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DISSOLUTION RATES OF CARBAMAZEPINE AND NITRAZEPAM UTILIZING SUGAR SOLID DISPERSION SYSTEM

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ABSTRACT

The dissolution of carbamazepine and nitrazepam from its solid dispersions using anhydrous lactose, mannitol, galactose, PEG 6000 and coprecipitate using polyvinyl-pyrrolidone (PVP) 40,000 was investigated. The dissolution process of capsules containing either carbamazepine or nitrazepam as solid dispersion or coprecipitate followed an apparent first order process. The combination of carbamazepine with sugars (mannitol, lactose, and galactose) caused, in every case, an increase in the dissolution rate of the drug. Carbamazepine-PVP coprecipitate gave the higher dissolution rate than that of the solid dispersions with sugars and PEG 6000. Nitrazepam-lactose system gave higher dissolution rate than the other dispersions and coprecipitate. This enhancement in dissolution rate was much more obvious for the solid dispersions and coprecipitate than for the physical mixtures.

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INTRODUCTION

Many reports show variations in clinical response between two or more orally administered dosage forms containing equivalent amounts of a drug, usually of limited aqueous solubility. Tolbutamide and its sodium salt is a clear example of the difference in biological response that may result from administering two chemical forms of the same drug (1). The rate of absorption of certain drugs from hard gelatin capsules may be highly dependent on formulation factors. The influence of crystal modification on the bioavailability and dissolution of two crystalline forms of carbamazepine was studied (2). They found that the only difference in pharmacokinetics between the two forms of carbamazepine was somewhat higher absorption rate for the dihydrate.

Carbamazepine is widely used anti-epileptic drug, and is marginally soluble in water or diluted hydrochloric acid (0.11 $mg.ml^{-1}$) and as expected, its absorption upon oral administration has been shown to be dissolution-rate limited (3-5).

Nitrazepam is a highly lipophilic compound as seen from the solubility (1.4×10^{-4}) and partition (2.12) data previously determined (6). The effect of cyclodextrin on the solubility of benzodiazepines in aqueous solutions was studied (6). They found that, the increase in solubility of benzodiazepines was due to the formation of inclusion complexes.

The importance of dissolution to the bioavailability of these drugs is undisputed. Therefore, the purpose of this investigation was the enhancement of dissolution rate of carbamazepine and nitrazepam from their solid dispersions and coprecipitate.

EXPERIMENTAL

Materials - The following materials were used :

Nitrazepam, Wyeth; carbamazepine, Ciba-Geigy; polyethylene glycol 6000 (BDH chemicals, Ltd., England); polyvinylpyrrolidone (Luviskol K_{30}, mol.wt. 40,000,B.A.S.F., Germany); D-Galactose (Prolabo); Anhydrous lactose and Mannitol (BDH chemicals, Ltd., England). All other chemicals were analytical reagent grade.

METHODS

Preparation of solid dispersion.

The melting procedure was used as follows : The calculated amount of the powdered drug was then accurately weighed, and added to the melted carrier (PEG 6000, galactose, mannitol, or anhydrous lactose)with constant stirring. Cooling was affected at room temperature and the product was placed in a dessicator over silica gel. The solidified product was then transferred to a suitable clean mortar, powdered and passed through a sieve of 80 micron mesh size. The incorporation of the drug in the melted carriers resulted in a one phase system. The drug carriers weight ratio was 1:3 and it was analytically confirmed. The drug content was between 95 and 102%.

Preparation of coprecipitate.

PVP 40,000 was accurately weighed and dissolved in 100 ml absolute ethyl alcohol. The powdered drug was accurately weighed and dissolved in another 100 ml of absolute ethyl alcohol by the aid of magnetic stirrer. The two solutions of the drug and carrier were mixed together in a porcelain dish, the solvent was evaporated and the residue kept in an incubator at 40° to constant weight. The mass was placed in a dessicator over silica gel and then transferred to a suitable clean mortar , powdered and passed through sieve of 80 micron mesh size.

Dissolution rate study.

