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DESIGN DEVELOPMENT AND EVALUATION OF FAST DISSOLVING ORAL FILMS OF RANITIDINE

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Key Words

Ranitidine HCl, superdisintegrants, HPMC, CCMS.

ABSTRACT

The objective of the present research work is to formulate and evaluate the fast releasing oral thin films of Ranitidine Hydrochloride to achieve a safe, rapid and effective dosage form with enhanced drug dissolution and oral bio availability. Ranitidine hydrochloride is Histamine H2-receptor antagonist. It has only 50% oral bioavailability due to hepatic first pass metabolism to enhance the bioavailabity and increase the patient compliance oral films are formulated by using HPMC, PVA, Hypromellose as film forming polymers. CCMS, CP, SSG, as disintegrating agents. Polymers like PEG 200, PG are used as plasticizers, sodium saccharin as sweetening agent, Mannitol and citric acid as flavoring agents. Films were formulated by using solvent evaporation technique. Preformulation studies revealed there was no interaction between drug and excipient. Films were evaluated for various physical parameters and were found good. Disintegration time of all formulations was ranging from 9 to 29 sec, formulations with CCMS showed less disintegration time and higher drug release 99%±1% when compared to other superdisintegrants.

INTRODUCTION:

Before designing a new dosage form, the biopharmaceutical factors need to be considered. First pass metabolism is one of the important biopharmaceutical parameter to be considered for formulating oral drug delivery. Ranitidine hydrochloride is Histamine H2-receptor antagonist. It has only 50% oral bioavailability due to hepatic first pass metabolism when given orally. To avoid the first pass metabolism and to enhance the bioavailability, formulation of Fast disintegrating oral films is one of the approaches, which quickly disintegrate and facilitate the fast absorption of the drug into systemic circulation it also increases the patient compliance as oral drug delivery is most acceptable and advantageous when compared to the other routs of administration[14,18,19].

MATERIALS AND METHODS

Materials: Materials/chemicals required for

designing and developing of Ranitidine Hcl fast dissolving oral films are Ranitidine HCl procured from S.M.S pharmaceuticals, HPMC-E6 ,Hypromellose-E3 obtained as gift sample from Hetero labs, Crosscamellose sodium, crosspovidone, SSG obtained as gift sample from Aurobindo pharma company, Carbinol, PEG-200, propylene glycol obtained as gift sample from Finar chem limited, PVA, Mannitol, Citric acid, sodium saccharin are obtained as gift sample from INR chemicals, Sd fine chem., NR fine chem., Rolex company.

Preformulation studies:

Calibration curve for ranitidine hydrochloride

10mg of Ranitidine Hydrochloride was dissolved in 100ml of distilled water to obtain a 100mcg/ml concentration of Ranitidine Hydrochloride in solution. This solution was subjected to scanning between 200 – 400 nm[21](100 mcg/ml) was prepared and further diluted to 2,4,6,8 and 10 mcg/ml absorbance values were at 315nm

Drug-Excipient Compatibility Studies by FTIR

The IR spectrum of pure drug and physical mixture of drug and polymer were studied by making a KBr disc (ratio of 1:100). Observed for the spectrum in FTIR.

Differential scanning calorimetry [DSC]:

Differential scanning calorimetry was performed using differential scanning calorimeter [DSC 200 PC]. The instrument was calibrated using indium (156^0C), Tin (232^0C) and zinc (419.5^0C) as internal standards. Samples of 2-10mg were placed in aluminum pans and sealed. The probes were heated from 0-300^0C. Samples were heated in an open pan at a rate of 10^0C min^{-1} under a nitrogen flow of 10K/min under nitrogen atmosphere.[2, 3]

Swelling Studies of Super Disintegrants

Although not all effective disintegrants swell in contact with water, swelling is believed to be a mechanism in which certain disintegrating agents (such as starch) impart the disintegrating effect. By swelling in contact with water, the adhesiveness of other ingredients can be overcome and allows the film to get easily disintegrated.[6]

PREPRATION OF FILMS

The fast dissolving films of Ranitidine hydrochloride were prepared by the solvent casting technique. The fast films were prepared using polymers like Hypromellose, HPMC, and PVA. Propylene glycol is used as plasticizer. The calculated amount of polymer was dispersed in three-fourth volume of solvent with continuous stirring using magnetic stirrer and the final volume was adjusted. The calculated amount Ranitidine hydrochloride was incorporated in the polymeric solutions after levigation with required volume of PEG. The solution was casted onto the petridish and kept them in hot air oven at 40^0c for about 24hrs.The films were cut into 2×2cms films.[6]

POST FORMULATION PARAMETERS

Weight uniformity of the films: Three films of 2×2 cms were weighed individually using digital balance and average weights were calculated.

