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Adsorption–desorption effect of microcrystalline cellulose on ampicillin and amoxycillin

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Summary

Three grades of microcrystalline cellulose (Avicel PH 105, 103 and 102) were used to elucidate their effects on both ampicillin monohydrate and amoxycillin trihydrate, both in water and in 0.1 N HCl media. The studies were undertaken to determine the effect of specific surface area, pH as well as the type of antibiotic on the adsorptive capacity of microcrystalline cellulose. In addition, desorption of the antibiotics from the adsorbate was carried out in distilled water and in 0.1 N HCl solution at various elution stages. The minimum inhibitory concentration (MIC) and minimum biocidal concentration (MBC) were determined against the standard sensitive test microorganism (*Sarcina lutea* ATCC 9341) for each of the selected antibiotics in absence and presence of each of the microcrystalline cellulose grades. Studies revealed that the smaller the particle size of microcrystalline cellulose the more drug was adsorbed, a property which is more apparent in aqueous ampicillin solution while amoxycillin was highly adsorbed in acid solution. Higher rates of antibiotic elution were obtained in acid solutions than in aqueous media. Amoxycillin showed higher elution relative to ampicillin to the extent of complete desorption in gastric pH solution. The MIC of the tested antibiotics increased in presence of microcrystalline cellulose with decreased particle size.

Introduction

Microcrystalline cellulose was introduced in tablet manufacture as diluent, disintegrant and directly compressible vehicle (Lamberson and Raynor, 1976; Enezian, 1972; Lerk et al., 1974; Bolhus and Lerk, 1973). It could also be used as a tablet excepient in formulation prepared by wet granulation (Wallace, 1978a), and as problem solver in tablet coating (Rowe, 1977; Bolhus et al., 1975). In addition microcrystalline cellulose could be used as capsule vehicle to solve problems related to mixing and flowability especially for hydrophobic materials (Ho et al., 1977). More recently, the colloidal grades of microcrystalline cellulose (Avicel RC types) were recommended to be used as dispersants in regular and reconstitutible susensions (Wallace, 1978b). Such extensive applications of microcrystalline cellulose in pharmaceutical dosage forms necessitates an extensive investigation of the adsorptive–desorptive interactions with the drug(s) in combination. The adsorptive–desorptive interactions of microcrystalline cellulose with ampicillin monohydrate and amoxycillin trihydrate, formulated usually as capsule and reconstitutible suspension forms, are worthy to be studied. It was stated that ampicillin

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lin was 74% adsorbed onto Montmorillonite but the pharmacokinetic parameters and gastrointestinal availability of the drug were not altered (Fredi et al., 1983). On the other hand, irreversible uptake of ampicillin and amoxycillin by Attapulgite, magnesium trisilicate, veegum and kaolin was confirmed (Khalil et al., 1984a). Urinary excretion data showed decreased bioavailability of ampicillin and amoxycillin on prior administration of kaolin (Khalil et al., 1984b).

This study was undertaken to define whether microcrystalline cellulose of different specific surface areas may interfere in the antibacterial efficiency of these antibiotics through surface adsorption interactions.

Experimental

Materials

Ampicillin monohydrate (El-Nasr Pharm. Co., Egypt) and amoxycillin trihydrate (Instit. Biochemical Italiano, Milano). Microcrystalline cellulose samples, Avicel PH 105, 103 and 102 of the particle size grades 20, 50 and 90 μm (FMC, Philadelphia, PA), HCl (A.R.).

Test organisms

Sarcina lutea (ATCC 9341) was used for the determination of MIC and MBC of the tested antibiotics.