Dissolution rates of the pure, solid dispersions and coprecipitate of carbamazepine and nitrazepam were studied. This was carried out using in vitro dissolution apparatus as described by the USP. The calculated amount (100 mg) of powdered drugs contained in hard gelatin capsule was rapidly introduced. The dissolution rates were studied in 200 ml 0.1 N hydrochloric acid at $37 \pm 1^{\circ}$. Five ml samples were removed as a function of time and analysed for drug content. Five ml of the dissolution medium was added back to the beaker after each sampling. The absorbance of the solutions was measured spectrophotometrically using a Shimadzu UV-150 spectrophotometer at 285 nm for carbamazepine and at 260 nm for nitrazepam against a blank solution. The total amount of the medicament in solution at time of sampling was determined. The drug concentration in solution was determined from

the standard Beer's law plot prepared previously and the amount dissolved calculated. Each dissolution profile is the average of three individual determinations.

RESULTS AND DISCUSSION

The intrinsic dissolution rate of carbamazepine, nitrazepam and their solid dispersions were determined in 0.1 N hydrochloric acid.

To examine the kinetics of the dissolution process of capsules containing drug, the log of the percentage undissolved in the capsule was plotted as a function of time. A linear relationship was obtained indicating an apparent first order process.

Figure 1, represents the dissolution rate of carbamazepine from its solid dispersions. It is evident that coprecipitate gave higher dissolution rate than pure carbamazepine and other drug-carrier systems. During the first hour of dissolution, lactose dissolved somewhat more quickely than the other solid dispersions and coprecipitate. After one hour, in fact, whilst only 7% carbamazepine had dissolved with regard to the pure product, the figure reached 39% for dispersion with lactose, 35.5% for coprecipitate, 32% for dispersion with mannitol, 24% for dispersion with polyethylene glycol 6000 and 21% for dispersion with galactose.

The dissolution rate of carbamazepine solid dispersions and coprecipitate during the first two hours was not in a regular manner, but after that time it becomes

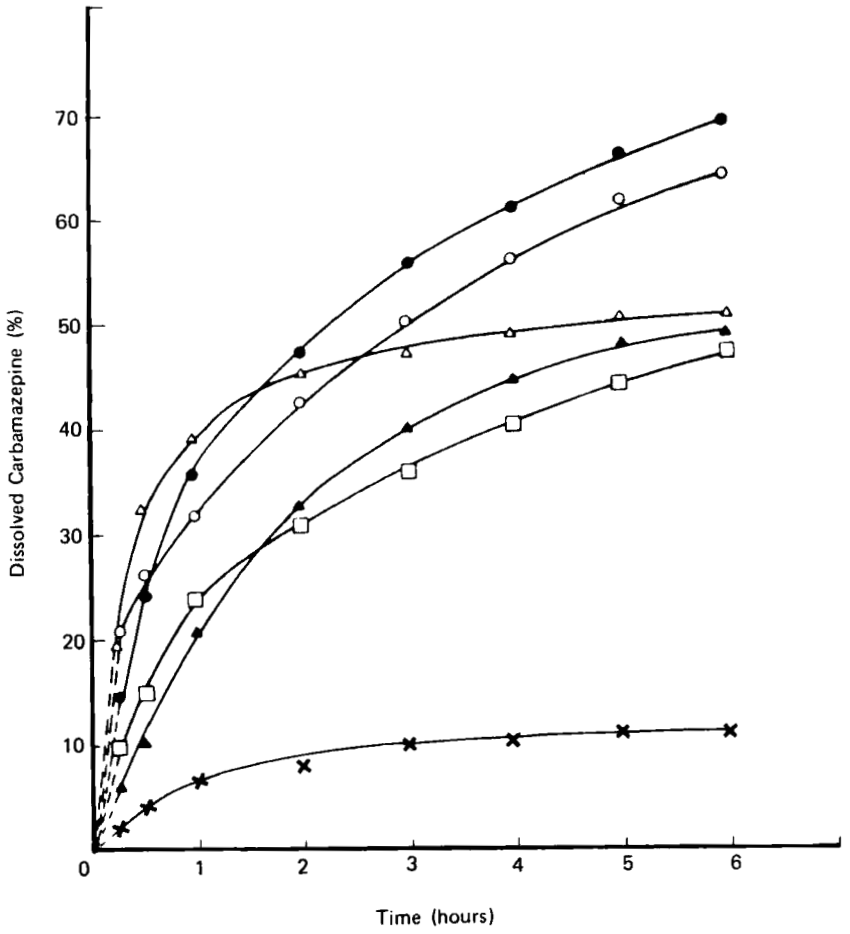

FIGURE 1

Dissolution of Carbamazepine from its Solid Dispersions and Coprecipitate.