Thickness uniformity of the films: Thickness of the films was measured using screw guage with a least count of 0.01mm at different spots of the films. The thickness was measured at three different spots of the films and average was calculated.

Folding endurance of the films: The flexibility of the films can be measured quantitatively in terms of what is known as folding endurance. Folding endurance of the films was determined by repeatedly folding

a small strip of films at the same place till it broke.

pH studies: pH was determined by dissolving a film in 2 ml of distilled water and then the pH of the obtained solution was measured by pH paper.

SEM Analysis: Morphology of the prepared film was observed under a scanning electron microscope (SEM).The samples were attached to the slab surfaces with double-sided adhesive tapes and the scanning electron photomicrograph was taken at 1000X magnification.

***In vitro* Disintegration Time:** Disintegration test was performed in the USP disintegration time testing apparatus. Water was used as medium. The films were placed in the tubes of the container and the disk was placed over it[6].

Content Uniformity: A film of size 2 cm diameter was cut and placed in a beaker.10 ml of phosphate buffer solution (pH6.8) was placed. The contents were stirred in magnetic stirrer to dissolve the film. The contents were transferred to a volumetric flask (10 ml). The absorbance of the solution was measured against corresponding blank solution at 315 nm.[8,9]

Dissolution Studies: The dissolution for the prepared Ranitidine films was performed by using USP2 Paddle type apparatus with 900 ml of 6.8pH phosphate buffer as medium which was maintained at 37±0.5 °C temperature and paddle speed was 50 rpm. 5ml of sample was collected for every 2 min and absorbance was measured at 315 nm.

Similarity Factor: The similarity factors are determined for comparison of dissolution profiles. The similarity factor (f2)is a logarithmic transformation of the sum-squared error of differences between the test Tj andreference Rj products over all time points.

$$f_2 = 50 \times \log\{[1 + (1/n)\sum_{j=1}^{n} w_j |R_j - T_j|^2]^{-0.5} \times 100\}$$

RESULTS AND DISCUSSION

Pre formulation Studies:

IR Spectroscopy: The IR spectrum of the pure drug was found to be similar to the standard spectrum of Ranitidine Hcl. The spectrum of Ranitidine HCl showed the following functional groups at their frequencies. All the formulations i.e, F6, F18 and F24 are showing their drug peaks in all the IR spectras which are within the characteristic range, hence it shows no Drug – excipient compatibility.

Differential scanning calorimetry: The DSC thermograms of Ranitidine exhibited an endothermic peak at corresponding to its melting point. The DSC thermograms of Ranitidine Hcl. with other excipients does not show profound shift in peaks which indicates compatibility. The DSC thermograms of individual drug and drug with HPMC-E_6, PVA, and Hypromellose-E_3 were shown in the fig.

All the formulations were showing uniform weights ranging between 0.22 to 0.48, variations in thickness was very negligible ranging from 0.12 to 0.43 due to change in concentration of polymers, Drug content of all the formulations was found to be between 92.6% -99.6%,Disintegration time of all formulations lies between 29 min to 11 min disintegration time was decreased with increase in concentration of super-disintegrating agents.

Scanning electron microscopy: The prepared film containing Ranitidine Hydrochloride was clear.The scanning electron photomicrograph of the film at 40X magnification showed smooth surface and without any transverse striations. The SEM pictures were shown in the fig.