Methods

Adsorption isotherms

Adsorption isotherms were determined for both drugs using either of the Avicel suspensions where the external medium was distilled water as well as an aqueous medium of pH 2.1. The preparation of a series of drug–microcrystalline cellulose suspensions involved the addition of 90 ml of distilled water or hydrochloric acid solution of pH 2.1 to each of six 250 ml G.S. flasks containing 1 g of the appropriate grade of microcrystalline cellulose. The suspensions were then shaken for 1 min to ensure dispersion. To each suspension was added 1, 2, 3, 4, 5 or 6 ml of a stock solution of the appropriate antibiotic. The contents of each flask was completed to 100 ml with the appropriate solvent used. Blanks were prepared at the same drug concentration in the appropriate solvent, only containing no microcrystalline cellulose. The suspensions and blanks were equilibrated at 25°C in a thermostatically controlled mechanical shaker water bath for 1 h. Equilibrium was attained within this period. After centrifugation, the supernatants and blanks were assayed for their antibiotic contents spectrophotometrically at 261 nm and 272 nm for ampicillin and amoxycillin, respectively, against blanks treated in the same manner. The average of two separate readings performed on each sample was used. The amount of drug adsorbed to the microcrystalline cellulose was calculated as the difference between the total drug concentration in the respective blank and the total concentration in the supernatant.

Desorption of the drug from its adsorbate

One gram of the dried drug–microcrystalline cellulose was transferred to 100 ml conical flask, with 40 ml of eluting system which was either to be distilled water or hydrochloric acid solution of pH 2.1. The system was shaken for 5 min, equilibrated, centrifuged and the supernatant assayed for its drug content as previously described. The elution procedure was repeated 3 times on each drug–microcrystalline cellulose sediment using each time, 40 ml of the eluting medium shaking for 5, 5, 15 min, respectively. Each elution was performed on two separate samples and the values were averaged.

Microbiological investigation of the antibiotic–microcrystalline cellulose interactions

Such a study was achieved through the determination of both the minimum inhibitory conc. (MIC) as well as the minimum biocidal conc. (MBC) of both antibiotics in presence and absence of each of the microcrystalline cellulose grades tested.

Determination of the minimum inhibitory concentration (MIC)

Two-fold serial dilutions were made from the antibiotic solution alone and from a similar antibiotic solution to which the microcrystalline cel-

lulose under test was added in the ratio 1 : 30 in test tubes each containing 5 ml of double-strength nutrient broth (Difco) supplemented with 1% dextrose. The tubes were incubated for 4 h at 25 ± 1°C on a shaker before being inoculated each with one drop of a fresh suspension of the test microorganism (10^8 c.f. U./ml). The inoculated tubes were incubated at 35°C for 24 h. After incubation the tubes were examined for signs of growth and the MIC end-point was determined.

Determination of the minimum biocidal concentration (MBC)

This was carried out following the same procedure mentioned above. Subcultures (one drop each) were made from tubes showing no growth in the MIC on fresh tubes of nutrient broth dextrose.

The inoculated tubes were incubated at 35°C for 24 h. After incubations the tubes were examined for signs of growth and the MBC end-point were determined.

Results and Discussion

Adsorption study

It has been established that certain adsorbents whether present as formulation additives or for their therapeutic potentials result in a decrease in bioavailability of co-administered drugs. Such an interference in the systemic availability of a drug is brought about by its adsorption on the activated surface of the solid adsorbent, thus preventing the adsorbed fraction of the drug from permeating through the gastrointestinal mucosa into the blood stream.

In this study, the adsorptive effect of microcrystalline cellulose of different grades on two structurally related antibiotics, namely ampicillin and amoxycillin was elucidated. Figs. 1–4 illustrate the adsorption isotherms of the two antibiotics in both water and hydrochloric acid solution. It is evident that the amounts of drug adsorbed increased in the following order: Avicel PH 105 > 103 > 102. This is probably a function of the total surface area of the adsorbent. Furthermore, the adsorption efficiency of either of the microcrystalline cellulose grades towards ampicillin is higher than that for amoxycillin. The presence of the polar phenolic group in amoxycillin may explain this behaviour (Khalil et al., 1984a). In the mean time the amounts of drug adsorbed by the microcrystalline cellulose from aqueous solution is apparently higher than that from the solution at pH 2.1, which is highly detectable in ampicillin adsorption results. The two drugs possess the same pK_a values for the carboxyl and α-amino groups (2.6 and 7.2, respectively), hence the percent ionization of the ionic groups and the net charge will be the same within each system studied (Khalil et al., 1984a). Also, it seems that the ionized carboxyl group, formed by the oxidation of the hydroxyl group of the glucose units ($pK_a \simeq 4$) are responsible for the surface adsorption efficiency of cellulose at higher pH of distilled water pH ≃ 5–6 (Franz and Peck, 1982). These two facts explained the assumption that the

