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ENHANCEMENT OF SOLUBILITY AND DISSOLUTION RATE OF FAMOTIDINE WITH HYDROPHILIC POLYMERS BY SOLID DISPERSION TECHNIQUE

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ABSTRACT: Objective: In the present study to enhance solubility and in vitro dissolution of poorly aqueous soluble drug Famotidine by preparing solid dispersions using the Kneading method. **Methods:** Solid dispersions of the drug were prepared by the kneading method using Kollidon and Povidone K30 (as a carrier). Eight different drugs: Carrier ratios were prepared by Factorial design taking three factors, i.e., the concentration of Famotidine (X1), Kollidon (X2), and Povidone K30(X3). **Results:** DSC, FTIR spectroscopy, powder X-ray diffraction (XRD), and SEM studies were used to characterize solid dispersions. In vitro release was carried out using the USP II dissolution apparatus. Multilinear regression analysis was applied to develop a mathematical model to estimate cumulative drug release. The batch F4 was found to be best batch as it showed maximum solubility and *in-vitro* dissolution after 30 min. Improvement in the dissolution behavior of solid dispersion batches was observed due to the conversion of a crystalline form of drug to amorphous form as confirmed by DSC, FTIR studies, and XRD studies. SEM photographs of batch F4 showed porous nature of particle surface. **Conclusion:** Solid dispersion prepared via Kneading method was proved to be beneficial in enhancement of dissolution rate of poorly- aqueous soluble drug using hydrophilic carriers. Respectively, this model can further be utilized to design solid dispersions for desired release characteristics.

INTRODUCTION: Oral drug delivery is the simplest and easiest way of administering drugs. Because of the greater stability, smaller bulk, accurate dosage, and easy production, solid oral dosage forms have many advantages over other types of oral dosage forms. Therefore, most of the new chemical entities (NCE) under development are intended to be used as a solid dosage form that originates an effective and reproducible *in-vivo* plasma concentration after oral administration^{1,2}.

In fact, most NCEs are poorly water-soluble drugs and are not well absorbed after oral administration, which can detract from the drug's inherent efficacy^{3,4}. Consequently, if these drugs are not completely released in the gastrointestinal area, they will have a low bioavailability⁵. Therefore, one of the major current challenges of the pharmaceutical industry is related to strategies that improve the water solubility of drugs⁶. The techniques/approaches that have commonly been used to overcome drawbacks associated with poorly water-soluble drugs, in general, include micronization, salt formation, use of surfactants, and use of prodrug⁷. However, all these techniques have potential limitations. Solid dispersion is the most successful strategy to improve the drug release of poorly soluble drugs.

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Solid dispersion improves the solubility through decreased particle size, increase surface area, improved wettability, and increased amorphous state of water-insoluble compound⁸. Sekiguchi and Obi first introduced the concept of using solid dispersions to improve the bioavailability of the poorly water-soluble drug in 1961. Chiou and Riegelman defined the term solid dispersion as “a dispersion of one or more active ingredients in an inert carrier or matrix, prepared by the melting, solvent, or melting solvent method⁹. Solid dispersion (SD) technique has been widely used to improve the solubility, dissolution rate, and oral absorption of poorly water-soluble drugs^{10,11}.

Famotidine is a poorly water-soluble H₂ receptor antagonist and acid-reducing drug. The drug has been classified as a class IV drug as per the biopharmaceutical classification system (BCS) as a result of its low solubility and oral bioavailability. Low water-soluble drugs often exhibit low dissolution profile and oral bioavailability problems^{12, 13}. Therefore, the objective of the present study was to improve the solubility and in vitro dissolution profile of Famotidine using solid dispersions by Kneading method through factorial design.

MATERIALS AND METHODS:

Materials: Famotidine was a gift sample from Milan Laboratories (India) Pvt. Ltd. Kollidon was purchased from Research lab fine chem. Industries (India). Povidone K30 purchased from Pallav Chemicals Pvt. Ltd. (India). All chemicals used were of analytical grade.

Preparation of Physical Mixture (PM): A physical mixture (PM) of Famotidine with Kollidon or Povidone K30 in 1:1 ratio was prepared by thoroughly mixing the accurately weighed quantity of drug and carrier in by using glass mortar and pestle for 5 min. This mixture was then subsequently passed through mesh no. 40 and stored in desiccators for 48 h.