FC	Ranitidine.HCl (gms)	HPMC E6 gms	PVA gms	Hypro mellose-E3 gms	CCMS gms	CP gms	SSG gms	Na.saccharin gms	Citric Acid gms	Mannitol gms	PEG 200 ml	PG ml
F1	0.49	0.4	-	-	-	-	-	0.2	0.2	0.4	3	1.5
F2	0.49	0.4	-	-	0.1	-	-	0.2	0.2	0.4	3	1.5
F3	0.49	0.4	-	-	0.2	-	-	0.2	0.2	0.4	3	1.5
F4	0.49	0.4	-	-	0.3	-	-	0.2	0.2	0.4	3	1.5
F5	0.49	0.4	-	-	-	0.1	-	0.2	0.2	0.4	3	1.5
F6	0.49	0.4	-	-	-	0.2	-	0.2	0.2	0.4	3	1.5
F7	0.49	0.4	-	-	-	0.3	-	0.2	0.2	0.4	3	1.5
F8	0.49	0.4	-	-	-	-	0.1	0.2	0.2	0.4	3	1.5
F9	0.49	0.4	-	-	-	-	0.2	0.2	0.2	0.4	3	1.5
F10	0.49	0.4	-	-	-	-	0.3	0.2	0.2	0.4	3	1.5
F11	0.49	-	0.3	-	-	-	-	0.2	0.2	0.4	3	1.5
F12	0.49	-	0.3	-	0.1	-	-	0.2	0.2	0.4	3	1.5
F13	0.49	-	0.3	-	0.2	-	-	0.2	0.2	0.4	3	1.5
F14	0.49	-	0.3	-	0.3	-	-	0.2	0.2	0.4	3	1.5
F15	0.49	-	0.3	-	-	0.1	-	0.2	0.2	0.4	3	1.5
F16	0.49	-	0.3	-	-	0.2	-	0.2	0.2	0.4	3	1.5
F17	0.49	-	0.3	-	-	0.3	-	0.2	0.2	0.4	3	1.5
F18	0.49	-	0.3	-	-	-	0.1	0.2	0.2	0.4	3	1.5
F19	0.49	-	0.3	-	-	-	0.2	0.2	0.2	0.4	3	1.5
F20	0.49	-	0.3	-	-	-	0.3	0.2	0.2	0.4	3	1.5
F21	0.49	-	-	0.5	-	-	-	0.2	0.2	0.4	3	1.5
F22	0.49	-	-	0.5	0.1	-	-	0.2	0.2	0.4	3	1.5
F23	0.49	-	-	0.5	0.2	-	-	0.2	0.2	0.4	3	1.5
F24	0.49	-	-	0.5	0.3	-	-	0.2	0.2	0.4	3	1.5
F25	0.49	-	-	0.5	-	0.1	-	0.2	0.2	0.4	3	1.5
F26	0.49	-	-	0.5	-	0.2	-	0.2	0.2	0.4	3	1.5
F27	0.49	-	-	0.5	-	0.3	-	0.2	0.2	0.4	3	1.5
F28	0.49	-	-	0.5	-	-	0.1	0.2	0.2	0.4	3	1.5
F29	0.49	-	-	0.5	-	-	0.2	0.2	0.2	0.4	3	1.5
F30	0.49	-	-	0.5	-	-	0.3	0.2	0.2	0.4	3	1.5

