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ADSORPTION OF ISONIAZID ON INSOLUBLE TABLET EXCIPIENTS AND CHARCOAL

M.S. Mesiha & S. Shawky

Departments of Industrial Pharmacy and Pharmaceutics, Faculty of Pharmacy, University of Assiut, Assiut, Egypt.

ABSTRACT

The adsorption of isoniazid onto the insoluble directly compressible tablet excipients: Emcompress, Avicel pH 101, Elcema P 50, P 100, G 250, ethyl cellulose and STA-Rx as well as talc, magnesium stearate and charcoal was studied. The adsorption followed the Langmuir equation over initial concentrations of 80-200 mmole/L of isoniazid solution in water or in buffer solutions of pH 2.1 and 7.2. The adsorption capacities were of the following sequence: charcoal > starch > celluloses and talc > ethyl cellulose > Emcompress. No measurable adsorption was noted on magnesium stearate or glassware. The possible mechanisms of adsorption were discussed.

The kinetics of isoniazid release from compressed tablets using Emcompress, Avicel, ethyl cellulose and starch as the excipients did not correlate with the adsorption data, but the extent of release of drug had a good correlation with the adsorptive capacities of the excipients.

A survey of pharmaceutical literature shows that certain materials used as pharmaceutical adjuncts may adsorb significant amounts of various drugs[1-4]. Although most of the previously studied drugs are administered in the tablet form, the tablet excipients were generally ignored as being potential adsorbents for drugs.

The *in-vitro* adsorption of various pharmaceuticals to montmorillonite was studied by MeGinity and Lach[5]. This clay was studied for use as disintegrant, binder and lubricant[6] and was also proved to adsorb some antibiotics[7].

An increasing number of water-insoluble materials have been suggested as directly compressible vehicles for tablets[8-12]. These include microcrystalline cellulose[8-10], dicalcium phosphate dihydrate[11] and starch[12]. These vehicles were usually mixed with drugs, together with a suitable disintegrant and a lubricant if they were not themselves self-disintegrating or self-lubricating[8-10].

The purpose of this study was to determine the extent of isoniazid adsorption onto various insoluble tablet excipients in distilled water and in two buffer solutions of physiological pH values 2.1 and 7.2. Isoniazid was chosen as a model water soluble drug of long term use. The excipients were of different chemical characters. Celluloses of different origin, ethyl cellulose, starch, dibasic calcium phosphate, magnesium stearate and talc were the studied potential adsorbents. Charcoal was also studied for comparison, as it is a widely used cassical adsorbent and its coadministration with drugs may interfere with their biological availability[17-19].

Adsorption of isoniazid on insoluble tablets excipients and charcoal.

Isoniazid tablets were prepared using four of the studied excipients to elucidate if the adsorption has an effect on the kinetics of drug release from tablets.

EXPERIMENTAL

Materials:

Isoniazid (Bayer, donated by CID laboratories,Cairo), activated charcoal (E.Merck, Darmstadt), dibasic calcium phospnate dihydrate (Emcompress special, E. Mendell Co., Carmel, New York), microcrystalline cellulose(Avicel pH 101, FMC corporation, Philadelphia), microfine (P 50, P 100) and granular (G 250) celluloses (Elcema, Degussa, Frankfurt), ethyl cellulose (Searle Co., HW, Essex), compressible starch (STA-Rx 1500 starch, Staley Co., Ilinoy), sodium starch glycolate (Primojel, E. Mendell Co., Carmel, New York), talc, magnesium stearate and buffer components were pharmaceutical grades or analytically pure chemicals.

Emcompress, Avicel and ethyl cellulose were separately passed through a standard sieve of aperture size 200 µm before use. Other chemicals were used as received.

Methods:

Adsorption experiments:

One gram of the adsorbent was placed in 30-ml stoppered glass tube and 10 ml of isoniazid solution of appropriate concentrations ranged from 80-200 mmole/L in distilled water, or hydrochloric acid buffer (USP XX) of pH

2.1 or in phosphate buffer (USP XX) of pH 7.2. Suspensions were shaken for 24 hours in a constant temperature shaking water bath (GFL, D. Burgwedel) at 60 strokes per minute, at 37°C. The suspensions were centrifuged for 5 min at 3000 rpm, 2 ml portions of the supernatant solutions were removed and assayed for isoniazid concentration.