Key: ●— P V P Coprecipitate. ×— Plain.
○— Mannitol Carrier. □— P E G 6000 Carrier.
△— Lactose Carrier. ▲— Galactose Carrier.

regular (coprecipitate gave the highest dissolution rate and PEG 6000 gave the lowest).

The dissolution rates of the corresponding physical mixtures were somewhat more rapid than that of the plain control drug (Figure 2).

Figure 3 represent the dissolution rate of nitrazepam from its solide dispersions and coprecipitate. It was found that, during the first two hours, galactose gave higher dissolution rate of nitrazepam than that with lactose, mannitol, PEG 6000, and coprecipitate. After six hours (experimental time) only 16% nitrazepam had dissolved with regard to the pure drug, the amount released reached 70% for dispersion with lactose; 54% for dispersion with mannitol; 51% for dispersion with galactose; 50% for dispersion with PEG 6000 and 48% for coprecipitate.

On the other hand, the dissolution rates of the corresponding physical mixtures were somewhat more rapid at the initial time of the dissolution, followed by a slower release of nitrazepam after the first three hours (Figure 4). At the end of the experimental time, the amount of the drug released from physical mixture containing lactose was 50%, 47% for the system containing mannitol, 42.5% for the system containing galactose, 33% for the system containing PEG 6000 and 25% for PVP.

Table 1, illustrates the 50% dissolution times in hours for both drugs. Polyvinylpyrrolidone coprecipitate produced the least dissolution time for 50% carbamazepine,

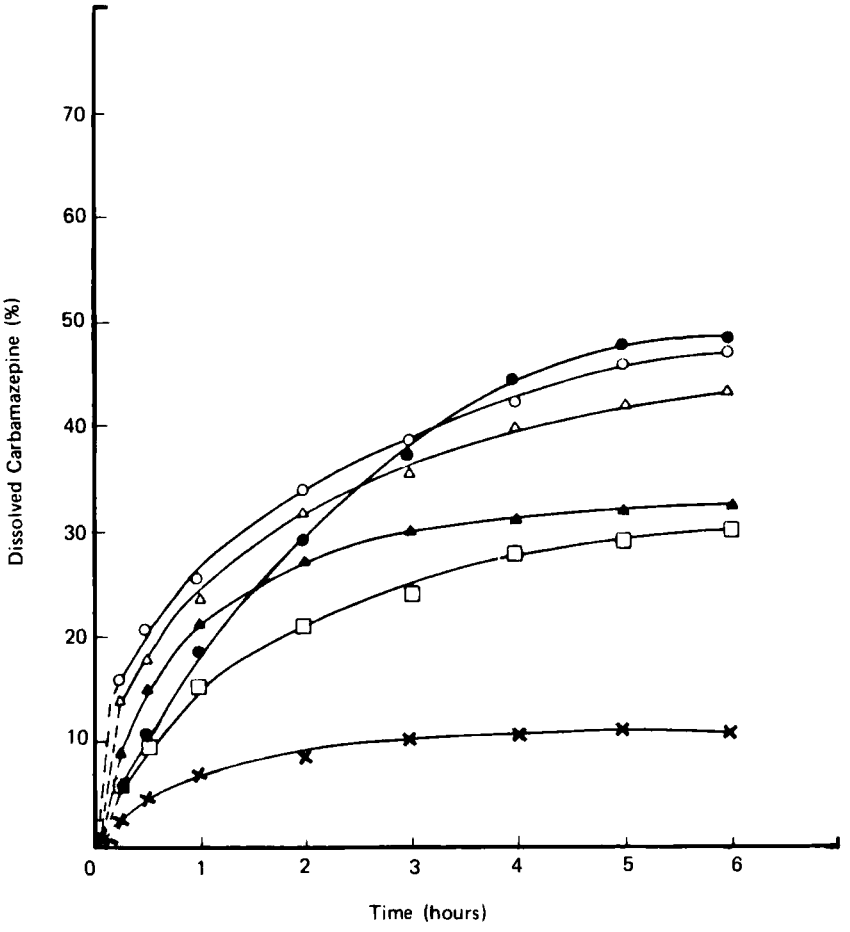

FIGURE 2

Dissolution of Carbamazepine from its Physical Mixture.