Experimental Design: Solid dispersion was formulated according to the factorial design to study the effect of three independent variables on the *in-vitro* dissolution profile of Famotidine. The three factors analyzed during the study were the concentration of the drug (X1), the concentration of

Kollidon (X2), and the concentration of Povidone K30(X3) **Table 1**.

Preparation of Solid Dispersion (SDs): The Kneading method (KM) was used for the preparation of solid dispersion. Eight different Drug: Carrier ratios (1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7 and 1:8) were used. F1 to F8 corresponds to preparations containing Kollidon, and F9 to F16 corresponds to preparations containing Povidone K30. Famotidine and Kollidon or Povidone K30 were weighed according to these weighed ratios. Famotidine and Kollidon were triturated using a small volume of methanol to give a thick paste, which was kneaded for 30 min and then dried at 40 °C in an oven. The dried mass was then pulverized, passed through mesh no. 30, stored in vacuum desiccators (48 h), and passed through mesh no. 60 before packaging in an airtight container¹⁴.

Determination of Solubility: Phase solubility was performed as described by Higuchi and Connors. Excess amounts of solid dispersion were added to 25 ml phosphate buffer (pH 7.4) taken in a stopper conical flasks, and the mixture was shaken for 24 h in a rotary flask shaker. After shaking to achieve attain an equilibrium, 2 ml aliquots were withdrawn at 1 hr intervals and filtered through Whatman filter paper no 40. The filtrate was analyzed spectrophotometrically at 265 nm. Shaking was continued until three consecutive reading was the same¹⁴.

Fourier Transforms Infrared Spectroscopy: Infrared spectra of pure Famotidine, carriers, and solid dispersions were recorded using the FTIR spectrometer (Thermo Nicolet 380, USA) to ascertain the presence of different functional groups. A small amount of the powdered solid (1-2 mg) was added to pure potassium bromide powder and grounded up as fine as possible. This was then placed in a small die and put under pressure mechanically to form KBr pellet. Pellet was then scanned in the range from 400 to 4000 cm⁻¹¹⁵.

Differential Scanning Calorimetry: The melting behavior of the pure drug, carrier, and solid dispersions was evaluated by using DSC instrument (DSC Mettler Tolado). Samples were heated under nitrogen atmosphere on an aluminum pan at a rate of 10 °C/min. over the temperature range of 30 to 300 °C¹⁶.

In-vitro Dissolution Studies: Drug release studies were performed in triplicate using United States Pharmacopoeia Type II dissolution test apparatus, employing phosphate buffer (pH 7.4) as dissolution media at a temperature of 37 ± 0.5 °C and at a speed of 50 rpm. Dissolution studies were performed on the pure drug (4 mg) and the different solid dispersions containing an equivalent amount of drug. Aliquots of the periodically withdrawn samples (5 ml) were analyzed spectrophotometrically at 265nm and were replaced with an equal volume of dissolution medium¹⁷.

Powder X-ray Diffraction Studies: XRD patterns were recorded using BRUKER-axs D8-ADVANCE, model generator Powder X-ray diffraction patterns were traced for Famotidine, various carriers, and solid dispersion. The position

and intensities of diffraction peaks were considered for the identification and comparison of crystallinity of the drug or carrier¹⁸.

Scanning Electron Microscopy: Sample of pure Famotidine drug and solid dispersions were mounted onto the stubs using double-sided adhesive tape and then coated with gold-palladium alloy (150-200 Å) using fine coat ion sputter (Joel, JPC-1100). The samples were subsequently analyzed under the scanning electron microscope for external morphology¹⁹.

RESULTS AND DISCUSSION: Three factors, *i.e.*, the amount of drug and carriers (Kollidon and Povidone K30) were studied at two levels, and sixteen batches (F1-F16) of SDs were formulated using factorial design.

