

Enhancement of Solubility characteristics of Alprazolam

Sandeep.M^{1*}, Das Saumya¹, Joe Cherry Divya², J. Tarun¹, B. Kiran kumar¹

¹Department of Pharmaceutics, Vikas College of Pharmaceutical Sciences, Rayanigudem, Suryapet, Nalgonda, Andhra Pradesh, India

²Department of Pharmaceutics, Nalanda College of Pharmaceutical Sciences, Cherlapally, Nalgonda, Andhra Pradesh, India

*sandeepm005@gmail.com



ABSTRACT

Alprazolam is an anti-anxiety with sedative and hypnotic actions and used in treatment of anxiety and panic disorders. It is practically insoluble in water and hence has a less bioavailability. In the present study attempt has been made to prepare and characterize inclusion complexes of alprazolam with HP- β -CD and PEG6000 (Polyethylene glycol6000). The phase solubility analysis indicated the formation of 1:1 molar inclusion complex of alprazolam with HP- β -CD and PEG6000. The inclusion complexes were prepared by two different methods viz. physical and kneading methods. The complexes were characterized using Fourier transform infrared spectroscopy and differential scanning calorimetry. The complexes prepared by physical method with HP- β -CD exhibited greatest enhancement in solubility and fastest drug release of 90.29% and kneading method with PEG6000 exhibited greatest enhancement in solubility and fastest drug release of 90.19%.

Keywords: HP- β -CD, Alprazolam, PEG6000, Physical method, kneading method

INTRODUCTION¹

Cyclodextrins (CDs) are cyclic oligosaccharides and were discovered approximately hundred years ago. In the beginning only small amounts of relatively impure cyclodextrins could be generated and high production cost prevent their industrial usage^[1]. Recent biotechnological advancements in the production of cyclodextrins have reduced the cost of production and improved solubility of various water insoluble drugs. Before a drug can pass through a biological membrane it must be first be solubilized in the fluids bathing the membrane. It is well known that the drug efficacy can be severely limited by poor aqueous solubility. The rate limiting step of poorly water soluble drugs is dissolution which is governed by solubility^[2].

Methods of enhancement of solubility can be done by different methods like^[3,4]:

- Increasing the effective surface area of the drug
- Incorporation of surface-active agents in formulation
- Alternation of the pH of the surrounding medium
- Solute-solvent complex reaction
- Eutectic mixture and solid solution techniques
- Dispersion techniques
- Use of salt forms
- Complexation with cyclodextrins

Among all the approaches, complexations with cyclodextrins have proved to be most effective in enhancing solubility. Anti-anxiety with sedative and hypnotic actions and used in treatment of anxiety and panic disorders. Side

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effects of alprazolam tablets are generally observed at the beginning of the therapy and usually disappear upon continued medication. In usual patients, the most frequent side effects are likely to be an extension of the pharmacologic activity of alprazolam i.e., drowsiness or light-headedness. The main problem associated with alprazolam is its poor water solubility. Hence the present work aims at preparing efficient water soluble complexes of alprazolam, HP- β -Cyclodextrins and PEG6000 to improve bioavailability.

MATERIALS AND METHOD

Materials

Alprazolam was obtained as a gift of Cipra Pharmaceutical, Pune. Hydroxy propyl β cyclodextrin(HP- β -CD) was obtained from Gangwal Chemicals, Mumbai. Polyethylene glycol(PEG6000) was obtained from S-d Fine Chemicals, Mumbai. All the rest chemicals used were of analytical grade.

Methods

a) Preparation of complexes^[1,2]

Physical Mixture

Alprazolam with HP- β CD and PEG6000 in ratios 1:1, 1:2, 1:3 were mixed in a mortar for about one hour with constant trituration. The mixture was passed through sieve no. 80 and stored in dessicator over fused calcium chloride.

b) Kneading Method

Alprazolam with HP- β CD and PEG6000 in ratios 1:1, 1:2, 1:3 were taken. Hydroxy propyl β cyclodextrin is added to the mortar and triturated with small quantity of 50% ethanol to prepare a slurry. Slowly the drug is incorporated into the slurry with constant trituration. The prepared slurry is then air dried at room temperature for 48hrs. The resultant product is pulverised and passed through sieve no. 80 and stored in dessicator over fused calcium chloride.

