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EFFECT OF THE HYDROPHOBIC NATURE OF TRIACETYL B-CYCLODEXTRIN ON THE DISSOLUTION PROPERTIES OF FENOPROFEN CALCIUM DIHYDRATE PREPARED BY KNEADING AND CO-EVAPORATING METHODS

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ABSTRACT
Fenoprofen calcium dihydrate is a non- steroidal, anti- inflammatory, anti-arthritic drug. It is slightly soluble in water and indicated for the treatment of mild to moderate pain, the recommended dosage is 200 mg given orally every 4 to 6 hours. Therefore, the **aim** of this study was to attain a prolonged therapeutic effect and a reduced incidence of side effects, sustained or controlled release formulations of fenoprofen calcium dihydrate have been developed to maintain a suitable plasma level for a long period of time with minimal frequency of daily administration. **Method:** Fenoprofen calcium dihydrate: triacetyle b-cyclodextrin (TABCD) was prepared as physical mixture and solid binary systems were performed by kneaded and co-evaporated methods in different ratios 1:1, 1:2, 1:3, 1:4. **Results:** The most appropriate technique was co-evaporating using the drug: TABCD in a ratio of 1:3. **Conclusion:** The lowest DE was found for the co-evaporated complex which contains (Drug: TABCD) in a ratio of 1:3.

KEYWORDS: Fenoprofen calcium dihydrate, TABCD, dissolution.

1. INTRODUCTION
Fenoprofen calcium dihydrate, a non- steroidal, anti-inflammatory, anti-arthritic drug. It is slightly soluble in water, with pk_a 4.5 at 25°C and indicated for the treatment of mild to moderate pain, the recommended dosage is 200 mg given orally every 4 to 6 hours, as needed. For the relief of rheumatoid arthritis or osteoarthritis, the recommended dose is 300 to 600 mg given orally, 3 or 4 times a day.[4] Fenoprofen calcium is readily absorbed from the gastrointestinal tract; bioavailability is about 85% but food and milk may reduce the rate and extent of absorption. Peak plasma concentrations of 50µg/ml occur one to 2 hours after a dose.[4] The plasma half-life is about 3 hours. Fenoprofen calcium is about 99% bound to plasma proteins. About 90% of a dose is excreted in the urine in 24 hours[5]

Cyclodextrins are cyclic oligosaccharides with six, seven or eight D (+) –glucose by α-1, 4-glucose bonds. Depending on the number of sugar units, the three unmodified CDs are (α), beta (β), and gamma (-γ), which correspond n=6, 7 and 8, respectively obtained by degradation of starch by cycloglucanotransferase (CGTase) enzyme. CD natural host molecule are known to accommodate various guest molecules into their hydrophobic cavity in aqueous solution. The natural CDs are great interest as molecular hosts, many utility in supra molecular chemistry are derived from their structural modification. On the other side unmodified CDs may be considered as molecular scaffolds on which functional groups and/or other substitutes of increasing sophistication can be assembled with controlled geometry.[1,20]

CDs, due to their ability either to complex drugs or to act as functional carrier materials in pharmaceutical formulations, can serve as potential candidates for efficient and precise delivery of required amounts of drugs to targeted site for a necessary period of time. β-CD derivatives are classified as hydrophilic, hydrophobic, and ionizable derivatives.[21]

The hydrophilic derivatives improve the aqueous solubility and dissolution rate of poorly soluble drugs, while the hydrophobic derivatives retard the dissolution rate of water-soluble drugs from vehicles. Therefore, the hydrophilic and hydrophobic CD derivatives are used in the formulation of immediate and prolonged release type formulae, respectively**.** The ionizable CD derivatives, on the other hand, improve inclusion capacity, modify drug dissolution rate, and alleviate drug irritation.[2] Hydrophobic CDs, such as alkylated and acylated

derivatives, are useful as slow-release carriers in prolonged release formulations of water-soluble drugs and those with short biological half life.[3,22]

The most applied preparation method of complexes with hydrophobic CDs is definitely the kneading technique. Thus, we decided to compare this method with the co-evaporating one, which has not yet been used for this kind of complexes.