TABLE 1: FORMULATION OF SOLID DISPERSION

Famotidine- Kollidon			Famotidine- Povidone K30		
Formulation code	Polymer	Drug: Polymer ratio	Formulation code	Polymer	Drug: Polymer ratio
PM1	Kollidon	1:1	PM2	Povidone K30	1:1
F1	Kollidon	1:1	F9	Povidone K30	1:1
F2	Kollidon	1:2	F10	Povidone K30	1:2
F3	Kollidon	1:3	F11	Povidone K30	1:3
F4	Kollidon	1:4	F12	Povidone K30	1:4
F5	Kollidon	1:5	F13	Povidone K30	1:5
F6	Kollidon	1:6	F14	Povidone K30	1:6
F7	Kollidon	1:7	F15	Povidone K30	1:7
F8	Kollidon	1:8	F16	Povidone K30	1:8

Solubility Studies: The solubility profile of Famotidine was found to be 0.006 mg/ml, and drug release was found to be only 41.13% during *in-vitro* dissolution study, suggesting a strong need to enhance the solubility and dissolution of Famotidine. Therefore, a solid dispersion technique using Kollidon and Povidone K30 was employed for solubility and dissolution enhancement of Famotidine in the present investigation. The improvement in solubility was observed with for all

solid dispersion, Increase in weight fraction of surface-active carrier resulted in an increase in the solubility of all dispersions. Maximum solubility enhancement was found in 1:4 ratio of Famotidine: Kollidon prepared by the kneading method. Enhancement in saturation solubility was found to be in the order of Kollidon > Povidone K30. The solubility of Famotidine was determined in phosphate buffer pH 7.4 by shake flask method.

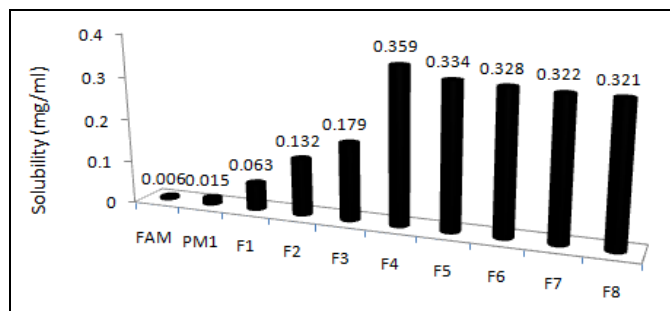


FIG. 1: SOLUBILITY OF FAMOTIDINE, PM1, SDs- KOLLIDON

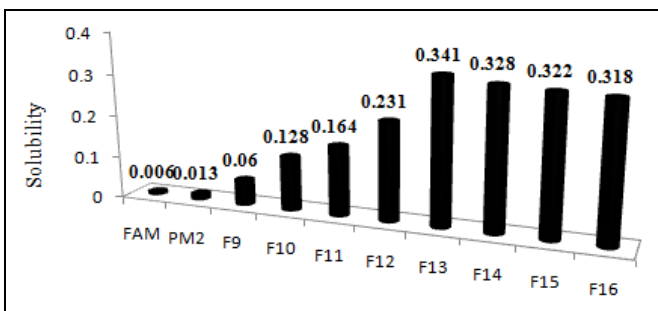


FIG. 2: SOLUBILITY OF FAMOTIDINE, PM2, SDs- POVIDONE K30

Differential Scanning Calorimetry: Famotidine exhibited a characteristic, sharp exothermic peak at 167.58 °C, which is associated with the melting point of the drug and indicates the crystalline nature of the drug; degradation was indicated by an endothermic peak at 124.2 °C. However, the characteristic exothermic peak, corresponding to

drug melting, was broadened and shifted toward a higher temperature with reduced intensity in solid dispersions. DSC studies also showed that there no interaction between drug and carrier at a molecular level in solid dispersions. Indicate that the entire drug has been converted to its amorphous form.

