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RESEARCH ARTICLE

DESIGN AND DEVELOPMENT OF SOLID DISPERSION SYSTEM OF ZOLMITRIPTAN

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ABSTRACT

Zolmitriptan is a potent anti-migraine drug. The bioavailability of Zolmitriptan is about 40% via oral dosage forms and problem arises from its low water solubility and dissolution rate. The present study deals with formulation of solid dispersions of variying ratios of Zolmitriptan (ZMP) and urea or poly vinyl pyrrolidone K-30 (PVP K-30) or PEG-6000 were prepared by hot melt and solvent evaporation methods in an effort to increase the dissolution rate as well as bioavailability of the drug. The properties of solid dispersions were characterized by FTIR , XRD and DSC. FTIR analysis demonstrated the presence of intramolecular hydrogen bonds between Zolmitriptan and PVP K-30 in solid dispersions. Dissolution studies indicated that the dissolution rate were markedly increased in these solid dispersions systems compared with those in physical mixtures. The increase in dissolution rate strongly depended on the type, ratios of drug to carriers and selection of the method of preparations of solid dispersions. The solid dispersions compound prepared in the ratio of 1:5 by the PVP K-30 showed the higest improvement in wettability and dissolution rate of ZMP. XRD studies proved that the amorphous ZMP-PVP K30 solid dispersions was formed only at the 1:5 drug to PVP weight ratio. This formulation was found to show a significant improvement in terms of the drug release with complete release of drug compared to physical mixtures and other formulations. So this amorphous solid dispersions may be useful further to formulate in a suitable dosage form.

Keywords: Solid dispersion, Zolmitriptan, Urea, Polyvinyl Pyrrolidone K-30, PEG-6000, Dissolution Studies.

INTRODUCTION:

Zolmitriptan is an anti migraine drug. It is widely used for the acute treatment of migraines with or without aura. Solid dispersion technique has been extensively used to increase the solubility of a poorly water-soluble drug [1]. A drug is thoroughly dispersed in a water-soluble carrier by suitable method of preparation. The mechanism by which the solubility and the dissolution rate of the drug is increased includes, the particle size reduced to submicron size or to molecular level, the drug is changed from crystalline to amorphous form, the high energetic state, the wettability of the drug particle is improved [2-3]. Solid dispersions are generally prepared by one of two methods, co-melting of drug carrier mixtures or dissolving drug and carrier in a mutual solvent followed by solvent removal. Neither method, as traditionally used, is ideal from the perspective of scale up. However, well-known processing techniques from the polymer industry, such as melt extrusion, compression molding, transfer molding and injection molding, could be imported and tailored for highly efficient and controlled production of pharmaceutical products [4-6]. For example, direct extrusion of melts into hard gelatin capsules, or the compression moulding of transdermal patches, could be possibilities for large scale manufacturing [7-9].

The bioavailability of Zolmitriptan is about 40% via oral dosage forms & its problem arises from its low water solubility and dissolution rate. Oral Zolmitriptan administration is characterized by slow absorption. Zolmitriptan is available in the market as a tablet, conventional dosage form. But this formulation suffers from the bioavailability problem [10-12]. The main goal of this experiment was to improve its bioavailability. The solid dispersion technique was applied in order to improve the dissolution rate of Zolmitriptan. PEG-6000, PVP-K30 and Urea were selected as carriers. The formulations were optimized at various drugs to carrier weight ratio, because if the bioavailability of drug increases the dose sizes can be reduced. These reduced dose sizes produces less adverse effects and prices of dosage form can also be minimized

MATERIALS AND METHODS:

Zolmitriptan was obtained from Glenmark Pharmaceutical Ltd., Mumbai as a gift sample. Urea (Rankem, New Delhi), PEG-6000 (Qualigens, Mumbai) and PVP K30 (Loba Chemicals Pvt. Ltd., Mumbai) were

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employed in this study. All other reagents were of analytical grade.