Evaluation

Phase solubility analysis^[3]

Phase solubility studies for alprazolam complexes were performed to determine the stoichiometry of drug. Complexes containing 10mg of the drug were taken and added to 20ml proportions of distilled water in volumetric flasks, each containing variable amount of hydroxypropyl β -cyclodextrin (HP- β -CD) such as 3, 6, 9, 12 and 15x10⁻³ moles/liter. The above solutions were shaken for 72hrs on a rotary shaker. Then the solutions were filtered and absorbance's were recorded at 226nm. The solubility of alprazolam in every solutions were calculated.

Drug content estimation^[4]

50mg of complex was accurately weighed and transferred to 50 ml volumetric flask and volume was made up to the mark with methanol. From this 1ml was taken in 10ml volumetric flask and the volume is adjusted up to the mark with same solvent. The absorbance of the solution was measured at 226 nm using appropriate blank.

Preparation of Alprazolam-HP- β -CD & Alprazolam-PEG6000 complex tablets^[5]

The complexes each separately single polymer (HP- β -CD), second polymer (PEG6000) super disintegrant (crosscarmellose sodium), filler (microcrystalline cellulose), lubricant (magnesium stearate) and glidant (talc) were blended together by dry mixing in a laboratory mixer (poly bag) for 10 mins. The mixture was then compressed using 8mm standard concave punch and die set (Pilot Press 12 station) at compression force 6 ton. The formulations of the tablets with their code are listed in table no. 2 and 3. Total tablet weight is kept at 300 mg.

Hardness and friability^[6]

Hardness of the tablets was tested using Monsanto hardness tester for each formulation. The friability of the tablets was determined

using Veego Friabilator. From each formulation six tablets were subjected to the test.

Disintegration Studies^[2]

The prepared tablets were subjected to disintegration test using disintegration apparatus.

Dissolution Characteristics^[7]

In-vitro dissolution of alprazolam inclusion complex was studied in USP II dissolution apparatus (Lab India) employing a paddle stirrer. 900 ml of distilled water was used as dissolution medium. The stirrer was adjusted to rotate at 50 rpm. The temperature of

dissolution media was previously warmed to $37 \pm 0.5^\circ\text{C}$ and was maintained throughout the experiment. 1 ml of sample of dissolution medium were withdrawn by means of syringe fitted with prefilter at known intervals of time and analyzed for drug release by measuring the absorbance at 226nm after suitable dilution.

Weight variation test^[5]: 20 tablets were selected randomly from each formulation and weighed individually to check for weight variation. The U.S Pharmacopoeia allows a little variation in the weight of a tablet. The following percentage deviation in weight variation is allowed.

Table No.1 Percentage deviation in weight variation

Average weight of a tablet	Percentage deviation
130 mg or less	± 10
More than 130 mg and less than 324 mg	± 7.5
324 mg or more	± 5

Table No.2 Formulation code table

Method	Drug to Carrier	Drug to Carrier ratio	Code
Physical Mixture	ALP:HP- β -CD	1:1	FP1
	ALP:HP- β -CD	1:2	FP2
	ALP:HP- β -CD	1:3	FP3
Kneading Method	ALP:HP- β -CD	1:1	FK1
	ALP:HP- β -CD	1:2	FK2
	ALP:HP- β -CD	1:3	FK3
Physical Mixture	ALP:PEG6000	1:1	PFP1
	ALP:PEG6000	1:2	PFP2
	ALP:PEG6000	1:3	PFP3
Kneading Method	ALP:PEG6000	1:1	PFK1
	ALP:PEG6000	1:2	PFK2
	ALP:PEG6000	1:3	PFK3

Table No.3 Formulation table of tablets containing Alprazolam:HP- β -CD complexes.

