

**DISSOLUTION RATE ENHANCEMENT OF POORLY SOLUBLE BICALUTAMIDE USING  $\beta$ - CYCLODEXTRIN INCLUSION COMPLEXATION**M V SRIKANTH<sup>1</sup>, G V MURALI MOHAN BABU<sup>2</sup>, N SREENIVASA RAO<sup>1</sup>, S A SUNIL<sup>1</sup>, S BALAJI<sup>1</sup> and KV RAMANAMURTHY<sup>1</sup><sup>1</sup>University college of pharmaceutical sciences, Andhra University, Visakhapatnam-530003, India. <sup>2</sup>Unichem Laboratories Ltd, Pilerne Industrial Estate, Bardez, Goa-403511, India, E-mail: venkatasrikanth\_meka@yahoo.com**ABSTRACT**

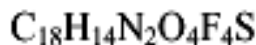
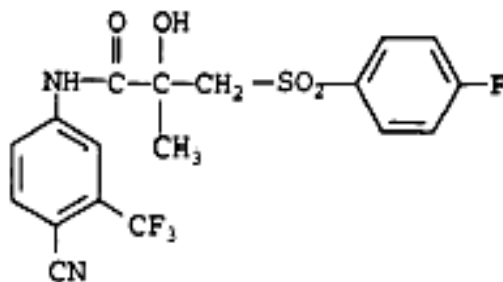
The purpose of this study was to improve the dissolution rate of poorly soluble bicalutamide drug with cyclodextrin complexation by following different techniques like spray drying, solvent evaporation and kneading method. Bicalutamide is a non-steroidal anti androgen. The effect of  $\beta$ -cyclodextrin on the dissolution rate of bicalutamide was investigated by evaluating inclusion complexes. The present invention relates to the inclusion complexes made by  $\beta$ -cyclodextrins and the methods for enhancing the bioavailability of bicalutamide. Solid inclusion complexes were prepared by conventional methods like spray drying, solvent evaporation and kneading techniques. Optimized complex was characterized by using powder x-ray diffractometry, and FTIR. *In vitro* studies showed that the dissolution rate of bicalutamide was significantly improved by the complexation with  $\beta$ -cyclodextrin with respect to the drug alone. In contrast, kneading complexes showed highest dissolution rate than the other conventional techniques.

**Keywords:** Bicalutamide,  $\beta$ -cyclodextrin, Complexation, Inclusion complex, Dissolution rate

**INTRODUCTION**

Poorly water-soluble drugs are associated with slow drug absorption leading eventually to inadequate and variable bioavailability. Bicalutamide is a poorly water soluble drug. The chemical name of the bicalutamide is propanamide, N- [4-cyano-3-(trifluoromethyl) phenyl]-3-[(4-fluorophenyl) sulfonyl]-2-hydroxy-2-methyl-, (+-) (Fig 1). It is a non-steroidal antiandrogen with a pKa of

approximately 12<sup>1</sup>. It competitively inhibits the action of androgens by binding to cytosol androgen receptors in the target tissue. The aqueous solubility of bicalutamide is low at 5  $\mu\text{g/mL}$  when determined in vitro at pH 7 and 37°C<sup>2</sup>. Since the pKa<sub>a</sub> of bicalutamide is 12, the solubility of the drug is low at physiological pH. Thus, it is important to enhance the solubility and dissolution rate of bicalutamide to improve its oral bioavailability.