Preparation and Evaluation of Tablets:

Four batches of isoniazid compressed tablets were prepared, each contained 25% isoniazid, 2.5% sodium starch glycolats as disintegrant , 1% magnesium stearate as lubricant and 71.5% of either Emcompress, Avicel, ethyl cellulose or STA-Rx as the excipient. These powder ingredients were blended and compressed into 8-mm diameter flat tablets using an eccentric tablet press (Korsch Maschinenfabrik, Berlin) adjusted for each excipient to produce 200 mg tablets containing 50 mg isoniazid.

The tablets were evaluated for uniformity of weight, uniformity of drug content, hardness, friability, disintegration time and dissolution rate (Erweka Apparatebau, Heusentamm). The dissolution was determined in 500 ml hydrochloric acid buffer (USP XX) pH 2.1 at 37°C, stirred at 50 rpm. Samples were withdrawn for isoniazid determination every minute over 10 min, then every 5 min over total dissolution time of 60 min.

Assay of isoniazid:

Suitable dilutions of the samples taken from the adsorption or dissolution studies were made with 1% hydrochloric acid. Measurements of the absorbance were made at wavelength of 265 nm, using 1-cm cell (Pye Unicam SP6-400 Spectrophotometer).

RESULTS AND DISCUSSION

Adsorption isotherms

Preliminary determination of equilibrium time for isoniazid adsorption onto different substances studied indicated that equilibrium was achieved between 6 and 12 hours. To ensure equilibrium, all samples were allowed to agitate for 24 hours. The analysis of isoniazid samples in control experiments indicated the absence of measurable adsorption of the drug onto the glassware and degradation during equilibration.

The data obtained from the adsorption experiments were treated according to the linear form of Langmuir equation[20]:

$$C_e/(x/m) = 1/ab + C_e/b$$

where x/m is the millimoles of isoniazid adsorbed per gram of adsorbent, C_e is the equilibrium molar concentration of the drug, a and b are constants. Constant a is the adsorption coefficient, while constant b is the limiting adsorptive capacity of the adsorbent. Linear adsorption isotherms with a slope of 1/b and an intercept of 1/ab were obtained (Figures 1-5) by plotting $C_e/(x/m)$ versus C_e. The b values or limiting adsorptive capacities were calculated from the reciprocal of the slope of the regression line equation (Table 1).

It was necessary, in most cases, to use one-gram samples of the adsorbents to find adherence to the Langmuir

equation over a wide isoniazid concentration range. When less than 1 g of adsorbent was used, deviations from linearity occurred at low concentrations of isoniazid. Higher concentration of the drug may creat new sites for adsorption by forcing the adsorbate molecules through porous structure of adsorbent[21].

Activated charcoal was demonstrated to be the most effective adsorbent for isoniazid (Figure 1). This is also clear from the high values of the adsorptive capacity of charcoal compared with other materials (Table 1). The binding capacity was maximum at pH 7.2, followed by pH 2.1 and water (pH 5.6). These data indicate that the less ionized species of isoniazid, of pK_1 =2.13, pK_2 = 3.81, pK_3 = 11.03[22] is more preferably adsorbed than its ionized or protonated species in solution. The lipophilic pyridine moiety of isoniazid probably promotes drug adsorption through hydrophobic interaction with the activated surface of charcoal. Such a possibility is similar to previous findings on the nature of carbon surface[13,23].

Adsorbents other than charcoal showed less adsorption at all conditions than charcoal, probably due to smaller surface area and consequently smaller interfaces available for accumulation of solute molecules than in case of charcoal.

The dibasic calcium phosphate (Emcompress showed(Fig. 2) minimum adsorptive capacity of the drug from water and from acid buffer media. This may be due to lack of porosity, or the valence requirements may be fully satisfied by binding with other surface atoms[24].

Talc was supposed to carry a negative charge on its

surface due to deficiency of certain cations in its crystals[25]. This may explain the higher adsorption of isoniazid onto talc than on cellulose or ethyl cellulose (Table 1) specially in acid medium (Figure 3). The decreased adsorption of isoniazid from buffer solutions compared to water may be attributed to the preferential adsorption of buffer ions onto the surface of the adsorbent.

Significant amounts of isoniazid were adsorbed from water onto STA-Rx, cellulose (Avicel and Elcema), ethyl cellulose (Table 1, Figures 4,5). The polyhydroxy groups of these polysaccharides may be responsible for hydrogen bonding with isoniazid. This may explain the decreased adsorption onto the ethylated cellulose. The relative position of free OH groups in α and β glucose molecules in cellulose and starch respectively may contribute to the ease of adsorption onto starch relative to cellulose , as shown from the adsorptive capacities in Table 1.

