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EFFECTS OF CYCLODEXTRINS AND PHOSPHOLIPIDS IN ENHANCING DISSOLUTION OF INDOMETHACIN

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ABSTRACT

Inclusion complexes of indomethacin (IND) and ß-cyclodextrins (ß-CD) were prepared by the freeze drying methods. Solid dispersion of IND and Dimyristoylphosphatidylcholine (DMPC) was prepared as coprecipitate (CPPT) by the solvent method. These formulations were characterized by X-ray diffractometry and dissolution rate determinations. Dissolution of IND from ß-CD inclusion complex was found to be 133 times faster than the corresponding pure IND, whereas it was about 4 times faster from a DMPC CPPT sample. Various derivatives of ß-CDs showed variable rates of dissolution of IND. ß-CD and most of the other derivatives showed almost instantaneous dissolution of IND at a molar ratio of 1:1 (IND:ß-CD) except dimethyl-ß-cyclodextrin (DMB) derivative, which showed a fairly constant release of IND over 90 minutes. DMB may, therefore, have the potential for use in the formulation of a constant-release preparation. X-ray diffraction spectra showed that indomethacin remained as amorphous state in CPPT or in inclusion complex. Thus, these formulations may have the potential to produce faster onset of action, reduced dosing and decreased GI irritation.

INTRODUCTION

Indomethacin (IND), an indoleacetic acid derivative, is a non-steroidal anti-inflammatory drug which has analgesic, antipyretic, and antiphlogistic actions[1]. It is a poorly water-soluble drug with a saturation solubility of 0.4 mg/ml[2]. Although absorption of IND appears to be complete only in small

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intestine in adults, but it takes several hours. Since it is recommended to be taken with food, its absorption is variable among individuals and depends on the effect of the food on gastric pH. In premature neonates, unlike adults, absorption of oral IND appears to be poor and incomplete; bioavailability is reportedly only about 20%[3]. Recently, molecular encapsulation method by cyclodextrin (CD) inclusion complex is being investigated in the field of pharmaceutics to improve aqueous solubility, chemical stability, and bioavailability of drug molecules[4]. γ-CD has the largest internal diameter which allows easy entrapment of molecules. However, the expensive process required for the production of γ-molecules has made ß-CDs the first choice in almost all studies. Disadvantages of limited internal diameter and relatively low water solubility of ß-CD have led to the production of ß-CD derivatives with increased internal diameter and solubility. These characteristics have been obtained by alkylation of the hydroxyl groups (methyl-, hydroxyl-, and also hydroxyethyl -CDs), substitutions of primary hydroxyl groups by saccharide (glycosyl- and maltosyl-CDs), or polymerization of CDs[5-9].

The aim of this study was to investigate the effects of different derivatives of CD on the release characteristics of IND and also to compare the results with the dissolution behavior of dimyristoylphosphatidylcholine (DMPC) coprecipitate (CPPT) formulation.

MATERIALS

L-α-DMPC and IND was purchased from Sigma Chemical Company, St. Louis, MO. All cyclodextrins and their derivatives such as : dimethyl-ß-cyclodextrin (DMB), 2-hydroxypropyl-ß-cyclodextrin (HPB), and glucosyl-ß-cyclodextrins (MG1B) were purchased from Pharmatec Company, Alachua, Fl. Chloroform, methanol, ethanol and other solvents were reagent grade solvents. Demineralized distilled water was used throughout.

METHODS

Preparation of CD-IND Inclusion Complex : A modified method of Kurozumi et al.[10] was used to prepare the inclusion complex of CD-IND because of its superiority over other methods[10-11]. In short, appropriate quantities of IND and CD (or derivatives) were dissolved in water and few drops of 28% aqueous ammonium solution were added. It was then freeze-dried using a laboratory freeze dryer and dried at 50°C for 2 hours. It was washed with ethyl ether, the residue was dried in vacuum at room temperature and finally the powder so obtained was triturated and sieved through #80 mesh screen for use in dissolution studies.

Preparation of DMPC-IND CPPTs and Physical Mixtures : CPPT of DMPC-IND was prepared by the solvent method[12] using chloroform in a jacketed beaker by constant stirring, which were subsequently dried and sieved through

a #80 mesh screen and examined within 24 hours. Physical mixtures were prepared by triturating drug and DMPC in a small mortar then transferring to a vacuum desiccator until ready for use.