**Fig. 1: Chemical structure of bicalutamide.**

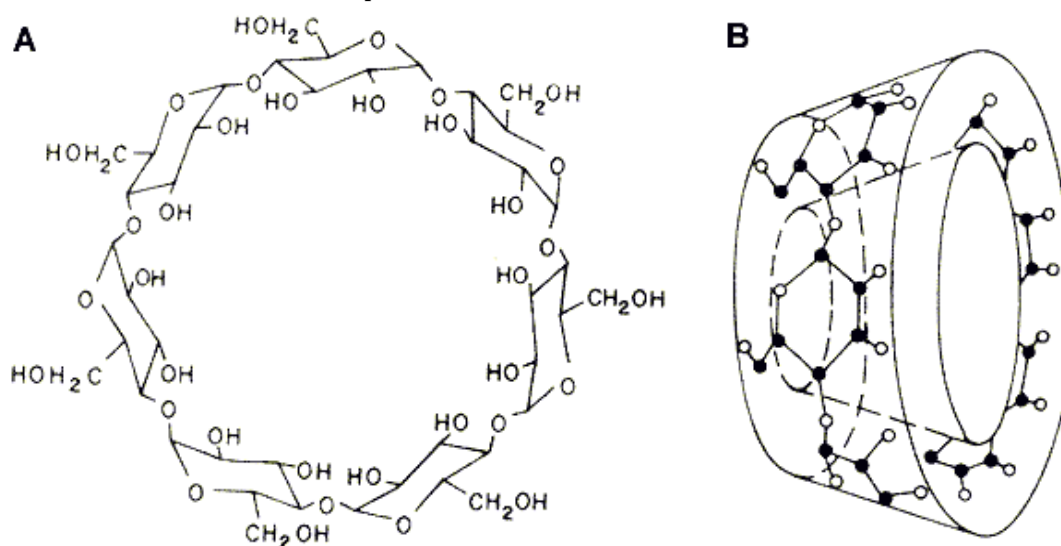
The solubility of poorly soluble drug can be altered in many ways, such as modification of drug crystal forms, addition of co solvents, addition of

surfactants, complexation with cyclodextrins (CD), etc<sup>3, 4,5,6,7</sup>. Among the possibilities, the cyclodextrin approach is of particular interest. The

complexation with cyclodextrins involves simple manufacturing steps, cost effective and industrial feasibility.

Cyclodextrins are cyclic ( $\alpha$ -1, 4)-linked oligosaccharides of  $\alpha$ -D-glucopyranose, containing a relatively hydro-phobic central cavity and hydrophilic outer surface<sup>8</sup>. Owing to lack of free rotation about the bonds connecting the glucopyranose units, the cyclodextrins are not perfectly cylindrical molecules but are toroidal or cone shaped<sup>8</sup>. Based

on this architecture, the primary hydroxyl groups are located on the narrow side of the torus, while the secondary hydroxyl groups are located on the wider edge (Figure 2). The chemical structure (A) and the steroidal shape (B) of the  $\beta$ -cyclodextrin molecule (7  $\alpha$ -1, 4 -linked glucopyranose units form a cone with a hydrophilic outer surface and a lipophilic cavity in the center).



**Fig. 2: The chemical structure (A) and the steroidal shape (B) of the  $\beta$ -cyclodextrin molecule**

During the past two decades, cyclodextrins and their derivatives have aroused considerable interest in the pharmaceutical field because of their potential to form complexes with many varieties of drug molecules<sup>9, 10</sup>. When cyclodextrins are used to enhance the solubility of water insoluble drugs, it is generally assumed that the solubilization proceeds through inclusion complex formation<sup>11</sup>. The hydrophobic cavity of cyclodextrins is capable of trapping a variety of molecules within to produce inclusion complexes. Numerous scientific articles describe the advantages of drugs complexed with cyclodextrins in this

way: increased solubility; enhanced bioavailability; improved stability; masking of taste or odor; reduced volatility; transformation of liquid or gas into solid form; reduced side effects; reduced haemolysis and prevent admixture incompatibilities<sup>8,12,13,14</sup>. In this study, investigations were performed on the possibility of complexation of bicalutamide with  $\beta$ -cyclodextrin for improving the solubility and dissolution rate, thereby increasing the oral bioavailability. In the present investigation, complexation of bicalutamide with  $\beta$ -cyclodextrin was prepared by solvent evaporation, spray drying and kneading technologies at

stoichiometric ratios. Out of these techniques, best method was optimized depending upon their highest dissolution rate. Selective physicochemical determinations based on powder x-ray diffractometry (PXRD) and Fourier transform infrared spectroscopy (FTIR) were used to characterize the complexes. *In-vitro* dissolution profiles of the complexes were performed.