Table 1: Composition of fast dissolving oral film of ranitidine

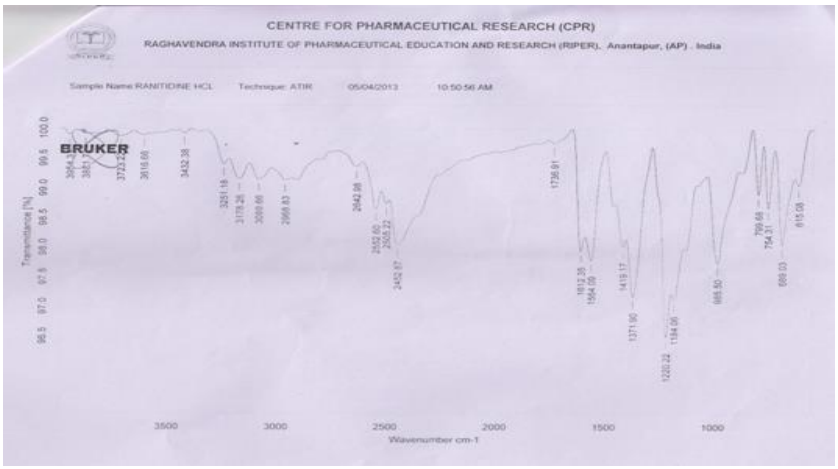


Fig: 1 IR spectra of Ranitidine Hydrochloride

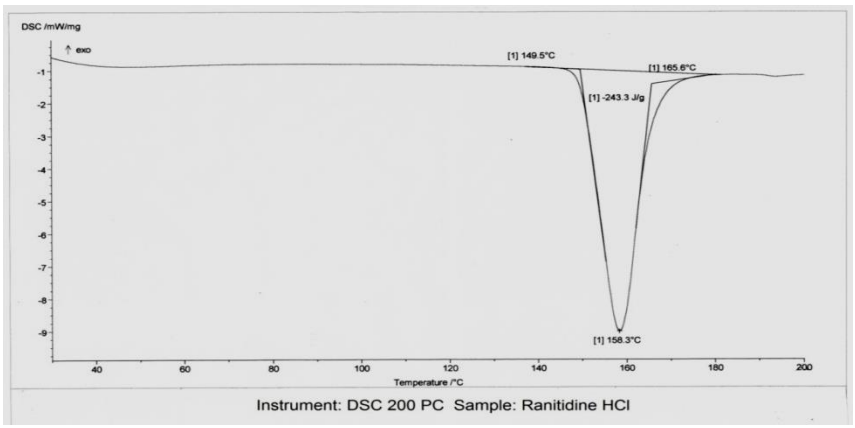


Fig 2: DSC of pure drug

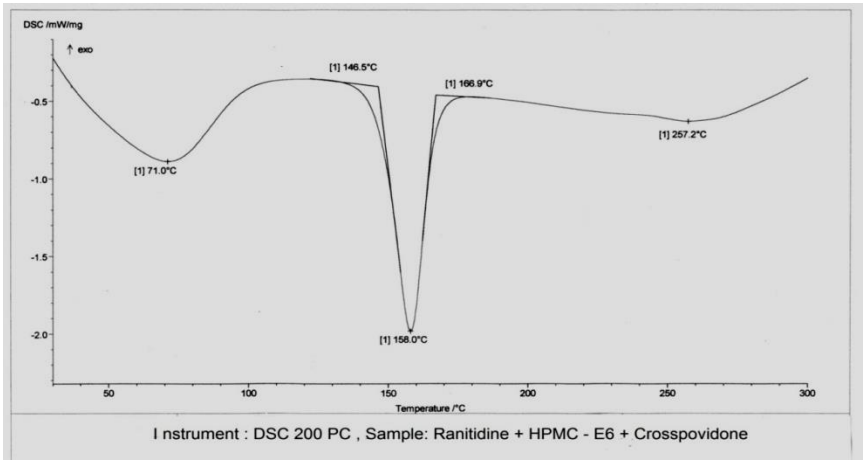


Fig 3: DSC of film using HPMC-E6

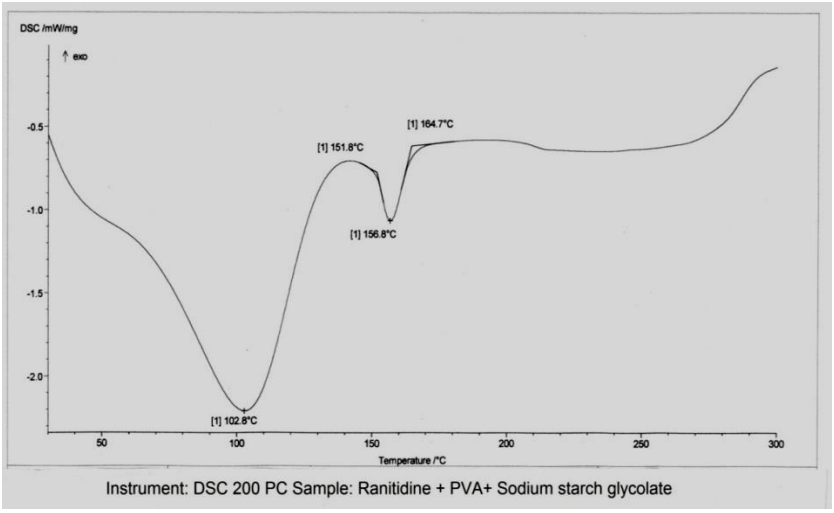


