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### Formulation and Evaluation of Solid binary systems of an Antipsychotic Drug by Using a modified Carrier

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#### ABSTRACT

*The aim of the study was to formulate and evaluate solid binary systems of the poorly water-soluble novel antipsychotic drug ziprasidone hydrochloride. The solid binary systems were prepared by using a new carrier (modified starch such as starch phosphate) for improving the dissolution properties. Starch phosphate was prepared by a reported method. The solid binary systems were prepared by kneading method in different drug to carrier molar ratios (1:1, 1:3, 1:9 and 1:19). Evaluation of the solid binary system was performed using dissolution studies, Differential thermal analysis, Infrared Spectroscopy and X-ray powder diffraction studies. All the solid binary systems showed dissolution improvement when compare to pure drug and physical mixture to varying degrees, binary systems prepared by kneading method in 1:9 drug to carrier ratio exhibited the highest drug release. Mathematical modeling of in vitro dissolution data indicated the best fitting with Korsmeyer-Peppas model and the drug release kinetics primarily as Fickian diffusion.*

**Key words:** Anti psychotic drug, starch phosphate, solid binary systems, kneading method, mathematical modeling.

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#### INTRODUCTION

Starch phosphate (SP) is a modified starch that has been chemically processed to insert phosphate group in place of hydroxyl group. Though many modified starches have been studied [1-4] widely for their pharmaceutical applications, SP has not been investigated thoroughly. The objective of the present investigation is to evaluate SP as a carrier for formulating solid binary systems for a poorly soluble antipsychotic drug ziprasidone hydrochloride to improve the dissolution rate and efficiency of ziprasidone.

Aqueous solubility of a drug can be a critical limitation to its oral absorption. Poorly water-soluble drugs are associated with slow drug absorption leading eventually to inadequate and variable bioavailability [5, 6]. Nearly 40% of the new chemical entities currently being discovered are poorly water-soluble drugs [7, 8]. Based upon their solubility and permeability characteristics, the Biopharmaceutical Classification System (BCS) categorizes drugs in two major classes, class II and IV [9]. The BCS class II drugs are poorly water-soluble entities with high permeability. They pose serious delivery challenges like incomplete release from the dosage form, poor bioavailability, increased food effect and high inter-patient variability [10]. The enhancement of oral bioavailability of poorly water-soluble drugs remains one of the most challenging aspects of drug development although salt formation, solubilization and particle size reduction have commonly used to increase the dissolution rate that in turn improved drug absorption or bioavailability. Preparation of solid binary systems is another popular approach used to improve the oral bioavailability of poorly water-soluble drugs [11-13].

Ziprasidone (ZPR), Diethyl (E)-4-{2-(*tert* butoxy-carbonyl)vinyl}phenyl-1,4-dihydro-2,6-dimethyl pyridine-3,5-dicarboxylate. It is a novel antipsychotic with high affinity for dopamine D2 and D3, serotonin 5HT2A, 5HT2C and 5HT1D receptors and high affinity for the 5HT1A receptor, where it acts as a potent agonist [14, 15]. ZPR was chosen as a model candidate because of its low solubility [16].

The aim of the present study was to prepare and characterize the solid binary systems of ZPR with modified starch (starch phosphate), which was prepared in the laboratory by a reported method [17]. The current studies exploring the mechanism of drug release through mathematical modeling for all the solid binary systems and solid-state characterization of the most promising one. The results obtained for the solubility and dissolution enhancement of this model drug can be rationally extrapolated to other poorly soluble therapeutic agents too.

## MATERIALS AND METHODS

### Materials

Ziprasidone was obtained as gift sample form Dr. Reddy's laboratories, Hyderabad. Starch, mono sodium phosphate dihydrate were procured from S.D. fine chemicals, Mumbai. Starch phosphate was prepared in the laboratory. All other materials were of analytical grade.

### Preparation of starch phosphate (SP)[17]:

Disperse 1 mole of starch into the 1/2 mole of mono sodium phosphate dihydrate solution and stir the slurry for about 10 min. Swollen starch granules were collected by filtration and filter cake was broken up and dried in the air for 30 min. The dried starch lumps were heated in a vacuum oven at 135°C for 3 hours. The dried mass was crushed, pulverized and sifted through mesh no. 120.

