PREPARATION AND CHARACTERIZATION OF ZAFIRLUKAST- β-CYCLODEXTRIN COMPLEXES USING SOLID DISPERSION TECHNIQUES

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ABSTRACT

Zafirlukast is an oral leukotriene receptor antagonist used in the treatment of asthma. Poor solubility in biological fluids is the major problem with this drug which results in poor bioavailability after an oral administration. The rate of absorption and the extent of bioavailability for such a poor soluble drug is controlled by rate of dissolution in gastrointestinal fluids. Hence an attempt has been made to enhance the solubility of the drug by preparing its complex with β-cyclodextrin. FT-IR studies were performed. Drug-complexing agent interactions were investigated using differential scanning calorimetry(DSC) . The study clearly shows that the dissolution rate of zafirlukast may be enhanced to a great extent by solid dispersion technique using kneading method. This is due to the reason that the cyclodextrins increased the aqueous solubility of poorly soluble drug by forming inclusion complexes with their apolar molecules and functional groups.

Keywords: Zafirlukast, Solid dispersions, Physical mixing, Solvent evaporation, kneading method.

INTRODUCTION

Zafirlukast is chemically cyclopentyl N-[3-[[2-methoxy-4-[(2-methylphenyl) sulfonylcarbamoyl] phenyl] methyl]-1-methylindol-5-yl]carbamate. It is an oral leukotriene receptor antagonist widely used for the treatment of asthma[1]**.** Zafirlukast blocks the action of the cysteinyl leukotrienes on the CysLT1 receptors, thus reducing construction of the airways, build-up of mucus in the lungs and inflammation of the breathing passages[2, 3]. Zafirlukast is a poorly water soluble drug. In the case of poorly water soluble drugs, dissolution is the rate limiting step in the process of drug absorption. The rate of dissolution can be increased by increasing the surface area of the available drug. There are many techniques that have been used to improve the dissolution and bioavailability of poorly water soluble drugs which includes the use of surfactants, micronization phenomena, complexation etc[4-6].For the dissolution enhancement of poorly water soluble drugs solid dispersion technique is widely used[7].

Cyclodextrins are mainly used to increase the aqueous solubility and dissolution rate of drugs [8-10]. αCD, βCD and γCD, are commonly known as parent Cyclodextrins (CDs), consisting of six, seven, and eight α- (1,4)-linked glucopyranose units, with a relatively hydrophobic central cavity and a hydrophilic outer surface respectively. They are often depicted as hollow truncated cones with primary and secondary hydroxyl groups orientated outwards. As a result, CDs have an electron rich hydrophobic internal cavity and a hydrophilic exterior [11]. This unique cavity enables CDs to accommodate a wide range of non-polar molecules via the formation of reversible non-covalent inclusion complexes. CDs not only offer protection to the encapsulated molecule from the outer environment but also improve properties such as bioavailability, stability and taste masking [12]. Cyclodextrins can also be used to prevent drug-drug and drug additive interactions, convert liquid drugs into microcrystalline powder, decrease volatility, modify gastrointestinal or ocular irritation and mask of objectionable taste or odor of drugs [13, 14].

The main purpose of the present investigation is to increase the solubility and dissolution rate of Zafirlukast by the preparation of the complex with β-CD using physical mixing, solvent evaporation and kneading methods.

MATERIALS AND METHODS

Materials:

Zafirlukast was obtained as a gift sample from Dr. Reddy's Laboratories, Hyderabad, β-cyclodextrin was obtained from Roquette, France and all other ingredients used were of pharmaceutical grade.

Methods:

Complexation with cyclodextrin has been reported to enhance the solubility, dissolution rate and bioavailabilty of poorly water soluble drugs. Among the cyclodextrin, β-cyclodextrin is the most widely studied compound for drug complexation. To improve solubility and dissolution rate of zafirlukast via complexation with β-cd, different ratios (1:0.5,1:0.75,1:1) were prepared using physical mixing ,solvent evaporation and kneading method.

a) *Physical mixtures*:

Accurately weighed quantities of drug and β-cd were taken in a glass mortar and were mixed thoroughly. The resultant mixture was passed through sieve number 100 and was stored in a desiccator for complete removal of moisture and was tested for content uniformity.