Fig 4: DSC of film using PVA

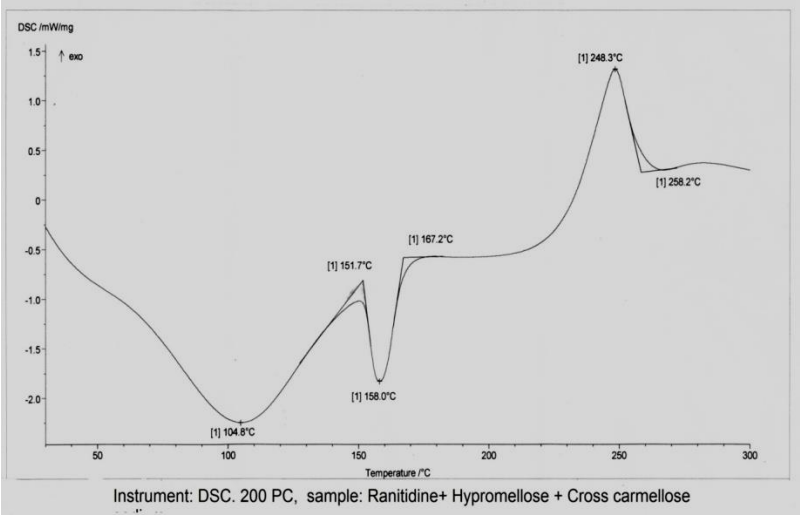


Fig 5: DSC of film using Hypromellose-E3

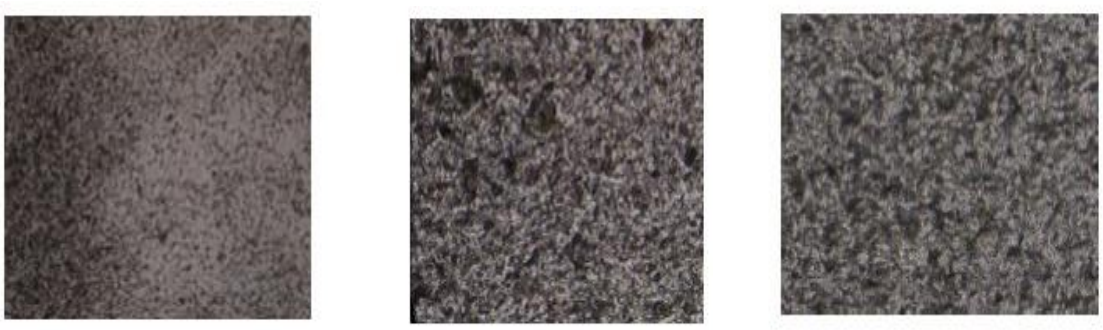
Table 2: Swelling Studies of Super Disintegrants in Purified Water:

Super Disintegrate	% Increase in Volume
Cross Carmellose Sodium	850
Sodium Starch Glycolate	600
Crosspovidone	2.83

