DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 20(15), 2381-2393 (1994)

USE OF DEHYDRATED BETA-CYCLODEXTRIN AS PHARMACEUTICAL EXCIPIENT

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ABSTRACT

Cyclodextrins, and expecially beta ones, are widely used in the pharmaceutical field for their ability of improving the solubility and the stability of drugs by complex formation at the solid state. Such phenomenon occurs only when cyclodextrin has a certain water content, being the removal of water from internal cavity essential for the interaction between the drug and the excipient. Anyway, the dehydration of beta cyclodextrin leads to a product with peculiar properties, which is reported to be not able to form inclusion complex at the solid state, but is very effective in increasing the rate of complex formation in solution with a consequent strong influence on dissolution performances of drugs. This approach is extremely interesting for obtaining fast dissolving tablets of drugs that are able for their own characteristics, to form stable solid inclusion complexes only in solution, but not at the solid state. The formulation process is extremely simple and of low cost involving only the physical mixing of the drug with the

excipients before tableting or other pharmaceutical processes.

INTRODUCTION

Cyclodextrins (CDs) are cyclic oligosaccharides made up of 6,7 and 8 D-glucose residues for α, ß and y CDs respectively; these compounds are well known for their ability of including in their hydrophobic cavity various kinds of molecules.

This interaction greatly depends on the hydrophobicity of the guest molecule, the steric hindrance between the drug and the cyclodextrin, and the size of the cyclodextrin cavity. This kind of encapsulation confers new physicochemical properties to the drug, and is extensively used by researcher in the pharmaceutical field to improve the solubility and stability of drugs (1,2).

More generally, this procedure has been used to improve the bioavailability of active molecules presenting a very low water solubility but a good absorption rate through biological membranes (3).

Various methods for preparing solid inclusion compounds, such as kneading (4), co-grinding (5), co-precipitation (6) and freeze-drying (7) are suitable: no rules are available to choose preliminarly which one of them is the best in terms of yields and reproducibility, for the formation of a complex at the solid state, since each drug has its own peculiarities and each tecnique of complex preparation shows both advantages and disadvantages.

Anyway, water has a strong influence in the formation of a complex. When a drug interacts with CDs, the driving force for complex formation is the removal of water from the internal cavity by guest molecules and the London dispersion interaction (8). The formed complex has a

definite stoichiometry and usually can be isolated at the solid state.

It is also well described in the literature that, under a certain water content, CDs are not able to form stable inclusion compounds at the solid state (9), and that the dehydrated form of CDs is not stable unless a very low degree of relative humidity is present in the enviroment. Moreover we have noticed that even if the formation of a complex with a drug is not reached at the solid state, anhydrous CDs have properties which differ from those of hydrate ones and which improve drug dissolution performances, and can be easily used as excipients by simple physical mixing (10). Better performances were obtained especially with drugs that are not able to form a solid complex like, for example, a large number of benzodiazepines (11).

The purpose of our work was to evaluate more precisely the differences between hydrate and dehydrated CDs.

MATERIALS AND METHODS

FCE24578 (2-cyano-3-(1,4-dihydro-1-phenyl-(1)-benzothiopyran-(4,3-C)-pyrazol-3-yl)-3-oxo-N-phenyl-propanamide), FCE24304 (6-methylen-androsta-1,4-diene-3,17-dione) and Temazepam were from FARMITALIA CARLO ERBA. ß-CD was purchased in its hydrate form (about 12-14% of water) by SPAD-ROQUETTE. Dehydrated ß-CD was obtained by simply heating the commercial cyclodextrin in a oven at 130°C under light vacuum in presence of a non-interacting dissecant agent (silica gel) till constant weight was reached. Physical mixtures were prepared cosieving and then tumble mixing the powders with a Turbula mixer.

The co-ground systems were obtained by grinding the physical mixtures in a laboratory high energy mill (Giuliani IGW2) for about 2 hours. The powders were

sieved and tumble mixed before use. When dehydrated CD is present, materials were manipulated in controlled relative humidity conditions.

The influence of increasing cyclodextrin concentration on Temazepam solubility was determined as previously described (12).

Dissolution rate tests were carried out on free flowing powders according to USP XXII (paddle method) in different standard conditions depending on the drug tested. The dissolved drug was determined either by U.V. or H.P.L.C. tecnique.