b) *Solvent evaporation method*:

In this method, accurately weighed quantities of carriers in the stated proportions were carefully transferred into boiling test tubes, and dissolved in acetone. To these solutions, accurately weighed quantities of drug were added, and allowed to dissolve. The solution was transferred to a petridish, the solvent was allowed to evaporate at room temperature, and the dispersions were dried at room temperature for 1 h, and then dried at 65^0c for 6h in a hot air oven. The mass obtained in each case was crushed, pulverized, and sifted through 100 mesh.

c) *Kneading method:*

Drug and β-cyclodextrin were triturated separately at different ratios in a mortar with a small volume of methanol: water (3:2) solvent blend. The thick slurry was kneaded for 45 mins, and then the mass was further dried in a desiccator for 2 days. The dried product was crushed, pulverized and sieved through 100 mesh. The solid dispersions thus obtained were stored in a well closed container and kept in a desiccator.

Phase solubility studies:

Solubility studies were performed according to the Higuchi and Connors method. An excess amount of Zafirlukast was placed into 50ml flask containing different concentration of β-cyclodextrin in distilled water. All flasks were closed with stopper and covered with cellophane membrane to avoid solvent loss. The flasks were kept in the incubator shaker for 72 hr. After 72 hr the content of each flask was then filtered through Whatman filter paper. The filtrate was diluted and assayed spectrophotometrically for Zafirlukast content at 238 nm. All solubility measurements were performed in triplicate.

Drug content analysis:

An accurately weighed quantity of solid dispersion equivalent to 10 mg of Zafirlukast, was taken into a 100ml volumetric flask and dissolved in acetonitrile. The stock solutions were filtered, suitably diluted and assayed for drug content using a double beam UV/VIS spectrophotometer at 238 nm.

In vitro dissolution studies:

In-vitro release rate of Zafirlukast solid dispersion of different samples was determined using LABINDIA DISSO 2000, an eight stage dissolution rate testing apparatus with paddle. The dissolution medium consisted of 0.5% Sodium lauryl sulfate in water. Solid dispersion equivalent to 10 mg of drug was spread onto the surface of 900 ml of preheated dissolution medium at 37 ± 0.5^0C. Aliquots of 5 ml were withdrawn at regular intervals of time i.e (10, 20, 30, 45, 60, 90 min) and the sample is replaced with the fresh dissolution medium each time. The samples obtained were filtered through Whatman filter paper and the absorbance was measured at 238 nm.

Fourier transform infra-red spectroscopy:

FT-IR spectra (400-4400cm^{-1}) were obtained on a Perkin-Elmer FT-IR spectrophotometer with a resolution of 4 cm^{-1} KBR pellets were prepared gently by mixing the 1 mg sample with 100 mg potassium bromide.

Differential scanning calorimetry:

Differential scanning calorimeter measurements were carried out using a thermal analysis instrument DSC Q 20 V 24.2 Build 107 equipped with a liquid nitrogen sub ambient accessory. Samples were weighed in aluminium pans, hermetically sealed and scanned at a heating rate of 10^0C/min over a temperature range of 25^0C-300 ^{0} C under a nitrogen gas stream.

RESULTS AND DISCUSSION

Drug content:

The zafirlukast solid dispersions were tested for drug content and it was found that the drug was within the compendial limits 95-101% w/w. All the solid dispersions were uniform in drug content. The results were shown in Table1.

Table 1: Drug content and percent drug release of Zafirlukast solid dispersions

Zafirlukast:β-cd	Ratio	Product name	Percent drug content present	% cumulative drug release (90 min)
Physical Mixture	1:0.5	Z-1	97.2±1.06	34.2±1.32
	1:0.75	Z-2	99.6±0.08	38.7±1.56
	1:1	Z-3	96.9±0.03	43.4±0.95
Solvent evaporation method	1:0.5	Z-4	99.5±0.05	60.9±0.65
	1:0.75	Z-5	83±0.05	73.0± 0.35
	1:1	Z-6	95.0±0.07	76.1± 1.05
Kneading method	1:0.5	Z-7	96.1±0.04	78.2±0.82
	1:0.75	Z-8	98.4±0.08	81.0±0.91
	1:1	Z-9	99.1±0.09	99.0± 0.94