### Preparation of physical mixtures

Physical mixtures of ZPR with different concentrations of starch phosphate (1:1, 1:3, 1:9 and 1:19) were prepared by geometric mixing, by triturating ZPR and starch phosphate by using the mortar and pestle, sifted through the sieve no 120 and stored in dessicator under vacuum [18].

**Preparation of solid binary systems**

Solid binary systems of ZPR with different concentrations of starch phosphate (1:1, 1:3, 1:9 and 1:19) were prepared by using kneading method [19]. Accurately weighed quantities of ziprasidone and starch phosphate were taken in a mortar and mixed thoroughly. The mixture was kneaded with 2 times their amount of methanol for one hour. The resulting paste was dried at 40° for 2 hours. The dried mass was crushed, pulverized and sifted through mesh no. 120 and stored in dessicator under vacuum.

**Solubility study**

Solubility measurements were performed in triplicate [20]. An excess amount of ziprasidone, solid binary systems and physical mixtures in different ratios were added to 25 mL of double distilled water in a series of 50 mL Stoppard conical flasks. The flasks were sealed and shaken 24 h at room temperature on a rotary flask shaker. To get equilibrium the flasks were kept aside for 24 h filtered through 0.45 µm membrane filter. The filtered samples were diluted and analyzed spectrophotometrically at 219 nm.

***In vitro* dissolution studies**

*In vitro* dissolution studies of ziprasidone in pure form and from various binary systems were performed using USP XXI six-station dissolution rate test apparatus (LABINDIA, DISSO 2000) with paddle stirrer. Sample equivalent to 20 mg of ziprasidone in 900 mL of 1% sodium lauryl sulphate (SLS) in phosphate buffer of pH 7.4 maintained at  $37 \pm 0.5$  °C with a speed of 50 rpm were used in each case. A 5 mL aliquot was withdrawn at different time intervals, filtered through 0.45µm nylon disc filter and replaced with 5 mL of fresh dissolution medium. The filtered samples were suitably diluted and estimated spectrophotometrically at 219 nm. The dissolution experiments were conducted in triplicate.

**X-ray diffraction studies**

X- ray diffraction (XRD) patterns of samples were recorded at room temperature on Bruker X-ray diffractometer (AXS D8 Advance) employing Cu-K<sub>α</sub> radiation, wavelength 1.5406 Å°. The diffractometer was run at 3° /min in terms of 2θ angle.

**Differential thermal analysis** DTA thermograms of the drug, carrier, solid binary systems and its corresponding physical mixture were obtained by using Perkin Elmer, Diamond TG/DTA. Samples were heated under nitrogen atmosphere on an aluminium pan at a heating rate of 10o /min in range 30-300°.

**Infrared spectroscopy**

Infra red (IR) spectroscopy was employed to further characterize the possible interactions between the drug and the carrier in the solid state on a Shimadzu IR-281 spectrophotometer by the conventional KBr pellet method. The scanning range was 400-4000 cm<sup>-1</sup> and the resolution was 1 cm<sup>-1</sup>.

**Scanning Electron Microscopy**

SEM monograph is representative of the surface topography and distribution of elemental composition on the surface. Samples of the drug, carrier, solid binary system formulation and its corresponding physical mixture were mounted onto the stubs using double-sided adhesive tape

and then coated with gold film (thickness 200 nm) under reduced pressure (0.001 torr) to render them electrically conductive. The samples were observed under a Scanning Electron Microscope (JEOL Model JSM – 6390LV).