Intrinsic dissolution rates were carried out on tablets using the "Rotating Disk" method (13).

The penetrating volume of distilled water was detected as a function of time using a powder bed of sample packed and analyzed with an Enslin Apparatus according to Nogami (14).

Thermal analyses were carried out using a Mettler TA 3000 system equipped with a DSC 20 cell under nitrogen flow.

X-ray diffractograms were obtained irradiating powder samples with a Siemens P500TT (CuKα as radiation source).

Surface area measurements were carried out using a mercury porosimeter apparatus (Carlo Erba Instruments) according to Carli (15).

RESULTS AND DISCUSSION

Anhydrous ß-CD is a white crystalline powder structurally different from the original hydrate one.

In Figure 1 the differences between scanning calorimetric curves of hydrate and dehydrated ß-CD are evident: after dehydration the low temperature peak disappears and a new endothermal event, due to solid-solid transition, becomes visible.

When the dehydrated ß-CD is exposed to humidity this peak disappears and the thermogram pattern comes back to that of the hydrate form.

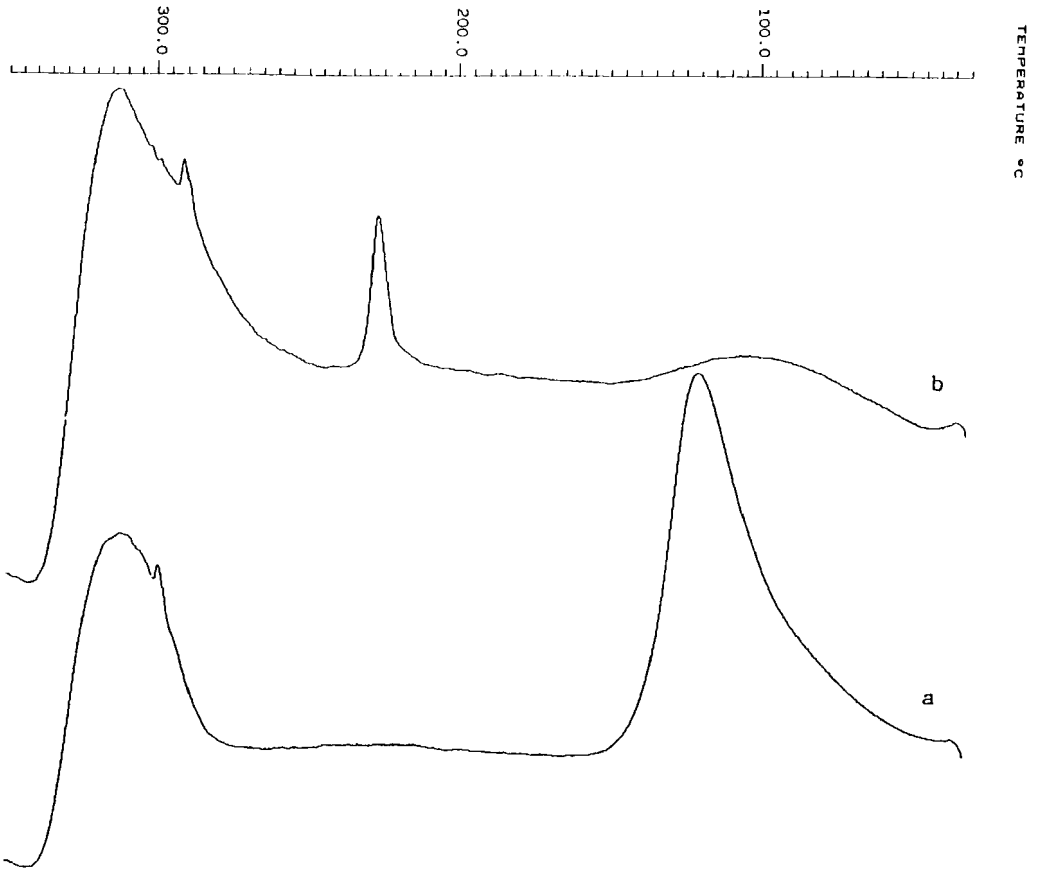

FIGURE 1
Scanning calorimetric pathways of hydrate (a) and dehydrated (b) ß-CD.