Table 2: Dissolution parameters of Zafirlukast and its β-cd complexes prepared by physical mixing (PM), Solvent evaporation (SE), Kneading methods (KM)

Inclusion complex	DE_{30}%	DE_{60}%	T_{50} (min)	%Dissolved in 10 min
Pure drug	3.9	10.69	>90	3.5
Zaf: β-cd(1:0.5)PM	10.4	18.7	>90	8.4
Zaf: β-cd(1:0.75)PM	11.5	20.5	>90	8.6
Zaf: β-cd(1:1)PM	17.8	24.4	>90	19.3
Zaf: β-cd(1:0.5)SE	24.6	39.0	35	22.2
Zaf: β-cd(1:0.75)SE	32.3	48.9	25	42
Zaf: β-cd(1:1)SE	43.1	57.5	22	44.1
Zaf: β-cd(1:0.5)KM	47.7	61.3	10	50
Zaf: β-cd(1:0.75)KM	53.6	65.3	9	61.4
Zaf: β-cd(1:1)KM	57.5	72.7	7	63

Phase solubility studies:

The phase solubility diagram for the complex formation between Zafirlukast and β-cd was shown in Figure 1. The aqueous solubility of the drug increased linearly as function of β-cyclodextrin concentration. At all the concentrations of β-cd used for the preparation of the inclusion complexes showed significant increase in the solubility of Zafirlukast. As the concentration of the β-cd increased, the solubility of the drug was found to be increased.

In -vitro dissolution studies:

Zafirlukast release from the solid dispersion and alone was studied upto 90 minutes. The average percentage release of the pure drug was found to be 34.2% in 90 minutes. In the solid dispersions formulation, β-cyclodextrin was used as carrier and the dissolution rate increased with increased amount of β-cd. The best results among solid dispersions with β-cd were obtained for the complex Z-9 (Figure-2). Dissolution parameters of zafirlukast and its cyclodextrin complexes prepared by three methods in different ratios were given in (Table 2). The increased dissolution rate may be due to the higher solubility of β-cd in dissolution medium and better wettability of Zafirlukast in the complex.

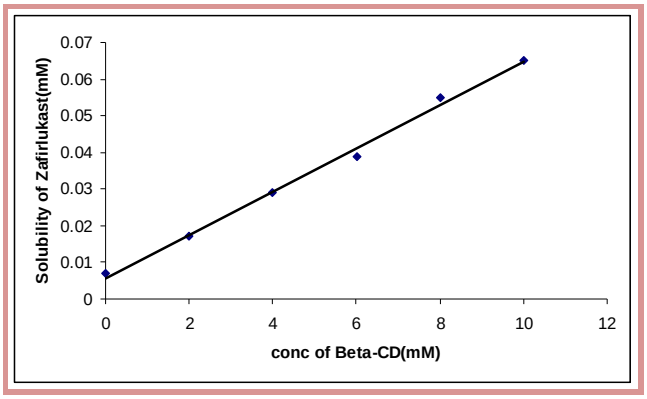


Figure 1: Phase solubility diagram of Zafirlukast in aqueous β-cyclodextrin solution