Selection of carriers, solvent, drug polymer ratio and methods of preparation of solid dispersions and physical mixtures:

The PVP K30, PEG-6000 and Urea were selected as carriers. These carriers were used for the preparation of the solid dispersions and physical mixture, but for solvent evaporation methods anhydrous methanol was selected as a solvent. The 1:1, 1:5 and 1:8 drug polymer ratio were selected for both melt method and solvent method to prepare of solid dispersions. Out of these formulations PVP K30 physically decomposed when the temperature rose to 150°c and the color of the PVP K30 crystal gradually changed from white to yellowish-brown and its became too sticky, that's why melt method by using PVP K30 was discarded, therefore only solvent method was selected for PVP K30 for preparation of solid dispersions [13].

Preparation of Physical mixtures:

Physical mixtures (PMs) were prepared by mixing Zolmitriptan (ZMP) with urea or PEG-6000 or PVP K30 at 1:1, 1:5 and 1:8 weight ratios, using glass mortar and pestle. The mixture was passed through a 60 mesh sieve [14].

Preparation of Solid dispersions:

Melting method:

The PMs were heated by stirring at 150°c in an oil bath to achieve a homogenous dispersion. When the solid was completely dissolved, the hot liquid was shifted to a water bath (99°c) with continued stirring. It was then subsequently cooled under the ice cooling. The congealed mass was pulverized, passed through 30 meshes, stored in desiccators (48h) and passed through 60 meshes before packing in an airtight container [15].

Solvent evaporation method:

The PMs were dissolved in a minimal volume of anhydrous methanol, and the solvent was removed by slow evaporation under reduced pressure. The dried co-precipitate was passed through 30 meshes, stored in desiccators (48h) and passed through 60 meshes before packing in an airtight container [16].

Fourier transforms infrared spectroscopy:

FTIR spectra were recorded on a Perkin-Elmer Fourier transform infrared spectrophotometer with resolution of 2 cm^{-1} from 4000 to 400 cm^{-1}. Samples for analyzing were prepared by gently mixing the test samples with KBr. Polystyrene was used to check the Spectrophotometer Calibration.

Powder X-ray diffraction studies:

XRD were obtained using a powder X-ray diffractometer (Ultima III, Rigaku) by employing a CuK_{α} radiation source operating at 40 kV, 20 mA, collimated by a 0.080 divergence and a 0.20 receiving slit and 30 min^{-1} scanning rate over the 50 to 500 (2θ) range. The positions and intensities of diffraction peaks were considered for the identification and comparison of crystallinity of the drug or carrier.

Differential Scanning Calorimetry:

Thermal analyses were performed in a Perkin-Elmer DSC-7 differential scanning calorimeter. Samples were accurately weighed (5–8 mg) into aluminum pans and thermo grams obtained at a heating rate of 10°C min^{-1} over a temperature range of 20–300°C under nitrogen atmosphere.

Dissolution studies:

The dissolution behavior of physical mixtures and ZMP solid dispersions were investigated by using the USP XXII rotation basket method, (VEEGO VDA-6D) at 50 rpm. Powder samples of physical mixtures and ZMP solid dispersions containing 2.5 mg equivalent weight of ZMP were filled into capsules. The dissolution medium consisted 900 ml of 0.1(N) HCl was filled into glass vessels as a dissolution medium and temperature was maintained at 37±0.5°C stirring at 50 rpm. 5 ml of aliquot was taken out at predetermined intervals and the same volume of fresh dissolution medium at the same temperature was replaced. The concentration of ZMP in the solution was determined spectrophotometrically at 283 nm. Each test was performed in triplicate [12-14].

Stability studies:

A stability study of selected best formulation was carried out by keeping at ambient room temperature condition for 3 months. Best formulation was subjected to physical examination and drug content analysis before and after stability study [14].

Data analysis:

Results are expressed as mean values and standard deviation (±S.D.) and the significance of the difference observed was analyzed by the Student's t-test. In all tests, a probability value of $P < 0.05$ was considered statistically significant.

RESULTS AND DISCUSSIONS:

The solid dispersions of drug; ZMP: urea or PVP K30 or PEG 6000 at various ratios (1:1, 1:5 and 1:8) was prepared and their dissolution rates and physical state properties were characterized. Solid dispersions formulations were prepared by melting and solvent methods. The results of the studies showed that the dissolution rate of ZMP increased markedly when present in solid dispersions in comparison with the physical mixtures and the pure drug. There were large differences between various types of solid dispersions. The amounts of dissolved ZMP after 180 mins dissolution were measured. The data showed that the amount and type of the carriers has big influenced on the dissolution of the drug in ZMP: carrier system. According to the dissolution rate studies, the best results were obtained with 1:5 mixing ratio of PVP K 30 in solvent method, which showed the most significance improvement in dissolution rate, 99 % drug released within 1 hr.

