Bull. Pharm. Sci., Assiut University, Vol. 27, Part 1, June 2004, pp. 19-24.

MODIFICATION OF THE RELEASE OF DIPYRIDAMOLE FROM CERTAIN POLYMERIC SYSTEMS

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الهدف من هذه الدراسة هو تحوير معدل انطلاق الدايبيريدامول لكى نتغلب علي امتصاصه الغير منتظم والغير مكتمل في القناة الهضمية حيث ان إذابة العقار تعتمد علي الرقم الهيدروجيني للمحاليل. وقد تحقق هذا التحوير باستخدام بوليمر يؤخر انطلاق العقار في الوسط المماثل للمعدة مثل سيللوز اسيتات فيثالات (كاب) واستخدام مادة تسرع الانطلاق في الوسط المماثل للامعاء مثل الدايميثيل بيتا سيكلوديكسترين والهيدروكسي بروبيل بيتا سيكلوديكسترين. وهذه الطريقة قد عدلت من الانطلاق المفاجئ لهذا العقار القاعدى في الوسط الحمضى. وقد تم تحضير المتراسب المتزامن للعقار مع كل من الدايميثيل بيتا سيكلوديكسترين والهيدروكسى بروبيل بيتا سيكلوديكسترين في نسبة جزيئيه (١:٢ عقار الي سيكلوديكسترين)، ثم بعد ذلك حضرت الحبيبات المحورة للدايبيريدامول بكسوة تلك المتراسبات بواسطة بوليمر الكاب بطريقة التحبب في نسبة وزنيه (١:٣ عقار الي بوليمر).

وقد أظهرت النتائج أن الحبيبات المحورة للدايبيريدامول قد عطلت انطلاق العقار في الوسط المماثل للمعدة ذو الرقم الهيدروجيني ١,٣ في حين أن معدل انطلاقه قد تحسن ووصل الي ١٠٠% في الوسط المماثل للامعاء ذو الرقم الهيدروجيني ٦,٨ بالرغم من أن العقار شحيح الذوبان في ذلك الوسط. ويعزى ذلك الي تأثير الكاب في حماية العقار من الانطلاق من حبيباته في الوسط الحمضي، ثم تبع ذلك تحرر انطلاق العقار بسهولة من حبيباته في الوسط المماثل للامعاء بعد إذابة الكاب في ذلك الوسط.

*The objective of the present study is to modify the release of dipyridamole (DIP); which has a pH dependant solubility in order to overcome its irregular and incomplete absorption from the gastrointestinal tract. This was achieved by incorporation of a dissolution retarder such as cellulose acetate phthalate CAP and a dissolution enhancer such as cyclodextrins; (dimethyl beta cyclodextrin DM-*βCD and hydroxypropyl betacyclodextrin HP-βCD). This was *an effective mean of moderating the drastic dissolution behaviour of that basic drug at acidic pH. Coevaporates of DIP with DM-*βCD and DIP with HP-β*CD in 1:2 molar ratio were prepared, followed by coating of these coevaporates by an enteric polymer (cellulose acetate phthalate, CAP) in 1: 3 drug : polymer weight ratio. In vitro release study was performed for capsules containing the modified granules at pH values of 1.3, 5 and 6.8. It was found that the drug release from the modified granules was decreased in a simulated gastric fluid and was enhanced in a simulated intestinal fluid and reached up to 100%. This could be attributed to the protecting effect of CAP for the drug granules in the acidic medium, followed by dissolving of CAP coat in the intestinal fluids which lead the drug to be released easily from the granules.*

INTRODUCTION

Basic drugs having a pH-dependent solubility as dipyridamole (DIP) has bioavailability problems, because, after oral administration, the different pH values of the gastrointestinal tract result in a drastic change in drug solubility, as DIP is soluble in acidic media and practically insoluble in pH higher than 5.[1, 2]

It may, then, be necessary to increase the drug release as the dosage form progresses through the intestine, so as to compensate the decrease in absorption which generally occurs in the colon with the conventional sustained release dosage forms.[3]

Coprecipitate systems have been extensively used as a mean of enhancing the dissolution of poorly water soluble drugs using water soluble carriers,[4-6] or alternatively to