### Statistical analysis

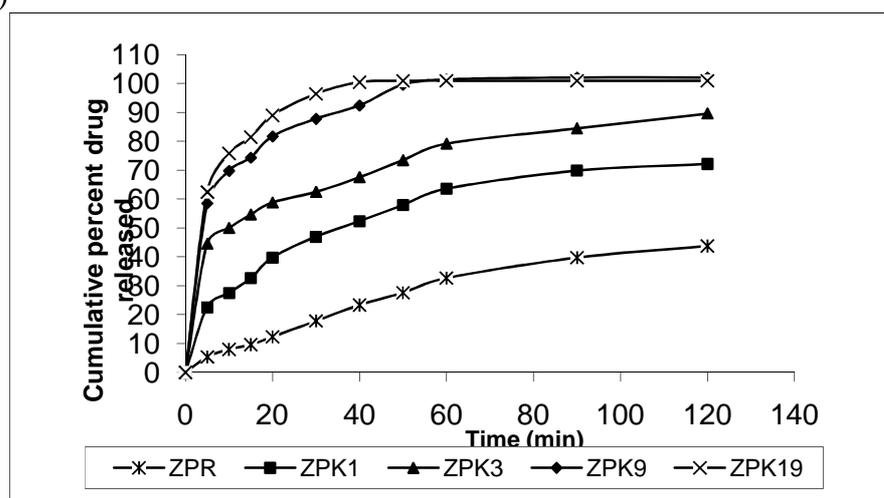
*In vitro* drug release data of different solid binary systems of ZPR were subjected to the one way ANOVA to find out whether there was any significant difference between the formulations. Statistical analysis of the data was performed using the PRISM soft ware (Graphpad, USA). A t-test was performed to find out if there was any significant difference in the release pattern of solid binary systems and physical mixture of ZPR (ZPP9 and ZPK9) having same amount of carrier (SP).

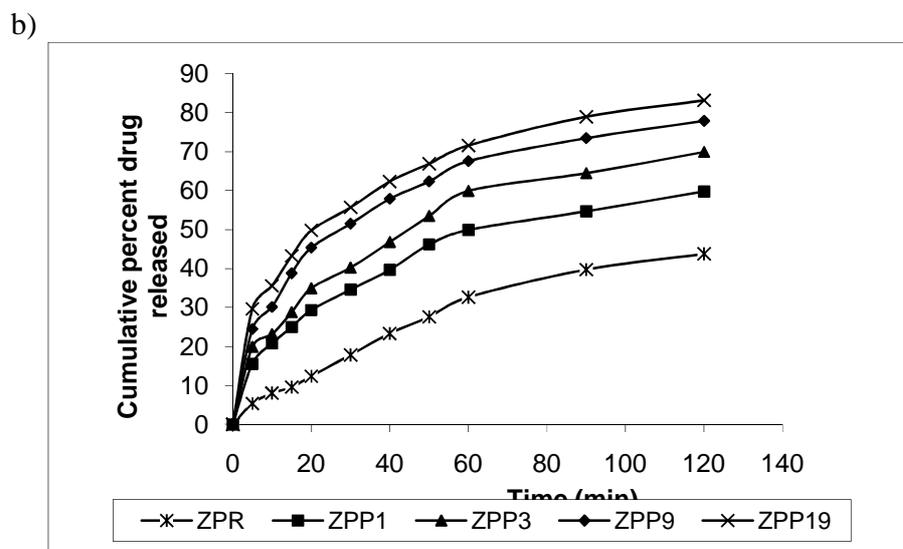
## RESULTS AND DISCUSSION:

A simple method to prepare starch phosphate was adopted. The method employed produced SP in fine free flowing powder form with more hydration capacity. The SP was easily dispersible in purified water. The pH of 10% w/v slurry in water was 6.4. The density (g/cc), bulk density (g/cc), porosity (%), compressibility index (%) and swelling index (%) of SP prepared were 1.412, 0.508, 64.03, 19.13 and 98.5. Solid binary systems of ZPR were prepared by kneading method and by physical mixing using SP as a carrier in different drug, carrier ratios of 1:1, 1:3, 1:9 and 1:19. Percent practical yield increased as the amount of carrier added to each formulation increased. The drug content of the prepared binary systems was found to be in the range of 95.67-100.54% indicating the application of the methods for the preparation of solid binary systems have high content uniformity.