An alternative explanation of the mechansim of isoniazid adsorption onto these polyhydroxylate molecules is the ability of these compounds to absorb water [10,12]. The free solubility of isoniazid in water may suggest the adsorption to take place through the complement effect of water molecules.

In spite of the difference in the apparent particle size of Elcema celluloses, their adsorptive capacities (Table 1) are not significantly different. It seems that microcrystalline celluloses are more or less equally porous, or become porous after water uptake[10].

Properties of isoniazid tablets:

The properties of the compressed tablets prepared using four different excipients were summarized in Table 2. The tablets were uniform in weight and in drug content, as can be seen from the very low standard deviation values. These results reflect good mixing of the powders and no segregation during manipulation or compression. The good flow properties of the matrix also help to lower the standard deviation[26].

Avicel-based tablets were the best batch concerning the mechanical properties, least disintegration time and fastest dissolution. No correlation was observed between such parameters and the adsorption data. The adsorption data were correlated with the amount of drug retained after dissolution over 30 min. These amounts increased parallel with the adsorptive capacities of the excipients.

The primojel was added in equal weights to all tablet formulations to aid fast disintigration of tablets to simulate normal formulation conditions. Magnesium stearate was added after quantitative study of its ability to adsorb isoniazid. The change in drug concentration was extremely small after 24 h equilibration. Its use in the formula was necessary to ensure smooth ejection of the tablets from the die.

Table 1: Limiting adsorptive capacities of tablet excipients for isoniazid (mmole.g^{-1}) in different media

Adsorbent	*distilled water pH 5.5*	*HCl buffer pH 2.1*	*Phosphate buffer pH 7.3*
Charcoal	351.91	366.80	409.12
Talc	24.69	10.94	8.97
Emcompress	3.02	1.10	8.58
Avicel pH 101	28.72	5.21	7.49
Elcema P 50	23.55	-	-
Elcema P 100	30.03	-	-
Elcema G 250	26.06	-	-
Ethyl cellulose	17.50	6.28	18.37
STA-Rx	88.38	-	-

Table 2: Effect of excipients on the properties of isoniazid tablets

	Weight (mg)		*Drug content*[2]		*Erweka Hardness*[2] (Kg)		*Friability* (% loss)	*Disintgration time*[2]		$t^{4}_{50\%}$ (min)	*Retained drug*[5] %
	x	*s.d.*	*x*	*s.d.*	*x*	*s.d.*		*x*	*s.d.*		
Emcompress	202.6	5.1	49.2	1.7	1.8	0.45	3.80	7.2	0.67	8.10	0.1
Avicel	200.8	2.1	49.3	1.5	5.5	0.32	0.05	6.8	0.81	0.45	3.8
Ethyl cellulose	206.2	2.6	49.5	1.6	1.9	0.12	0.86	8.9	1.31	8.11	1.2
STA-Rx	200.0	3.9	50.1	1.6	1.0	0.08	1.70	3.2	0.44	4.35	6.4

1- Mean of 20 tablets individually weighed
2- Mean of 10 tablets determined individually
3- Mean of 3 determinations using 20 tablets in Erweka Friabilator
4- Time of 50% release, mean of 3 determinations
5- Calculated from the cumulative drug release after 30 min relative to the mean drug content.

