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PREPARATION AND EVALUATION OF IRBESARTAN-CYCLODEXTRIN INCLUSION COMPLEXES

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ABSTRACT

In the present work effect of methyl-β-cyclodextrin (MβCD) on physical properties and dissolution rate of Irbesartan (IRB) was studied.Based on A_L-type ofphase solubility diagram obtained; solid binary systems of the drug with MβCD were prepared in 1:1 molar ratio by various methods. Complexes were characterized using Differential Scanning Calorimetry and powder X-Ray Diffractometry. It could be concluded that IRB can form inclusion complex with MβCD. The dissolution profiles of inclusion complexes were compared with those of IRB alone and the physical mixture. The dissolution rate of IRB was increased remarkably by MβCD inclusion complexation.

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INTRODUCTION:

Irbesartan (IRB) is used in the treatment of hypertension. Its poor aqueous solubility leads to limited bioavailability after oral administration[1, 2]. Cyclodextrins (CDs) are macrocyclic oligosaccharides with six to eight D-glucose units called α- cyclodextrin, β- cyclodextrin and γ-cyclodextrin and have been widely used to improve the solubility and dissolution rate of poorly soluble drugs[3]. Significant improvement in the solubility resulting in increased rate of dissolution and absorbability is obtained by use of methylated βCD.

Co-evaporation, co-grindingandkneadingmethods were used to prepareinclusion complexes. Instrumental techniques like X-Ray Diffraction (XRD) and Differential Scanning Calorimetry (DSC) were used for characterization of complexes. Dissolution patterns of plain drug, physical mixtures and inclusion complexes were evaluated.

MATERIALS AND METHODS:

Materials: IRB was kindly supplied byAarati Drugs Ltd., India. MβCD (D.S. = 1.8 and M. W. = 1310) was gifted by Wacker fine chemicals.

Methods: Method described by Higuchi and Connors was used to conduct phase solubility studies[1]. An excess amount of IRB was added to MβCD aqueous solution (0-10mM) and subjected to shaking. After equilibrium attainment, concentration of IRB was determined. The apparent stability constant Ks was calculated from the phase solubility diagram according to the following equation:

$$Ks = \frac{Slope}{S_o(1 - Slope)}$$

S_0 is the solubility of IRB in absence of MβCD.

Preparation and evaluation of Binary Systems of IRB–MβCD:

Various methods such as co-grinding (CG), kneading (KN) and co-evaporation (CE) were used to prepare binary systems of IRB-MβCD with 1:1 molar ratio. The physical mixture (PM) was also prepared for the purpose of comparison. Intense trituration of IRB and MβCD was carried out to obtain CG product. Trituration of IRB with MβCD in glass mortar followed by kneading with 66% alcohol for 45 minresulted in KN product. The pasty mass obtained was dried at 60°C. The dried mass was passed through sieve no.80 and stored overnight in desiccator. For preparation of CE product, equimolar amounts of MβCD and IRB were dissolved in minimum volume of 1:1 mixture of 66% ethanol and water. The final solution was stirred with the help of magnetic stirrer at 60°C till pasty mass was obtained. The pasty mass was treated as above to get the dry sample.

Binary systems were characterized by DSC, XRD alongwith dissolution studies. Dissolution rate studies of IRB alone and from various IRB-MβCD systems were conducted using USP XXIII dissolution apparatus type-II (6 stations, VDA-6DR, Veego Scientific, India) at 37 ± 0.5°C stirring at 50 rpm. Seventy five mg of IRB or its equivalent amount of IRB-MβCD binary system was added to 1000 ml of distilled water. At predetermined time intervals, the samples were withdrawn and analyzed spectrophotometrically.

RESULTS AND DISCUSSION:

The phase solubility profile of IRB-MβCD as presented in Figure1 is classified as A_L type. The curve showed a linear increase in IRB solubility as a function of MβCD concentration with a slope of 0.0904 (R^2 = 0.999) in the concentration range (0-10 mM) investigated. The apparent stability constant $K_{1:1}$ was 177.8 M^{-1}. Slope value was lower than one indicating inclusion complex in the molar ratio of 1:1.

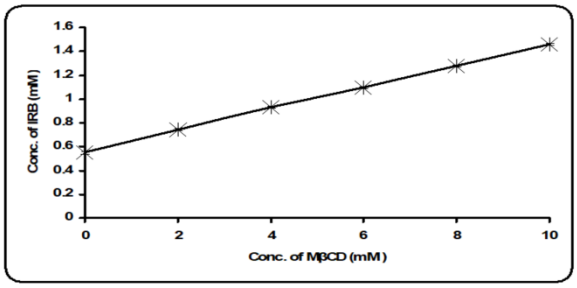

Figure 1: Phase solubility profile of IRB-MβCD in water

Thermograms of IRB and the binary systems are shown in Fig. 2. The thermogram of IRB was typical of a highly crystalline compound, characterized by a sharp endothermic peak at 181°C, corresponding to its melting. A broad endotherm in the range of 100-120°C in case of MβCD indicated release of water molecule from its cavity. PM and CG systems showed retention endothermic peaks corresponding to drug whereas it was shifted to lower temperature in the case of CE system. KN system showed a significant shift in location of endothermic peak of IRB to 158.9ºC with substantial broadening which can be attributed to complex formation [5].