Key: P V P Coprecipitate. Plain.
Mannitol Carrier. ier P E G 6000 Carrier.
Lactose Carrier. Galactose Carrier.

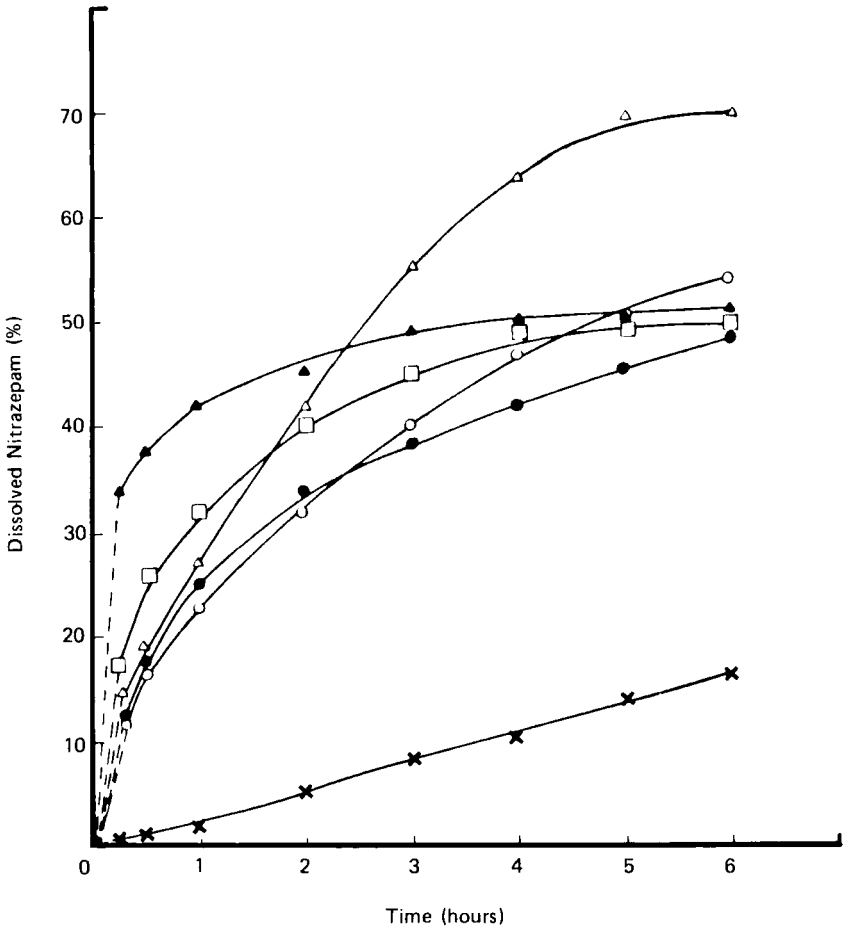

FIGURE 3

Dissolution of Nitrazepam from its Solid Dispersions and Coprecia

Key: ●— P V P Coprecipitate. ×— Plain.
○— Mannitol Carrier. □— P E G 6000 Carrier.
△— Lactose Carrier. ▲— Galactose Carrier.