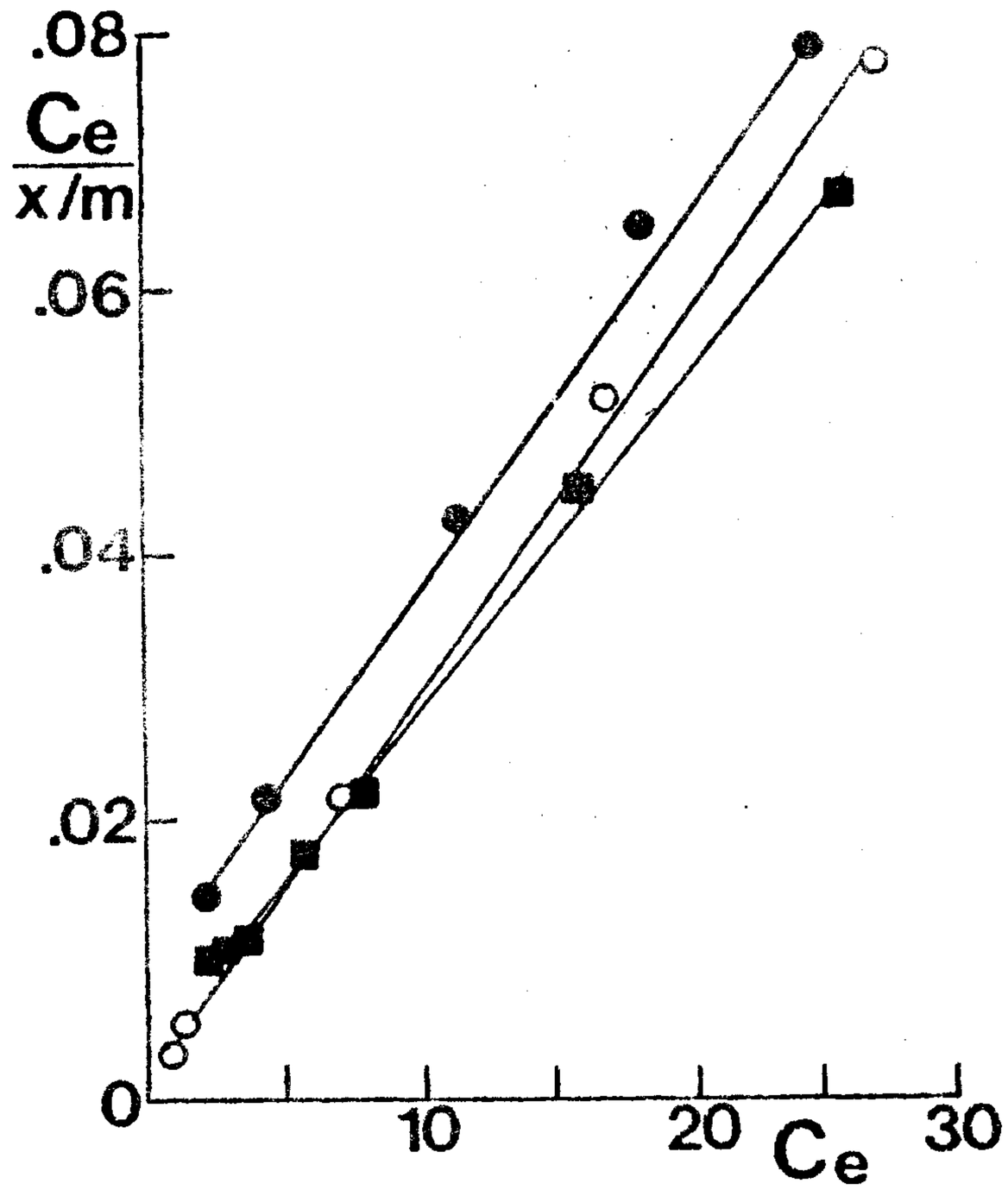

Fig. 1: Langmuir isotherm for adsorption of isoniazid by activated charcoal.

Key: C_e Concentration of isoniazid at equilibrium (mmol. l^{-1}).

x/m: Millimoles of isoniazid adsorbed per gram of solids.

o—o Distilled water

●—● Hydrochloric acid buffer

■—■ Phosphate buffer.