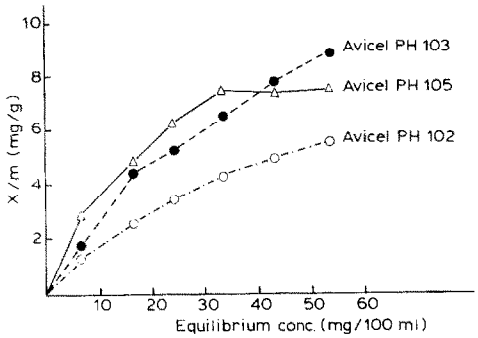

Fig. 1. Adsorption isotherm of amoxycillin trihydrate on Avicel in water at 25°C.

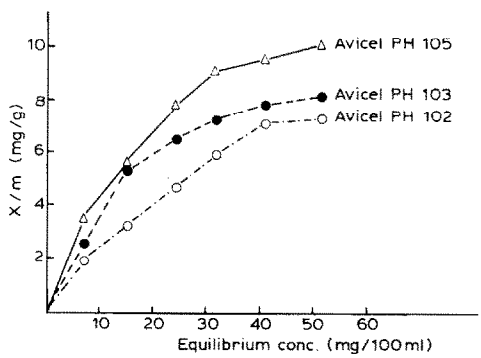

Fig. 2. Adsorption isotherm of amoxycillin trihydrate on Avicel at pH 2.1 and at 25°C.

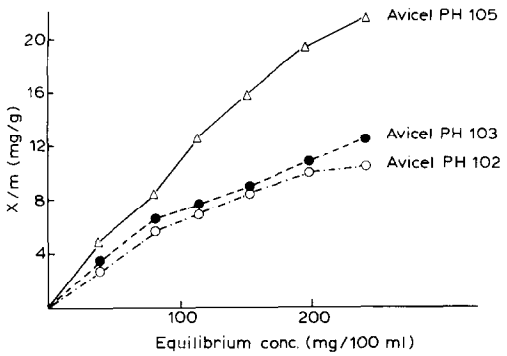

Fig. 3. Adsorption isotherm of ampicillin monohydrate on Avicel in water at 25°C.

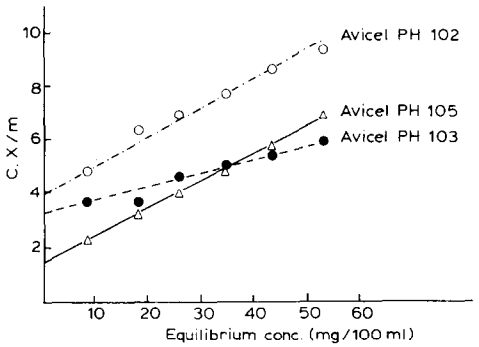

Fig. 5. Langmuir plots for the adsorption of amoxycillin trihydrate on Avicel in water at 25°C.

two drugs tested are merely physically adsorbed on the microcrystalline cellulose surface, despite the cationic nature of the drugs and the surface anionic activity.

The adsorption results of the two drugs in either of the microcrystalline cellulose suspensions adhered to the theoretical Langmuir equation:

$$\frac{C_{eq}}{X/m} = \frac{1}{K_1K_2} + \frac{C_{eq}}{K_2}$$

where C_{eq} is the equilibrium concentration of the antibiotic in the supernatant, X/m is the amount of the drug adsorbed in mg/g of the microcrystalline cellulose and K_1 and K_2 are constants. The constant K_2 is the limiting adsorptive capacity, i.e. the maximum amount of the drug adsorbed by the adsorbent (mg/g). The value K_1K_2 could be used as a measure of the relative affinity of the adsorbate to the adsorbent. Figs. 5–8 represent the Langmuir relations of the two antibiotics to the different grades of the adsorbents in distilled water and in HCl solution of pH 2.1. In the mean time Table 1 shows the constants obtained from the different isotherms calculated according to the least-squares method. The constants calculated contain the previously concluded findings that the adsorptive capacity of Avicel increased with decreased particle size, ampicillin was adsorbed more efficiently than amoxycillin, and the adsorption efficiency of microcrystalline cellulose was higher from aqueous solution in comparison to that from acidic solution of pH 2.1.