Also X-ray analysis (Figure 2) confirms these structural differencies by showing a completely different diffractografic pattern.

These structural changes have a broad influence on pharmaceutical properties of CDs. The lack of water in the crystalline structure leads to a higher affinity towards water (higher wettability and higher rate of solubilization), and also to a product that is more easily crushed and reduced to fine particles by milling.

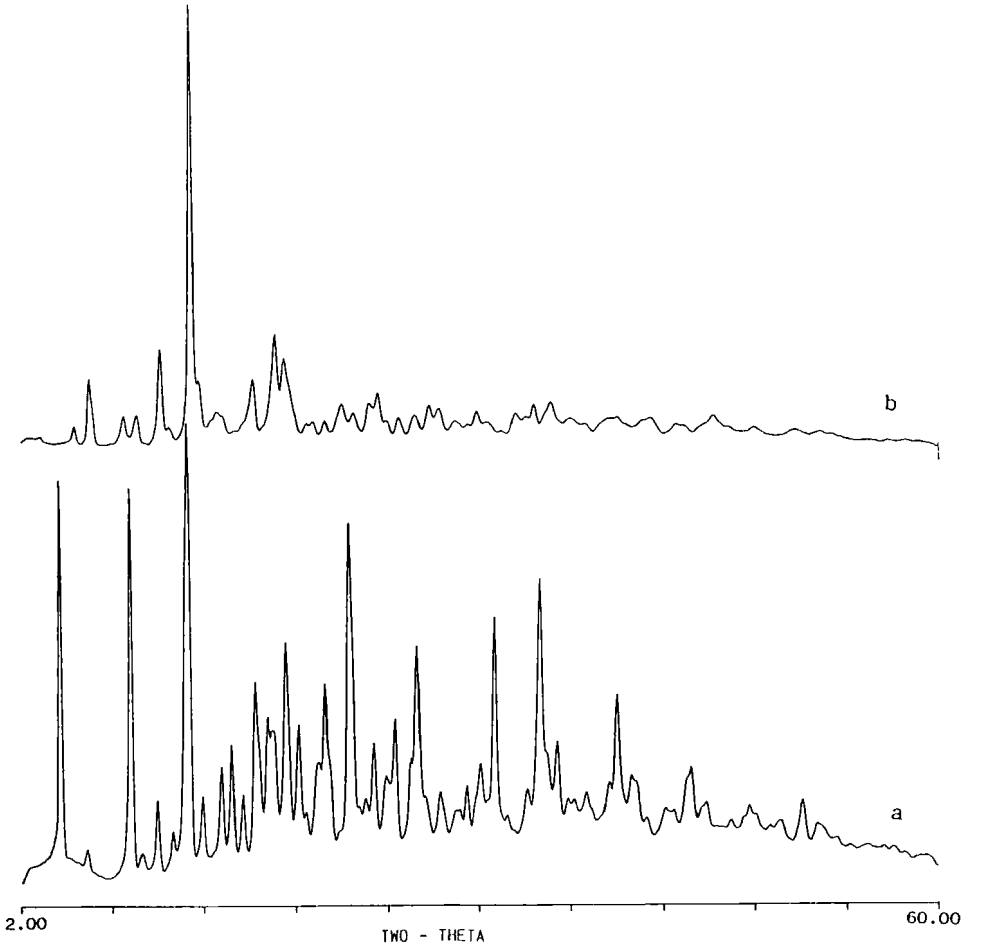

FIGURE 2
X-ray analysis of hydrate (a) and dehydrated (b) ß-CD.

As shown in Table 1, dehydration itself leads to a higher surface area of CDs; the grinding of the dehydrated excipient magnifies this difference, giving a product with very high surface area.

For quantifying the improved wettability of dehydrated versus hydrated ones the penetrating volume of water was detected as function of time, with an Enslin Apparatus,

TABLE 1

Surface area measurements by mercury porosimetry tecnique

Sample	Surface Area
Hydrate ß-CD	0.10 m^2/g
Dehydrated ß-CD	0.36 m^2/g
hydrate ß-CD after grinding	0.68 m^2/g
dehydrated ß-CD after grinding	8.71 m^2/g

TABLE 2

Penetration rate constant of water into a powder bed of sample bed of CD (Enslin Apparatus)

Hydrate CD	Dehydrated CD
$4*10^{-4}$mL/g*sec	$3*10^{-3}$mL/g*sec

and the penetration rate constant was calculated.

