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SOME PHARMACEUTICAL STUDIES ON SUSTAINED RELEASE COPRECIPITATES OF AMPICILLIN TRIHYDRATE WITH ACRYLIC RESIN (EUDRAGIT(R)-RS).

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ABSTRACT

Coprecipitates of Ampicillin trihydrate with acrylic resin (Eudragit(R) - RS) were prepared. Comparative dissolution rate studies of the coprecipitates and pure ampicillin showed that, the coprecipitates slowed down the release rate of the drug. Bioavailability studies in human subjects using urinary excretion method indicated a lower rate and extent of drug absorption from the tablet formulation containing coprecipitated drug, as compared to the tablets formulated from the pure drug. Both the in-vitro and the in-vivo results suggest that the embeddment of ampicillin trihydrate in Eudragit-RS by the coprecipitation technique, show a great promise in sustaining the drug's release in a matrix controlled drug delivery system.

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INTRODUCTION

Just about four decades ago, sustained release products were introduced as a new class of pharmaceutical products. These products have received a considerable attention in recent years (1 - 6).

The major objective of a sustained release product is to attain drug efficacy and safety, by increasing the duration of drug action and reducing the required multiple dosing. Frequent dosing of drugs is often accompanied with poor patient compliance, which may lead to drug failure, as pointed out by Porter (7), and drug resistance in the case of antibiotics.

Ampicillin, is a semisynthetic penicillin which is acid resistant and therefore can be given orally. Relatively short biological half life times of 0.9 and 0.75 - 2 hours have been reported by Dettli (8) and Ritschel (9) respectively. It was therefore considered interesting to design a sustained release formulation of ampicillin by utilizing a selected acrylic resin, with an objective of improving patient compliance and increasing the efficacy of the drug. The retardant effects of acrylic resins on drug release from solid dosage forms have been reported in the pharmaceutical literature (10 - 13). This paper discusses the results obtained from studies on sustained release ampicillin formulation, and attempts to establish correlationship between the in-vitro and in-vivo results.

EXPERIMENTAL

Materials: Ampicillin trihydrate (Beecham Pharmaceuticals England), acrylic resin - Eudragit(R)-RS PM (Rohm Pharma

Darmstadt, West Germany), Microcrystalline cellulose-Avicel PH 101 (Fluka AG), Stearic acid (BDH-England). The materials listed above were used as received. All other materials and chemicals used were obtained from standard sources and were of analytical grade.

Methods:

1. Preparation of drug-resin coprecipitates - Coprecipitates of ampicillin trihydrate and acrylic resin (Eudragit-RS) in drug: polymer ratio of 2:1 and 1:1 were prepared by dissolving together appropriate quantities of the drug and polymer in methanol. The cosolvent was evaporated at room temperature in a vacuum dessicator[1] containing anhydrous calcium chloride. Precipitated ampicillin trihydrate alone was similarly prepared. After allowing drying to constant weight, all preparations were powdered and screened through a 150 μm sieve. Powder samples of precipitated drug, drug/polymer 1:1 and 2:1 designated I, II and III respectively, were selected for dissolution rate studies.

2. Stability Studies

(a) TLC: Methanolic solutions of pure drug, precipitated drug and its coprecipitates were spotted on a 0.25 mm Silica Gel G chromatographic plates and developed by a solvent system of Ethylacetate: Formic acid: Methanol: Water (65:5:20:10) as described by McGilveray et al (14). After drying, the plates were placed in an iodine tank. Detection of the spots was done by viewing the plates under a U.V. lamp at 254 nm.

(b) IR Spectra: Liquid paraffin mulls of the drug and its coprecipitates were prepared. Infra-red spectra of the prepared mulls were scanned by using Perkin Elmer Spectrophotometer[2] at slow speed to achieve the maximum resolutions.