Table 3: Evaluation parameters of ranitidine films

FC	Weight [gms]	Thickness [mm]	Avg Folding Endurance	Avg. Drug content [%]	Disintegration time [secs]	Surface pH
F1	0.23±0.031	0.24±0.016	42 ± 0.042	97.2 ±0.065	19± 0.051	6.7± 0.014
F2	0.41±0.024	0.32±0.005	51 ± 0.084	98.8 ±0.032	16± 0.035	6.8± 0.041
F3	0.42±0.096	0.32±0.022	28 ± 0.063	99.4 ±0.044	12± 0.064	6.9± 0.013
F4	0.47±0.044	0.34±0.019	72 ± 0.056	94.8 ±0.038	09± 0.049	6.5± 0.036
F5	0.22±0.182	0.21±0.005	67 ± 0.025	95.9 ±0.061	18± 0.089	6.6± 0.063
F6	0.28±0.052	0.20±0.015	41 ± 0.033	98.9 ±0.095	15± 0.047	6.1± 0.051
F7	0.26±0.021	0.26±0.003	73 ± 0.076	98.6 ±0.057	12± 0.078	6.2± 0.026
F8	0.41±0.053	0.24±0.010	39 ± 0.037	97.8 ±0.037	19± 0.069	6.3± 0.062
F9	0.38±0.032	0.26±0.028	29 ± 0.051	96.9 ±0.084	16± 0.076	6.7± 0.046
F10	0.38±0.067	0.18±0.022	61 ± 0.073	99.3 ±0.035	12± 0.038	6.9± 0.059
F11	0.41±0.035	0.20±0.065	65 ± 0.061	92.8 ±0.079	29± 0.071	6.6 ±0.026
F12	0.48±0.062	0.18±0.072	32 ± 0.054	96.4 ±0.059	16± 0.016	6.8 ±0.074
F13	0.31±0.048	0.22±0.069	56 ± 0.035	94.7 ±0.014	15± 0.043	6.7±0.036
F14	0.41±0.032	0.21±0.054	44 ± 0.041	99.1 ±0.037	10± 0.038	6.1±0.015
F15	0.41±0.054	0.12±0.063	38 ± 0.037	98.3 ±0.076	21± 0.040	6.6 ±0.026
F16	0.34±0.069	0.18±0.031	67 ± 0.046	97.5 ±0.058	19± 0.051	6.4 ±0.047
F17	0.31±0.057	0.14±0.044	43 ± 0.027	99.9 ±0.042	18± 0.018	6.6±0.064
F18	0.30±0.049	0.24±0.012	52 ± 0.019	97.9 ±0.061	26± 0.027	6.5±0.072
F19	0.39±0.028	0.26±0.052	70 ± 0.046	99.6 ±0.047	22± 0.043	6.3±0.051
F20	0.45±0.059	0.23±0.036	69 ± 0.023	98.1 ±0.038	21± 0.031	6.3±0.022
F21	0.41±0.015	0.43±0.051	28 ± 0.021	98.3 ±0.046	24± 0.016	6.2± 0.012
F22	0.44±0.056	0.37±0.036	34 ± 0.030	97.6 ±0.018	15± 0.024	6.4± 0.036
F23	0.32±0.034	0.34±0.026	19 ± 0.048	98.2 ±0.035	16± 0.018	6.8± 0.094

F24	0.39±0.042	0.19±0.019	37 ± 0.026	96.2 ±0.049	11 ± 0.03	6.4± 0.045
F25	0.37±0.095	0.31±0.026	41 ± 0.019	97.8 ±0.053	18± 0.028	6.± 0.061
F26	0.34±0.015	0.24±0.051	29 ± 0.082	99.6 ±0.073	16± 0.042	6.4± 0.078
F27	0.38±0.044	0.32±0.063	36 ± 0.051	98.5 ±0.081	14± 0.019	6.3± 0.032
F28	0.37±0.027	0.38±0.041	51 ± 0.046	96.9 ±0.057	23± 0.024	6.6± 0.019
F29	0.34±0.054	0.41±0.017	32 ± 0.037	99.1 ±0.037	21± 0.031	6.9± 0.062
F30	0.47±0.061	±0.008	46 ± 0.028	98.3 ±0.076	20± 0.022	6.9± 0.031