Received in 8/1/2004 & Accepted in 30/3/2004

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control the release of drugs by the same technique, but using insoluble materials.[7]

Cyclodextrins have the ability to entrap drug molecules of appropriate size and polarity in their cavity to form non covalent inclusion compounds.[8,9] This may lead to useful modifications of the physical and chemical properties of the guest molecules, allowing the improvement of stability, increasing solubility of poorly water soluble drugs, enhancement of dissolution rate, improvement of membrane permeability and assisting of drugs bioavailability.[10,11]

The aim of this study is to prepare the inclusion complexes of dipyridamole with either DM-βCD or HP-βCD by coevaporation method. In addition, modified granules of dipyridamole were prepared by granulation of its coevaporates with the above mentioned CDs, using an enteric coating polymer (cellulose acetate phthalate, CAP) to prevent the drug release in the acidic pH of stomach. As the modified granules of the drug reach the intestine of pH 6.8, the enteric coat of CAP will dissolve leaving the drug to be released easily from its inclusion complex.

EXPERIMENTAL

Materials

Dipyridamole was obtained from Chemical Industries Development Company (CID), Cairo, Egypt.

Dimethyl beta cyclodextrin (DM-βCD) was obtained from Toshin Chemicals, CO. Japan.

2-Hydroxypropyl beta cyclodextrin (HP-βCD) with molar substitution of 0.6 was obtained from Pharmatec, INC, Alachua, Florida, U.S.A.

Cellulose acetate phthalate (CAP) was obtained from Estman Chemical products, INC., U.S.A.

The solvents and the buffer components were of analytical grade. Deionized distilled water was used throughout this study.

Equipment

USP dissolution apparatus, Hanson Researches Corporation Chatsworth, California, USA.
UV-VIS Spectrophotometer, JAS CO., Japan.
Differential Scanning Calorimeter, DSC-50I, Shimadzu, Japan.
X-Ray Diffractometer, Philips, PW1710 X-ray, Netherland.

Methods

1- Preparation of coevaporates

Coevaporates of DIP with DM-βCD and HP-βCD were prepared in 1:2 molar ratio using the solvent evaporartion technique. An appropriate amount of CD was dissolved in ethanol and DIP was dissolved in minimum amount of ethanol and added to the CD solution while stirring. The solvent was allowed to evaporate at room temperature till a dough mass was obtained. The mass was passed through a sieve of 600 μm and dried at 37° for 24 h. Complete drying was attained by obtaining a constant weight and the samples were kept in a dessicator over calcium chloride till used.

2- Preparation of the modified granules

The dried coevaporates of DIP and CDs were granulated by a solution of the CAP which was prepared by dissolving CAP and drug in 1:3 weight ratio in a mixture of acetone and isopropanol (1:1 volume ratio). The wet mass was sieved through 1600 μm mesh screen to obtain granules which were dried in an oven at 40°. After a proper drying, the granules were resieved through 1000 μm mesh screen. The produced granules were kept in a dessicator over calcium chloride till used.

3- Differential scanning calorimetric investi-gation of the prepared samples (DSC)

The DSC thermograms were obtained at a scanning rate of 10°/min and N_2 purge at 40 ml/min. The instrument was calibrated with an indium standard and the samples were examined in the temperature range 20-300°. The weight sample is 2-5 mg using aluminium pans.

4- X-ray diffraction for the prepared samples (XRD)

Powder X-ray diffractometry was carried out under the conditions of CU/Kα radiation (40 Kv, 30 MA, Slite 1.5) over 4- 60 2θ range.

5- Release studies for the prepared samples

The USP XX**III** dissolution test apparatus 2 (paddle type) was used at 100 rpm and

temperature of 37°. Capsules containing the modified granules with equivalent amounts of 25 mg of dipyridamole were tested. Dissolution media of pH 1.3, 5 and 6.8 buffer solutions were used. At appropirate time intervals, 5 ml aliquots were withdrawn, filtered, and analysed spectrophotometrically at 288 nm for dipyridamole. After each sampling, 5 ml of the same buffer, maintained at 37°, was added to keep the dissolution volume constant. Three replicates were performed for each sample of the modified granules and the average drug release was calculated within 8 hours.

