formulation	Poured* density[3] (gm/ml)	Tapped density*[3] (gm/ml)	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

Table 4: Results of granular properties

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

Table 5: Results of tablet properties of formulations (F1-F18)

S.NO	Formulation	Wt. variation	Wetting time*	Drug content uniformity ± SD
1	F1	PASS	12.88±2.045	74.50±0.008
2	F2	PASS	10.55±1.002	74.38±0.015
3	F3	PASS	6.79±1.712	74.60±0.007
4	F4	PASS	13.69±0.560	75.00±0.041
5	F5	PASS	11.17±0.850	74.80±0.006
6	F6	PASS	22.66±0.995	74.93±0.020
7	F7	PASS	21.42±1.100	74.63±0.014
8	F8	PASS	22.28±1.564	75.05±0.005
9	F9	PASS	21.87±1.014	75.20±0.011
10	F10	PASS	27.74±1.001	76.00±0.008
11	F11	PASS	29.88±2.045	74.59±0.009
12	F12	PASS	30.55±1.563	75.03±0.023
13	F13	PASS	32.23±1.462	75.00±0.014
14	F14	PASS	29.12±1.025	52.05±0.025
15	F15	PASS	27.84±1.456	48.30±0.012
16	F16	PASS	32.46±2.488	50.02±0.004
17	F17	PASS	30.00±1.123	49.00±0.035
18	F18	PASS	29.36±1.745	48.85±0.023

Table 6: Table no-6 Results of tablet properties of formulations (F1-F18)

S.NO	Formulation	Thickness [A] (mm)	Hardness [B] $(Kg/cm)^2$	Friability (%)	Disintegration[C] time (sec)
1	F1	4.10±0.07	3.17±0.30	0.44	15.40±0.469
2	F2	4.11±0.05	3.12±0.34	0.63	12.27±0.782
3	F3	4.11±0.07	3.53±0.25	0.75	8.40±0.369
4	F4	4.10±0.03	3.14±0.20	0.32	17.52±0.469
5	F5	4.10±0.06	3.23±0.15	0.42	13.85±0.813
6	F6	4.10±0.04	3.36±0.12	0.54	10.91±0.671
7	F7	4.11±0.07	3.23±0.27	0.73	29.66±0.125

8	F8	4.11±0.06	3.26±0.19	0.66	25.96±0.0145
9	F9	4.11±0.08	3.45±0.22	0.51	23.67±0.160
10	F10	4.12±0.04	3.13±0.29	0.83	75.32±0.258
11	F11	4.12±0.05	3.10±0.23	0.48	53.12±0.215
12	F12	4.11±0.03	3.58±0.25	0.72	37.76±0.189
13	F13	4.12±0.04	3.11±0.26	0.62	85.35±0.956
14	F14	4.11±0.05	3.21±0.18	0.83	61.46±0.483
15	F15	4.12±0.01	4.00±0.13	0.6	42.25±0.146
16	F16	4.12±0.02	3.14±0.17	0.4	87.13±0.364
17	F17	4.11±0.06	3.67±0.14	0.5	65.40±0.469
18	F18	4.12±0.07	3.76±0.24	0.3	44.37±0.782

Table 7: *In-Vitro* Dissolution of F1-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

Table 8: *In-Vitro* Dissolution of F10-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

Table 9: 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 10: 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

4. Conclusion

Nizatidine is a H2 receptor antagonist used to treat gastric and duodenal ulcers and gastroesophogeal reflux disease. The Complexes of Nizatidine-Eudragit E100 prepared by two different methods i.e. solvent evaporation method and spray drying method and were characterized by IR, SEM and DSC. The complexes tablets. Tablets were prepared by direct compression method using three different superdisintegrants. Desired results 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 .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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