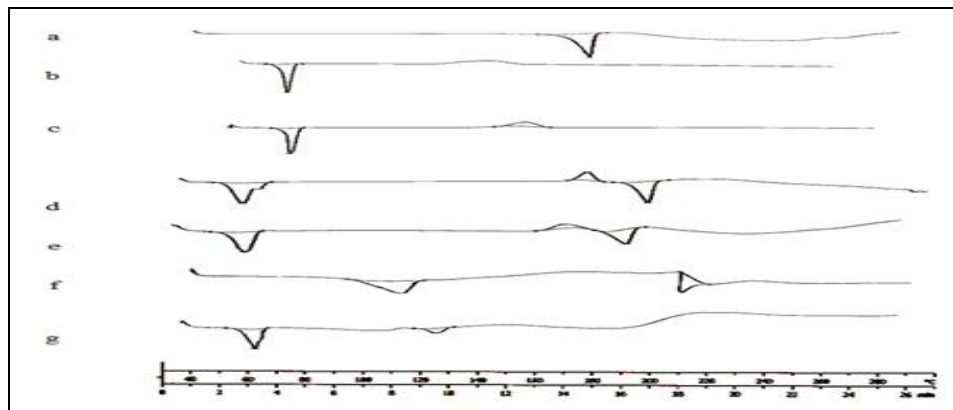
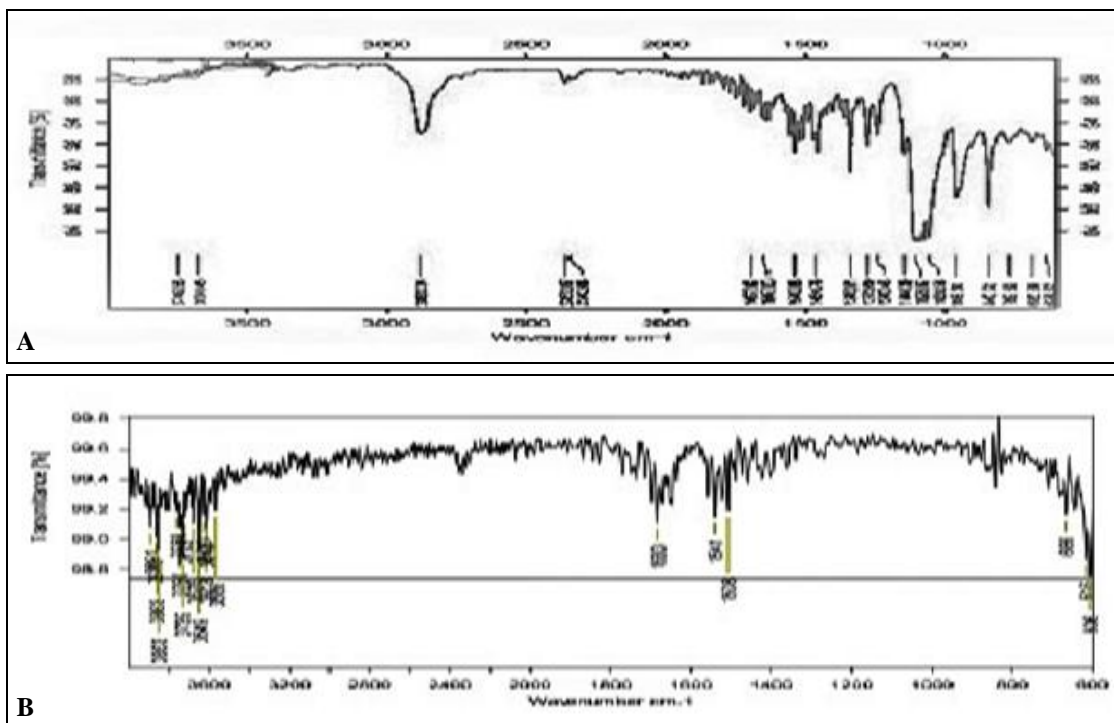


FIG. 3: DSC THERMOGRAMS (A) FAMOTIDINE (B) KOLLIDON (C) POVIDONE K30 (D) PM1 (E) PM2 (F) SDs F4 (G) SDs F13

Fourier Transform Infrared Spectroscopy: FTIR of pure Famotidine showed characteristic sharp peaks 3398, 2883, 2359, 2342, 1636, 1535, 1466, 1459, 1342, 963, 821 cm^{-1} . Kollidon showed characteristic absorption peaks at 3918, 3902, 3890, 3869, 3863, 3613, 3566, 1683, 1541.1762, 1507, 666, 643 and 616 cm^{-1} . Povidone K30 showed characteristic absorption peaks at 1646, 1457, 1519, 1540, 1418, 1285, 837, 742, 680 and

613 cm^{-1} . Whereas SDs F4 peaks were observed at 3398, 2883, 1749, 1716, 1698, 1541, 1469, and 610 cm^{-1} and SDs F13 showed characteristic absorption peaks at 1527, 1436, 1425, 1284, 1274, 1240, 1143, 1113, 847, 772, 745, 685, 666, 605 cm^{-1} . **Fig. 4.** These spectrum observations indicated no interaction between the drug and carrier used in solid dispersion.