The **FTIR spectrum** (fig. 1) of Zolmitriptan exhibited characteristic signals at 1369.7 cm^{-1} (C-N stretching vibrations), 2974 cm^{-1} (C-H stretching vibrations), 1735.8cm^{-1} (C=O stretching vibrations), 1257.8cm^{-1} (C-O stretching vibrations) and 3348.8cm^{-1} (N-H stretching vibrations) respectively. PEG-6000 exhibited a broad O-H stretching vibration at 3431.9cm^{-1}, C-H stretching of OC_2H_5 groups at 2886.2 cm^{-1}. ZBP5 showed superimposed spectra of ZMP and PEG-6000. The transmittance intensities of N-H stretching band of ZMP were reduced markedly and broad OH stretching band of PEG-6000 slightly shifted to lower frequency 3422.7cm^{-1} in ZBM5. PVP-K30 showed a broad C-H stretching vibration at 3337.2 cm^{-1}, C=O stretching at 1643.9 cm^{-1} and C-N stretching at 1464.3cm^{-1}. ZCP5 showed superimposed spectra of ZMP and PVP-K30. ZCS5 showed the reduced transmittance intensities of C=O stretching band of ZMP and N-H stretching band of ZMP shifted to lower frequency. From these results, it can be speculated that drug–carrier hydrogen bonding existed in ZBM5 SDs, causing reduced drug recrystallization. The spectra of PMs were indicating that no interaction occurred between drug and carriers. Spectra of ZBM5 and ZCS5 showed that some interaction occurred between the drug and carriers but these did not seem to affect the drug release from the formulations.

XRD patterns for ZMP, PVPK30, physical mixture (ZCP5) and solid dispersion (ZCS5) were shown in fig. 2. PVP K30 is an amorphous powder having no-crystalline structure. Characteristic peaks of ZMP appeared at a diffraction angle of 2θ at 19.4, 22.1, 23.6 and 28.4. The XRD patterns of ZMP were similar to those of physical mixtures indicating that the crystallinity of ZMP did not change in the physical mixtures. This was consistent with the results obtained by FTIR studies. The XRD pattern of solid dispersion was different from those of ZMP and physical mixtures (fig.2). Less no. of detectable diffraction peaks were observed for drug: PVP K30 (1:5) solid dispersion, indicating the presence of the drug may be due to in an amorphous form. The certain of intermolecular hydrogen bonding interaction between ZMP and PVP by FTIR analysis possibly retarded drug recrystallization and causing ZMP to be precipitated out in an amorphous form. The relatively intense peaks of the ZMP also present in the physical mixture of ZCP5, but the intense diffraction peaks of ZMP were less prominent in the ZCS5 (solid dispersion). These results may be suggested that some portion of ZMP till existed in the same crystal structures of pure drug. The lack of numerous distinctive peaks of the drug in the solid dispersion (ZCS5) demonstrated that a high concentration of drug was dissolved in the solid-state carrier matrix in an amorphous structure. The peaks height showed the crystallinity of formulations. In SDs the intensity of peaks were lower than the PMs, these showed that the ZMP present in the SDs would be mostly in amorphous state.

DSC thermograms for ZMP shown in fig. 3. Pure ZMP gave a melting endotherm at 137.08^{o}C. DSC tharmograms of PVP K30, solid dispersions and physical mixtures showed the broad endotherms due to water removal.