The value for dehydrated systems, as shown in table 2, was ten fold higher than for the hydrate ones.

The penetration rate constants had quite the same value when CDs were physical mixed with drugs.

Coupling the above characteristics, which are extremely positive for improving drug dissolution, dehydrated CDs could be proposed as an innovative pharmaceutical excipient.

As first drug model, we have chosen Temazepam, a benzodiazepine known from the literature for not being able to form an inclusion complex with CDs at the solid state but only in solution (16).

A solubility determination of Temazepam in presence of increasing concentrations of ß-CDs has been carried out (figure 3). A linear relationship between benzodiazepine solubility and ß-CDs concentration was found; however, the equilibrium situation was reached at different times using hydrate or anhydrous CDs. After 15 minutes, the amount of the dissolved drug was higher for dehydrated CDs but this difference was no longer seen after 4 hours, when CD was completely solubilized eliminating physico-chemical differences that exist at the solid state.

A confirmation of this quick complex formation in solution was obtained by dissolution rate tests in which simple physical mixture with hydrate or dehydrated ß-CDs were compared (Figure 4).

Similar results were obtained with FCE24578, an immunomodulating agent, in which the poor solubility (25 mcg/mL) is coupled with an absolute lack of wettability. For that reason, the simple hydrate ß-CD/FCE24578 physical mixture had no better dissolution performances than the drug as such, and dehydrated CD improved only slightly the dissolution rate. When an intimate mixture of the drug with ß-CDs was obtained (amorphization or molecular dispersion of the drug by cogrinding with CDs) the differences were clear (figure 5), being the drug/CD system more wettable as showed by contact angle measurements (from 86° of the physical mixture to 69° degrees of the coground system).

The same behavior was also observed with Griseofulvin (data not shown).

Different considerations could be taken into account for FCE24304, an aromatase inhibitor.

Analyzing FCE24304/ß-CD systems, the dissolution performances of simple physical mixtures with both hydrate or dehydrated ß-CD were not better than those of a solid state inclusion complex already formed by