The dissolution rate of ZPR and from various solid binary systems was studied in 1% sodium lauryl sulphate (SLS) in phosphate buffer of pH 7.4. *In vitro* release profiles of the drug, solid binary systems are shown in Figure 1.

a)





ZPR: Ziprasidone, ZPK1: 1:1 kneading, ZPK3: 1:3 kneading, ZPK9: 1:9 kneading, ZPK19: 1:19 kneading, ZPP1: 1:1 physical mixture, ZPP3: 1:3 physical mixture, ZPP9: 1:9 physical mixture, ZPP19: 1:19 physical mixture

**Figure 1: Dissolution profile of ziprasidone, physical mixtures and solid binary systems in various ratios with SP**

The drug exhibited a slow dissolution, suggesting that its absorption *in vivo* would be dissolution rate limited, where as solid binary systems showed a marketed enhancement in dissolution rate. Thus, dissolution of up to 100% was recorded with solid dispersions in contrast to the enhancement of 51% observed with physical mixtures. Further, the dissolution profile of solid binary systems in four different mixing ratios also demonstrated variability and it was found to be dependent on drug-carrier ratio. Hence, as the proportion of carrier in the solid binary systems increased, the dissolution rate also increased. For comparative analysis of all the formulations, %DE values at three different times, representing early, middle and late phase of dissolution study, were computed. The %DE values in the initial time period of dissolution study (%DE10) provide comparative information for very fast releasing formulations, where as % DE30 values furnish relative information about both fast and slow releasing formulations and % DE60 values, provides information about slow releasing formulations. The value of %DE10 (pure drug 4.06) was enhanced from miniscule (12.85 for ZPP1) to very high (48.42 for ZPK9) high carrier concentration. Analogous to %DE10 values, the value of RDR30 was least for ZPP1 system (1.99) and maximum for ZPK9 system (5.21). For all the methods, the maximum dissolution was documented for the drug to the carrier ratio of 1:9 (ZPK9, ZPP9). Among these, ZPK9 prepared by kneading method exhibited maximum release compared to ZPP9. Table 1 enlists the dissolution parameters of ZPR solid binary system of various methods.

**Table 1: Dissolution parameters of ziprasidone and various solid dispersions formulated**

S.No	Formulation	Dissolution parameters						
		%DE <sub>10</sub>	%DE <sub>30</sub>	MDT <sub>30</sub>	RDR <sub>30</sub>	Amount released in 30 min	T <sub>50</sub> (min)	K <sub>1</sub> (min <sup>-1</sup> )
1	ZPR	4.06	9.43	14.15	1	3.57	>120	-0.0058
2	ZPK1	18.22	32.36	10.19	2.74	9.80	45.29	-0.0153
3	ZPK3	35.88	52.14	6.25	3.69	13.17	23.97	-0.0289
4	ZPK9	48.42	72.10	6.71	5.21	18.58	7.07	-0.0980
5	ZPK19	51.28	75.50	6.16	5.32	19.00	6.41	-0.1081
6	ZPP1	12.85	23.74	9.97	1.99	7.11	67.94	-0.0102
7	ZPP3	15.66	27.92	9.95	2.34	8.35	51.33	-0.0135
8	ZPP9	19.93	36.60	9.62	3.02	10.78	38.71	-0.0179
9	ZPP19	24.19	41.17	8.86	3.27	11.68	32.38	-0.0214

Solid binary system formulated with all the methods exhibited significant improvement in the dissolution parameters of ZPR. Table 2 enlists the regression parameters obtained after fitting various release kinetic models to the *in vitro* dissolution data. The goodness of fit for various models investigated for binary systems ranked in order of Korsemeyer-Peppas > Higuchi  $\approx$  first-order > Hixson-Crowell cube root  $\gg$  zero-order. All the kinetic models, other than the zero-order, fitted well at early periods. Since the extent of release at given time points varied largely between inter and intra drug carrier dispersions, modeling analysis was carried out by fitting the dissolution data until the time 90% of the drug was released.