## **MATERIALS AND METHODS**

### **Materials**

Bicalutamide was a generous gift sample from Dr. Reddy's Laboratories Ltd (Hyderabad, India).  $\beta$ -cyclodextrin was purchased from Fine chemicals, Hyderabad. All other reagents and chemicals were of analytical grade.

### **Preparation of Solid Complexes**

The preparation of solid complexes of bicalutamide with  $\beta$ -cyclodextrin was performed by different techniques, which are described below in detail.

### **Complexation with $\beta$ -cyclodextrins by solvent evaporation**

Bicalutamide &  $\beta$ -cyclodextrins complexes (1:1, 1:2 & 1:5) were prepared by conventional solvent evaporation method. In this method required quantity of

$\beta$ -cyclodextrins was dissolved in water-ethanol mixture. Water-ethanol mixture was prepared in the ratio of 3:1. An appropriate weight of bicalutamide was dissolved in acetone (15 %w/v). Both solutions were mixed, and the volume was adjusted with either water-ethanol mixture or acetone until the formation of a clear solution, if necessary. The solvents were evaporated at 50°C under reduced pressure in a rota evaporator and they were further dried in desiccators over silica gel for 24 hrs to remove all the residual solvents. The dried mass was collected and passed

through 60 #, and packed in a closed container.

### **Complexation with $\beta$ -cyclodextrins by spray drying technique<sup>15</sup>**

In the spray drying technique, Buchi nozzle type mini spray dryer was used for the preparation of bicalutamide &  $\beta$ -cyclodextrin inclusion complexes in the ratio's 1:1, 1:2 & 1:5. In this method water-ethanol mixture about 3:1 ratio was used for salvation of cyclodextrins. Required quantity of  $\beta$ -cyclodextrin was dissolved in water-ethanol mixture. An appropriate weight of bicalutamide was dissolved in acetone (containing 15 %w/v drug). Both solutions were mixed, and the volume was adjusted with either water-ethanol mixture or acetone until the formation of a clear solution, if necessary. The final clear solution was supplied to the dryer nozzle at a flow rate of 2 ml/min using a peristaltic pump and thereafter spraying and drying simultaneously at the inlet temperature of 50°C with flow rate of 4 ml/min. The residue of bicalutamide &  $\beta$ -cyclodextrin inclusion complex was collected and that complex was further dried in desiccators over silica gel for 24 hrs to remove all the excess residual solvents. The dried mass was collected and passed through 60 #, and packed in a closed container.

### **Complexation with $\beta$ -cyclodextrins by kneading technique<sup>16</sup>**

The bicalutamide &  $\beta$ -cyclodextrins complexes (1:1, 1:2 & 1:5) were prepared by kneading technique. In this method required amount of drug and  $\beta$ -cyclodextrin were taken and transferred to a mortar pestle. The mixture was size reduced by continuous stirring with pestle. Water-ethanol mixture (3:1) ratio was added to the above physical mixture and continuously stirred until the slurry mass was formed. Slurry mass was

collected and dried in a hot air oven for 2 hrs at 50 °C, dried mass was collected and further dried in desiccators over silica gel for 24 hrs to remove all the excess residual solvents. The dried mass was collected and passed through 60 # mesh, and packed it in a closed container.

