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EFFECT OF SUSPENDING AGENTS ON THE DISSOLUTION AND BIOAVAILABILITY OF AMPICILLIN

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ABSTRACT

The effect of various suspending agents viz., Methyl cellulose, Sodium carboxymethyl cellulose, Bentonite and Polyvinylpyrrolidone on the dissolution of ampicillin from its suspensions was studied. Methyl cellulose (MC) gave the best ampicillin suspensions as indicated by the highest sedimentation volume (F=0.78) while polyvinylpyrrolidone (PVP) gave the poorest suspensions (F=0.11). The effectiveness of the suspending agents decreased in the following order: MC > Bentonite > Sod. CMC > PVP. The in vitro dissolution studies showed that all the suspending agents decreased the dissolution rate of the drug. As the suspending agents concentration was increased, the retardation effect on drug dissolution increased. The bioavailability of ampicillin from its suspensions was studied in 6 healthy volunteers by urinary excretion method. Commercial product (Penbritin) was included for comparison. Both % dose excreted and maximum excretion rate were markedly reduced except in suspension containing Sod. CMC. However, the time for maximum excretion was not affected.

INTRODUCTION

Suspending agents are used in suspension formulation to increase the viscosity so that the sedimentation rate is slowed and the measurement of proper dose is simplified. Because a suspending agent alters the physical properties of suspension, it may concomitantly affect the absorption of the medicinal compound by the increased viscosity or by complexation. Many investigations have shown that about 20-30% bioavailability difference for ampicillin is due to formulation factors [1,2]. Shah and Seth [3] showed the reduced dialysis of nitrofurantoin from drug suspensions containing three viscosity grades of methyl cellulose polymers as suspending agents. Seager [4] who studied the effect of methyl cellulose on the excretion rate of nitrofurantoin, found that the amount of the drug excreted in 6 hours was significantly reduced and the bioavailability was impaired. Levy & Jusko [5] showed that methyl cellulose reduced the uptake of salicylic acid from ethanol-water mixtures by the ligated rate stomach.

Ampicillin is relatively stable in the acidic gastric secretion and is well absorbed from the gastrointestinal tract after oral administration. Peak concentrations in plasma are obtained in about 2 hours and following a dose of 500 mg by mouth are reported to range from 2 to 6 μg/ml. About 20% is bound to plasma proteins in the circulation and plasma half-lives of about 1 to 2 hours have been reported. About 30% of an orally administered dose is excreted unchanged in the urine in 6 hours; urinary concentration range from 0.25 to 1 mg/ml following a dose of 500 mg [6].

In this work, the effect of selected hydrocolloids on the dissolution and bioavailability of ampicillin suspension was investigated.

EXPERIMENTAL

1-Materials:

Ampicillin trihydrate, lot No. 2804502 (Biochemic Geselische M.B.H. Kundl/Tyrol/Austria); Penbritin, batch No. 22674d (Beecham research laboratories, Brenford, England); Methyl cellulose, Sod. Carboxymethyl cellulose, Polyvinylpyrrolidone and Bentonite (BDH chemicals ltd., Pool, England).

2-Preparation of hydrocolloids

Weighed amounts of hydrocolloid were taken and kept with water for 24 hours for swelling. The swollen hydrocolloids were agitated in a high speed mixer for a minute to get a uniform dispersion. The concentration of hydrocolloid dispersions used for preparation of ampicillin suspensions were as follows:

1-Methyl cellulose : 0.25, 0.50, 1.0, 2.0, and 3.0% w/v.

2-Sod. CMC : 0.25, 0.50, 0.75, 1.0 and 1.5% w/v.

3-Bentonite : 1.0, 2.0, 3.0, 4.0 and 5.0% w/v.

4-PVP : 2.0, 3.0, 5.0, 7.5 and 10% w/v.

Preparation of ampicillin suspensions:

2.5 g of ampicillin was added to the 50 ml of the above prepared dispersions and mixed thoroughly.

Viscosity measurements:

The viscosity of suspensions used in the study was determined by Brooke-field viscometer LTV model. The results are shown in Table (1).

3-Dissolution studies:

The dissolution study of the suspensions was carried out in a 500 ml beaker which was kept in a water bath at 37±1°C. A stirrer was lowered to a distance of 2 cm above the bottom of the beaker at a stirring rate of 100 rpm. The dissolution medium used was 0.1N HCl of pH 1.2.