Dissolution Studies : The dissolution rate measurements were carried out by using a fully automated Vanderkamp 600 dissolution test apparatus (paddle method). The flasks were immersed in a water bath maintained at 37°C. The 900 ml dissolution medium was continuously stirred at 200 rpm by an USP standard paddle. Sieved samples equivalent to 50 mg IND were sprinkled on the surface of the stirred medium. At different time intervals, samples were taken automatically to a Milton Roy Spectronic 1201 Spectrophotometer and absorbance reading were taken at 318 nm. The samples were returned to the dissolution flasks after the measurements were made.

X-ray Diffraction Study : Samples for low-angle powder X-ray diffraction studies were uniformly dispersed on a glass slide. Diffraction spectra were then obtained by using Scintag, USA X-ray diffractometer monochromated Cu-K_α radiation and run at a 2Θ angle.

RESULTS AND DISCUSSIONS

IND in ß-CD Inclusion Complex and in PL CPPTs : Figure 1 shows the effect of ß-CD-IND inclusion complex and DMPC-IND CPPT on the rate of dissolution of IND. Dissolution characteristics of a physical mixture of ß-CD:IND (1:1), pure IND, inclusion complex of ß-CD:IND (1:1) and CPPT of DMPC:IND (1:4) were compared. Physical mixture of ß-CD-IND and DMPC-IND showed similar results to pure IND. DMPC showed several fold increase in % drug dissolved both initially and at the 90 min period. At 10 min, the increase was 24.6 times and at 90 min 4.4 times. ß-CD displayed a dramatic increase in the % of drug dissolved both over pure IND and IND-DMPC CPPT. At 10 min, 90.4 % of IND in the inclusion complex of ß-CD was released and dissolved. This corresponds to approx. 133 times increase in the % IND dissolved over IND alone and 5.4 times over IND-DMPC CPPT. The release and dissolution of IND from ß-CD inclusion complex was immediate and almost complete within 10 minutes.

IND in Inclusion Complexes of ß-CD Derivatives : Figure 2 indicates the effect of different derivatives of ß-CD on the dissolution characteristics of IND. MG1B is indicating results comparable to that of the parent molecule ß-CD. There are no statistically significant differences in % drug dissolved at any time interval. HPB releases IND to a lesser extent than either ß-CD or MG1B. DMB shows even lesser effect on the release and dissolution of IND throughout the time period from 10 min to 90 min. But unlike ß-CD or other derivatives, release of IND from DMB was gradual. The fairly constant

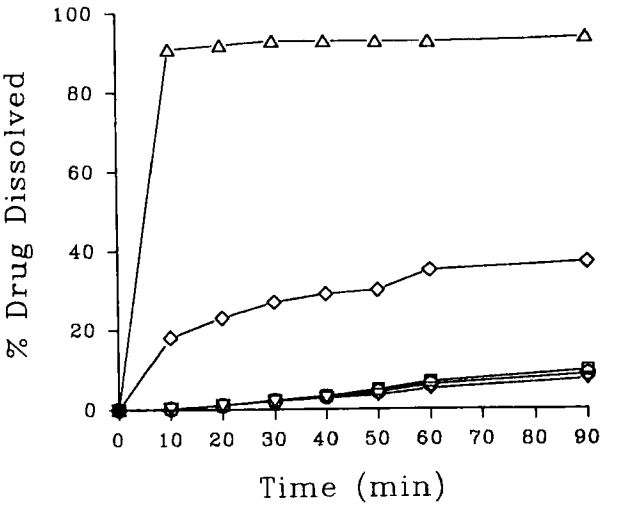

FIGURE I

Effect of CD-IND complex on the rate of dissolution of IND in distilled water and at 37°C. Key : (○) pure IND; (▽) CD-IND (1:1) physical mixture; (□) DMPC-IND (1:4) physical mixture; (◇) DMPC-IND (1:4) CPPT; (△) CD-IND (1:1) inclusion complex