### Evaluation of the complexes

#### Dissolution Rate Studies

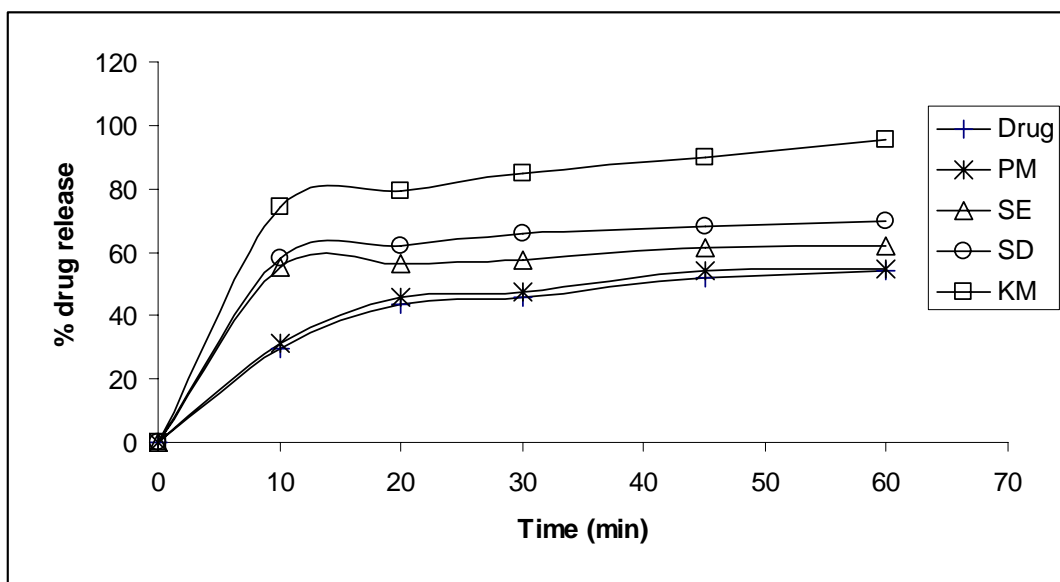
Dissolution studies were performed separately in 900ml of water with 1% SLS maintained at 37°±0.5°C using USP XXII type II dissolution test apparatus at the speed of 50 rpm which was official in FDA dissolution methods. The physical mixture or inclusion complexes, equivalent to 50mg of bicalutamide was taken for dissolution studies. The sample (5 ml) was withdrawn at different time intervals up to 1 hour, and replaced the same with fresh dissolution medium. The samples were estimated for amount of bicalutamide dissolved by measuring their absorbances at 272nm.

Fourier transform infrared spectroscopy (FTIR) was used to identify the drug excipient interaction. Samples were analyzed by potassium bromide pellet method in an IR spectrophotometer (Shimadzu, FTIR 8700) in the region between 4000-450 cm<sup>-1</sup>. Complex formation was evaluated by comparing the IR spectra of the solid complex with drug. XRD studies were also performed to identify the interaction of the drug with β cyclodextrins.