The main purpose of the present work was the preparation of different ratios of fenoprofen calcium dihydrate: TABCD in the solid state. The in vitro drug release behavior from the TABCD complexes was also investigated, anticipating their use as a novel sustained release drug carrier.

2. MATERIALS and METHODS

2.1 Materials

Fenoprofen calcium dihydrate (MW= 558.65) and TABCD (MW= 2017.75) were purchased from Lanxi (China) and Sigma-Aldrich (St. Louis, USA), respectively. Tri-sodium phosphate 12-hydrate (MW= 380.12) was kindly supplied from Carlo ErBA (Milano, Italy). All other chemicals and solvents were of reagent grade.

2.2 Methods

2.2.1 Preparation of Solid Binary Systems

The preparation of fenoprofen calcium dihydrate: TABCD solid binary systems was performed by kneading and co-evaporating methods**,** which are described below in detail.

2.2.1.1 Physical mixture

The ground components of fenoprofen calcium dihydrate-CD binary systems were prepared by mixing the individual powdered components together in the molar ratios (1:1, 1:2, 1:3 and 1:4 drug to CD ratio) in a mortar and then passed through a mesh sieve and collected in the size range of 63-160µm. They were stored in a desiccator, containing calcium chloride anhydrous as a desiccant, till further use.[6,7]

2.2.1.2 Kneading method

Triacetyl β-cyclodextrin was wetted in a ceramic mortar with ethanol: water 80: 20 (V/V) solution until a paste was obtained in the molar ratios (1:1, 1:2, 1:3 and 1:4 drug to CD ratio) (the solution formed about 30% of the total weight of TABCD and fenoprofen calcium dihydrate used).The required amount of drug was then added slowly whilst mixing, and the slurry was kneaded for about 45 minutes. During this process, an appropriate quantity of solvent was added in order to maintain a suitable consistency. Further, the product was dried at 40°C for 48 hours. The dried solid was pulverized and the 63-160 µm sieve granulometric fraction was collected.[6,8]

2.2.1.3 Solid dispersion / co-evaporated dispersion

TABCD was dissolved in a sufficient amount of ethanol: water, 80: 20 (V/V) solution. The drug was added using the molar ratios (1:1, 1:2, 1:3 and 1:4 drug to CD ratio). The drug was added with continuous stirring. The resulting mixture was stirred for 24 hours at room temperature and the obtained solution was subsequently evaporated to dryness under vacuum. The obtained product was sieved and the 63-160 µm granulometric sieve fraction was collected.[6,8,19]

2.2.2 In vitro dissolution studies

Dissolution studies were carried out in triplicate USP dissolution tester (rotating paddle apparatus) at a rotation of 100 rpm . Studies were carried out at 37 ± 0.5°C in 750 ml of 0.1N HCl (pH 1.2) for a period of two hours and then continued in pohsphate buffer (pH = 6.8) for six hours after shifting the pH from pH 1.2 to pH 6.8 by adding 250 ml of 0.20 M tribasic sodium phosphate.[9] Fenoprofen calcium dihydrate and its equivalent in CD complexes and physical mixtures were filled into capsules size 00. Each capsule was placed at the bottom of the dissolution cell using the mean of sinker to avoid its floating.[10,11,12,13] Five milliliter samples were taken after 1, 2, 3, 4, 5, 6, 7 and 8 hours. The samples were filtered through a 0.22 µm filter. The volume in the vessel was immediately maintained with fresh dissolution medium.[14] The samples were analyzed for fenoprofen calcium dihydrate content by measuring the absorbance at predetermined λ_{max} 270.8 nm against 0.1N HCl as blank for the first 2 hours and λ_{max} 270.6 nm against phosphate buffer (pH 6.8) as a blank for the remaining 8 hours.