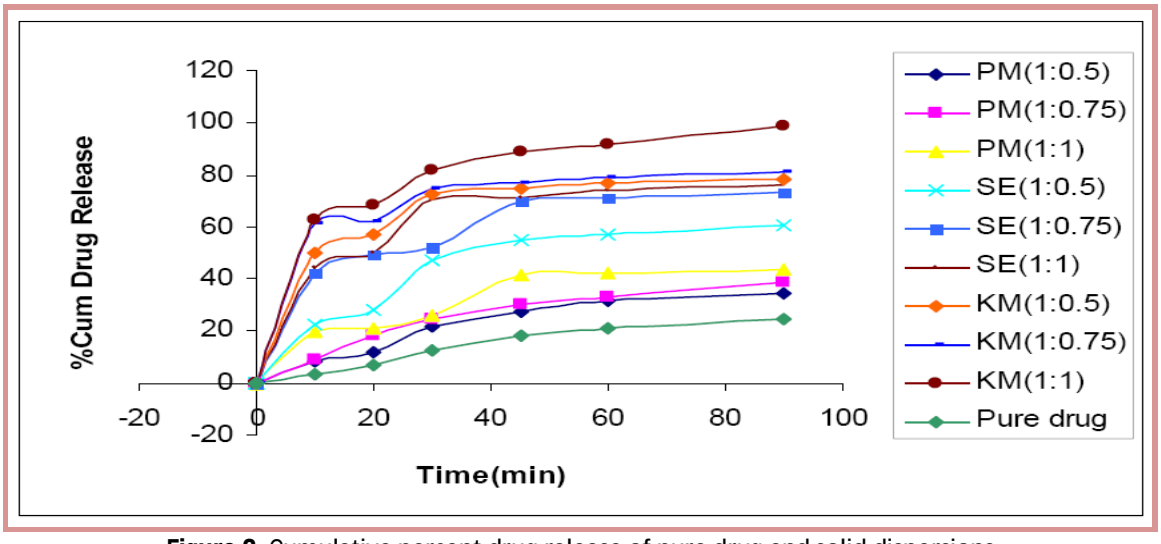
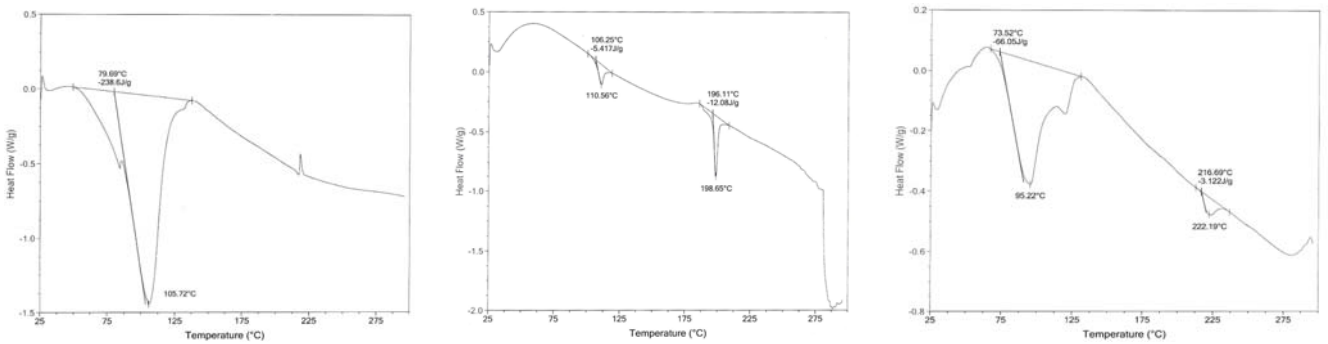


Figure 2: Cumulative percent drug release of pure drug and solid dispersions



(a) **(b)** **(c)**

Figure 3: Differential scanning calorimetry thermograms of (a)Zafirlukast, (b)β-CD, and (c)1:1 Zafirlukast: β-CD complex.