Desorption study

The desorption data showed that both antibio-

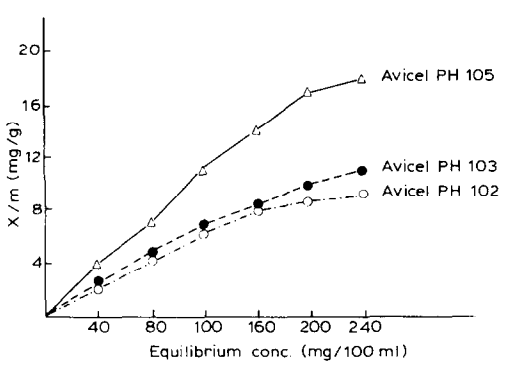

Fig. 4. Adsorption isotherm of ampicillin monohydrate on Avicel at pH 2.1 at 25°C.

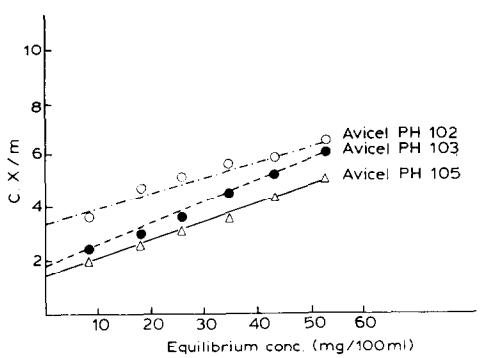

Fig. 6. Langmuir plots for the adsorption of amoxycillin trihydrate on Avicel at pH 2.1 and at 25°C.

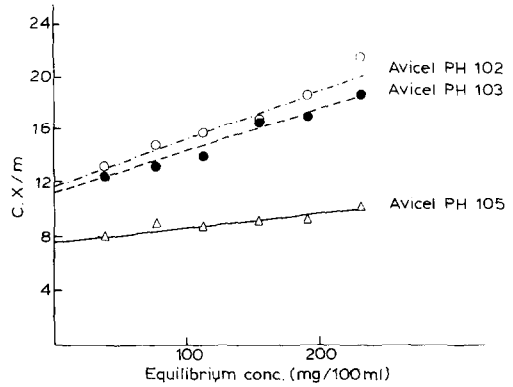

Fig. 7. Langmuir plots for the adsorption of ampicillin monohydrate on Avicel in water at 25°C.

tics are completely eluted in HCl solution of pH 2.1 in 30 min, while in distilled water about 60% of the adsorbed ampicillin and 70% of amoxycillin were desorbed. The desorbed amount of either of the two drugs showed insignificant differences from the desorbates of the different grades of microcrystalline cellulose. The desorption data were found to fit the first-order elution patterns as shown in Figs. 9 and 10. Tables 2 and 3 show the calculated first-order elution rate constants, in addition to the intercepts of the linear first-order elution plots with the y-axis as well as its correlation coefficients. It is clear that the elution rate constant decreased by increasing particle size of the microcrystalline cellulose particle especially in acidic desorption media. The calculated lower values of intercepts in acid media indicates higher drug flush during the first 5 min. These findings indicate that both ampicillin and amoxycillin are

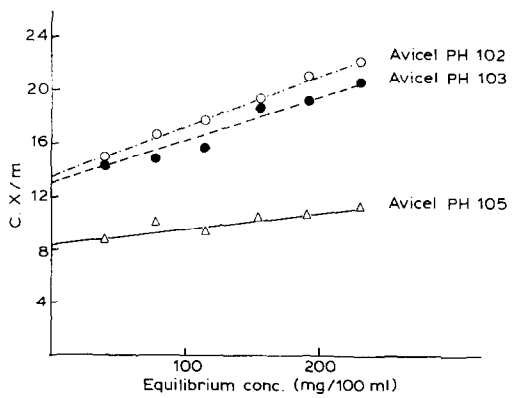

Fig. 8. Langmuir plots for the adsorption of ampicillin monohydrate on Avicel at pH 2.1 and at 25°C.