The **dissolution profiles** of ZMP: PVP K30, physical mixture and solid dispersions which are prepared by melting and solvent methods where shown in fig. 4 & 5. Solid dispersions of urea and PVPK30 exhibited faster dissolution rates than their corresponding physical mixtures. The enhanced dissolution rate of ZMP from the solid dispersions might be due to the increase in drug wettability and the drug: carrier interactions. The best dissolution rate was obtained with PVPK30. As shown in fig. 4 & 5 the drug PVP K30 solid dispersions with 1:5 mixing ratio in solvent method exhibited faster dissolution, 99 % of the dug being dissolved within 60 mins. The relative dissolution potency of the carriers with the drug, with the simple PMs might be ranked as PVP K30 > PEG 6000 > urea. The relative dissolution potency of the PMs was ZBP5 > ZAP1 > ZBP8 > ZAP5 > ZCP5 > ZCP1 > ZBP1 > ZCP8 > ZAP8. The relative dissolution potency of the different ratios was ZCS5 > ZCS1 > ZCS8 > ZBM5 > ZBS5 > ZAM1 > ZAS5 > ZBS8 > ZBS1 > ZAM5 > ZBM8 > ZBM1 > ZAS1 > ZAS8 > ZAM8. The percent drug released at the end of the study, of the every formulation was considered for statistical evaluation. Dissolution profiles of ZMP from the capsules are shown in figures 4 & 5. The solid dispersion capsules showed a more rapid dissolution

of ZMP than the physical mixture. The melts, as well as the co-precipitates with all the carriers and mixing ratios, had significantly improved dissolution rates than the corresponding PMs. Among the three carriers, PVP K30 showed the highest dissolution rate with respect to PMs for all mixing ratios and methods of preparation. As the 1:5 mixing ratio of PVP K30 in solvent method showed the most significant improvement in dissolution rate, 99% drug released within 1 hour. In different ratios of PEG 6000, 1:5 melt method showed the best result and in urea 1:1 melt method showed the best result. It was shown that the formulations did not follow only zero order, first order & Higuchi model kinetics, and it may be concluded that all formulations followed the mixed order release kinetics.

Solid dispersion prepared with PVP K30 (ZCS5) was selected as best formulation, which showed promising results. It was subjected to stability study at ambient room condition for 3 months. After 3 months, SDs did not show any change in physical appearance or drug content. It indicates that drug was stable in SDs even after 3 months of short term storage.

The **F-ratio** test was employed in order to find out whether the 24 sets of data obtained after dissolution study are the same or they differ from each other. For the F-ratio test, the % drugs released at the end of the study were taken into consideration. Tabulated value of F (23, 48) at 1% level of significance is 1.74. The calculated value is greater than the tabulated value. Hence the null hypothesis is rejected. It has been noted that all 24 sets of data differ from each other. Hence, it may be inferred that the test preparations are not the same, but are different in their formulations and carriers. Further, the **t-test** was then applied to find out whether the difference is significant or not. It is concluded from t-test that the level of significance is almost <0.001.

Table 1: Composition of various formulations (amount of ZMP & carriers in different ratio)

Drug: Carrier	*UREA* **(A)***(mg)*			*PEG-6000* **(B)***(mg)*			*PVP K30* **(C)** *(mg)*		ZMP **(Z)**(mg)
Ratio	MM **(M)**	SM **(S)**	PM **(P)**	MM **(M)**	SM **(S)**	PM **(P)**	SM **(S)**	PM **(P)**	
1:1 **(1)**	50*	50	50	50	50	50	50	50	50
1:5 **(5)**	250**	250	250	250	250	250	250	250	50
1:8 **(8)**	400***	400	400	400	400	400	400	400	50

MM-Melting Method, SM-Solvent evaporation Method, PM-Physical mixtures**,** Name of the formulations were given as for examples *ZAM1, **ZAM5, ***ZAM8.