SEM of Drug + HPMC-E_6 **SEM of Drug + PVA** **SEM of Drug + Hypromellose-E_3**

Fig 6: SEM pictures of ranitidine films

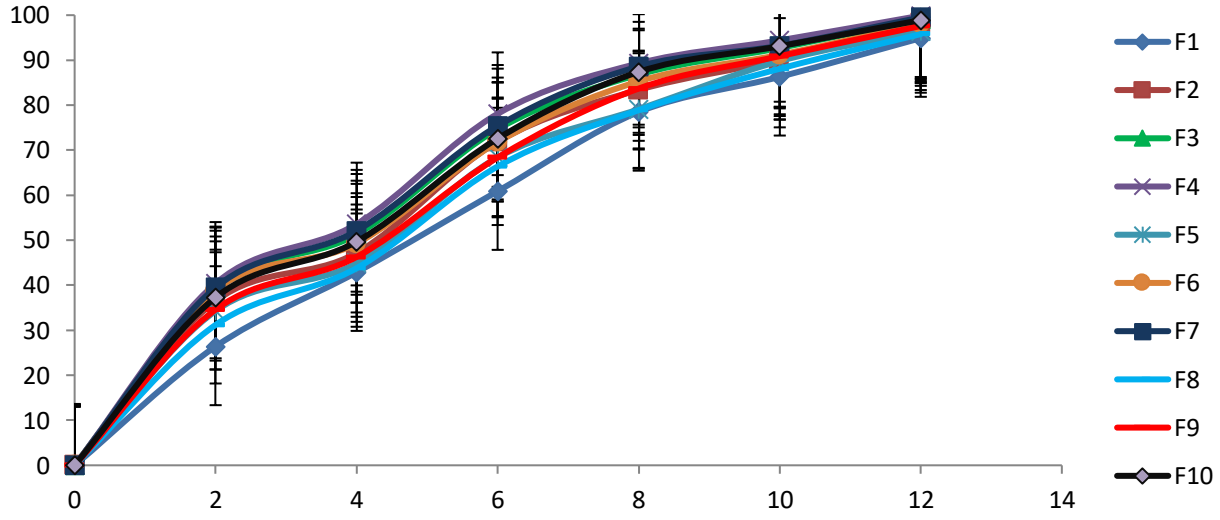


Fig 7: Comparison of *In-vitro* drug release profile of formulations– F_1, F_2, F_3, F_4, F_5, F_6, F_7, F_8, F_9, F_{10}

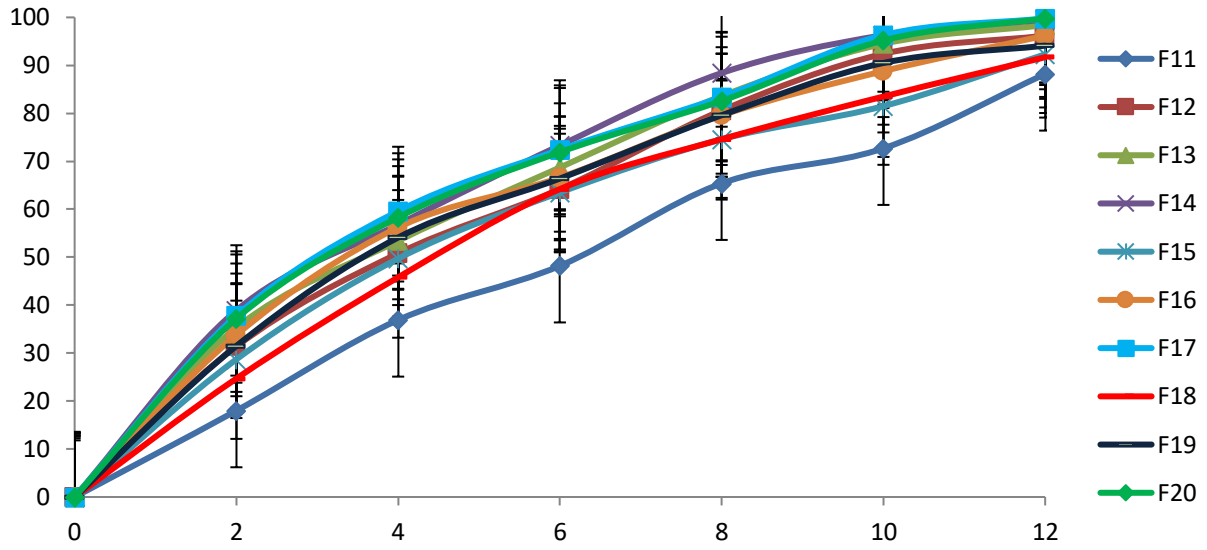


Fig 8: Comparison of *In-vitro* drug release profile of formulations– F_{11}, F_{12}, F_{13}, F_{14}, , F_{15}, F_{16}, F_{17},F_{18}, F_{19}, F_{20}