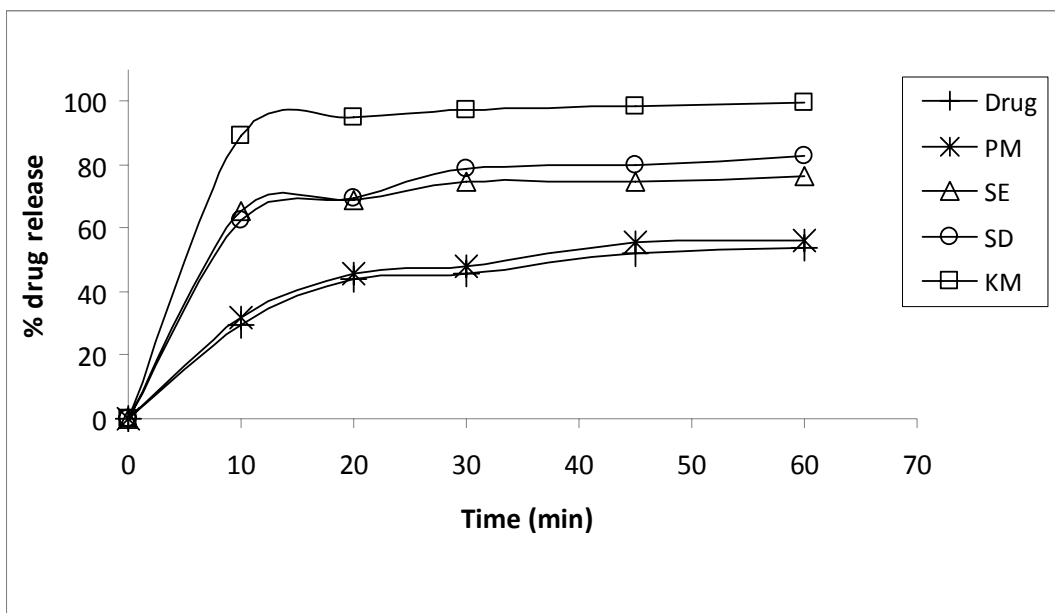
### RESULTS AND DISCUSSION

#### Drug dissolution from the inclusion complexes:

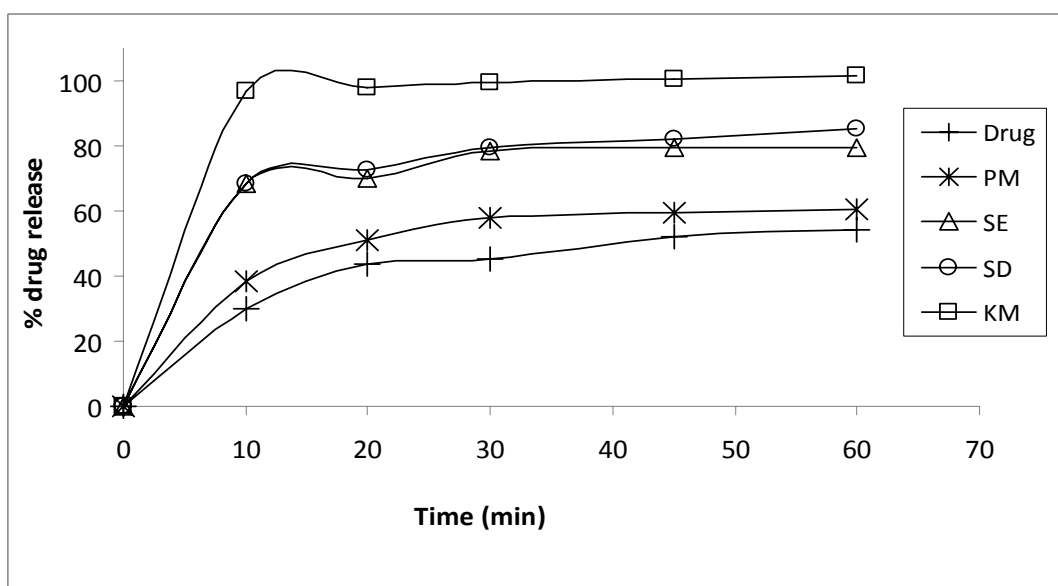
Dissolution rates of bicalutamide with β-cyclodextrin were conducted and the results were reported in Fig 3-5. The highest dissolution rate was found in the kneading method prepared complex, at the ratio of 1:5 (drug: β-cyclodextrin). Dissolution rate order with different techniques was found to be kneading method > spray drying method > solvent evaporation method > physical mixture > pure drug.



**Fig. 3: Dissolution profile of bicalutamide and β-cyclodextrin complex (1:1) ratio with different technologies. (+) Pure drug, (\*) physical mixture, (Δ) Solvent evaporation method, (o) Spray drying method, (□) Kneading method**



**Fig 4: Dissolution profile of bicalutamide and β-cyclodextrin complex (1:2) ratio with different technologies. (+) Pure drug, (\*) physical mixture, (Δ) Solvent evaporation method, (○) Spray drying method, (□) Kneading method.**



**Fig 5: Dissolution profile of bicalutamide and β-cyclodextrin complex of (1:5) ratio with different technologies. (+) Pure drug, (\*) physical mixture, (Δ) Solvent evaporation method, (○) Spray drying method, (□) Kneading method**

According to these results, pure drug released less than 60% of the active content at the end of 1hr because of its poor solubility, at the same time physical mixtures of different ratios were also released the active content less than 65% at the end of 1 hr, but the

inclusion complex prepared by kneading method at the ratio of 1:5 was released the drug more than 95% with in 10 min and complete drug was released at the end of the hour, indicating that the solubility of the drug was greatly increased by kneading