The dissolution profiles of the drug were characterized using the parameter of Dissolution Efficiency (DE). DE is defined as the area under the dissolution curve for a certain period of time using trapezoidal method, expressed as a percentage of the area of the rectangle that represents 100% dissolution at the same time interval.[15,16,17]

3. RESULTS AND DISCUSSION

The dissolution profiles of pure drug and 1:1 (drug: TABCD) binary systems are presented in fig. 1. The physical mixture and the kneaded product showed approximately the same dissolution profile of the drug, which was completely released after 5hrs, while the drug was completely released from the co-evaporated complex after 7 hrs. These results indicate that the dissolution rate for co-evaporated complex is lower than those of physical mixture and kneaded product. One the other hand, increasing TABCD fraction to 1:2 (drug: CD) did not show significant decrease in the dissolution rate of the three binary systems, as it is shown in fig. 2. The three binary systems showed approximately the same dissolution profile of the drug.

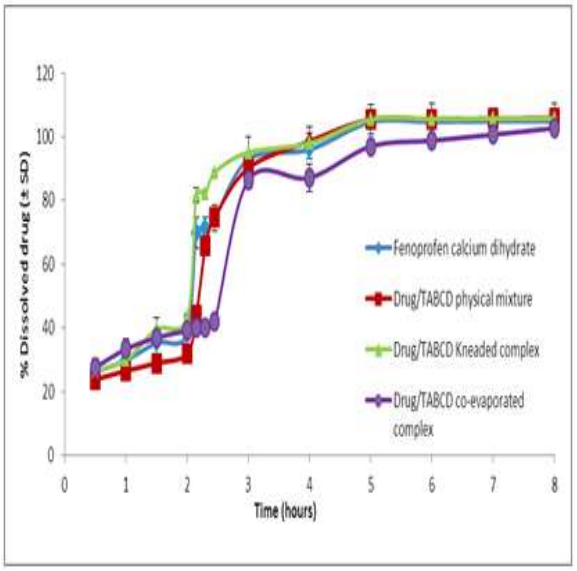

Figure (1): Effect of TABCD on the dissolution of fenoprofen calcium dihydrate (1:1 drug/CD molar ratio) at PH=1.2 for 2hrs and then continued in PH=6.8 for 6hrs.

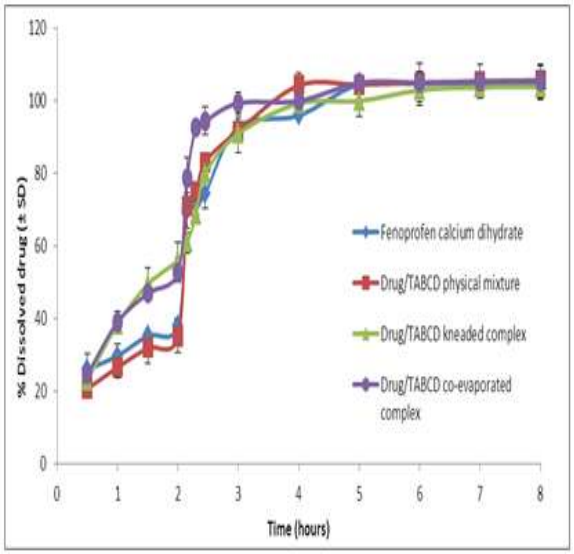

Figure (2): Effect of TABCD on the dissolution of fenoprofen calcium dihydrate (1:2 drug/CD molar ratio) at PH=1.2 for 2hrs and then continued in PH=6.8 for 6hrs.