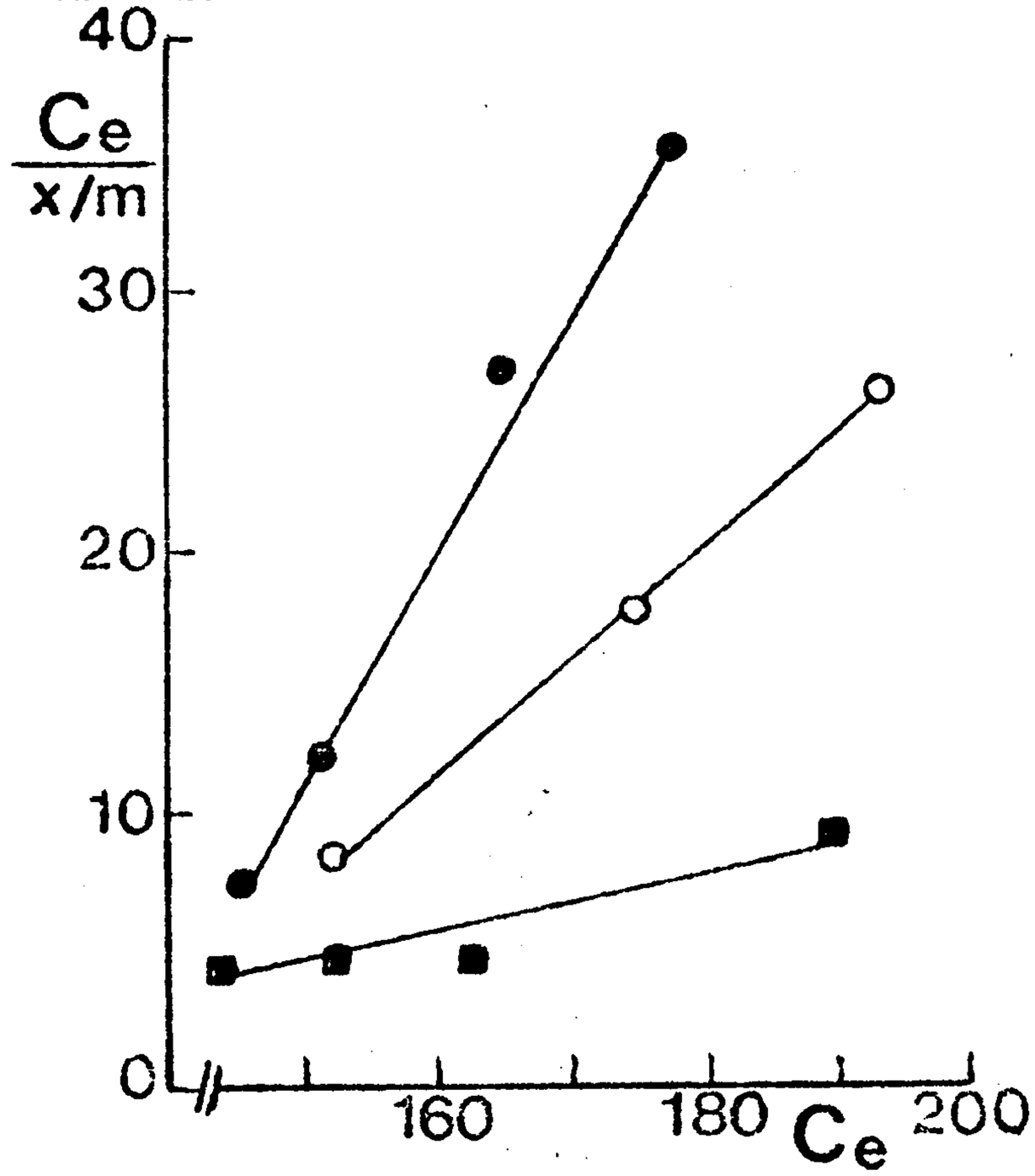

Fig. 2: Langmuir isotherm for adsorption of isoniazid by Emcompress.

Key: C_e Concentration of isoniazid at equilibrium ($mmol.l^{-1}$)