3. Powder Dissolution

The dissolution of the drug and its coprecipitates in powdered form was carried out by the tape method as described by Goldberg et al (15) with a slight modification. 50 mg - fine powder samples (size 0 - 150 μm) were spread essentially in a mono-layer on the adhesive side of a 5.5 x 3.5 cm cellotape[3]. The tape was held in a vertical position 3 cm from the centre of the dissolution vessel[4], with the powder sample facing a 6.3 x 2.5 cm stirring paddle. The paddle speed was 50 r.p.m. and the dissolution medium was 400 ml of distilled water equilibrated at 30 ± 0.5°C. After 15, 30, 60, 90, 120, 150, 180, 210 & 240 minutes, 5 ml samples were withdrawn from a fixed position in the dissolution medium and replaced with equivalent amount of distilled water maintained at the same temperature.

Assay of the drug in the samples was based on the spectrophotometric method according to the procedure described by Smith et al, (16).

Sample solutions were adequately diluted with pH 5.2 buffer containing 15 ug/ml of copper II ions. This solution had been prepared by adding 1.5 ml of a 0.393 % copper II sulphate pentahydrate solution to 98.5 ml of a buffer solution formed by mixing 464 ml (0.1M citric acid) with 536 ml (0.2M disodium hydrogen phosphate). Each sample

TABLE 1

Ampicillin Tablet Formulations: Quantities used for one tablet (mg).

Ingredients	Formulations		
	T-I	T-II	T-III
Ampicillin	100	200*	150**
Dextrose	40	40	40
Avicel PH 101	208	208	208
Stearic acid	2	2	2
Weight of each tablet	350	450	400

* and ** refer to coprecipitates of ampicillin trihydrate and Eudragit (R) - RS in (1:1) and (2:1) respectively.

was divided into two parts. One part was incubated at 75°C in a loosely stoppered tube for 30 min, cooled to room temperature in ice and the absorbance was measured at 320 nm against the un-incubated part in the reference cell.

4. Tablet Formulation

Three ampicillin tablet formulation T-I , T-II and T-III containing pure drug, drug/Eudragit (R) - RS (1:1) and (2:1) coprecipitates respectively were prepared. The details of the tablet formulations are given in Table 1.

Comprimates of 10 mm in diameter weighing 350, 450 and 400 mg for formulations T-I, T-II and T-III respectively, were produced by direct compression using a single punch

tabletting machine[5]. Physical properties of the tablets such as hardness and friability were satisfactory.

5. Tablet Dissolution

Tablet dissolution was carried out using the USP Method I with slight modification. Tablet sample was placed in the USP-basket held in 400 ml distilled water at 30 ± 0.5°C. The basket rotation speed was 100 r.p.m. Assay of withdrawn samples was carried out as described above. All dissolution experiments were replicated at least three times.

6. Bioavailability Studies:

Eight healthy male volunteers, 20 - 28 years old and weighing 66 - 68.5 kg were considered for this study. The volunteers had neither history of gastro-intestinal disease or surgery, nor kidney disorders. Also, they were not on any kind of medication for at least 2 weeks prior to the studies. The volunteers fasted overnight, but allowed free access to water before the experiments.

After collection of control urine samples, a single dose equivalent to 500 mg of ampicillin trihydrate from formulations T-I, and T-II[6] each at one time, was given orally to each subject at a fixed time along with 250 ml of water. After dosing, 100 ml of water was administered at 1, 2 and 3 hours, and each subject was given a uniform meal after 4 hours. Subjects' exercise was light and their movements were kept minimum. A balanced randomized crossover design for eight subjects (17), was employed in

these experiments such that, subjects 1 to 4 received formulation T-I, while the rest four (5 to 8) were given formulation T-II[6] in the first week. After a one week washout period subjects 1 to 4 were given formulation T-II[6] while subjects 5 to 8 received formulation T-I. Urine samples were collected at specified time intervals while recording the total volumes excreted. Drug assay was done according to the procedure of Angelucci and Baldieri (18) as follows: 0.1 ml urine was mixed with 0.1 ml of 20 % trichloroacetic acid solution. 4.8 ml of pH 5.8 citrate buffer[7] containing 15 µg/ml copper was immediately added to the solution. The final pH was 5.2. After thorough mixing and centrifugation, the supernatant was divided into two portions. One portion was incubated at 75°C for 30 min. After cooling, the resulted stable acid degradation compound was determined spectrophotometrically at 320 nm against the un-incubated portion as a blank.