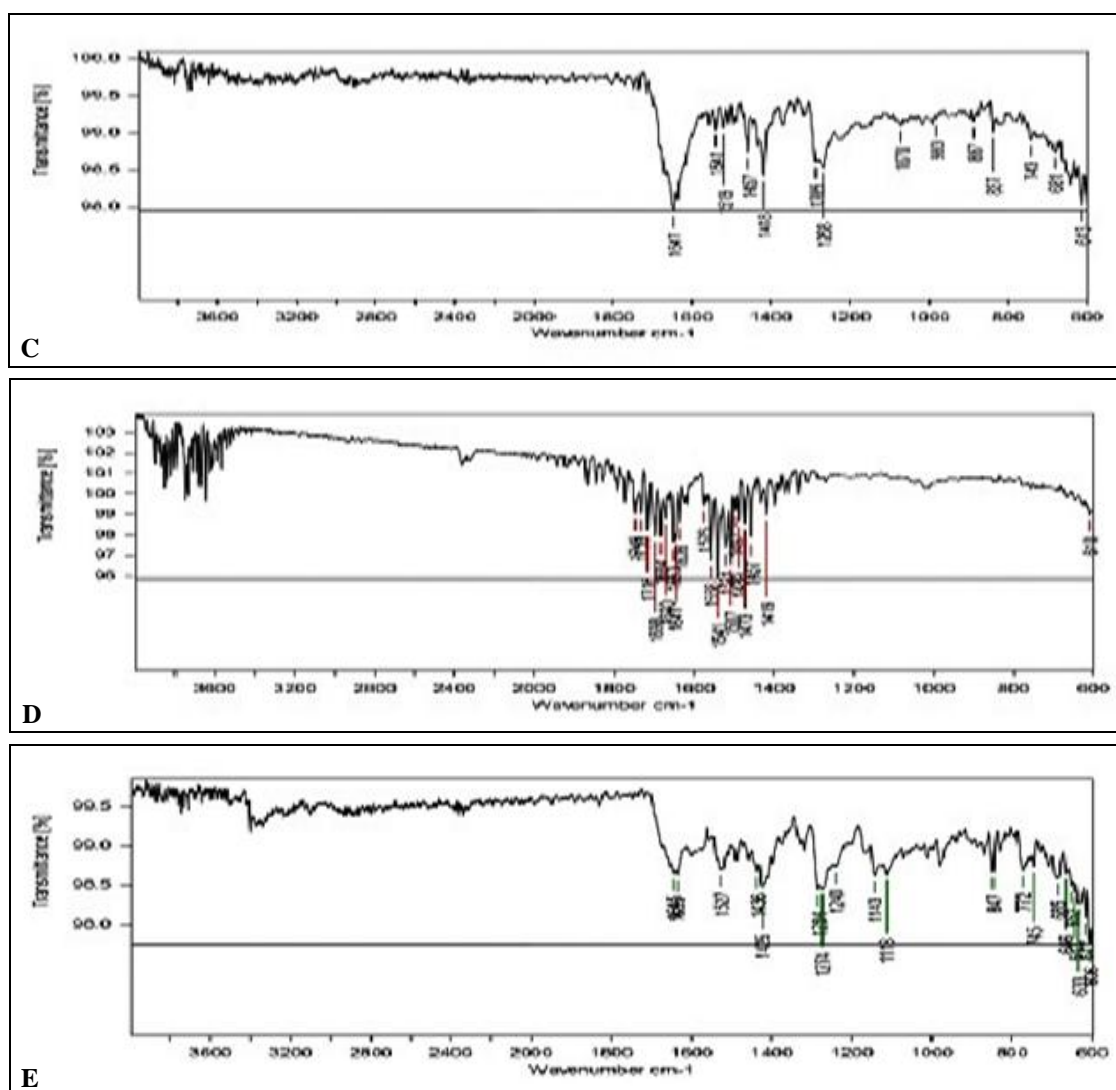


FIG. 4: FTIR SPECTRA A) FAMOTIDINE B) KOLLIDON C) POVIDONE K30 D) SDs F4 E) SDs F13

In-vitro Dissolution Studies: Studies of *in-vitro* dissolution rates allow a comparison to be made between pure drug, physical mixture, and solid dispersion. The *in-vitro* release profile of Famotidine from Kollidon and Povidone K30 solid dispersion (prepared by the kneading method) and physical mixture formulations are shown In vitro dissolution studies in **Table 2** and **3**, and the graph for the comparison of the cumulative percent release is illustrated in **Fig. 5** and **6**. According to observations, drug release was increased with