x/m: Millimoles of isoniazid adsorbed per gram of solids

o—o Distilled water

●—● Hydrochloric acid buffer

■—■ Phosphate buffer

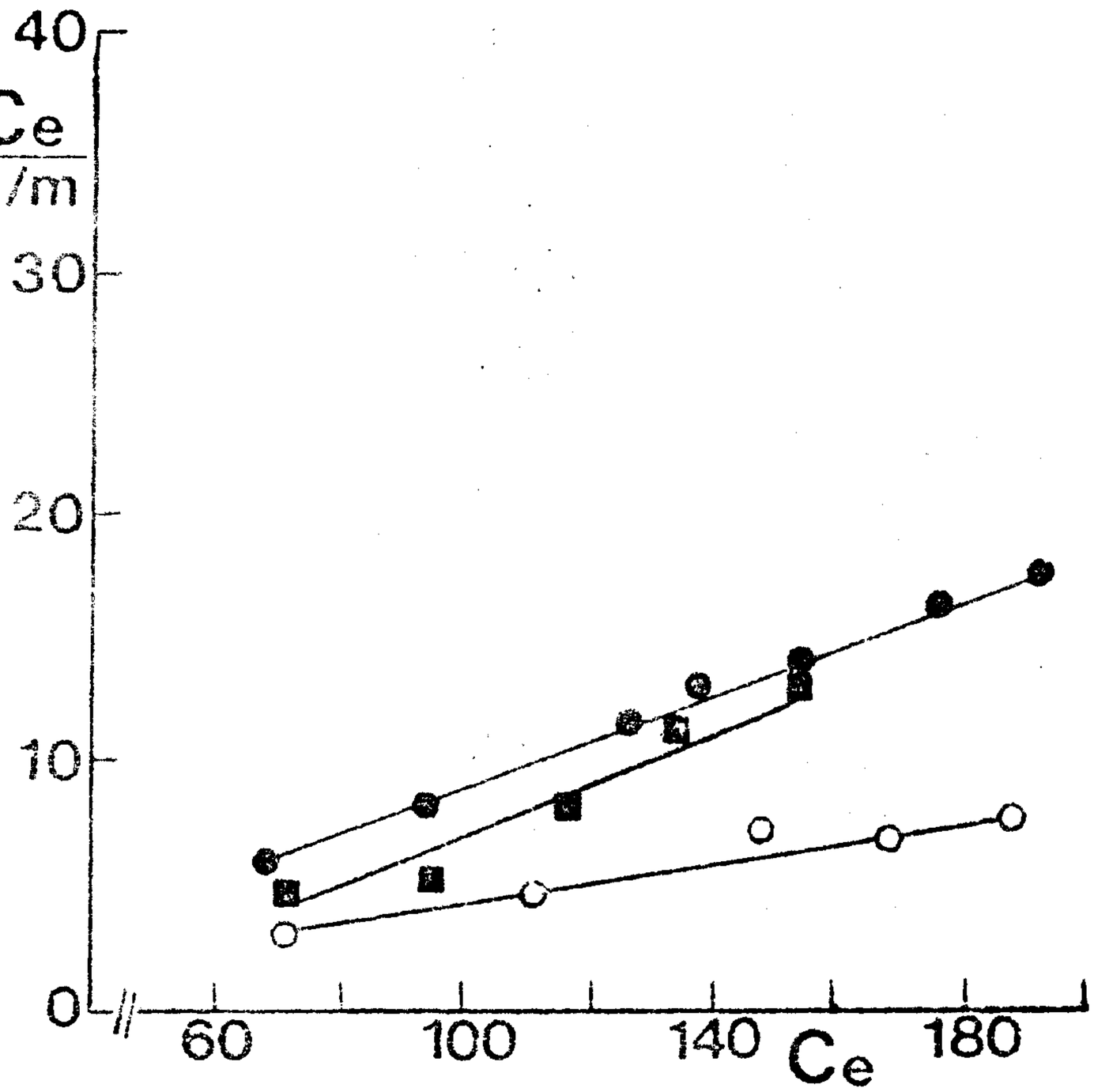

Fig. 3: Langmuir isotherm for adsorption of isoniazid of by talc powder

Key: C_e Concentration of isoniazid at equilibrium ($mmol.l^{-1}$)