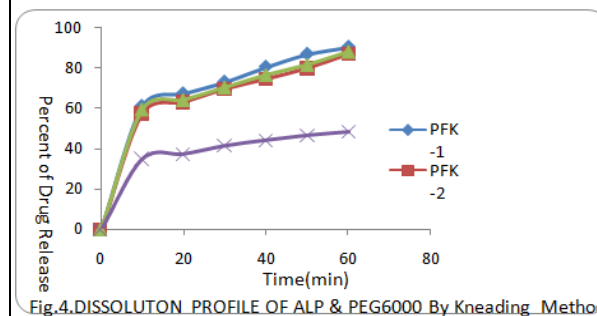
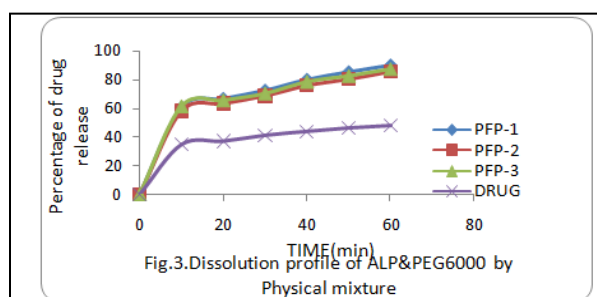
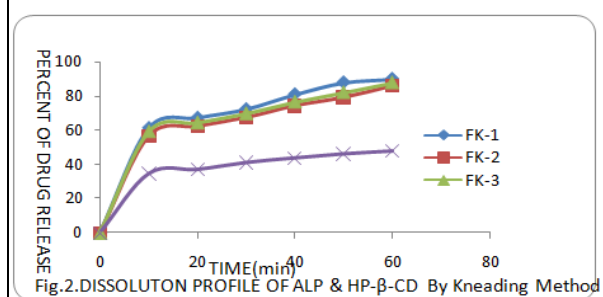
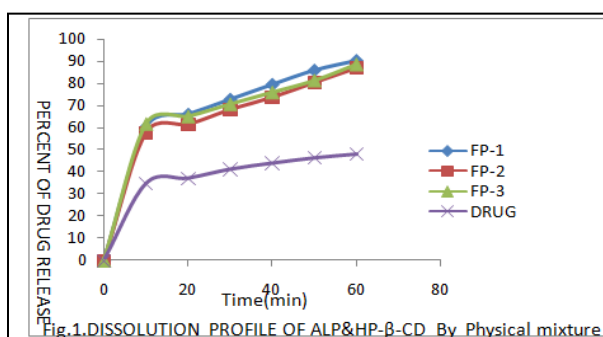
Ingredients(mg/tablet)	FP1	FP2	FP3	FK1	FK2	FK3
Drug Complex	74.87	59.76	40.70	49.89	54.34	43.77
Crosscarmellose sodium	50	50	50	50	50	50
Magnesium stearate	2	2	2	2	2	2
Talc	2	2	2	2	2	2
Microcrystalline cellulose	171.13	186.24	205.3	196.11	191.66	202.23
Final weight of tablet(mg)	300	300	300	300	300	300

Table No.4 Formulation table of tablets containing Alprazolam:PEG6000 complexes

Ingredients(mg/tablet)	PFP1	PFP2	PFP3	PFK1	PFK2	PFK3
Drug Complex	113.20	68.18	42-35	109.48	90.36	64.98
Crosscarmellose sodium	50	50	50	50	50	50
Magnesium stearate	2	2	2	2	2	2
Talc	2	2	2	2	2	2
Microcrystalline cellulose	132.8	177.82	203.65	136.52	155.64	181.02
Final weight of tablet(mg)	300	300	300	300	300	300

Table No.5 Evaluation tests

S. No	Formulations	Hardness(kg /cm ²) ±SD	Weight variation ±5%(mg) ±SD	Drug Content (%)±SD	Friability (%)	Disintegration (min&sec)
1	FP1	5.1±0.11	285±0.032	93.56±0.011	0.546	3m22s
2	FP2	5.4±0.19	296±0.151	89.63±0.067	0.967	3m30s
3	FP3	5.8±0.13	302±0.163	87.82±0.021	0.322	3m55s
4	FK1	5.2±0.21	289±0.088	91.09±0.031	0.636	10m9s
5	FK2	5.5±0.29	295±0.021	88.18±0.113	0.645	12m44s
6	FK3	5.3±0.23	298±0.121	86.72±0.046	0.636	14m57s
7	PFP1	5.1±0.21	300±0.171	90.28±0.136	0.655	15m34s
8	PFP2	5.7±0.14	303±0.045	86.75±0.023	0.333	18m49s
9	PFP3	5.4±0.20	297±0.192	83.46±0.011	0.980	20m57s
10	PFK1	5.6±0.18	301±0.059	89.77±0.041	0.636	21m51s
11	PFK2	5.9±0.25	319±0.103	87.09±0.083	0.974	22m40s
12	PFK3	5±0.16	315±0.048	85.32±0.121	0.896	24m59s