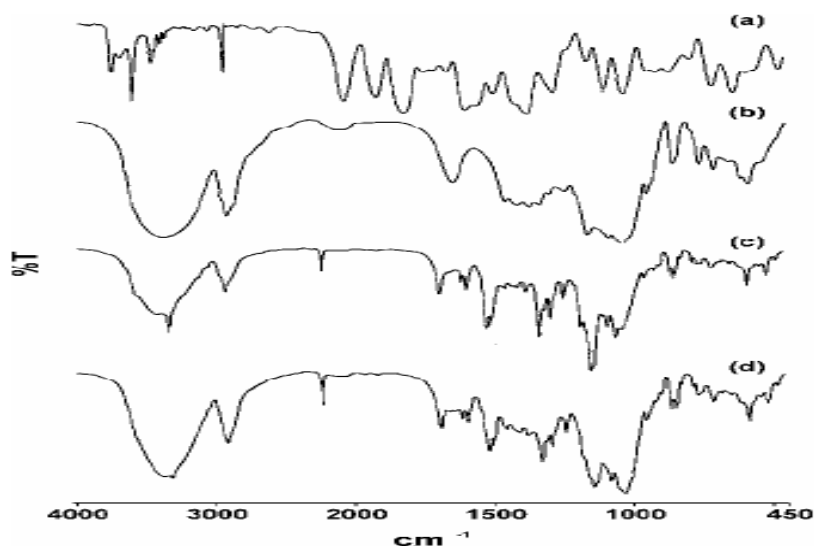
method. The kneading method prepared complexes at the ratio of 1:1, the dissolution rate was slightly increased as compared to physical mixture and drug alone, but at the ratios of 1:2 and 1:5 the dissolution rate was dramatically increased. Where as in case of solvent evaporation & spray drying methods, there was no significant change in the dissolution profile as compared to physical mixture, even though increasing the concentration of  $\beta$ -cyclodextrin. From the dissolution data concluded that dissolution rate was greatly improved by kneading method. This is because of higher hydrophilicity and wetting property of  $\beta$ -cyclodextrin.

### 3.2. Fourier transformation-infrared spectroscopy (FTIR)

Fig. 6 illustrates the FTIR spectra of bicalutamide,  $\beta$  cyclodextrin, physical mixture and inclusion complex in binary system. IR spectrum of bicalutamide (a) is identified by absorption peaks at  $3065\text{ cm}^{-1}$  (=C-H aromatic ring),  $2947\text{ cm}^{-1}$  (C-H stretch),  $2242\text{ cm}^{-1}$  (C $\equiv$ N

stretch),  $1699\text{ cm}^{-1}$  (C=O stretch),  $3587\text{ cm}^{-1}$  (H bonded O-H stretch),  $3345\text{ cm}^{-1}$  (Secondary amine N-H stretch), and  $1595\text{ cm}^{-1}$  (C=C stretch, aromatic ring). The IR spectrum of  $\beta$ -cyclodextrin (b) shows prominent peaks at  $3398\text{ cm}^{-1}$  (O-H stretch),  $2942\text{ cm}^{-1}$  (C-H stretch), and  $1652\text{ cm}^{-1}$  (C=O stretch).

In IR spectra of physical mixture (c), the peaks at  $3065\text{ cm}^{-1}$ ,  $2947\text{ cm}^{-1}$ ,  $3587\text{ cm}^{-1}$  of bicalutamide are not visible, whereas the peak at  $3345\text{ cm}^{-1}$  was shifted to  $3348\text{ cm}^{-1}$ . Compared to bicalutamide peaks, physical mixture peaks were smoothed indicating that a strong physical interaction exists in between bicalutamide &  $\beta$ -cyclodextrin. Those peaks were completely disappeared in IR spectra of inclusion complex (d). The broad peak of  $\beta$ -cyclodextrin (b) at  $3398\text{ cm}^{-1}$  was gradually reduces its intensity in physical mixture and in inclusion complex. It indicates that bicalutamide forms a strong inclusion complex with  $\beta$ -cyclodextrin in solid state.