Thus kneading method can be utilized for complexation of IRB using MβCD.

XRD patterns of IRB, PM and KN complex are illustrated in Fig. 3. Two broad diffused peak of MβCD indicated its amorphous nature. PM and CG systems showed peaks attributable to IRB. The KN and CE systems exhibited more diffused diffraction patterns, indicating loss of crystallinity. Similar disappearance of crystalline drug peak was observed by Bandi et al in case of HPβCD complexation of some drugs [5].

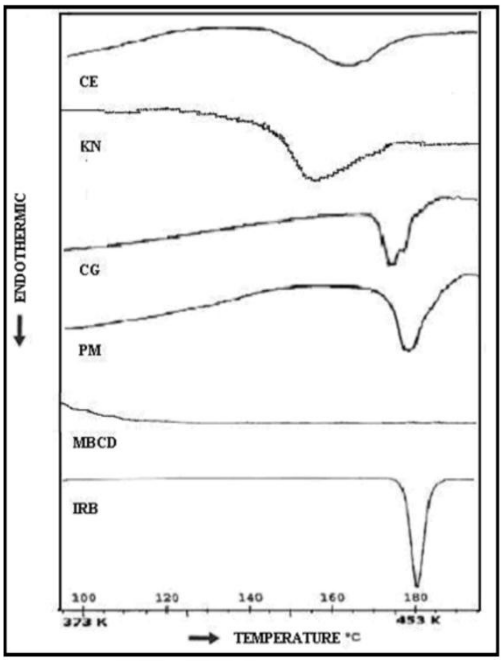

Figure 2: DSC thermograms of IRB-MβCD systems: Irbesartan (IRB), Methyl-β-cyclodextrin (MβCD), physical mixture (PM), co-ground (CG), co-evaporated (CE) and kneaded (KN) systems

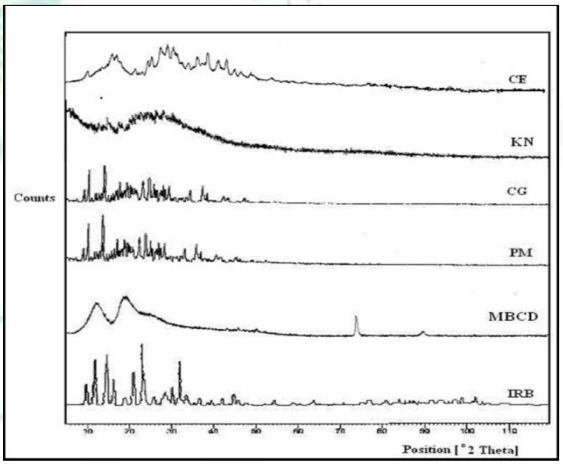

Figure 3: X-Ray Diffractograms of IRB-MβCD systems: Irbesartan (IRB), Methyl-β-cyclodextrin (MβCD), physical mixture (PM), Co-ground (CG), co-evaporated (CE) and kneaded (KN) systems

Dissolution Studies

Amongst the IRB-MβCD systems, KN system showed the highest improvement in the dissolution rate. Thus it can be concluded that KN method was more efficient in improving the solubility when using MβCD. The KN method is of the particular interest for industrial scale preparations because of the low cost and the simple process, which involves less energy, time and equipment.

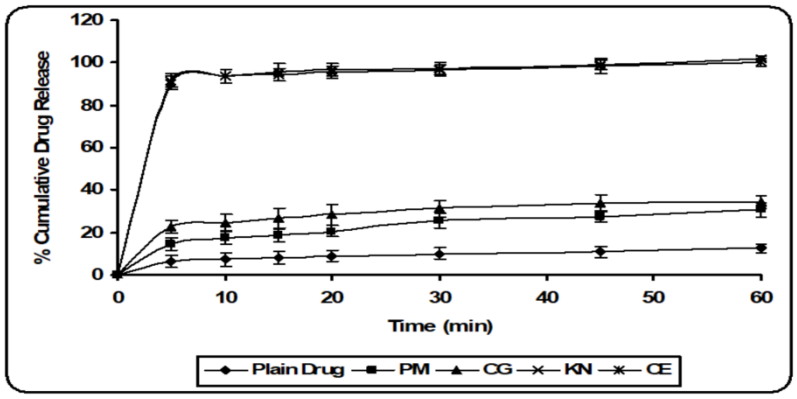

Figure 4: The dissolution diagram of IRB-MβCD systems

Irbesartan (IRB), physical mixture (PM), co-ground (CG), co-evaporated (CE), kneaded (KN) systems

CONCLUSION:

From instrumental methods of characterization, it can be concluded that IRB forms inclusion complexes with MβCD. The complexes exhibited improvement in solubility and dissolution rate of drug.

ACKNOWLEDGEMENT:

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