increasing the concentration of both polymer (*i.e.*, Kollidon and Povidone K30) up to a certain limit, and after that, then it almost becomes constant. Drug release from SDs and physical mixtures was faster than that from the pure drug. The dissolution of the drug from solid dispersion was found to be faster than that from physical mixtures; this may be due to the molecular and colloidal dispersion of drug in the hydrophilic carrier matrix. Among the formulations, batch F4 has shown maximum dissolution efficiencies of 98.00% after 30 min.

TABLE 2: DISSOLUTION PROFILE OF FAM, PM1 AND SDs- KOLLIDON

Time	Fam	PM1	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0	0	0
5	17.12	19.72	41.05	41.4	42.1	48	46.34	45	45.03	42
10	26.33	28.13	46.56	46.24	46.8	49.3	47.88	47	47.7	47.1
15	32.26	36.31	59.13	59.05	59.37	63.42	61.44	59	60.59	59.3
20	36.21	39.68	71.31	71.2	71.55	76.43	73.9	72.4	73.46	72.31
25	38.16	49.01	85.16	85	85.4	87.23	86.1	86	86.21	85.85
30	41.13	59.34	92.48	93.02	93.5	98.2	97.44	96.11	95.93	94.13

Solid dispersion batch F4 was selected for further SEM, and X-RD studies owing to the existence of drugs at the molecular level, as evidenced by the

absence of endothermic peak of the drug during DSC studies, absence of characteristic peak of the drug in the IR spectrum.

TABLE 3: DISSOLUTION PROFILE OF FAM, PM2 AND SDs-POVIDONE K30

Time	Fam	PM2	F9	F10	F11	F12	F13	F14	F15	F16
0	0	0	0	0	0	0	0	0	0	0
5	17.12	17.5	34.2	34.89	34.7	40.88	44.38	42.66	42.24	40.9
10	26.33	27.74	43.7	43.23	43.6	44.1	47.86	46.79	45.98	45.32
15	32.26	36.46	55.7	55.4	55.7	56.55	60.17	58.96	58.22	57.08
20	36.21	39.53	67.3	69.38	67.4	68.1	72.84	70.75	69.98	68.8
25	38.16	48.64	81.32	81.17	81.8	81.98	85.15	84.73	83.56	83.02
30	41.13	58.32	90.9	91.11	91.44	92.1	97.04	95.22	94.67	94.52