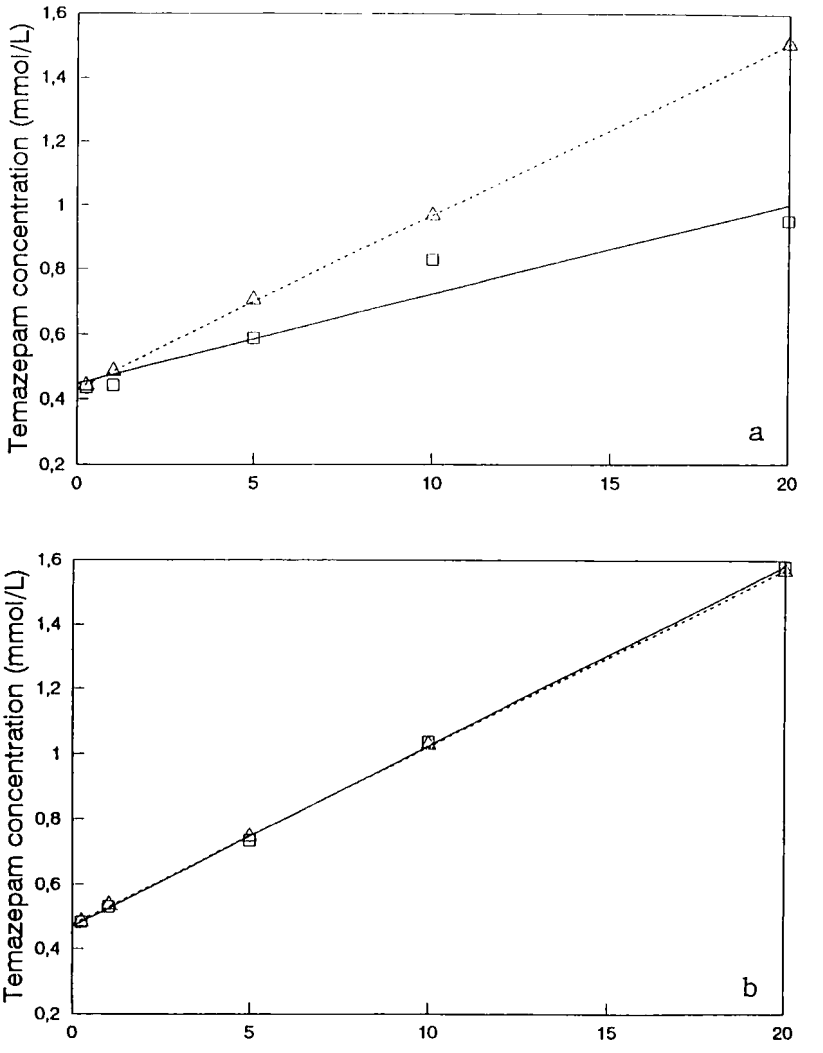

FIGURE 3
Solubility of Temazepam after 15 minutes (a) and after 4 hours (b) with increasing concentration of hydrate (□) and dehydrated (△) ß-CD.

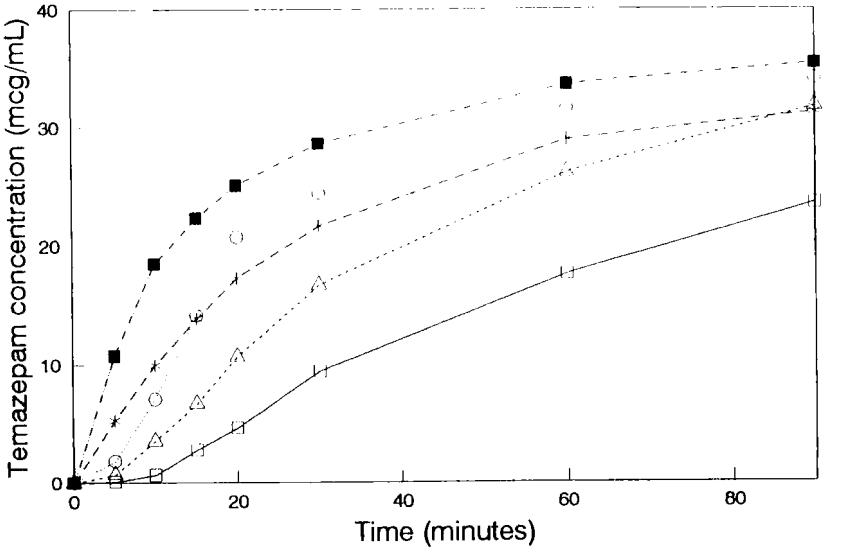

FIGURE 4
Dissolution rate performances of Temazepam (□) and its physical mixtures with hydrate (1:1 molar ratio △ ;1:2 molar ratio ✳) and dehydrated (1:1 molar ratio ○ ;1:2 molar ratio ■) ß-CD in acetate buffer pH 5.5.

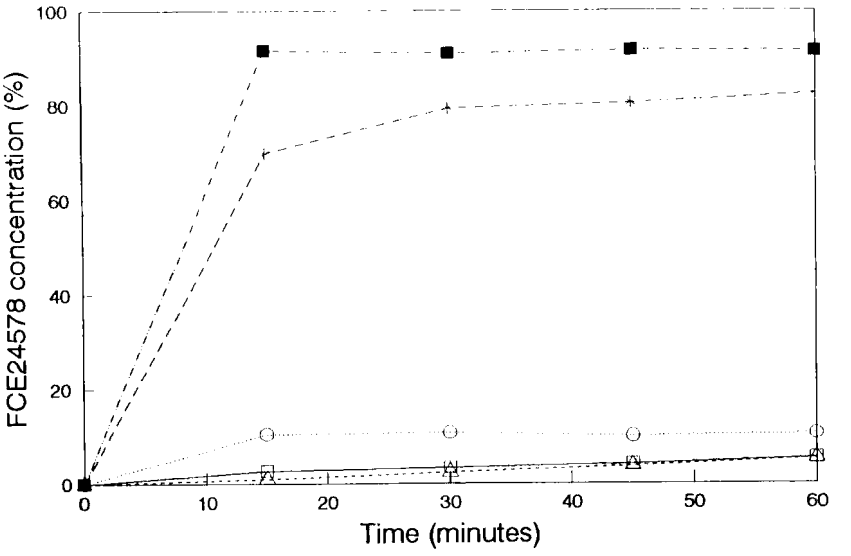

FIGURE 5
Dissolution rate performances of FCE24578 (□) in comparison with its equimolar physical mixtures with hydrate ß-CD (△), dehydrated ß-CD (○) and equimolar coground systems with hydrate (✳) and dehydrated (■) ß-CD in phosphate buffer pH 7.4.