To 450 ml of the dissolution medium, 5 ml suspension was added and the volume was made up to 500 ml with medium used for rinsing. Samples of 1 ml dissolution medium were withdrawn using a volumetric pipette connected with a cotton filter after 1, 2, 4, 6 and 8 minutes. The samples were completed with copper sulphate buffer, pH 5.2, and heated in a water bath at 75°C for 30 minutes, rapidly cooled to room temperature and the absorbance was measured at 320 nm using unheated buffered solution of ampicillin as a blank [7].

4-Bioavailability studies:

Six healthy female volunteers participated in the trials; average age 22 years and average body weight 55 kg. The participants did not take any other medication for one week before or during trial. An equivalent of 500 mg ampicillin of each suspension was taken by each volunteer in a cross-over design. After an over night, fast urine samples were taken prior to administration (control) and hourly for 8 hours post administration. Subjects were encouraged to drink water (200 ml) after each urine collection to effect diuresis. A wash-out period of seven days was allowed between trials. The ampicillin content were determined chemically on the same day of urine collection.

RESULTS AND DISCUSSION

The effect of suspending agent concentration on the sedimentation volume (F) of different ampicillin suspensions is shown in Table (2). The results show that physical stability of the investigated suspensions decreases in the following order : MC > bentonite > Sod. CMC > PVP. Generally, hydrocolloids and various polymers are known to form coherent films around the dispersed

particles. The film thickness could depend upon the bulk concentration of the hydrocolloid. This may be one of the reasons for the retarded dissolution at higher concentrations of the suspending agents as shown in Table (3). MC which gave suspensions with the highest sedimentation volume produced suspensions with the minimum dissolution rates. In suspensions containing sod. CMC, increasing the hydrocolloid concentration had gradually decreased the dissolution rate. Further interaction of the adsorbed sod. CMC with HCl of the dissolution medium may bring about reduction in its effect on retarding the dissolution of ampicillin [8]. In case of bentonite the relative reduction in the dissolution rate of ampicillin is probably due to the fact that bentonite at high concentration acts as a bulk viscosity imparting agent which may play a role in reducing the dissolution of the drug. On the other hand, PVP had only a slight effect on the dissolution rate. This may be due to the inadequate surface adsorption of the hydrocolloid, and its low viscosity even at high concentration compared to bentonite.

Tables (1&3) show a good correlation for viscosity versus drug dissolution in each suspension individually. But a combination of all the systems exhibited a poor correlation. This proves non prevalence of a general mechanism for the retardation of drug dissolution in the presence of different suspending agents, i.e. each system retarded dissolution by different mechanism.

Jusko and Lewis [9] demonstrated that a relationship exists in man between blood level of ampicillin and its rate of urinary excretion. Hence, the rate and extent of absorption of the drug can be determined by measuring the rate of appearance of unchanged ampicillin in urine.

The total amount of ampicillin excreted in urine over 8 hrs was used to describe the extent of ampicillin bioavailability. Table (4) reports the comparative bioavailability of ampicillin after oral administration of various suspensions (500 mg), expressed as % dose excreted in urine after 8 hrs. The mean maximum excretion rates (mg/hr) obtained after oral administration of various suspensions and the time (hr) to reach these maximum excretion rates are shown in Figure (1) and reported in Table (4).

Statistical analysis of main pharmacokinetic parameters of ampicillin suspensions relative to pure drug formulation indicates that these differences are very marked and significant ($P < 0.05$) with the exception of ampicillin suspensions containing 1.5% w/v sod. CMC and the commercial ampicillin suspensions (Penbritin) where the difference is non significant ($P > 0.05$).

Although reduced bioavailability, as indicated by % dose excreted in urine and maximum excretion rate, was observed for all suspensions, sod. CMC containing suspension was superior to the others and second only to the commercial ampicillin. The reduction of bioavailability in MC suspension was more pronounced compared to that of sod. CMC. Similar observations were seen for PVP containing suspension. Bentonite containing suspension presented the most unsatisfactory bioavailability of ampicillin from its suspension, where more than 50% reduction in ampicillin excretion was reported compared to pure drug suspension. This may be partly due to adsorption of the drug onto the suspending agent. Other mechanisms which may be involved are the modification of gastric emptying rate and/or intestinal transit rate and an effect on the movement of drug molecules

from the lumen to the absorption membrane.