x/m: millimoles of isoniazid adsorbed per gram of solids

o——o Distilled water

●——● Hydrochloric acid buffer

■——■ Phosphate buffer

Adsorption of isoniazid on insoluble tablets excipients and charcoat

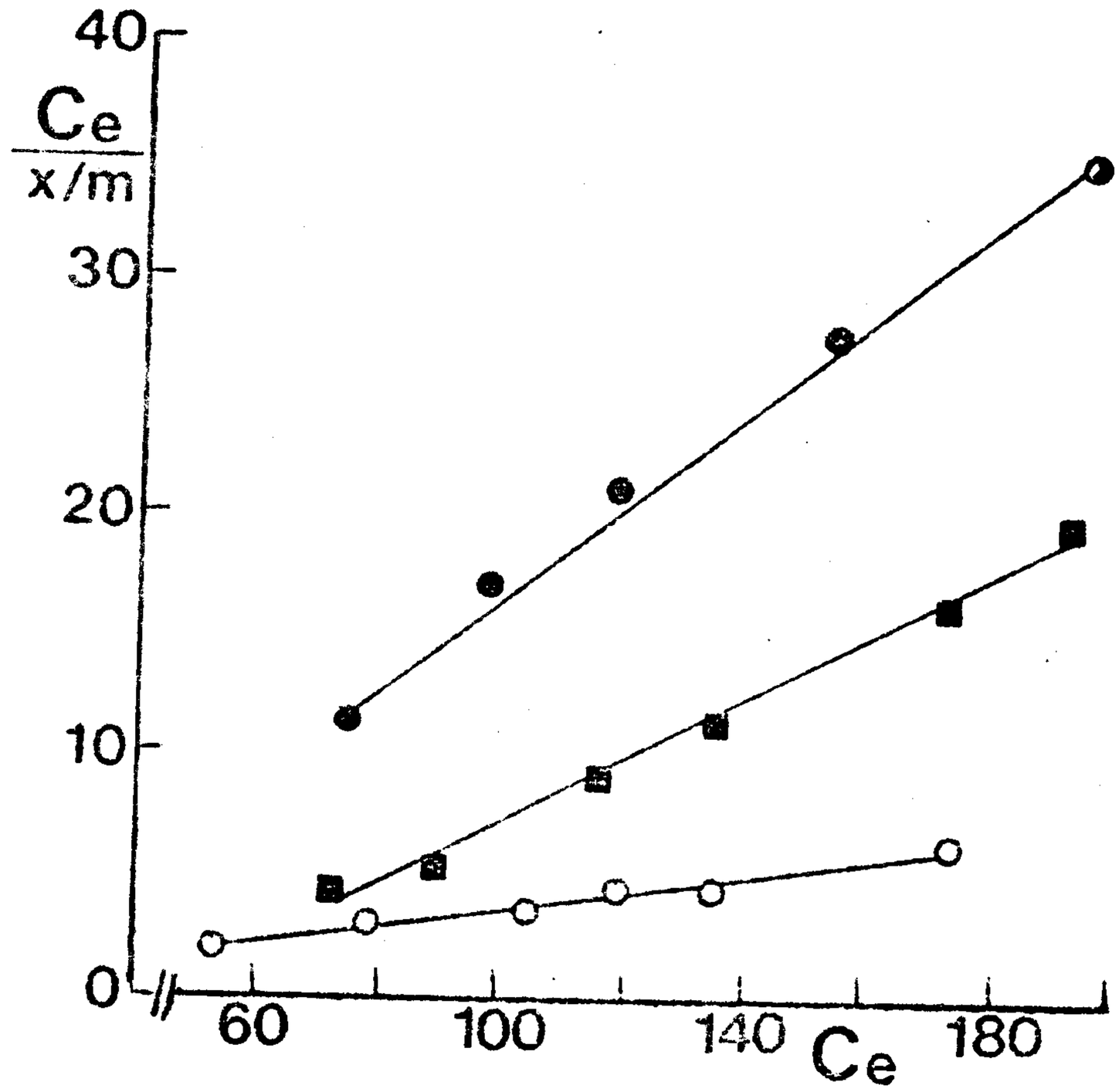

Fig. 4: Langmuir isotherm for adsorption of isoniazid by Avicel.

Key: C_e Concentration of isoniazid at equilibrium ($mmol.l^{-1}$)