RESULTS AND DISCUSSION

The physico-chemical properties of the modified granules of DIP were investigated using DSC and X-ray diffraction methods.

Differential scanning calorimetry (DSC)

Figure (1) shows the DSC thermograms of the pure DIP, the coevaporate with DM-βCD in 1:2 molar ratio, the modified granules and granules of DIP with CAP in 1:3 weight ratio. Pure DIP exhibits a sharp endothermic peak at 168.2° (curve A), corresponding to the melting point of DIP. This indicates that the latter is in its pure crystalline form. Curve B shows the DSC thermogram of the coevaporate of DIP with DM-βCD (1:2) molar ratio which shows very large reduction of the endothermic peak of DIP at 168.2°. This indicates that DIP was largely transformed into the amorphous state due to the interaction with DM-βCD.[12] The modified granules showed complete disappearence of the endothermic peak of DIP, as shown in curve C, which indicates that DIP became amorphous upon coating with CAP. Granules of the drug with CAP show no endothermic peak of the drug which indicates complete coating of DIP by CAP so the drug became completely amorphous (curve D).

Figure (2) shows the DSC thermograms of DIP alone, its coevaporate with HP-βCD in 1:2 molar ratio and the modified granules containing HP-βCD and CAP. The DSC thermogram of the coevaporate (curve B) shows a reduction in the endothermic peak of DIP which may be attributed to the reduction in drug crystallinity. Whereas the modified granules of DIP shows complete disappearance of the endothermic peak of DIP (curve C). Moreover, DSC curve D shows also disappearance of endothermic peak of DIP in case of its granules with CAP, which could be attributed to complete coating of drug particles by CAP. This assumption is confirmed by appearance of halo diffraction pattern in the x-ray diffractogram of modified granules of DIP.

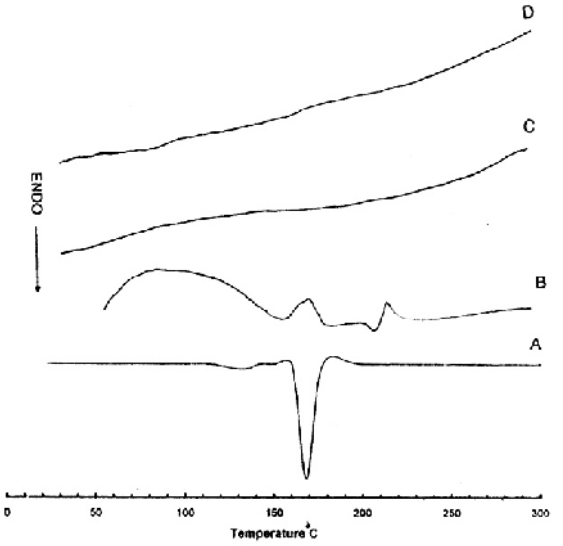

Fig. 1: DSC thermograms of dipyridamole with DM-βCD and cellulose acetate phthalate (CAP).
A- Dipyridamole alone
B- Coevaporate with DM-βCD 1:2
C- Modified granules
D- Granules with CAP 1:3

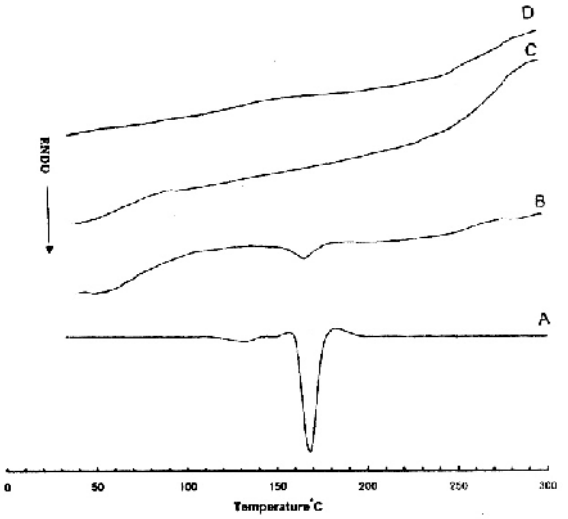

Fig. 2: DSC thermograms of dipyridamole with HP-βCD and cellulose acetate phthalate (CAP).
A- Dipyridamole alone
B- Coevaporate with HP-βCD 1:2
C- Modified granules
D- Granules with CAP 1:3