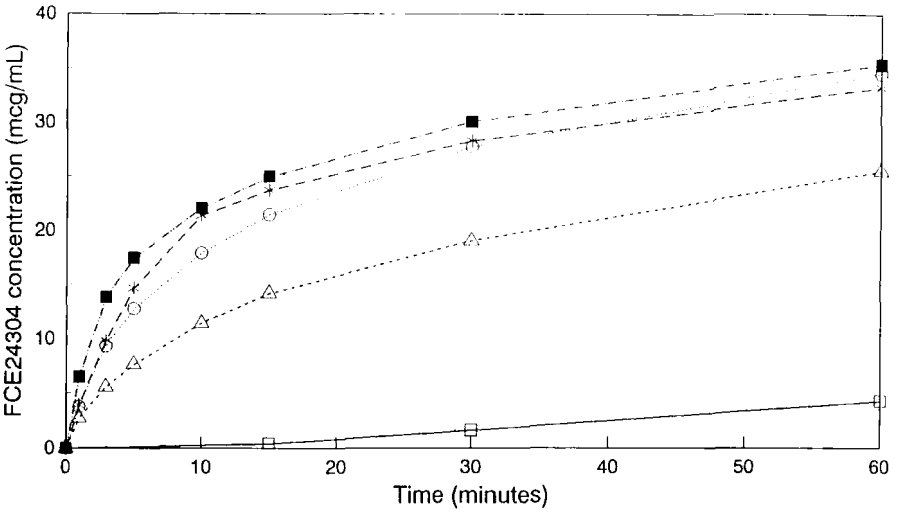

FIGURE 6
Dissolution rate performances of FCE24304 (□) in comparison with its physical mixture with hydrate (1:1 molar ratio △ ;1:2 molar ratio ○) and dehydrated (1:1 molar ratio ✳ ;1:2 molar ratio ■) ß-CD in phosphate buffer pH 7.4.

kneading (17); however the easy preparation of these systems (simple physical mixing) has made this technology interesting.

Looking at the dissolution profiles of simple physical mixture, has been evident that the same behaviour could be obtained with dehydrated-CD at low drug/excipient mole/mole ratio respect to hydrate-CD (figure 6).

Anyway the improved characteristics of the systems containing dehydrated CDs in comparison to those with hydrate ones were clearly demonstrated when an intrinsic dissolution rate test was carried out: the data in table 3 has confirmed that the intrinsic dissolution rate of FCE24304 was three fold improved for the equimolar mixture with hydrate-CD and five fold for the equimolar one with dehydrated-CD. The same conclusion was also reached for Temazepam (12).

TABLE 3

Intrinsic dissolution rate constants for FCE24304 and its physical mixtures with CDs

FCE 24304	$1*10^{-4}$ mg*cm^{-2}*sec^{-1}
FCE 24304/Hydrate-CD	$3*10^{-4}$ mg*cm^{-2}*sec^{-1}
FCE 24304/Dehydrated-CD	$5*10^{-4}$ mg*cm^{-2}*sec^{-1}

From these preliminary results a Temazepam/ßCD tablet has been developed with good "in vitro" dissolution performances and a very high stability. The poor compressibility of the mixture, determined by dehydrated CD, has been easily circumvented by an appropriate choice of other excipients suitable for tablet manufacturing. Tablets were prepared in a low humidity room (with R.H. below 30%) because at higher humidity CD was not stable (15).

CONCLUSIONS

Dehydrated CDs are a new interesting excipient under evaluation for improving biopharmaceutical properties of drugs. Their own peculiar characteristics lead to a quicker formation of complexes in solution with better dissolution performances for drugs, sometimes comparable to those of already formed complexes at the solid state.

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