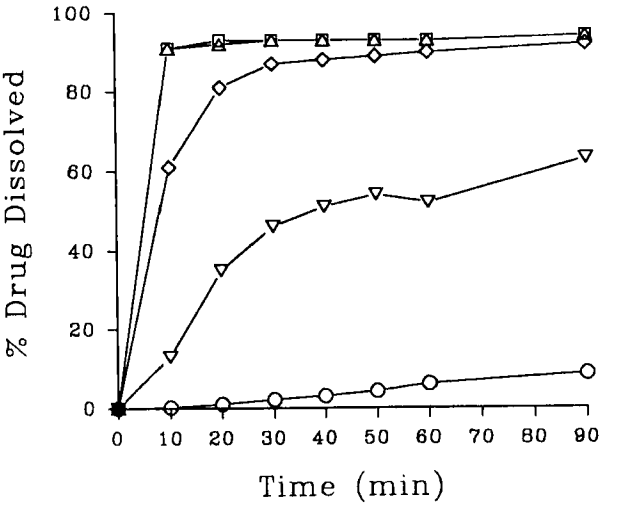

FIGURE II

Effect of various derivatives of CD on the rate of dissolution of IND in distilled water and at 37°C. Key : (○) pure IND; (△) CD-IND; (□) HPB-IND; (◇) MG1B-IND; (▽) DMB-IND.

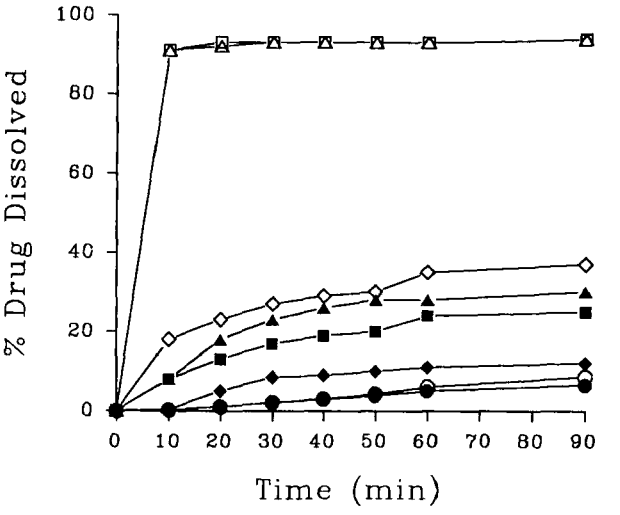

FIGURE III

Effect of pH of the medium on the rate of dissolution of IND at 37°C. Key : open = distilled water; closed = simulated gastric pH. (○ ●) pure IND; (◇ ◆) DMPC-IND (1:4) CPPT; (△ ▲) CD-IND (1:1) complex; (□ ■) MG1B-IND (1:1) complex.

release of IND from this derivative may make DMB a suitable candidate for controlled-release formulation of IND and perhaps other drugs. Further studies are required to investigate this property of DMB. The different results of CD derivatives on the release and dissolution of IND are thought to be due to the function of the spatial arrangement of each compound and the degree of interacting forces. The relatively more soluble derivatives of ß-CD did not improve the release and dissolution rate of IND. This ascertains that increase in the dissolution rate of the entrapped drug is not by mere increase in the CD solubility. Should this be the case, DMB or HPB would have shown better dissolution characteristics over ß-CD.

Effect of pH of the Medium : The lower dissolution rate of IND in low pH has been reported[3]. The increased contact time of gastro-intestinal mucosa with the drug at low pH results in irritation and ulcerogenicity. Figure 3 provides the results of the dissolution behavior of IND from complexes with ß-CD, its derivatives and from DMPC coprecipitate in the simulated gastric fluid. It also allows the comparison of % drug dissolved from each preparation between distilled water and simulated gastric fluid. As expected, all preparations showed lower % drug dissolved in gastric fluid relative to water. However, effect of lower pH was not similar for all preparations. At 10 and