x/m: Millimoles of isoniazid adsorbed per gram of solids

o—o Distilled water

●—● Hydrochloric acid buffer

■—■ Phosphate buffer

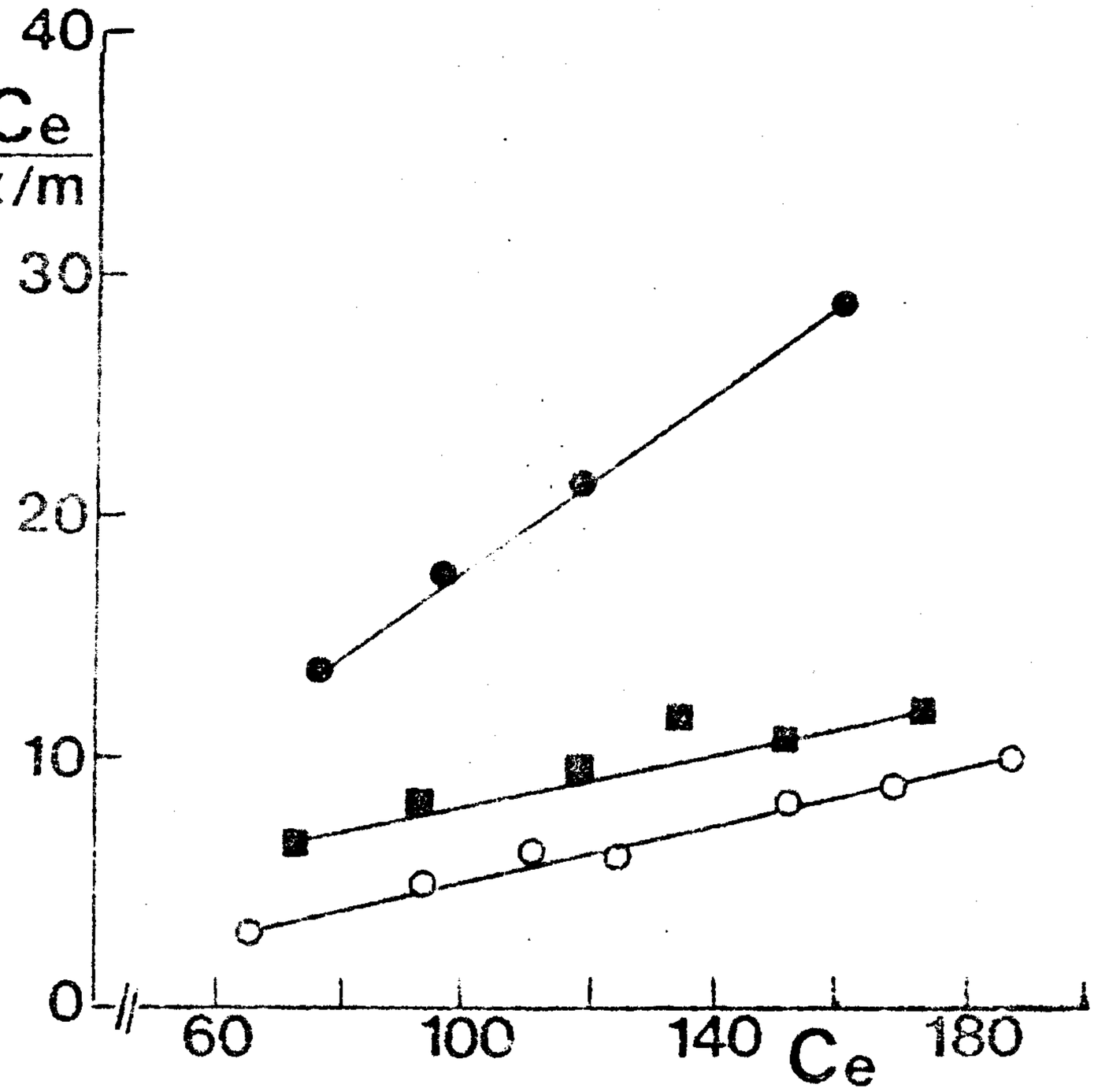

Fig. 5: Langmuir isotherm for adsorption of isoniazid by ethyl cellulose

Key: C_e Concentration of isoniazid at equilibrium ($mmol.l^{-1}$)

x/m: Millimoles of isoniazid adsorbed perggram of solids

o——o Distilled water

●——● Hydrochloric acid buffer

■——■ Phosphate buffer

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ادمصاص الايزونيازيد على مصوغات الاقراص التى لا تذوب وعلى الفحم

منير صبحى مسيحة - سوزان شوقى طوس
قسم الصيدلة الصناعية والصيدلانيات بكلية الصيدلة جامعة اسيوط

درس ادمصاص الايزونيازيد على مصواغات الكبس المباشر للاقراص التى لا تذوب مثل الامكومبرس وفوسفات الكالسيوم ثنائية القاعدية المائية) والافيسيل (سليلوز دقيق البللورات) والالسيما (مسحوق السليلوز وحبيباتة) وايثيل السليلوز ونشا ستاركس وكذلك التلك وشمعات الماغنسيوم والفحم المنشط .

وقد وجد ان الادمصاص يتبع معادلة لانجمير فى التركيزات التى بدىء بها والتى تتراوح بين ٨٠- ٢٠٠ ملليجرام جزيئى فى اللتر للايزونيازيد المذاب فى الماء المقطر او فى احد المحاليل المنظمة عند اس ايدروجينى ١و٢ و ٢و٧٠ وكانت اعلى مقدرة للادمصاص للفحم تلاها النشا ثم انواع السليلوز والتلك ثم ايثيل السليلوز واخيرا اقلها الامكومبرس وفسرت النتائج لكل حالة ولم يظهر اى ادمصاص على شمعات الماغنسيوم او على الزجاج المستعمل .

ولوحظ زيادة الادمصاص فى الماء عنه فى المحاليل المنظمة وعزى ذلك لتنافس ايوناتها للادمصاص على سطح الصواغات المدروسة مما يقلل ادمصاص الايزونيازيد .

ولوحظ ان الادمصاص اقل بصفة عامة فى الوسط الحمضى حيث يكون جزيئى .

ولم يظهر تاثير لمقدرة الادمصاص على خواص الاقراص المكبوسة الميكانيكية او معدل ذوبان المادة الفعالة ولكن ظهر تاثيره على كمية الايزونيازيد المنطلقة فقد زادت الكمية المحجوزه بزيادة قابلية المادة للادمصاص .

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