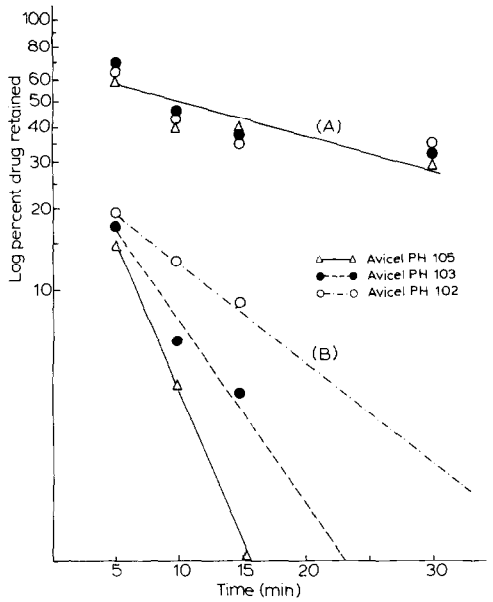

Fig. 9. First-order elution plot of amoxycillin trihydrate in distilled water (A) and in HCl solution of pH 2.1 (B).

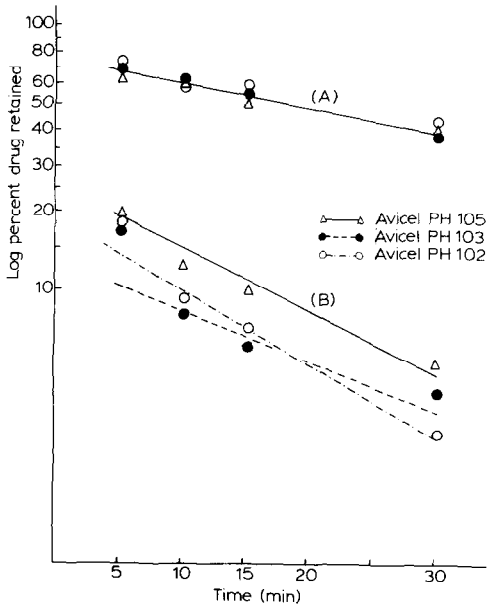

Fig. 10. First-order elution plot of ampicillin monohydrate in distilled water (A) and in HCl solution of pH 2.1 (B).

TABLE 1

SUMMARY OF CONSTANTS OBTAINED FROM FREUNDLICH AND LANGMUIR AND PLOTS FOR AMPICILLIN MONOHYDRATE AND AMOXYCILLIN TRIHYDRATE

	Ampicillin monohydrate						Amoxycillin trihydrate					
Medium:	Water			HCl pH2.1			Water			HCl pH 2.1		
Adsorbent:	Avicel I	Avicel II	Avicel III	Avicel I	Avicel II	Avicel III	Avicel I	Avicel II	Avicel III	Avicel I	Avicel II	Avicel III
Freundlich constant (K)	26×10^3	1.07×10^3	0.24×10^3	218.77	239.8	264.2	23.44	9.54	0.44	0.731	2.601	2.71
Affinity constant (N)	15.37	13.58	12.88	13.95	13.03	12.31	9.75	8.82	1.55	0.568	0.579	0.698
Langmuir constant: adsorptive capacity, K_2 (mg/g)	87.7	36.74	29.43	14.43	13.4	12.58	9.79	18.5	10.03	14.86	11.21	19.22
Affinity constant, K_1K_2	0.127	0.113	0.106	0.27	0.367	0.368	0.711	0.324	0.229	0.663	0.614	0.271

I = Avicel PH 105. II = Avicel PH 103. III = Avicel PH 102.