Powder X-ray diffraction patterns of the investigated samples

Figures (3) and (4) show powder X-ray diffraction patterns of DIP in different systems. The x-ray diffractogram of DIP crystals (curve A) had a characteristic crystalline diffraction peaks. In Fig. (3) curves B, C and D, no appearance of the characteristic diffraction peaks of DIP is recorded in case of its coevaporate, its modified granules containing DM–βCD and CAP as well as its granules with CAP. These results, thus, revealed the formation of amorphous state of drug in these systems. Fig. (4) shows the powder x-ray diffractograms of DIP with HP-βCD prepared systems. The diffractograms (curves B and C), of the physical mixture and coevaporate of DIP with HP-βCD are similar to their crystalline patterns. This means that both physical mixture and coevaporate showed the superposition of both components; DIP and HP-βCD. On the other hand, the x-ray diffractogram of modified granules of drug with HP-βCD coated by CAP (curve D), gave halo diffraction pattern which indicates the transformation of the drug from crystalline to amorphous state by coating. Also granules of DIP with CAP (Curve E) show a halo diffraction pattern. These x-ray diffraction data of DIP in different systems are in good agreement with the data obtained with DSC techniques of the respective samples.

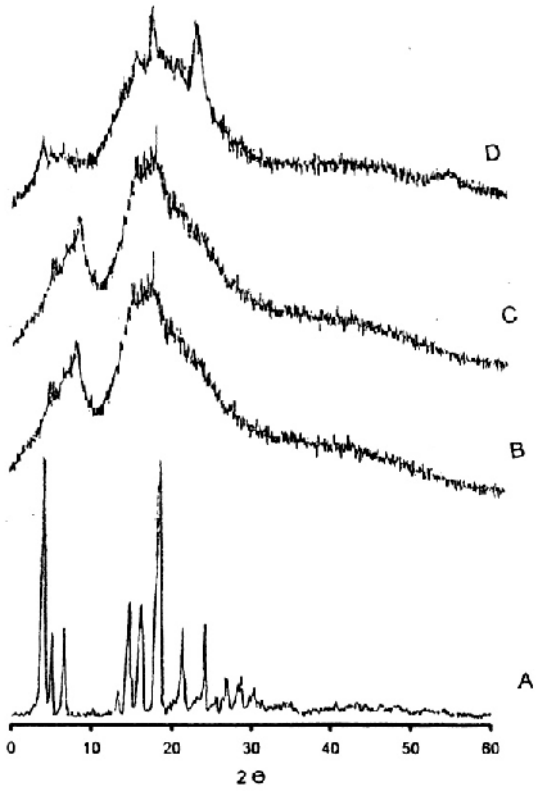

Fig. 3: X-ray diffraction patterns of dipyridamole with DM-βCD and cellulose acetate phthalate (CAP) systems.
A- Dipyridamole alone
B- Coevaporate with DM-βCD 1:2
C- Modified granules with DM-βCD and CAP
D- Granules with CAP 1:3