The contradiction between the *in vitro* and *in vivo* results emphasizes the needs for investigating the effect of suspending agents on the *in vivo* performance and *in vitro* dissolution of drugs. Accordingly, the formulator can select the suspending agents with the least effect on drug bioavailability.

Table 1: Measured viscosity of suspending agents at different concentrations.

% of suspending agent	Viscosity in CPS			
	MC	Sod. CMC	PVP	Bentonite
0.25	150	200	---	---
0.50	400	850	---	---
0.75	---	1400	---	---
1.00	1100	1600	---	200
2.00	1500	---	50	600
3.00	2000	---	100	1000
4.00	---	---	---	1350
5.00	---	---	250	1500
7.50	---	---	400	---
10.00	---	---	650	---

Table 2: Effect of various concentrations of suspending agents on the sedimentation volume (F) of ampicillin (aging for 7 days).

% of suspending agent	Sedimentation Volume			
	MC	Sod. CMC	PVP	Bentonite
0.00	0.06	0.06	0.06	0.06
0.25	0.078	0.089	----	----
0.50	0.089	0.133	----	----
0.75	----	0.178	----	----
1.00	0.111	0.200	----	0.067
1.50	----	0.289	----	----
2.00	0.156	----	0.067	0.133
3.00	0.780	----	0.067	0.667
4.00	----	----	----	0.689
5.00	----	----	0.111	0.711
7.50	----	----	0.111	----
10.00	----	----	0.111	----

Table 3: The effect of suspending agents on dissolution rate of ampicillin from suspension.

% of suspending agent	Dissolution Rate (% $min.^{-1}$)			
	MC	Sod. CMC	PVP	Bentonite
0.00	66.4	66.4	66.4	66.4
0.25	29.8	32.0	----	----
0.50	27.2	32.1	----	----
0.75	----	10.5	----	----
1.00	7.0	12.3	----	----
2.00	7.6	----	61.5	36.6
3.00	3.5	----	53.5	34.1
4.00	----	----	----	31.6
5.00	----	----	50.1	31.1
7.50	----	----	39.5	----
10.00	----	----	33.2	----

Table 4: Mean Pharmacokinetic Parameters for ampicillin after oral administration of the various suspensions (500 mg) of 6 subjects.

Type of suspension	% Dose excreted	Maximum excretion rate (mg/hr)		t max(hr)
Pure amp.	34.4 (±5.5)[a]	61.4 (±13.1)		1.5 (0)
Sod. CMC 1.5%	25.2 (±4.0)	52.4 (±15.3)	NS[b]	1.5 (0)
PVP 10%	21.5 (±1.6)	34.7 (±6.0)	S	1.5 (0)
MC 3%	21.0 (±3.6)	37.8 (±6.9)	S	1.7 (±0.17)
Bentonite 4%	16.5 (±1.4)	30.0 (±3.5)	S	1.7 (±0.17)
Commercial amp. (Penbritin)	31.8 (±5.0)	61.1 (±8.5)	NS	1.5 (0)

a = Standard error.
b = Non significant difference.
S = Significant difference.