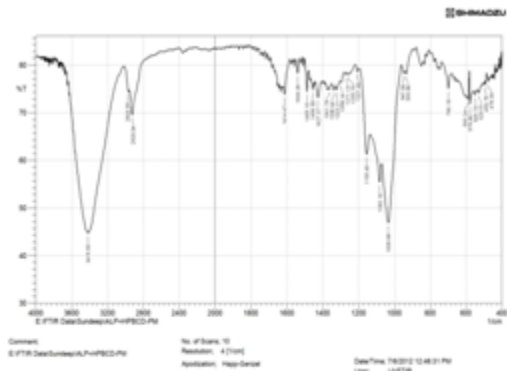


Fig.5. FTIR of formulation FP1

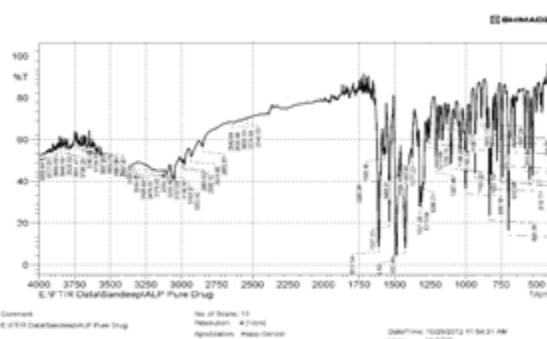


Fig.6. FTIR of Pure drug

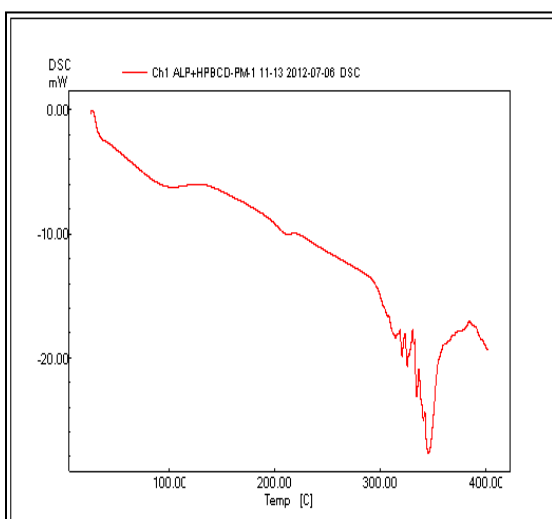


Fig.7. DSC Studies of Alprazolam VS Excipients Physical mixture (FP1)

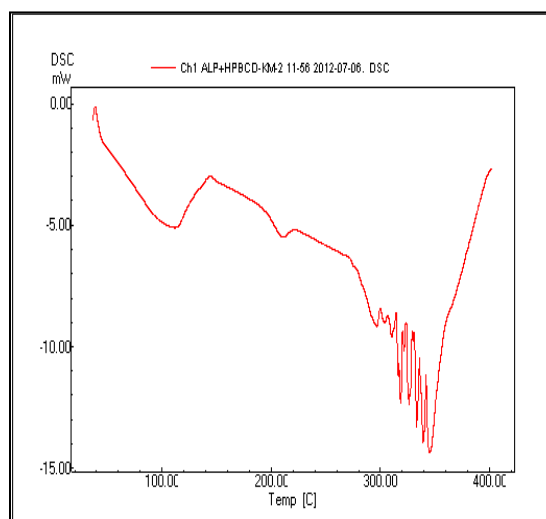


Fig.8. DSC Studies of Alprazolam VS Excipients Kneading method (FK1)