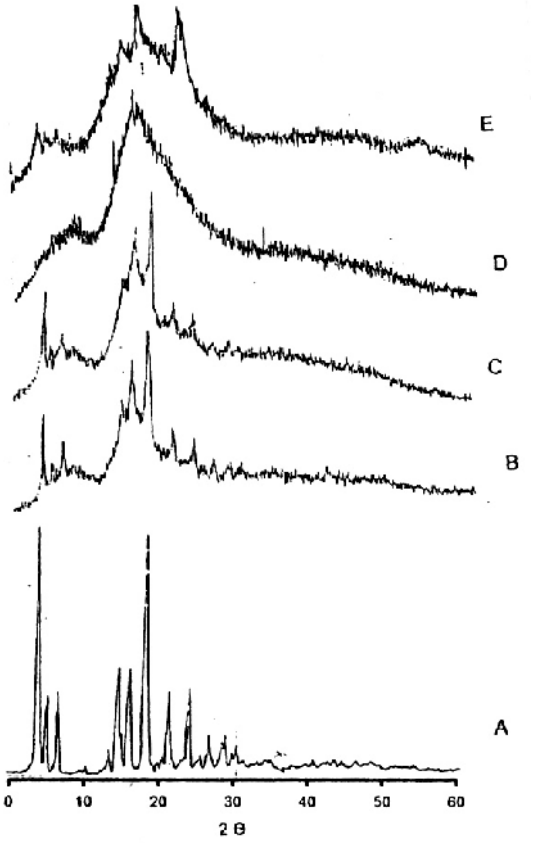

Fig. 4: X-ray diffraction patterns of dipyridamole with HP-βCD and cellulose acetate phthalate (CAP) systems.
A- Dipyridamole alone
B- Physical mix with HP-βCD 1:2
C- Coevaporate with HP-βCD
D- Modified granules with HP-βCD and CAP
E- Granules with CAP 1:3

Release studies

Figures (5-7) show the release profiles of the drug alone and capsules containing modified granules of DIP with DM-βCD, HP-βCD and CAP at the investigated buffer solutions of pH 1.3 & 5 & 6.8. At pH 1.3 a reduction in drug release rate was achieved within 90 min. As shown in Figure (5), the capsules containing modified granules of HP-βCD showed more retardation of DIP release than that achieved with the capsules containing modified granules of DM-βCD in pH 1.3. This may be attributed to the high capacity of DM-βCD to solubilize the drug. The release profiles at pH 5 are shown in Fig. (6). It is obvious that the granules containing DM-βCD enhanced the release of drug whereas that containing HP-βCD delayed the drug release. This may be attributed to the effect of coating with CAP which did not dissolve at pH 5.

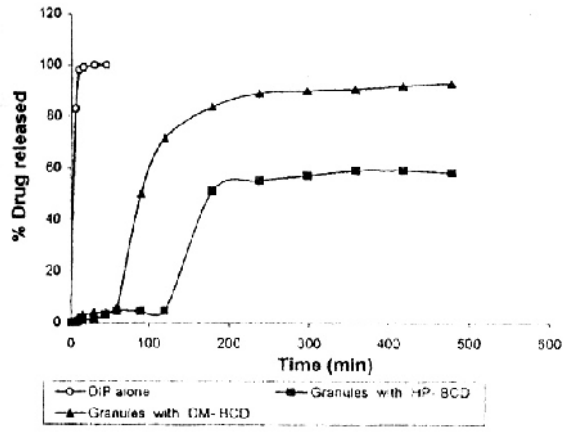

Fig. 5: Release profiles of DIP and the modified granules at pH 1.3.

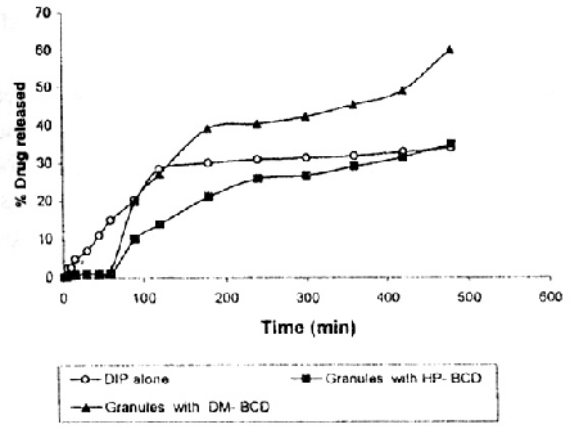

Fig. 6: Release profiles of DIP and the modified granules at pH 5.

Figure (7) shows the release profiles of the drug alone, capsules containing modified granules of DIP with CDs and CAP, and granules without CDs at pH 6.8. It is clear that a high change in DIP release was observed, where more than 90% of DIP was released after 3 hrs of dissolutin and about 98% of drug was released within 8 hrs of dissoluton. This is in contrast to the release of DIP alone where not more than 20% of the drug was released within the same period. The high increase of release rate may be attributed to the desintegration of the enteric polymer of CAP by the hydrolytic effect of simulated intestinal fluids and this allowed the drug–CD complex to play its role in enhancement of DIP dissolution in the intestinal fluids. Both types of the modified granules of DIP with either DM-βCD or HP-βCD and which are coated with CAP, showed a similar behaviour at pH 6.8.