Interpretation of the observed absorbances was based on a slope and intercept obtained by linear regression analysis of a series of standard solutions with known drug concentrations in urine which had been sampled shortly before drug administration. This procedure was carried out separately for every test subject.

RESULTS AND DISCUSSION

Stability Studies: Thin-layer Chromatographic studies and Infra-Red spectra gave no evidence of drug degradation or complexation in the prepared drug-polymer coprecipitates.

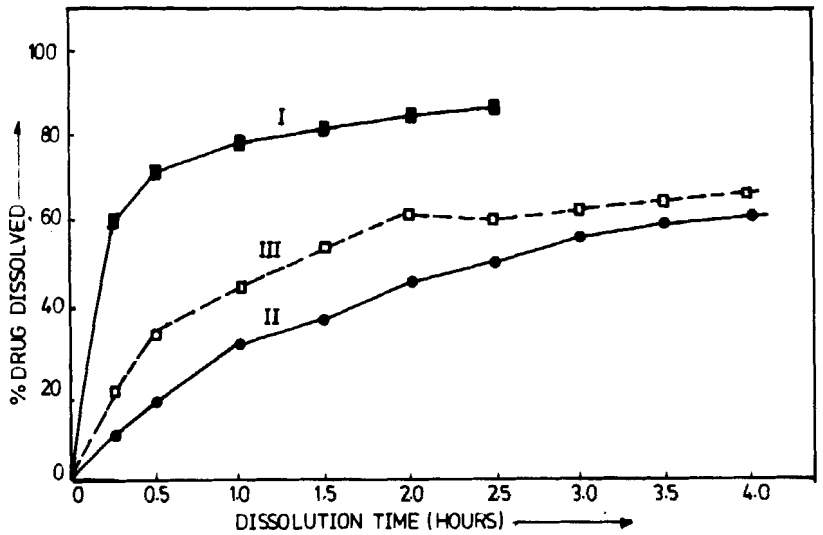

FIGURE 1.

Dissolution Rate Profiles of Ampicillin trihydrate coprecipitates I ——■—— = pure drug; II ——●—— = drug/Eudragit RS (1:1); III--□--□-- = drug/Eudragit RS (2:1)

On the TLC - plate each of the coprecipitates produced only one spot with R_f values identical to that of the pure drug. The IR spectra of pure drug and of drug in polymer coprecipitates were identical, ruling out any possible interaction between the drug and the carrier.

Dissolution Rate Studies: Fig. 1, illustrates profiles of the dissolution rate of ampicillin trihydrate alone and the release patterns from its coprecipitates with acrylic resin - Eudragit(R) - RS, by employing the tape method. The drug dissolution rate from powder I (pure drug) was rapid with the amount dissolved reaching 70 % in the first ½ an hour. The coprecipitates II and III gave the slowest release rates. The 70 % dissolution observed with powder I (after ½ hour)

was not attained by coprecipitates II and III even after the experiments were extended to four hours.

It is assumed that in the coprecipitates a considerably large amount of ampicillin was precipitated in fine particles embedded in the polymer matrix (19). Although water insoluble, Eudragit(R)-RS swells in aqueous natural and artificial digestive juices rendering itself permeable to these liquids (20). Apparently, the quantities of acrylic resin used were not sufficient to achieve 100 % drug embeddment. The mechanism of drug release therefore, would probably be through direct dissolution of the partially embedded drug by leaching mechanism and dissolution followed by diffusion of embedded drug via the matrix pores. The technique of coprecipitation of drug with water insoluble polymer (Eudragit(R)-RS) as employed in the present study, retarded the dissolution rate of ampicillin trihydrate. Such a retardation of the release rate would probably form a basis of formulating a sustained release solid dosage form.