**Table 2: Statistical parameters of various formulations obtained after fitting the drug release data to various release kinetic models**

S.No	Formulation	Mathematical models for drug release kinetics 'r'				
		Zero-order	First-order r	Higuchi	Korsemeyer-Peppas	
					r	n
1	ZPR	0.9516	0.9804	0.9638	0.9941	0.7904
2	ZPK1	0.5685	0.9004	0.9771	0.9926	0.4220
3	ZPK3	0.1346	0.9454	0.8582	0.9943	0.2443
4	ZPK9	0.3360	0.9803	0.9194	0.9973	0.2336
5	ZPK19	0.2149	0.9777	0.8436	0.9854	0.1924
6	ZPP1	0.6956	0.8903	0.9898	0.9956	0.4665
7	ZPP3	0.6952	0.9259	0.9883	0.9917	0.4580
8	ZPP9	0.4730	0.9139	0.9683	0.9914	0.4041
9	ZPP19	0.3102	0.9368	0.9554	0.9948	0.3603

However, in cases where the total drug release in the entire dissolution time span was below 90%, data until the last sampling time 120 min were taken into consideration. The values of diffusional exponent 'n' obtained from the slopes of the fitted Korsemeyer-Peppas model, ranges from 0.1924-0.7904. No clear trend was observed in the values of n among inter and intra drug-carrier systems. Except for a few cases all the solid binary systems tended to exhibit Fickian

diffusional characteristics, as the corresponding values of 'n' were lower than the standard value for declaring Fickian release behaviour i.e. 0.45, some formulations showed 'n' values marginally above 0.45 construing non-fickian release behaviour.

**X-ray powder diffraction:** Figure 2 shows the X-ray diffractograms for ziprasidone, starch phosphate and solid binary systems investigated. XRD of ziprasidone showed numerous distinctive peaks that indicated high crystallinity. In the physical mixture, the distinctive diffraction peaks of ziprasidone persisted with a marked decrease in their intensity compared to pure ziprasidone. The solid binary systems exhibited lesser and broader peaks, indicating that the drug was present in the amorphous form in the binary systems.

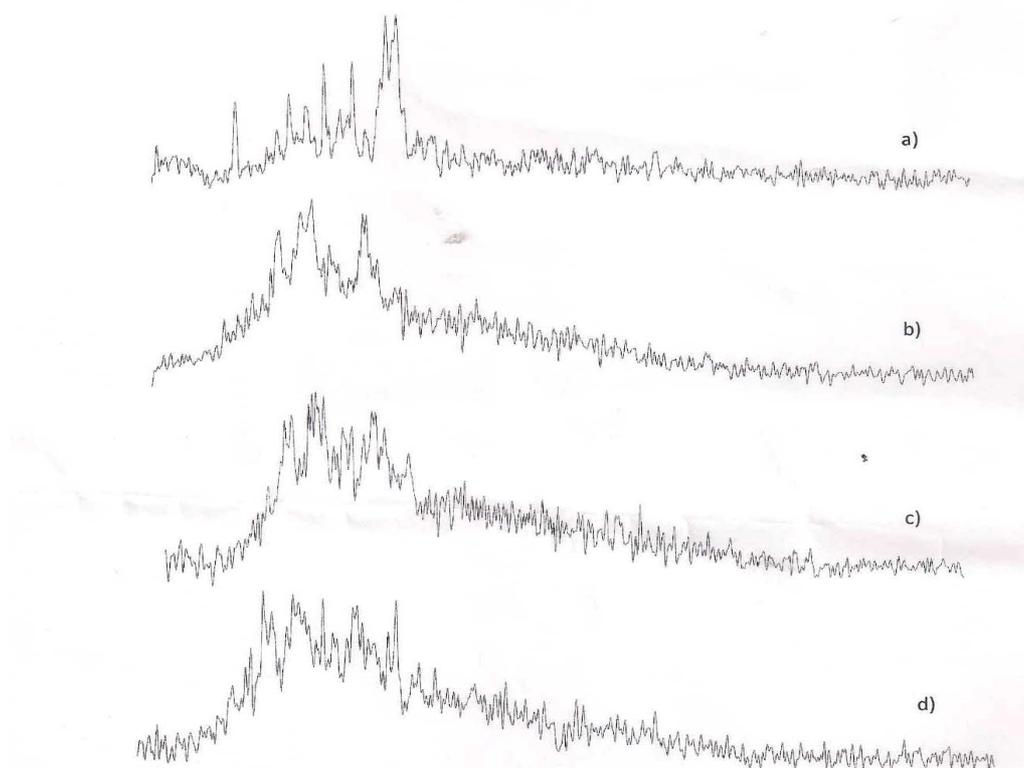


Figure 2: X- ray diffraction patterns of a) ziprasidone b) Starch phosphate c) solid binary systems (1:9) by kneading d) physical mixture (1:9)