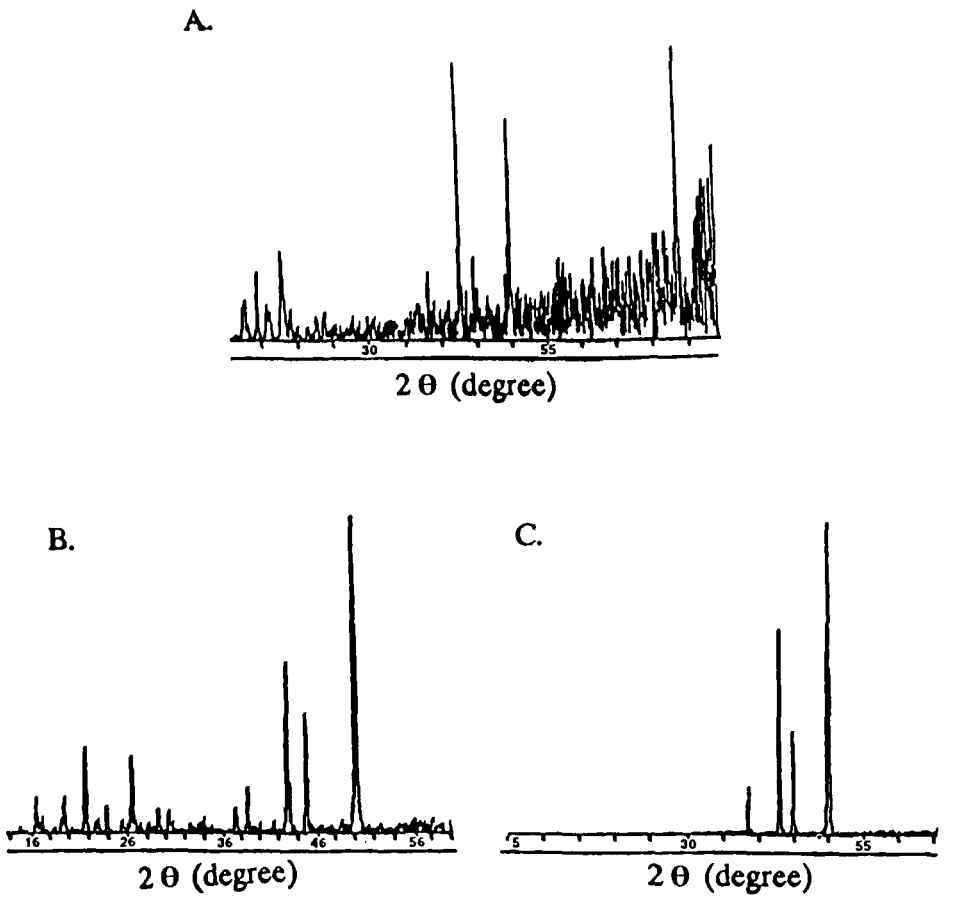

FIGURE IV
Low angle powder x-ray diffraction spectra of : (A) CD; (B) IND; and (C) CD:IND (1:1) complex.

90 minutes intervals, the rate of dissolution in gastric fluid from control IND were 2.8 and 1.7 times slower than in distilled water respectively. DMPC's ability to increase IND dissolution rate from control IND was reduced almost 14 times in gastric fluid compared to that in distilled water. ß-CD also showed reduced ability for the % drug dissolved in the gastric fluid, however, it still resulted 26 times improvement of dissolution rate relative to that of control IND. Unlike in water, MG1B releases IND at a slower rate than ß-CD in gastric fluid. If absorption of IND in-vivo is dissolution-rate limited, increased dissolution of IND in the gastric pH should improve the absorption of the drug. The undissolved drugs in the form of inclusion complex would not allow

prolonged irritation of the gastric mucosa. Use of vehicles such as CD causes more drug to absorb faster and protects the mucosa from the irritating agent.

X-ray Diffraction Patterns of IND:CD Inclusion Complexes: To gain insight into the several possibilities which may exist on the physical state of the CD compounds, X-ray diffraction spectra were performed. The crystalline properties of IND are characterized by two major and three minor peaks, whereas, ß-CD crystals show three major peaks. The positions of the diffraction peaks of IND were altered in the complex with ß-CD compared to that of pure IND or ß-CD (Figure 4). These clearly indicate that IND does exhibit polymorphism, eutectic or solid solution formation with CDs in the inclusion complex[13]. This also suggests that ß-CD synergetically inhibit the crystallization of the drug in the inclusion complex. Pl-IND CPPT showed similar results[13].

CONCLUSIONS

In conclusion, it can be stated that the rate of dissolution of IND can be increased several fold by using either PL CPPT or CD complexes. This study also shows that both PL or CD can be used to increase the rate of IND release but at a variable degree. Various derivatives of ß-CD showed variable results in the release of IND from the complexes. In particular, DMB derivative showed a fairly constant release of IND which may be utilized to formulate a constant-release preparation. It is, therefore, shown that these formulations may have potential to produce faster onset of action, reduced dosing and decreased GI irritation. In-vivo studies are needed to confirm these possibilities.

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