Fig. 2 depicts the release profiles of ampicillin from tablet formulations T-I, T-II and T-III containing the pure drug, 1:1 and 2:1 drug/polymer coprecipitates respectively. About 95 % drug dissolution was attained after two hours from formulation T-I (pure drug). Formulations T-II and T-III showed a significant retardation in the drug release rate. As the ratio of the resin was increased in the coprecipitate, the release rate of the drug decreased (Fig. 2).

Drug Bioavailability: Fig. 3 shows the average amount of ampicillin excreted by eight volunteers after oral

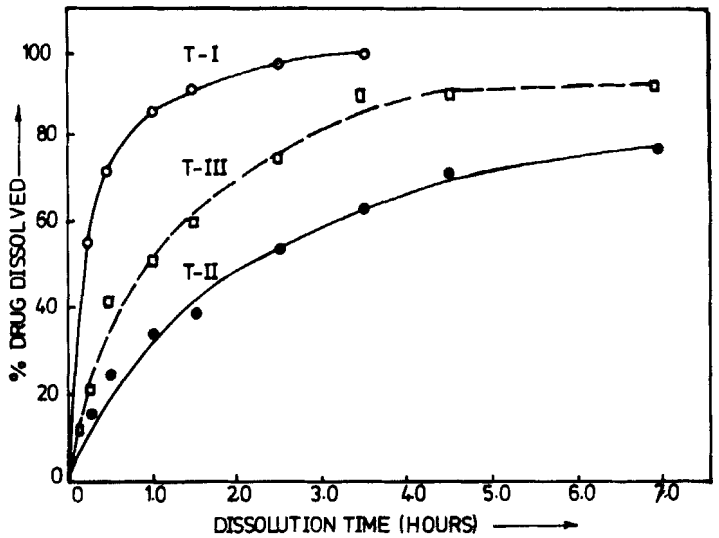

FIGURE 2.

Dissolution Rate Profiles of Ampicillin Trihydrate Tablets containing various forms of the drug. T-I —O—O— = pure drug; T-II —●—●— = drug/Eudragit RS (1:1); T-III — — □ — — □ — — = drug/Eudragit RS (2:1)

administration of tablet formulations T-I and T-II. The average increase rate of urinary drug concentration in the initial 1½ hours was about 0.42 mg/ml/hour for formulation T-I. Formulation T-II (drug coprecipitate) exhibited an excretion rate of 0.088 mg/ml/hour, an approximately five times slower rate which was maintained four 5½ hours. While formulation T-I produced a peak excretion of 0.665 mg/ml after 3½ hours, formulation T-II had a peak of 0.600 mg/ml attained after 10 hours, indicating a considerable delay in drug elimination. Both the reduced rate of excretion and a relatively lower urinary peak level of the drug in formulation T-II suggest a corresponding retardation in drug absorption rate, presumably due to reduced dissolution rate of the drug from the polymer matrix.