**Scanning electron microscopy:** Figure 3 shows the SEM photographs of ziprasidone, starch phosphate, physical mixtures and solid dispersions. The ZPR particles are in the form of irregular crystals with a relatively well defined outline and starch phosphate is in round shape pieces. The solid binary systems and physical mixture microphotos indicating that drug particles are adhered on the carrier. The carrier surface seems to be more porous in nature. Solid state characterization studies revealed partial loss of drug crystallinity which can bring about significant changes in the drug dissolution rate. However, other factors like reduced particle size, increased surface area,

and closer contact between the hydrophilic carrier and the drug may also be influential in enhancing drug solubility and dissolution rate observed with the solid dispersion particles.

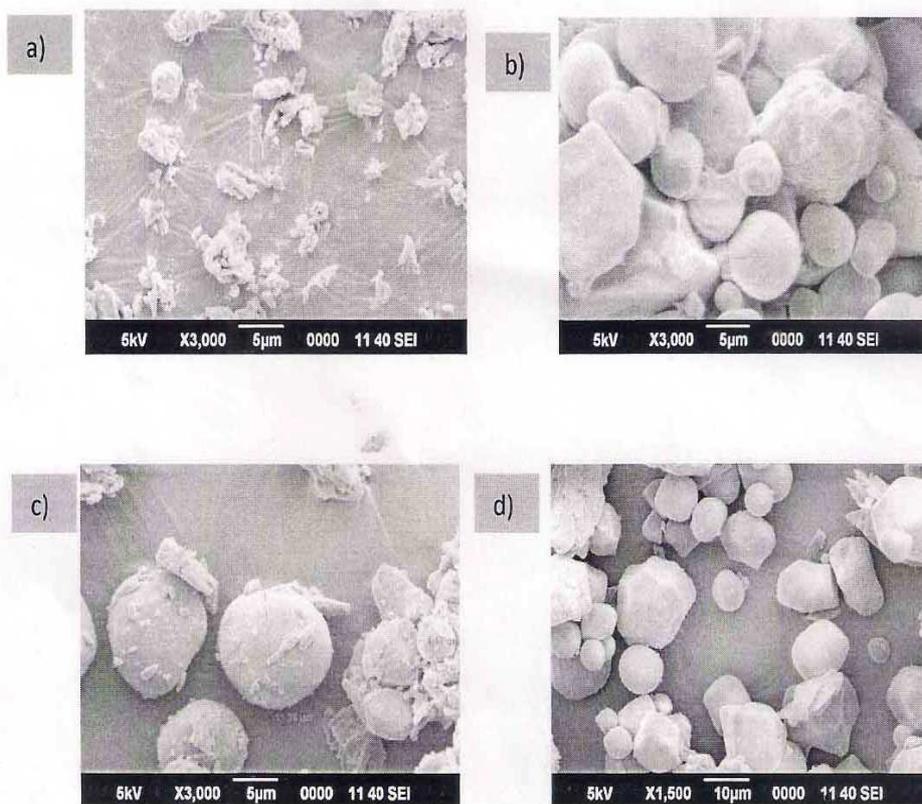


Figure 3: Scanning electron micrographs of a) ziprasidone b) Starch phosphate c) solid binary systems (1:9) by kneading d) physical mixture (1:9)

**Differential thermal analysis:** Figure 4 shows the DTA thermograms of ziprasidone, starch phosphate, physical mixtures and solid binary systems. The thermograms exhibited single endothermic peak at 254.14o, 255.42o, 252.87o and 248.93o respectively which corresponding to the melting point of ziprasidone. Thus, the DTA thermograms indicated no interaction between the drug and the carrier.