Fig. 3 illustrates the release profile of fenoprofen calcium dihydrate and 1:3 (drug: CD) binary systems. The physical mixture and kneaded product showed retardation in the dissolution rate of the drug. On the contrary, the drug dissolution rate was markedly retarded from co-evaporated complex. After 8 hrs, the percentage of dissolved drug from the co-evaporated complex was only nearly 70%, opposite to 90% dissolved from both the physical mixture and kneaded product.[18] This retardation in the drug dissolution rate when physically mixed, kneaded or co-evaporated with TABCD may be attributed to "In situ" formation of complexes in the dissolution medium. It was clearly observed that the dissolution profile of co-evaporated complex presented lower percentage of dissolved drug. It was found that, the ratio 1:4 (drug: CD) has no significant decrease in the dissolution rate of the three binary systems than 1:3 ratio. The percentage of drug dissolved from the physical mixture, kneaded and co-evaporated products was nearly 90% as illustrated in fig. 4.

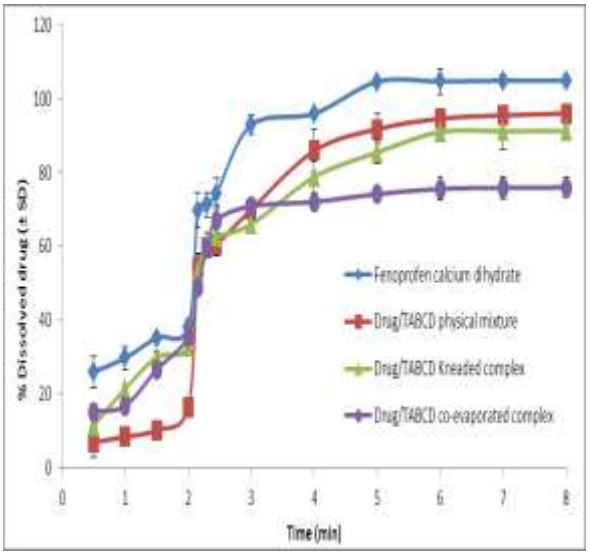

Figure (3): Effect of TABCD on the dissolution of fenoprofen calcium dihydrate (1:3 drug/CD molar ratio) at PH=1.2 for 2hrs and then continued in PH=6.8 for 6hrs.

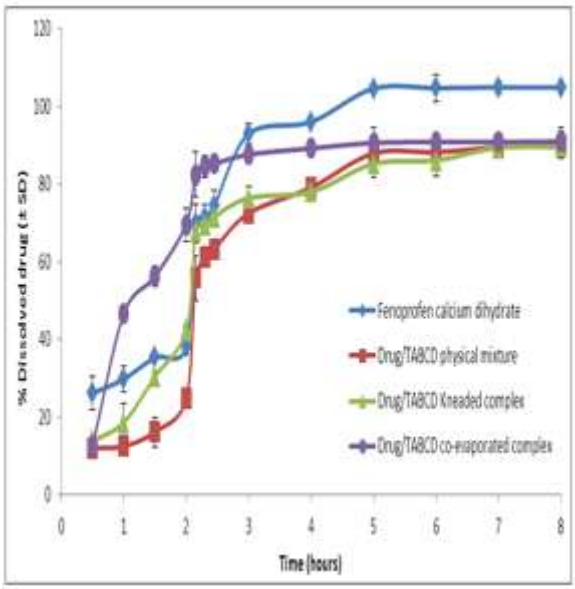

Figure (4): Effect of TABCD on the dissolution of fenoprofen calcium dihydrate (1:4 drug/CD molar ratio) at PH=1.2 for 2hrs and then continued in PH=6.8 for 6hrs.

Dissolution efficiency of the drug released was chosen for comparison between different prepared formulae. The lowest DE was found for co-evaporated complex which contains the drug and the TABCD in a ratio of 1:3. while, further increase in TABCD ratio to 1:4 did not

show significant decrease in DE. This indicates that 1:3 ratio remarks a significant decrease in dissolution profile of the drug.

4. CONCLUSION

1- The preparation technique and ratio of fenoprofen calcium dihydrate: TABCD deeply influence the drug dissolution behaviour.
2- The co-evaporating technique was more appropriate than kneading to achieve complexation between drug and TABCD when prepared in a ratio of 1:3.
3-The ratio 1:3 (drug: TABCD) showed significant decrease in DE with compared to the other ratios.

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