**Fig. 6: FTIR spectra of bicalutamide - $\beta$  cyclodextrin binary systems: (a) bicalutamide; (b)  $\beta$  cyclodextrin; (c) physical mixture; (d) inclusion complex**

### X-ray powder diffractometry (XRD)

From the Fig 7: found that the XRD pattern of bicalutamide showed sharp and intense peaks, indicating that drug is in crystalline nature. Bicalutamide (a) showed sharp peaks at  $17.05^\circ$  and  $23.90^\circ$  ( $2\theta$ ) with peak intensities of 358 and 460 respectively.

$\beta$ -cyclodextrin (b) showed only one sharp peak at  $19.90^\circ$  ( $2\theta$ ) with peak intensity of 465. The physical mixture (c) peaks were found to be less intensity compared to individual peaks, indicating reduction in the crystallinity. But in the case of inclusion complex the intensity was gradually decreased as compared with physical mixture.

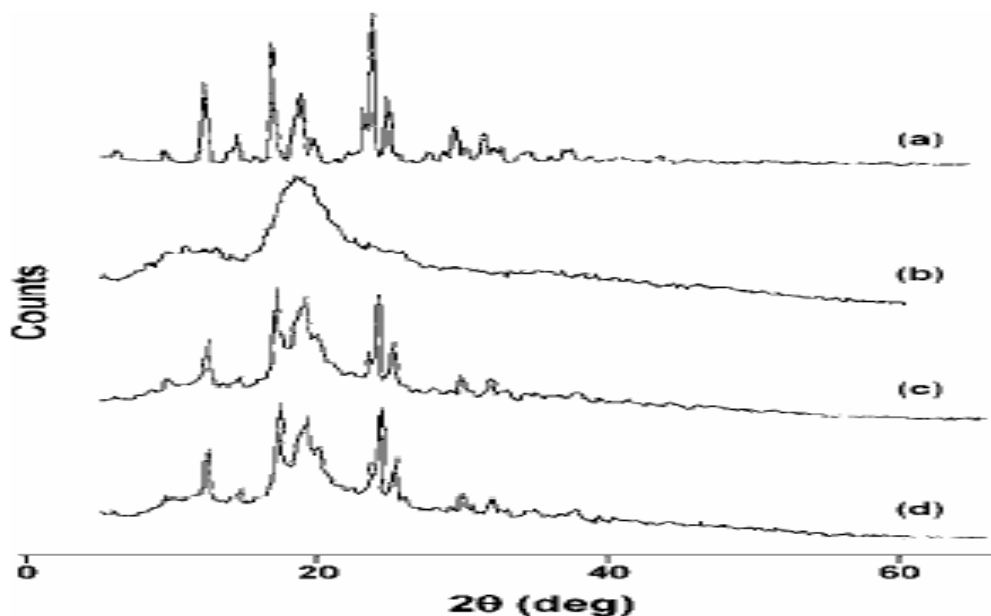


Fig. 7: XRD patterns of bicalutamide - $\beta$ -cyclodextrin binary systems

(a) bicalutamide; (b)  $\beta$ -cyclodextrin (c) physical mixture; (d) inclusion complex

### CONCLUSION

Inclusion complex of bicalutamide &  $\beta$ -cyclodextrin (1:5) prepared by kneading method exhibited higher rate of dissolution as compared to solvent evaporation method, spray drying method and physical mixture. Results obtained by different characterization techniques clearly indicate that the kneading method leads to formation of solid-state complexes between bicalutamide and  $\beta$ -cyclodextrin. The complexation of bicalutamide with  $\beta$ -cyclodextrin lends an ample credence for better therapeutic efficacy. From the results concluded that dissolution rate order with different techniques was found to be kneading method > spray

drying method > solvent evaporation method > physical mixture > pure drug. Finally it was concluded that the bicalutamide -  $\beta$ -cyclodextrin complexation results in increase in the solubility and dissolution rate of the bicalutamide, suggesting a possible enhancement of its oral bioavailability.

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