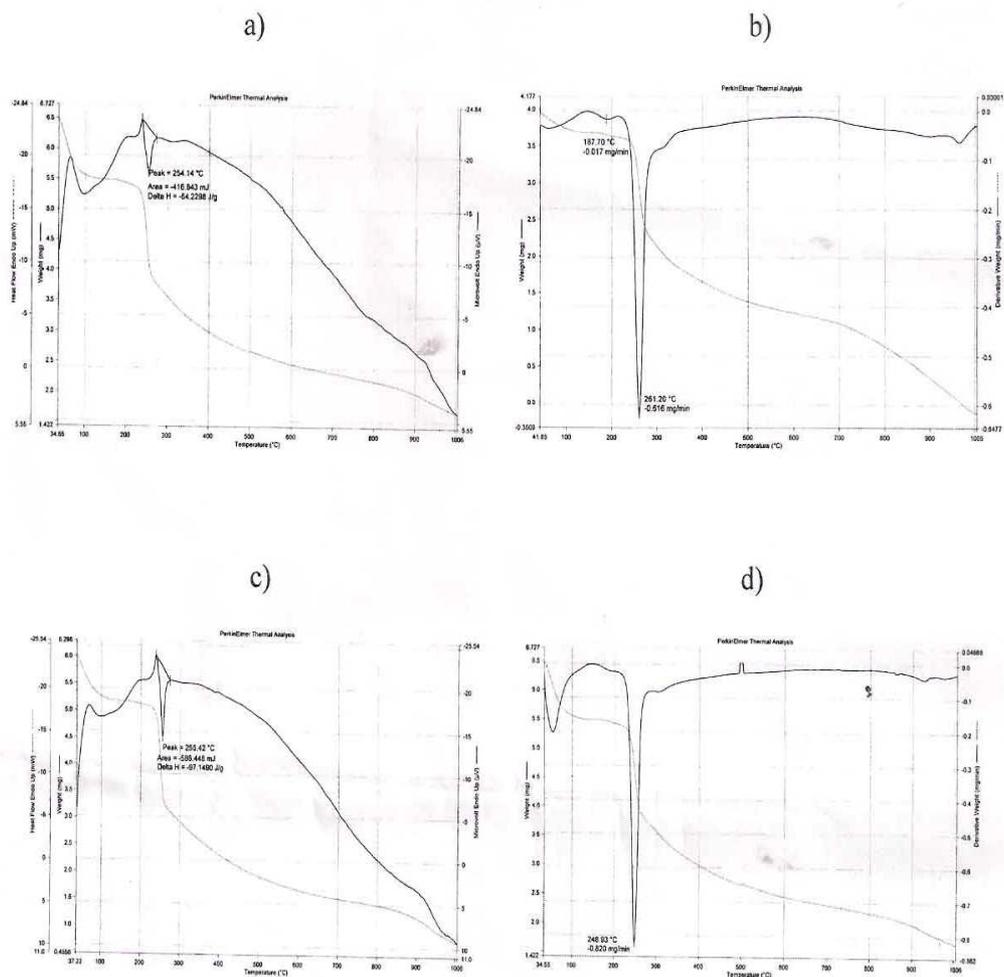


Figure 4: DTA thermograms of a) ziprasidone b) Starch phosphate c) solid binary systems (1:9) by kneading d) physical mixture (1:9)

**Infrared spectral analysis:** Figure 5 shows the FTIR spectra of the drug, carrier, solid dispersions and physical mixture. The principle IR absorption peaks of ZPR at  $3412\text{ cm}^{-1}$  for NH,  $2928\text{ cm}^{-1}$  for CH,  $1714\text{ cm}^{-1}$  for C=O,  $1629\text{ cm}^{-1}$  for C=N,  $1528\text{ cm}^{-1}$  for C=C,  $1383\text{ cm}^{-1}$  for CN and  $744\text{ cm}^{-1}$  for C-Cl were all observed in the spectra of ziprasidone as well as its binary systems in SP. Thus, these results ratify the absence of any well-defined interaction between ZPR and carrier as constructed by XRD study.