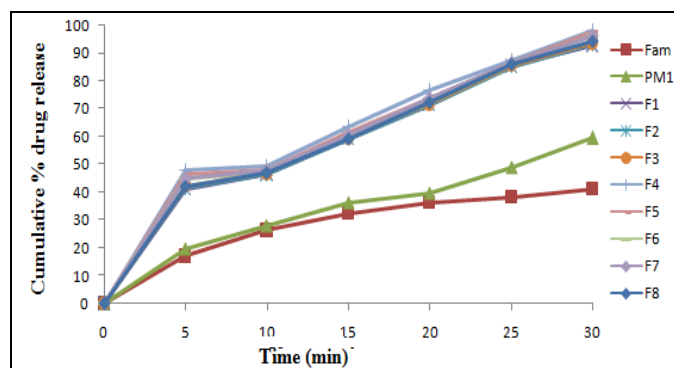


FIG. 5: IN-VITRO DRUG DISSOLUTION OF FAM, PM1 AND SDs FAM-KOLLIDON

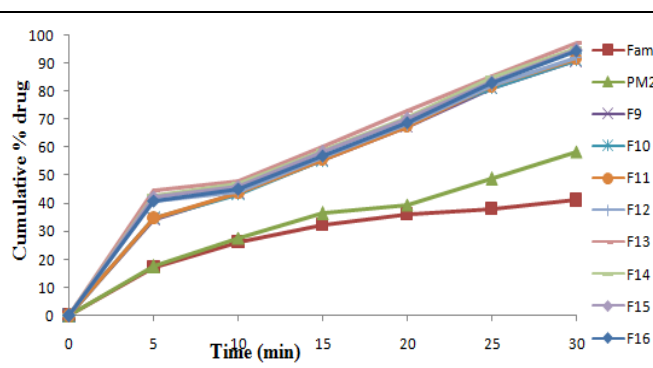


FIG. 6: IN-VITRO DRUG DISSOLUTION OF FAM, PM2 AND SDs FAM-POVIDONE K30

Powder X-ray Diffraction Studies: The XRD patterns of Famotidine, Famotidine - Kollidon and Famotidine - Povidone K30 Physical mixture and Famotidine - Kollidon and Famotidine - Povidone K30 SDs were shown in **Fig. 7**. In the X-ray diffractogram of pure Famotidine, a sharp peak is presented at a diffraction angle (2θ), are presented, and it confirms that the drug is in the crystalline form. Typical diffraction peaks of Famotidine in

physical mixture indicate the presence of free crystalline drugs, which were revealed by few broad peaks of low intensity, which emerged on the background of Kollidon as an amorphous carrier. The reduction in intensity and number of typical diffraction peaks of Famotidine in SD X-ray diffractogram suggests the reduction in the crystalline nature of the drug.

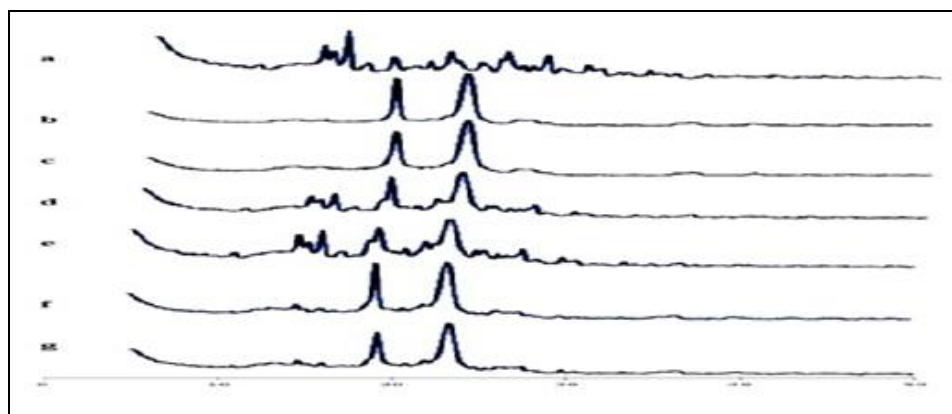


FIG. 7 XRPD PATTERNS OF (A) FAMOTIDINE (B) KOLLIDON (C) POVIDONE K30 (D) PM1 (E) PM2 (F) SDs F4 (G) SDs F13

Scanning Electron Microscopy: SEM scanning electron micrographs of pure Famotidine, pure Kollidon and SDs (F4) are shown in **Fig. 8**.

Famotidine was present in a crystal form. Kollidon was present in a globular form. The surface morphology of SDs indicates that Famotidine was

adsorbed into the Kollidon and homogeneously dispersed into the polymer. SEM pictures images suggested that the individual surface properties of

Famotidine and Kollidon were lost during kneading and the formation of effective SD systems.

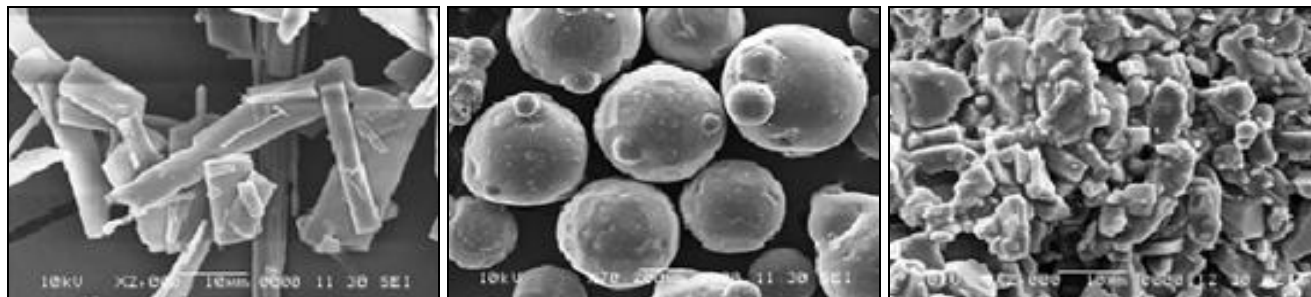


FIG. 8: SCANNING ELECTRON MICROGRAPHS (A) FAMOTIDINE (B) KOLLIDON (C) SDs F4

CONCLUSION: The study shows that the dissolution rate of Famotidine can be enhanced to a great extent by solid dispersion technique using an industrially feasible kneading method, without any physical and chemical interaction.