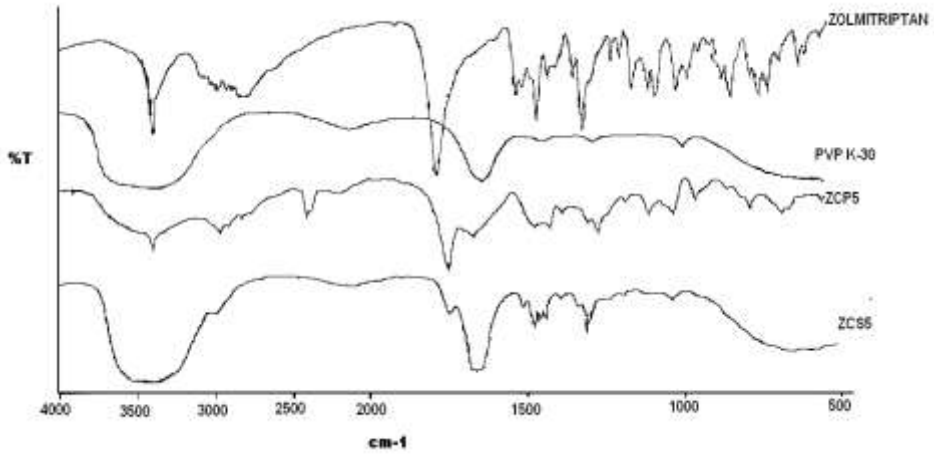

Figure 1: FTIR spectra of pure Zolmitriptan, PVP K-30, ZCP5 and ZCS5.

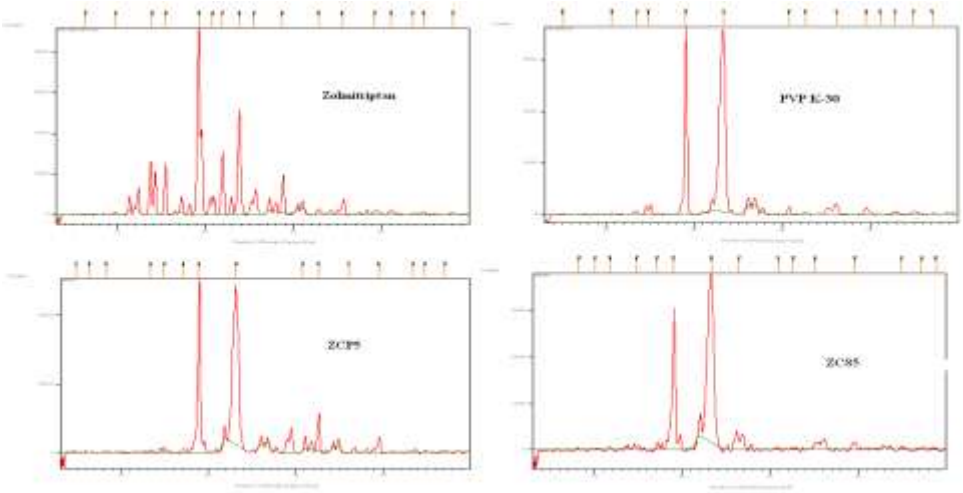

Figure 2: XRD patterns of pure Zolmitriptan, PVP K-30, ZCP5 and ZCS5.

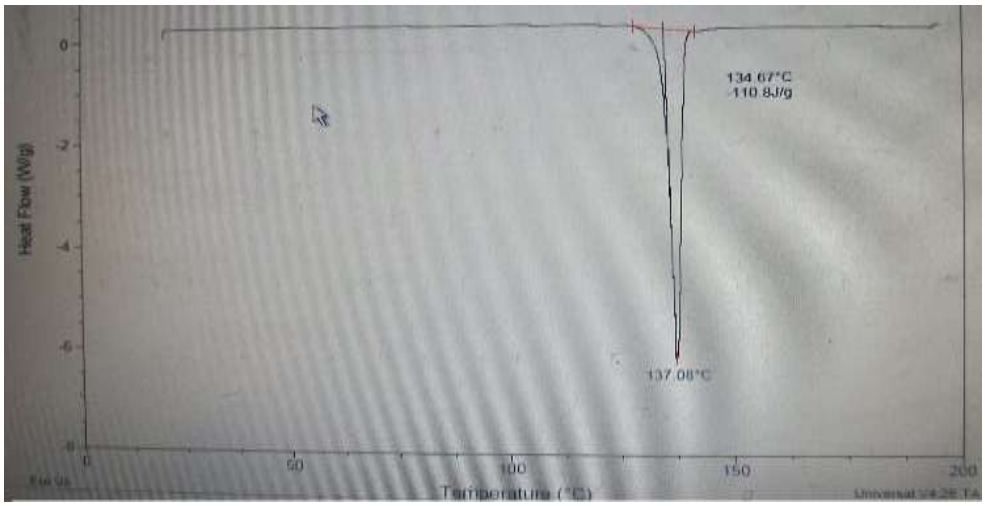

Figure 3: DSC patterns of pure Zolmitriptan.