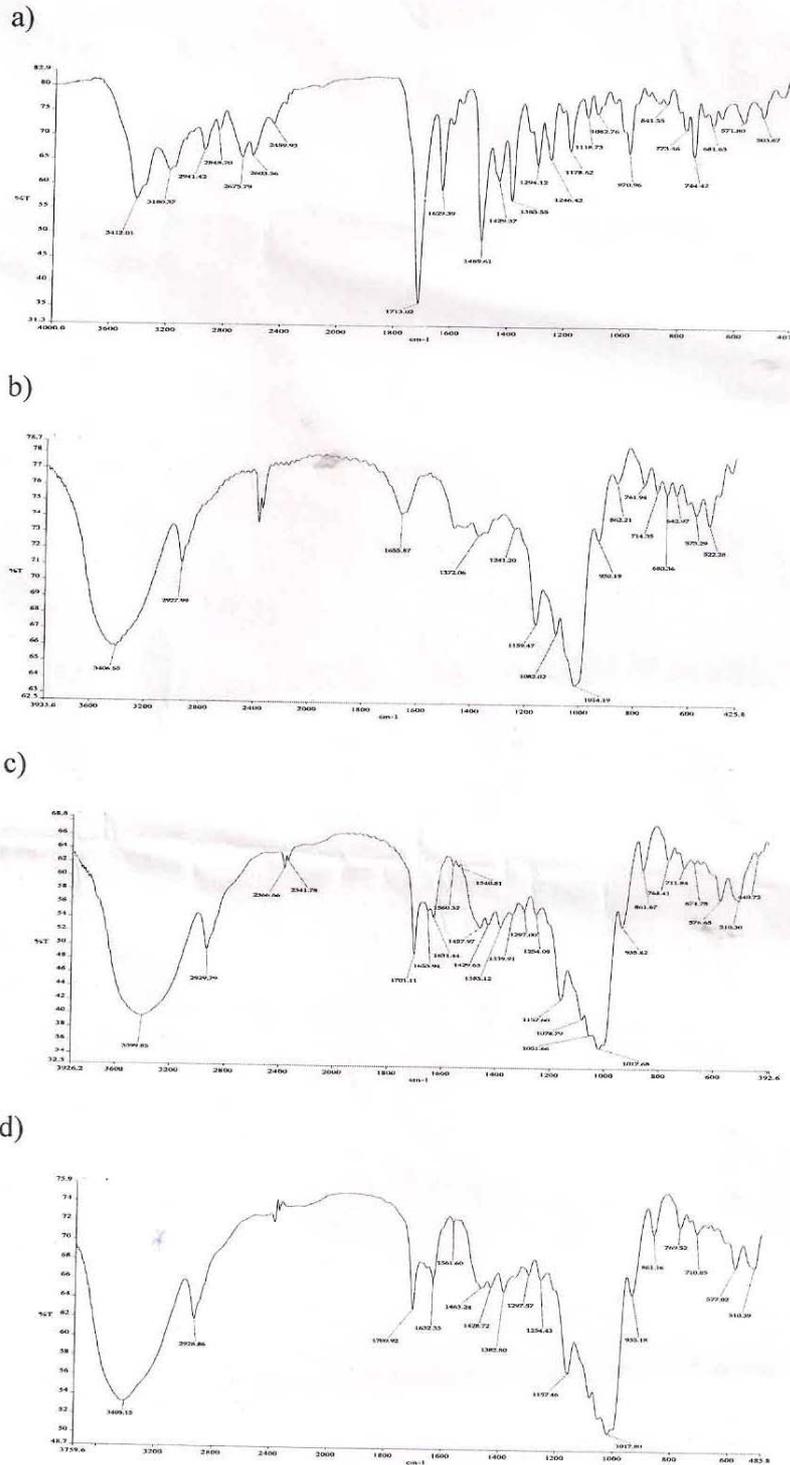


Figure 5: FTIR spectroscopy of a) ziprasidone b) Starch phosphate c) solid binary systems (1:9) by kneading d) physical mixture (1:9)

## CONCLUSION

This study shows that improvement in the dissolution of the water insoluble drug ziprasidone was achieved through solid binary systems using an inexpensive and laboratory made modified starch such as starch phosphate. The enhancement in solubility and dissolution characteristics of the drug is depends up on the concentration of the carrier. The Koresmeyer-Peppas model most aptly fits the *in vitro* data and gives and insight into the possible drug release mechanisms invariably predominated by Fickian diffusion. The results obtained with various carriers in the current studies can be extrapolated to other poorly soluble BCS class II drugs too.

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