Solid dispersion of Famotidine - Kollidon showed faster release than from that of Povidone K30. Solid dispersion of Famotidine - Kollidon (1:4) showed the maximum dissolution efficiency among all solid dispersion and physical mixtures.

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CONFLICTS OF INTEREST: There is no conflict of interest for all authors.

REFERENCES:

- Chiou WL and Riegelman S: Preparation and dissolution characterization of several Fast release Solid Dispersions of Griseofulvin. *J Pharm Sci* 1969; 58: 1505-10.
- Chiou WL and Riegelman S: Pharmaceutical applications of Solid Dispersion Systems. *J Pharma Sci* 1970; 1281-02.
- Chiou WL and Niazio S: Phase diagram and dissolution rate studies on sulpha thiazole-urea solid dispersions. *J Pharma Sci* 2006; 60: 1333-38.
- Dallob A, Hawkey CJ and Greenberg H: Characterization of Etoricoxib, a novel selective Cox-2 inhibitor. *J Clin Pharmacol* 2003; 43: 573-85.
- Kamal D, Ramana MV, Sara UVS, Himaja M and Garg V: Dissolution Enhancement of Aceclofenac through Solid Dispersions. *The Indian Pharmacist* 2002; 6: 70-72.
- Khan KA: The concept of dissolution efficiency. *J Pharma col* 1975; 27: 48-49.
- Leunerc and Dressman J: Improving drug solubility for oral delivery using solid dispersions. *Eur J Pharm Bio Pharm* 2000; 50: 47-60.
- Liu C and Desai KG: Characterization of Rofecoxib-PEG 4000 Solid Dispersions and tablets based on Solid Dispersions. *Pharma Dev Technol* 2005; 10: 467-77.
- Loyd V, Allen Jr, Levinson RS and Martono DD: Dissolution rates of Hydrocortisone and Prednisone utilizing sugars Solid Dispersion systems in tablet form. *J Pharma Sci* 2006; 67: 979-81.
- Chutimaworapan S, Ritthidej GC, Yonemochi E, Oguchi T and Yamamoto K: Effect of water soluble carriers on dissolution characteristics of nifedipine solid dispersions. *Drug Dev Ind Pharm* 2000; 26: 1141-50.
- Chen Y, Zhang G, Neilly J, Marsh K and Sanzgiri Y: Enhancing the bioavailability of ABT-963 using solid dispersion containing Pluronic F-68. *IJP* 2004; 286: 69-80.
- Anguiana-IS Otero-EFJ, Vila-Jato JL and Blanco- Mendez J: The properties of solid dispersions of clofibrate in polyethylene glycol. *Pharm. Acta Helv* 1995; 70: 57-66.
- Arias MJ, Gines JM, Moyano JR and Rabasco AM: Dissolution properties and in vivo behaviour of triamterene in solid dispersions with polyethylene glycols. *Pharm. Acta Helv.* 1996; 71: 229-35.
- Betageri GV and Makarla KR: Enhancement of dissolution of glyburide by solid dispersion and lyophilization techniques. *Int J Pharm* 1995; 126: 155-60.
- Ford JL: The current status of solid dispersions. *Pharm Acta Helv* 1986; 61: 69-88.
- Prasanthe NL, RamaRao N and Manikira SS: *Asian Journal Pharm Clin Res* 2010; 3(2): 95.
- Barzegar JM, Maleki N, Garjani A, Khandar AA and Haji HM: Enhancement of dissolution rate and anti-inflammatory effects of piroxicam using solvent deposition technique. *Drug Dev Ind Pharm* 2002; 28(6): 681-86
- Ginés M, Arias MJ, Moyano JR and Sanchez SPJ: Thermal investigation of crystallization of poly (ethylene glycol) s in solid dispersions containing oxazepam. *Int J Pharm* 1996; 143: 247-53.
- Williams AC and Timmins P: Disorder and dissolution enhancement: Deposition of ibuprofen on to insoluble polymers. *Eur J Pharm Sci* 2005; 26: 288-94.

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