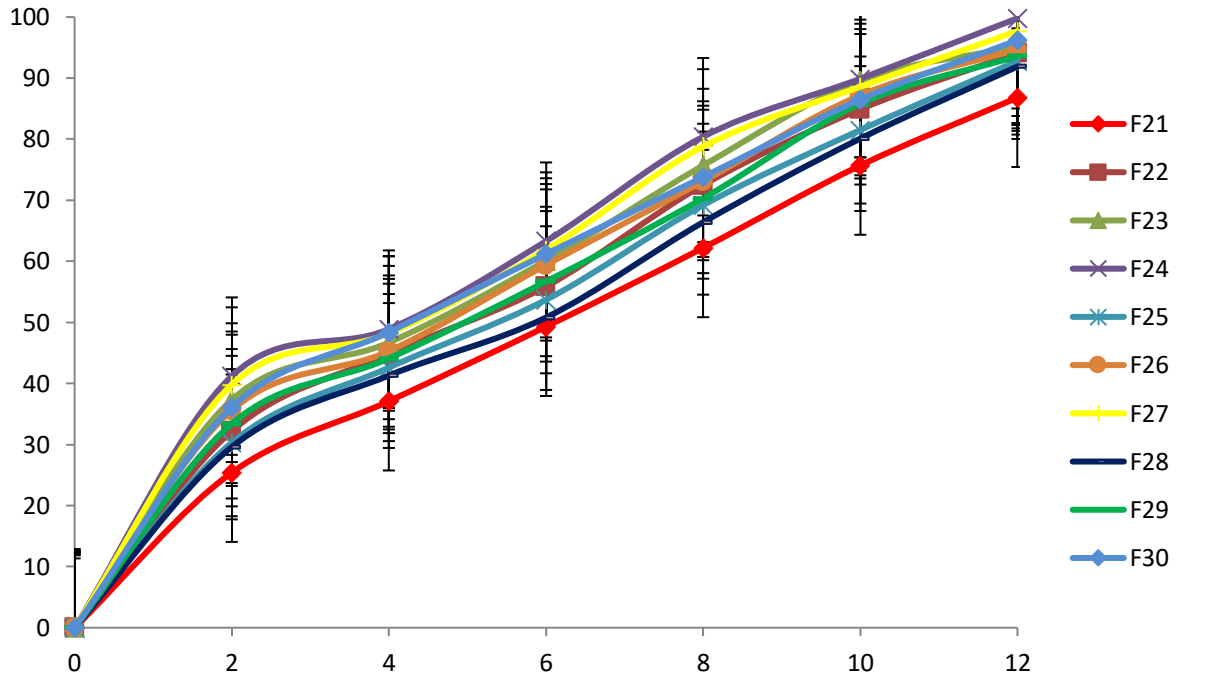


Fig 9: Comparison of *In-vitro* drug release profile of formulations– F_{21}, F_{22}, F_{23}, F_{24}, F_{25}, F_{26}, F_{27}, F_{28}, F_{29}, F_{30}

CONCLUSION:

In the present work fast dissolving films of ranitidine were prepared by solvent casting method using superdisintegrants such as Crosspovidone, croscarmellose sodium, sodium starch glycolate. The disintegration time of the films was reduced by using the super disintegrating agents.FT-IR and DSC studies revealed that there is no drug and excipient incompatability. The prepared film containing Ranitidine Hcl was clear as it shows smooth surface without any scratches in SEM analysis and the

formulated films has given satisfactory result for various evaluation parameters like weight uniformity, thickness uniformity, folding endurance, surface pH, drug content uniformity and Invitro disintegration studies revealed that upon increase in the concentration of super disintegrating agent reduces the disintegration time .From the invitro dissolution profiles the films made using 3% sodium starch glycolate had shown 96.2%, while with 3% Crosspovidone had shown maximum drug release of 99.8% while films made of croscarmellose sodium had shown 99.9% of drug release within 12 minutes. From the present study, it may be concluded that the fast dissolving films of Ranitidine Hcl. can be prepared by solvent casting method using superdisintegrants. Crosspovidone was found to be best when compared with other two disintegrants.

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