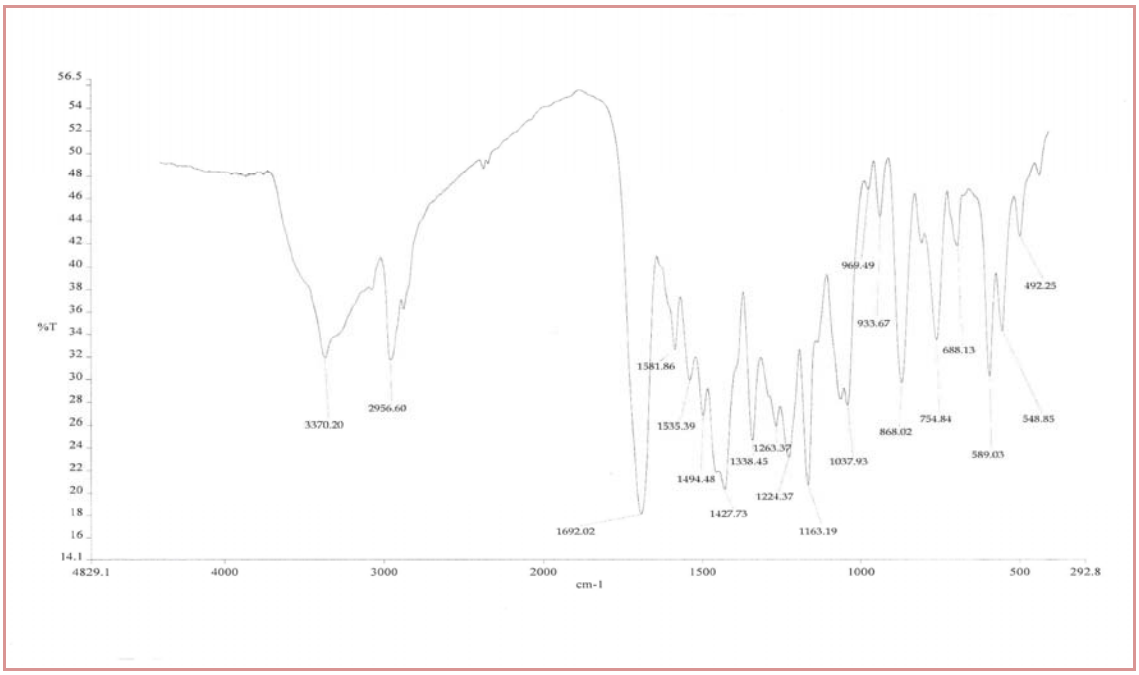


Figure 4 (a): FTIR Spectra of Zafirlukast

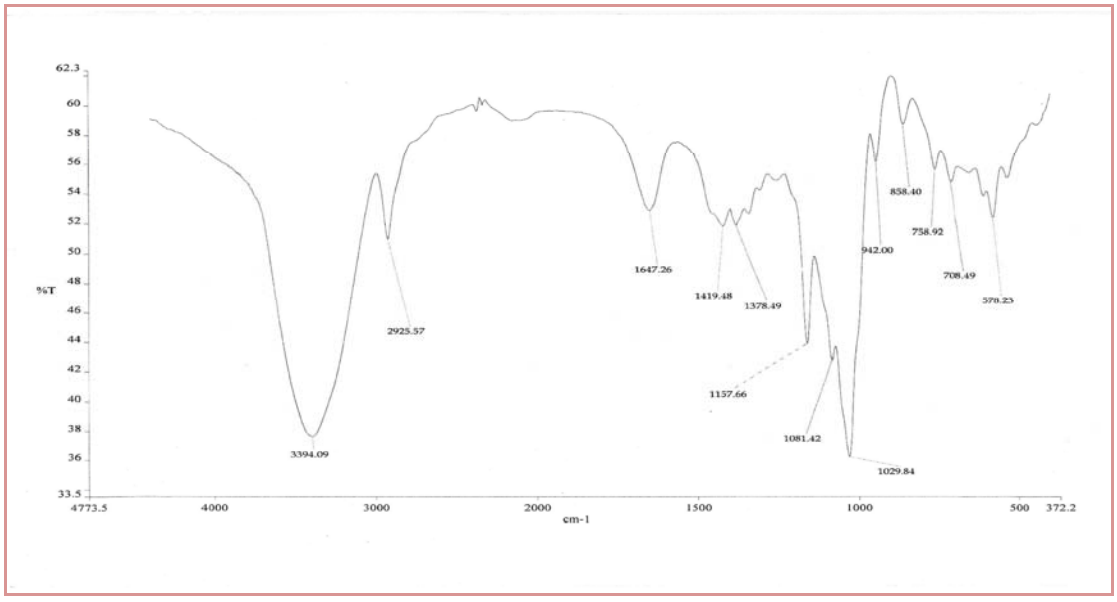


Figure 4 (b): FTIR Spectra of β-cd

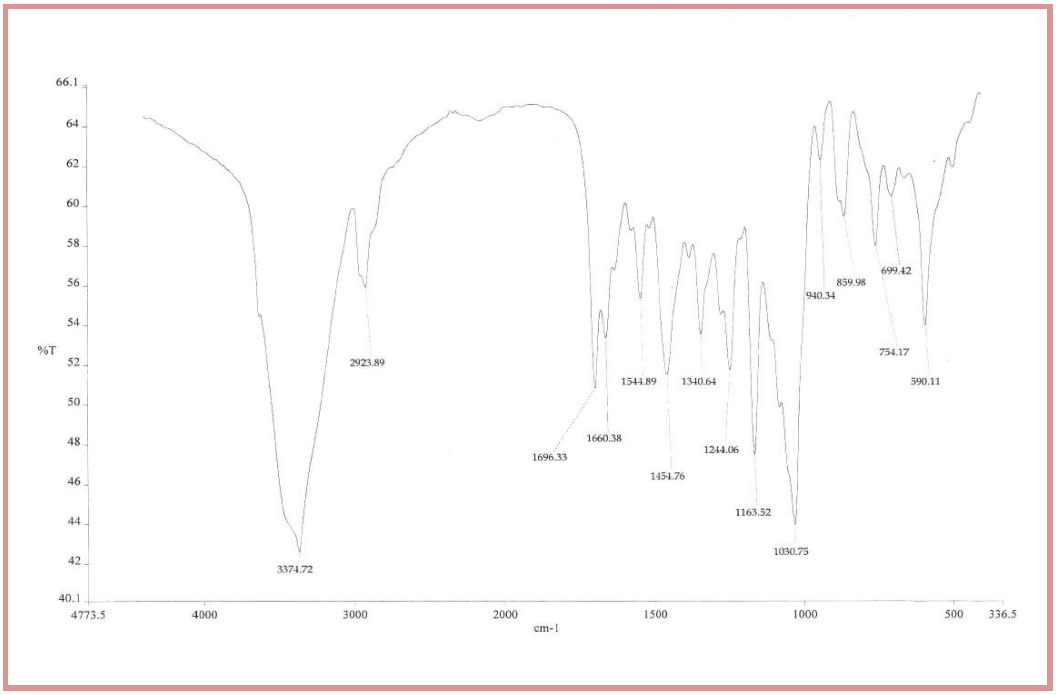


Figure 4 (c): FTIR Spectra of 1:1 Zafirlukast: β-cd complex

Differential scanning calorimetry:

Differential scanning calorimetry was used to characterize the Zafirlukast:β-cd complex. The DSC thermograms were shown in figure 3. The DSC thermogram of Zafirlukast exhibited an endothermic peak at 105.72^{0}C corresponding to its melting point. DSC thermograms of Zafirlukast: β-cd (1:1) inclusion complex prepared by Kneading method showed slight shift in peaks which indicates interaction between Zafirlukast and β-cd.

Fourier transform infra-red spectroscopy:

The IR spectrum of Zafirlukast, β-cd, and Zafirlukast: β-cd (1:1) complex were shown in figure 4.The IR spectrum of Zafirlukast exhibited peak at 3370 cm^{-1} due to N-H stretching, while peak at 1338cm^{-1} indicate SO_2 stretching. The IR spectrum of β-cd showed peak at 3394 cm^{-1}. The IR spectrum of Zafirlukast: β-cd (1:1) inclusion complex prepared by Kneading method has shown peaks at 3374 cm^{-1} and 1340 cm^{-1}. The shift in peaks indicates interaction between Zafirlukast and β-cd.

CONCLUSION

Zafirlukast is practically insoluble in water and aqueous fluids. As such dissolution is the rate limiting step in the process of drug absorption, to improve the dissolution of zafirlukast, solid dispersions if zafirlukast in β -cd were prepared and evaluated for their efficiency in increasing the dissolution rate of the drug. The study clearly shows that the dissolution rate of zafirlukast may be enhanced to a great extent by solid dispersion technique using kneading method. This is due to the reason that the cyclodextrins increased the aqueous solubility of poorly soluble drug by forming inclusion complexes with their apolar molecules and functional groups. The enhancement of zafirlukast from drug carrier systems is also due to the lack of crystallinity i.e., amorphization, increased wettability, dispersibility and particle size reduction.

Acknowledgements:

The authors wish to thank Dr. Reddy's Laboratories, Hyderabad for providing Zafirlukast gift sample, Management of K.V.S.R. Siddhartha college of pharmaceutical sciences for their constant support and encouragement.

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