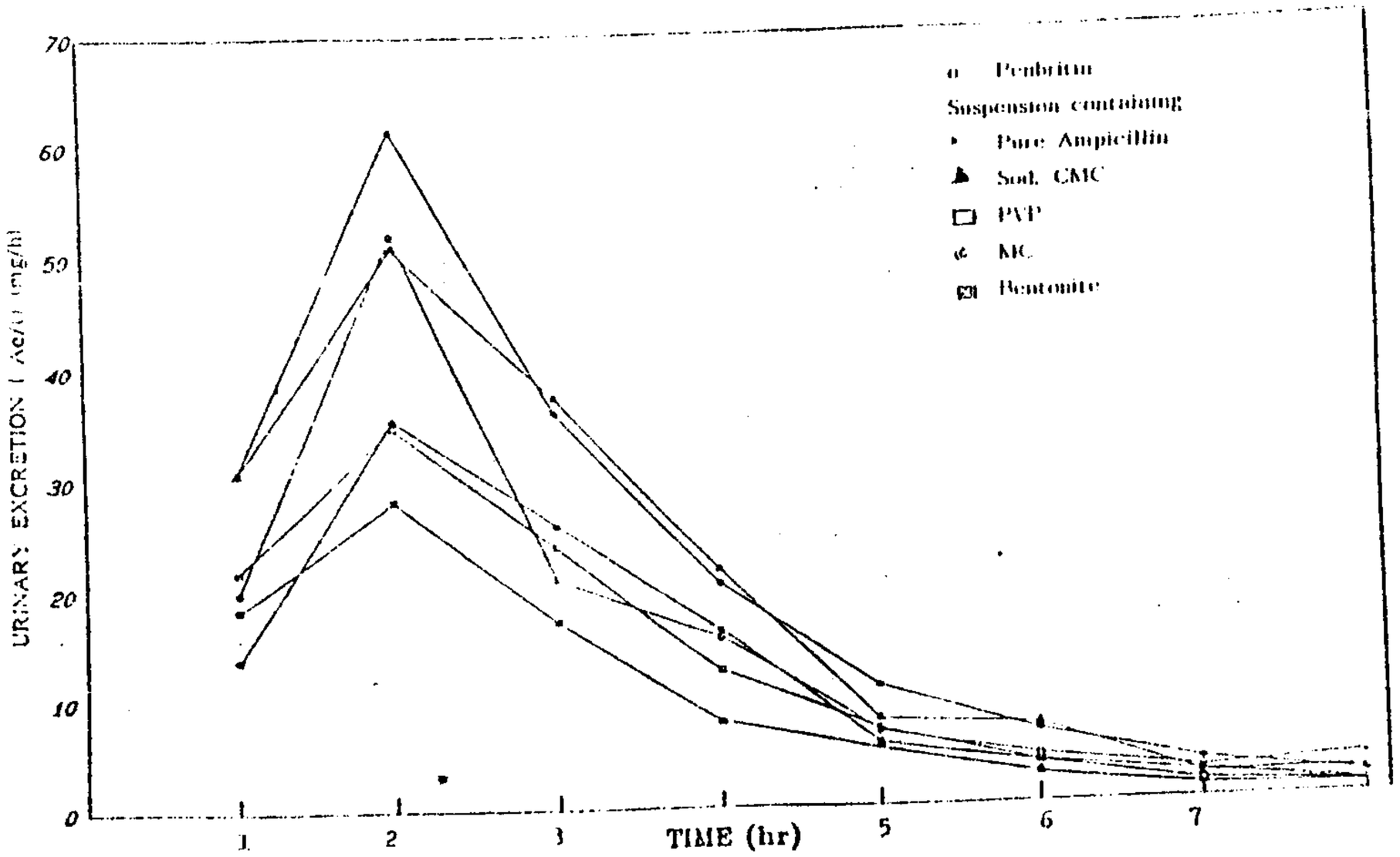

Fig. 1 • MEAN AMPICILLIN URINARY EXCRETION RATES (mg/hl AT VARIOUS TIMES AFTER ORAL ADMINISTRATION OF VARIOUS AMPICILLIN SUSPENSIONS (500 mg) TO 6 SUBJECTS.

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تأثير العوامل المعلقة على الاذابة والاتاحة الحيوية للامبسلين

احمد عبدالله بعيلة ـ محمود الصغير التريكى ـ محمود عبد الغنى مهدى ـ محمد سلامة محمد

تم دراسة تأثير العوامل المعلقة المختلفة مثل الميثيل سيليلوز ـ وصوديوم كاربوكسى ميثيل السيليلوز والبنتونيت والبولى فنيل بيروليدون على اذابة الامبسلين من المعلق وقد اعطى الميثيل سليلوز افضل معلق كما هو واضح من قيمة حجم الراسب العالى (٧٨ر٠) بينما اعطى البولى فنيل بيروليدون اقل معلق من حيث الجودة (حجم الراسب ١١ر٠) وبذلك يمكن ترتيب فاعلية العوامل المعلقة المستخدمة للامبسلين كالآتى : ميثيل السيليلوز- البنتونيت- صوديوم كاربوكسى ميثيل السيليلوز بولى فينيل بيروليدون كما تم دراسة الاتاحة الحيوية للامبسلين على ستة اشخاص اصحاء فى وجود العوامل المعلقة المختلفة بطريقة الاخراج البولى ، مع مقارنة النتائج بمستحضر تجارى مثل البنبرتين • وقد اشارت النتائج الى نقص ملحوظ فى كمية الامبسلين المخرجة ومعدل الاخراج فى وجود العوامل المعلقة المختلفة فيما عدا المعلقات المحتوية على صوديوم كاربوكسى ميثيل السيليلوز الا ان اقصى اخراج للامبسلين لم يتأثر بوجود العوامل المعلقة المختلفة •

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