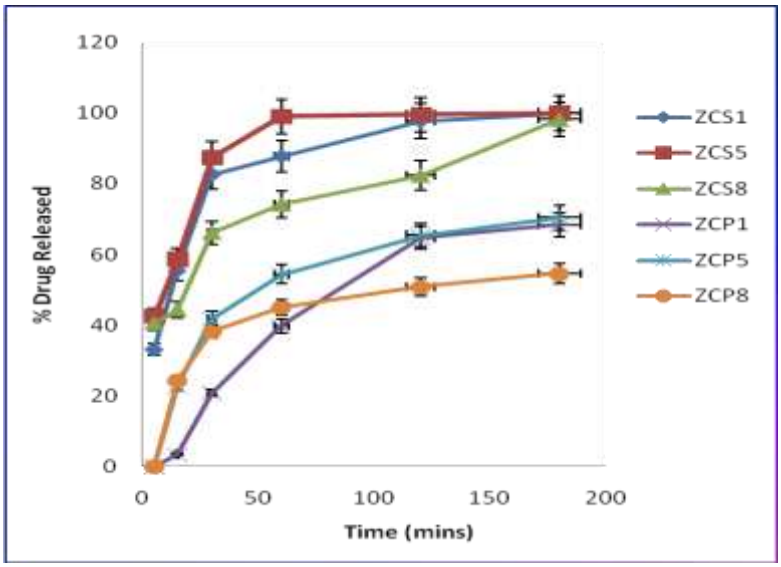

Figure 4: Zero order dissolution plots of physical mixtures and solid dispersions prepared by PVP K 30 in all ratios.

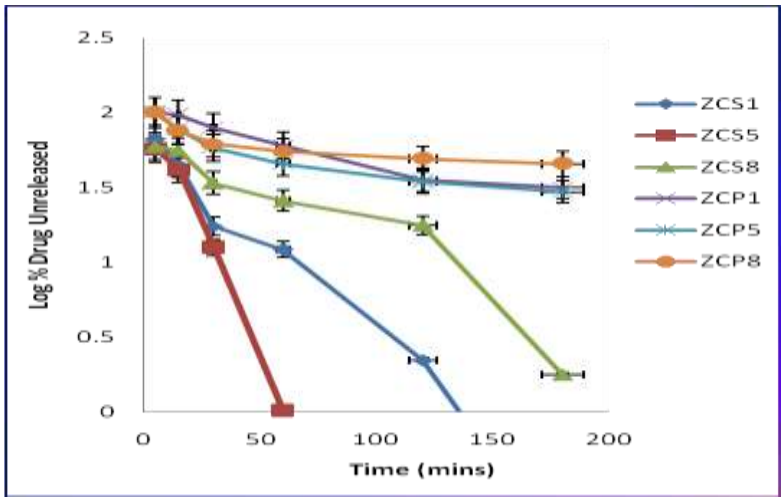

Figure 5: First order dissolution plots of physical mixtures and solid dispersions prepared by PVP K 30 in all ratios.

CONCLUSION:

Among numerous ways of enhancing drug dissolution, solid dispersion of drug in a water soluble polymer is one of the promising techniques. An obstacle of solid dispersion technology in pharmaceutical product development is that a large amount of a carrier, i.e. more than 50% to 80% w/w, was required to achieve the desired dissolution. This high percentage of carrier causes consistency of product performance at the time of manufacturing. This is a major consideration in that the number of market products arising from this approach has been less than expected. Recently, combined carriers have been used and a higher increase in drug dissolution was reported. However, those reported solid dispersions were still a very low percentage of drugs loading in the system, which required an extremely high amount of carrier. High drug loaded solid dispersion with high drug dissolution enhancement is not an easy task since the drug presented in such a system is in complete crystal has high crystallinity. Therefore, the strategy of high drug loaded solid dispersion systems with enhanced drug dissolution still needed to be improved. In this study Zolmitriptan solid dispersions were prepared with combination of three carriers PVP K30, PEG 6000 and urea in different drug to carrier ratios. These formulations were evaluated for in vitro dissolution studies, XRD, and FTIR spectroscopy. Solid state characterization indicated Zolmitriptan was present as amorphous material and entrapped in carriers matrix and it have some interaction with carriers but it not affects the drug release from the formulations. In contrast to the low solubility of pure drug and slow dissolution rate of physical mixtures of Zolmitriptan, the dispersion of the drug in the carriers considerably enhanced the dissolution rate. This can be attributed to improved wettability and dispensability, as well as decrease of the crystalline and increase of the amorphous fraction of the drug. Solid dispersion prepared with PVP K30 (ZCS5) showed the highest improvement in wettability and dissolution rate of Zolmitriptan.