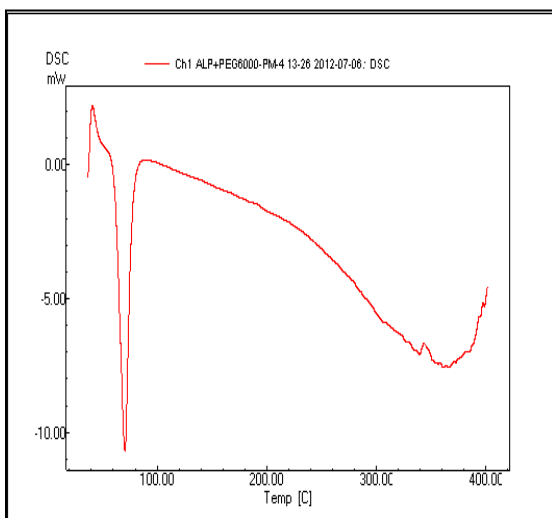


Fig.9. DSC Studies of Alprazolam VS Excipients Physical mixture (PFP1)

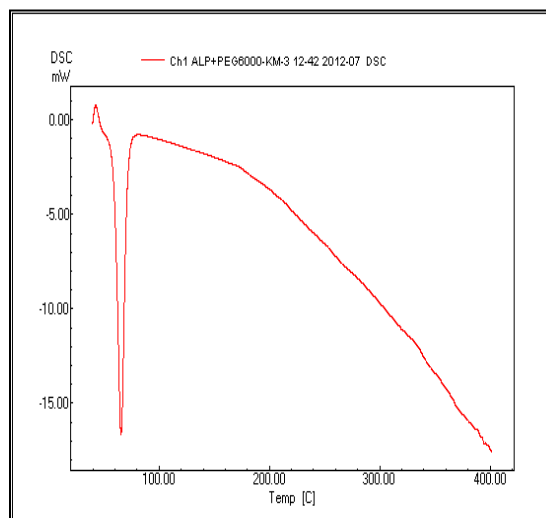


Fig.10. DSC Studies of Alprazolam VS Excipients Kneading method (PFK1)

Drug-Excipient Interaction Studies

The IR spectra of alprazolam and their complexes were obtained by KBr pellet method by SHIMADZU FT/IR-8400S spectrometer^[6,7].

The DSC graphs of alprazolam and their complexes were incorporated in their respective crystal lattice, their melting; boiling and sublimation points are usually shifted to a different temperature or disappear within the temperature range, where the respective complexes lattice is decomposed by SHIMADZU DSC60^[8].

Stability Study of Alprazolam Complexes

The stability studies of complexes were accessed according to ICH guidelines^[9].

RESULTS AND DISCUSSION

The HP- β -CD complexes were prepared successfully incorporating alprazolam. The physical characteristics were satisfactory. The colour of complexes was off white and of amorphous nature. The phase solubility analysis showed an increase in solubility of drug. The drug content was found to be in the range of 83.46% to 93.56%. The tablets containing different molar complexes were prepared. All the tablets had good physical characteristics. The hardness of all the formulations was found to be in the range of 5 to 6 kg/cm². The friability of formulations was within limits. The disintegration time of tablets was in between

3m22s to 24m59s due to the presence of disintegrant. The dissolution studies showed the release characteristics of the complexes. The formulation FP1 showed a highest dissolution profile of 90.29% in 60min due to the effective proportion of drug and HP- β -CD. All the other formulations showed an increase in dissolution but the drug release was extended due to higher ratios of HP- β -CD. The FT-IR spectra showed no change in peaks hence no interaction between drug and polymer. The stability studies showed no change in colour of the tablets. Both the Fig. 7&8 DSC graphs has shown a very good result similar to drug and but whereas in the Fig. 9 & 10 there is some interaction between drug and polymer (PEG6000) this is due to drug is insoluble in water and polymer is soluble in water. The dissolution studies after stability testing showed no remarkable change.

CONCLUSION

In the present study effective alprazolam- HP- β -CD complexes can be prepared by different methods. But the physical mixture yields good results when compared to kneading method. The tablets prepared by using these complexes showed fast releasing characteristics. Hence it can be concluded that HP- β -CD can be used to increase the solubility of water insoluble drugs.

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