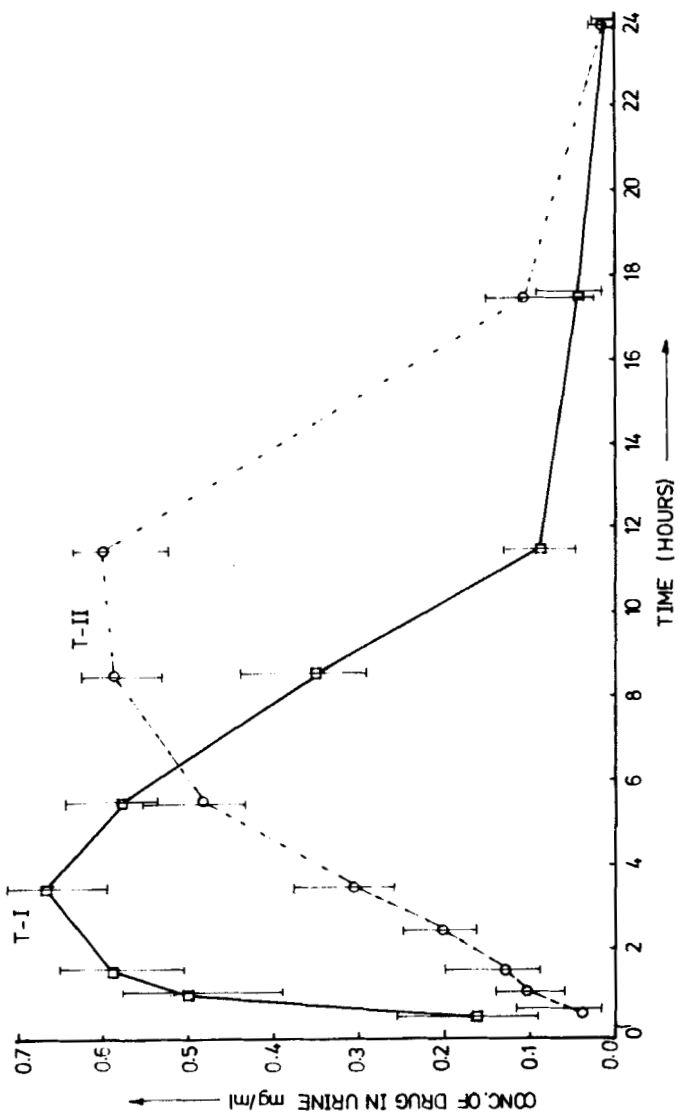

FIGURE 3.

Urinary excretion - time profiles for Ampicillin trihydrate tablet formulations containing: pure drug T-I—□—□— and drug/Eudragit RS (1:1) coprecipitate T-II—o—o— . Vertical lines represent the range of results for 8 subjects.

The amount of drug detected in the urine after 24 hours was insignificantly small. Renal clearance values for the eight volunteers were closely interrelated, and fell within the normal tolerances indicating normal kidney function and negligible inter subject variability in the excretory system. Assuming normal kidney function, the excreted cumulative amounts of about 38.3 and 32.2 % for formulations T-I and T-II respectively, were recorded and considered valid to estimate comparative drug bioavailability of the different two drug systems. A similar urinary drug recovery of about 39.7 % from a non-sustained 500 mg oral dose of ampicillin trihydrate had been obtained earlier by Loo et al (21).

The coprecipitation technique, as employed on ampicillin trihydrate with Eudragit(R)-RS and the selected tablet formulations have produced a considerable drug release retardation, both in-vitro and in-vivo. With appropriate modification of the formulation and design, a desired oral sustained release dosage form may be formulated. In cases were the drug suffers acid degradation or other instability in the gastrointestinal fluids, Eudragit(R)-RS would enhance stability, since it is insoluble in aqueous fluids and exhibits only little or limited pH-independent gastrointestinal fluid permeability.

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FOOTNOTES

1. A vacuum of about - 6kp.cm^{-2} was ensured by a vacuum pump compressor-type EB3A-Edwards High Vacuum (BOC Ltd), Crawley, England.
2. Perkin Elmer 710B IR Spectrophotometer, Norwalk, Connecticut, U.S.A.
3. Tesa film, Beirsdorf AG, Hamburg, FRG.
4. 500 ml PYREX-glass beaker (England)
5. KORSH-BERLIN: TYPE-EKO (ERWEKA-Apparatebau, FRG)
6. Formulation T-II was selected for this study following its better in-vitro retardant effect, while formulation T-III was excluded.
7. A mixture of 39.5 ml (0.1M citric acid) and 60.5 ml (0.2M Na_2HPO_4) formed 98.5 parts, while 0.393 % $CuSO_4.5H_2O$ solution formed 1.5 parts of the citrate buffer.

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