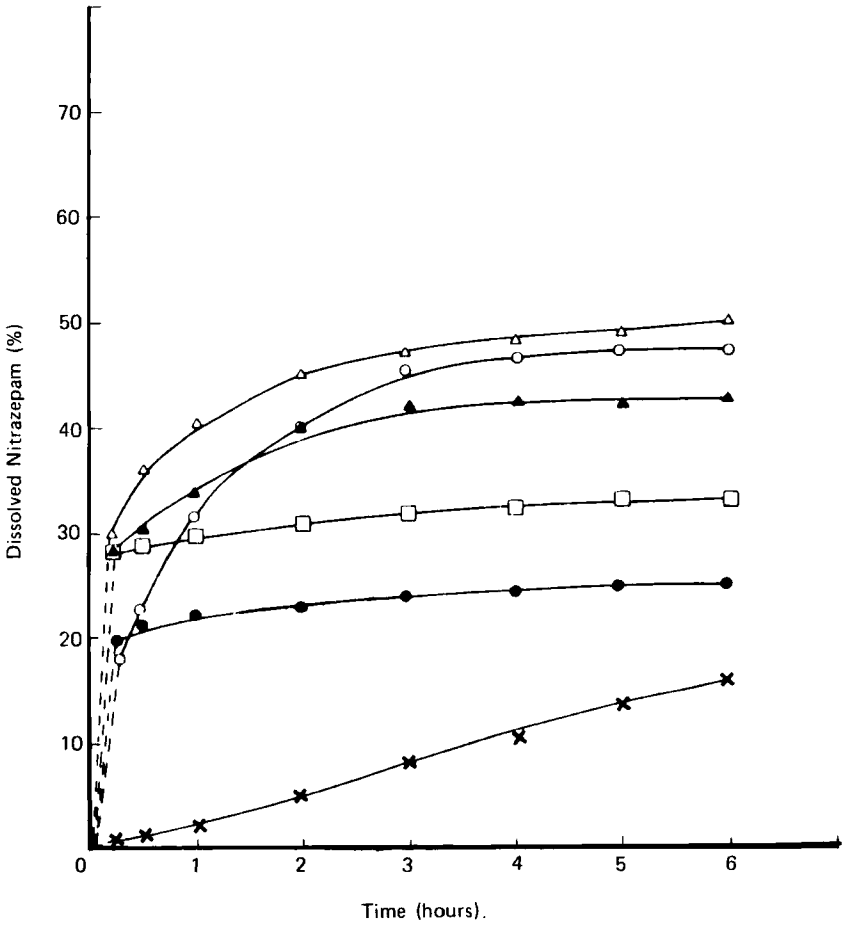

FIGURE 4

Dissolution of Nitrazepam from its Physical Mixtures.

Key: P V P Coprecipitate. Plain.
Mannitol Carrier. P E G 6000 Carrier.
Lactose Carrier. Galactose Carrier.

TABLE I

50% Dissolution Times (Hours) for Carbamazepine and Nitrazepam in Solid Dispersions and Physical Mixtures.

Drug-carrier Systems	Solid dispersion t_{50}	Physical mixture t_{50}
Carbamazepine	> 6	>6
Polyvinylpyrrolidone	> 2	>6
Mannitol	3	>6
Lactose	5	>6
Galactose	> 6	>6
PEG 6000	> 6	>6
Nitrazepam	> 6	>6
Polyvinylpyrrolidone	> 6	> 6
Mannitol	5	>6
Lactose	> 2	6
Galactose	4	>6
PEG 6000	6	>6

followed by mannitol and then lactose. While in case of nitrazepam, lactose gave the least dissolution time for 50% of the drug followed by galactose and then mannitol. The 50% dissolution time for the other systems were more than the experimental time (6 hours).

The sugar solid dispersion systems demonstrated a fast initial release, followed by slower prolonged release of carbamazepine and nitrazepam. Similar profiles were previously reported (7-9).

The rapid initial phase was attributed to the release of drugs present in a state of very fine subdivision, a portion of the drug probably was solubilized during preparation by the molten carrier and the another part was the most prolonged phase. This enhancement in the dissolution rate, can be attributed to the increased wettability of the two powdered drugs. Sugar carriers may act similarly as wetting agent. This may be due to that, sugars used in this investigation are readily soluble in an aqueous medium. Upon exposure of these systems to an aqueous medium, the sugar rapidly dissolved and a complete wetting of the drug occurred at the sametime.

The popularity of polyethylene glycol as a carrier was the main reason that the polyethylene glycol 6000 dispersion systems were used as a reference model when comparing the dissolution rates of the sugar dispersions. From the results obtained, it was found that the sugar dispersions had a faster dissolution rate than the polyethylene glycol dispersions.

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