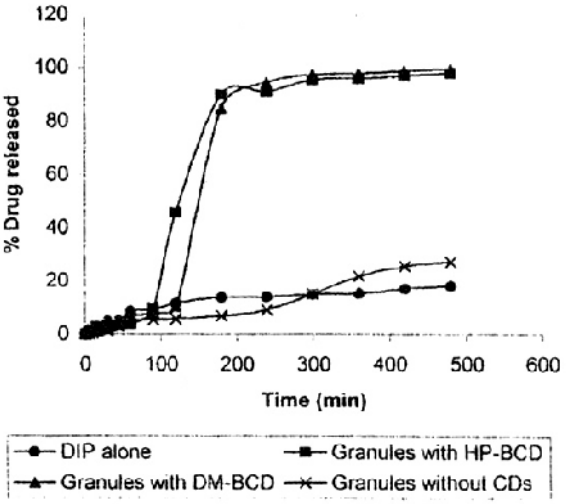

Fig. 7: Release profiles of DIP and the modified granules at pH 6.8.

Figure (8) shows the release profiles of DIP alone and of its modified granules at the investigated pHs, where dissolution was carried out at pH 1.3 from 0 to less than 2 hours, at pH 5 from 2 hours to 5 hours and at pH 6.8 from 5 to 8 hours. It was found that the release of the drug was highly decreased at a low pH based on the effect of enteric polymer (CAP) which is insoluble at acidic pH, thus acting as a barrier against drug release at this pH. Then, the release of drug was improved at a higher pH of simulated intestinal fluid, where the enteric polymer (CAP) was dissolved at pH above 5.5

allowing the drug to be easily released from its complex at such a high pH. The extent of modification of drug release from the modified granules verified the need to improve dissolution and absorption of drug through the various pHs of GIT.

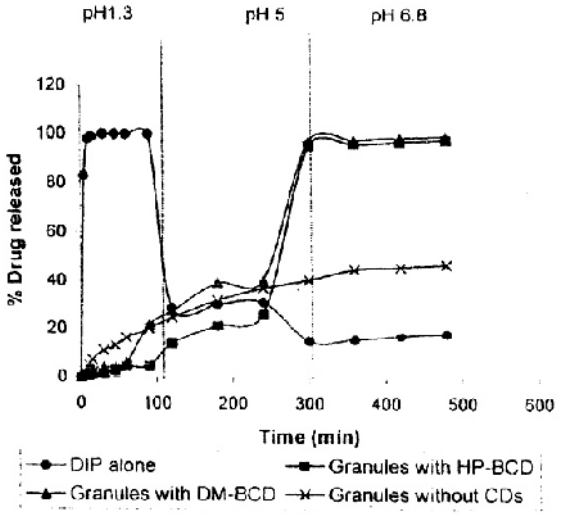

Fig. 8: Release profiles of DIP and the modified granules at pH 1.3, 5 and 6.8.

Figure (9) shows the histogram of the release profiles for DIP and the modified granules at the investigated pHs.

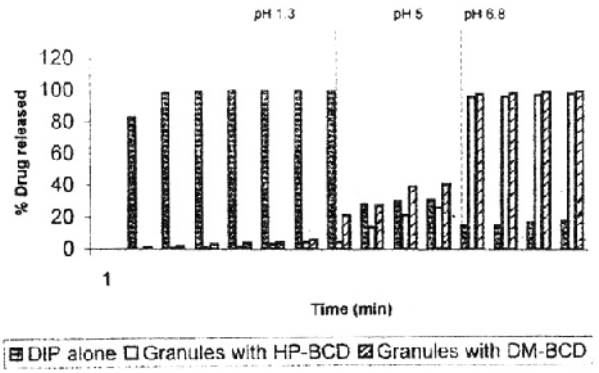

Fig. 9: Histogram of the release profiles of DIP and the modified granules at pH 1.3, 5 and 6.8.

Conclusions

The behaviour of drug release from the modified granules was profoundly altered in comparison with the pure drug, by moderating the drastic dissolution behaviors of a basic drug as dipyridamole at different physiological pH values. The modified granules of DIP containing either HP-βCD or DM-βCD and coated with the enteric polymer CAP achieved more retardation of drug release at acidic pH of 1.3 and enhancement of drug release at intestinal pH of 6.8.

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