REFERENCES:

1. MK Vadnere. Co precipitates and melts. In: Swarbrick J editor. *Encyclopedia of pharmaceutical technology*. Vol-2. USA: Informa Healthcare. 2007; PP. 774-81.
2. A Raza, TM Ansari, SB Niazi. A novel spectrophotometric method for determination of Zolmitriptan in pharmaceutical formulations. *Journal of the Chinese Chemical Soceity*. 2007; 54(6):1413-7.
3. Z Aydogmus, I Inanli. Extractive spectrophotometric methods for determination of Zolmitriptan in tablets. *Journal of AOAC International*. 2007; 90(5):1237-41.
4. SGV Kumar, DN Mishra. Preparation, characterization & In vitro dissolution studied of solid dispersion of Meloxicam with PEG 6000. *Yakugaku Zasshi*. 2006; 128(8):657-64.
5. S Okonogi, S Puttipipatkhachorn. Dissolution improvement of high drug –loaded solid dispersion. *AAPS Pharm Sci Tech*. 2006; 7(2):52.
6. VP Patel, NM Patel, BG Chaudhary. Effect of water soluble polymers on dissolution profile of Glipizide cyclodextrins complex. *Indian Drugs*. 2007; 44(10):761-6.
7. RP Patel, MM Patel. Physiological characterization and dissolution study of solid dispersion of Lovastatin with PEG 4000 & PVP K30. *Pharmaceutical Development and Technology*. 2007; 12(1):21-33.
8. KP Chowdhary, SS Rao. Dissolution rate and formulation studies on solid dispersion of

Itraconazole. *Indian Journal of Pharmaceutical sciences*. 2000; 62(6):471-4.

9. S Wook, J Kim, M Soo, Jo, Hyun G, Lee, Sibeum, Woo, Soo J, Park, Sook J, Hwang, S Joo. Cefuroxime Axetil solid dispersions prepared using solution enhanced dispersion by supercritical fluids. *Journal of Pharmacy and Pharmacology*. 2005; 57(12):1529-37.

10. K Goracinova, L Klisarova, A Simi, EF Kumbaradzi, K Meadenovska, M Glavas. Drug dissolution profiles and physico-chemical stability evaluation of controlled release solid dispersions granules. *Bulletin of the Chemists and Technologists of Macedonia*. 11998; 17(1):33-9.

11. P Dangprasirt, S Ponwai. Developent of Diclofenac Sodium controlled release solid dispersion powders and capsules by freeze drying technique using ethylcellulose and chitosan as a carrier. *Drug Dev Ind Pharm*. 1998; 24(10):947-53.

12. ATM Serajuddin. Solid dispersion of poorly water soluble drugs: Early promises, subsequent problems, and recent breakthroughs. *Journal of Pharmaceutical Sciences*. 2000; 88(10)1058-66.

13. KP Chowdhary, SS Rao. Investigation of dissolution enhancement of Itraconazole by solid dispersion in super disintegrates. *Drug Dev Ind Pharm*. 2000; 26(11):1207-11.

14. R Pignatello, M Ferro, G Puglisi. Preparation of solid dispersion of NSAIDS with acrylic polymers and studied on mechanism of drug polymer interactions. *AAPS Pharm Sci Tech*. 2002; 3(2):10.

15. F Sadeghi, HA Garekani, R Sadeghi. Comparison of ethylcellulose matrix characteristics prepared by solid dispersion technique or physical mixing. *Daru*. 2003; 11(1).

16. G Derricks, R Vandecryys, VD Conde, L Baert, J Peeters, ME Brewster. The use of three different solid dispersion formulations melt extortion, film coated beads, glass thermoplastic system to improve the bioavailability of a novel microsomal triglyceride protein inhibitor. *J Pharm Sci*. 2004; 93(5).