TABLE 2

CALCULATED FIRST-ORDER ELUTION RATE CONSTANTS AND LINEAR INTERCEPTS OF AMPICILLIN AND AMOXYCILLIN FROM THEIR MICROCRYSTALLINE CELLULOSE IN DISTILLED WATER

Parameter in water	Ampicillin			Amoxycillin		
	I	II	III	I	II	III
K (min^{-1})	0.017	0.015	0.014	0.405	0.278	0.274
Intercept (log%)	1.855	1.812	1.828	1.866	1.818	1.809
C.C.	−0.999	−0.899	−0.918	−0.999	−0.950	−0.939

K = Elution rate constant. I = Avicel PH 105. II = Avicel PH 103. III = Avicel PH 102.

TABLE 3

CALCULATED FIRST-ORDER ELUTION RATE CONSTANT AND LINEAR INTERCEPTS OF AMPICILLIN AND AMOXYCYLLIN FROM THEIR MICROCRYSTALLINE CELLULOSE IN HCl OF pH 2.1

Parameter in water	Ampicillin			Amoxycillin		
	I	II	III	I	II	III
K (min^{-1})	0.069	0.049	0.044	1.672	1.497	0.783
Intercept (log%)	1.288	1.221	1.352	1.539	1.471	1.453
C.C.	−0.914	−0.895	−0.982	−1.00	−0.912	−0.999

K = Elution rate constant. I = Avicel PH 105. II = Avicel PH 103. III = Avicel PH 102.

only physically adsorbed to microcrystalline cellulose and probability of chemisorption is too low despite the opposite charge nature of the drugs and microcrystalline cellulose surface.

Effect of microcrystalline cellulose on the MIC and MBC of ampicillin and amoxycillin

Tables 4 and 5 show the computed values of MIC and MBC of ampicillin and amoxycillin in the absence and presence of different grades of microcrystalline cellulose. It is apparent that the bacteriostatic and the bactericidal activity of either of the two drugs decreased in presence of microcrystalline cellulose. The effect is highly evident in amoxycillin systems where the MIC increased from 2.5 to 5 times that in presence of either of the cellulose grades, while that of ampicillin increased only to twice its concentration in the absence of adsorbents. The MBC values in the presence of Avicel systems ranges between equal and double its concentration in its absence. These results showed the significant reduction in the antimicro-

TABLE 4

THE MINIMUM INHIBITORY CONCENTRATION (MIC) VALUES IN μg/ml OF AMPICILLIN MONOHYDRATE AND AMOXYCILLIN TRIHYDRATE AQUEOUS AND ACIDIC SOLUTION OF pH 2.1 OF DIFFERENT AVICEL GRADES

Type of drug:	Ampicillin		Amoxycillin	
Type of adsorbent:	Water	pH 2.1	Water	pH 2.1
None	0.04	0.005	0.002	0.002
Avicel PH 105	0.08	0.005	0.01	0.005
Avicel PH 103	0.08	0.010	0.005	0.005
Avicel PH 102	0.08	0.010	0.05	0.050

TABLE 5

THE MINIMUM BIOCIDAL CONCENTRATION (MBC) VALUES IN μg/ml OF AMPICILLIN MONOHYDRATE AND AMOXYCILLIN TRIHYDRATE IN AQEUOUS AND ACIDIC SOLUTION OF pH 2.1 OF DIFFERENT AVICEL GRADES

Type of drug:	Ampicillin		Amoxycillin	
Type of adsorbent:	Water	pH 2.1	Water	pH 2.1
None	0.080	0.01	0.01	0.02
Avicel PH 105	0.165	0.02	0.02	0.02
Avicel PH 103	0.165	0.02	0.02	0.02
Avicel PH 102	0.080	0.02	0.01	0.02

bial activity of the two antibiotics in the presence of microcrystalline cellulose suspensions.

In conclusion, the concomitant presence of microcrystalline cellulose as directly compressible vehicle, diluent or disintegrant for tablets, as suspending agents in suspensions, or as filler in capsules may interfere in the bioavailability or local antimicrobial activity of ampicillin or amoxycillin. Despite the complete elution of either of the antibiotics through 30 min in simulating gastric pH, in vivo evaluation of these antibiotics in the presence of microcrystalline cellulose should be assessed to evaluate the extent of interaction.

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