International Journal of Pharmaceutics, 19 (1984) 307–321
Elsevier

IJP 00669

In vitro anticoagulant–antacid interactions

Said A. Khalil, Viviane F. Naggar, Iman A. Zaghloul and Assem A. Ismail

Department of Pharmaceutics, Faculty of Pharmacy, University of Alexandria, Alexandria (Egypt)

(Received March 18th, 1983)
(Modified version received December 16th, 1983)
(Accepted January 4th, 1984)

Summary

The adsorption characteristics of oral anticoagulants on some selected antacids were studied. The indanedione anticoagulants tested were: phenindione and diphenadione; while the coumarin anticoagulants tested were: dicoumarol, ethyl biscoumacetate, nicoumalone, phenprocoumon and warfarin.

The antacids or adsorbents used were: aluminium glycinate, aluminium hydroxide, bismuth carbonate, bismuth salicylate, bismuth subgallate, bismuth subnitrate, calcium carbonate, charcoal, dihydroxyaluminium sodium carbonate, magaldrate, magnesium carbonate, magnesium oxide, magnesium trisilicate and kaolin.

Adsorption of phenindione was significant on charcoal and magnesium oxide. Aluminium hydroxide, bismuth carbonate, subnitrate and salicylate adsorbed phenindione to a lesser extent. Other substances showed relative weak adsorption properties. Diphenadione, on the other hand, was adsorbed on most substances tested.

The extent of dicoumarol adsorbed was quite high on bismuth carbonate, salicylate and subnitrate as well as on magnesium oxide. It was intermediate on aluminium glycinate and magaldrate. The amount of the anticoagulant adsorbed on aluminium hydroxide, bismuth subgallate and magnesium trisilicate, under the experimental conditions, was quite low. Glycine was found to reduce the amount of dicoumarol adsorbed on bismuth carbonate and to a lower extent on magnesium oxide, while it had a negligible effect on the amount adsorbed on bismuth subnitrate. The other coumarin derivatives showed no or very low adsorption tendencies for the substances tested, with the exception of charcoal, bismuth subnitrate and salicylate.

Adsorption isotherms were plotted for phenindione and dicoumarol.

The dissolution of phenindione decreased in the presence of the adsorbing

Correspondence: S.A. Khalil, Dept. of Pharmaceutics, Faculty of Pharmacy, University of Alexandria, Alexandria, Egypt.

substance especially in acidic medium. The dissolution of dicoumarol in the presence of magnesium oxide was also decreased.

Introduction

Oral anticoagulants are derivatives of either indane-1,3-dione or 4-hydroxycoumarin. The indandione derivatives, phenindione and diphenadione, are commonly used oral anticoagulants. Due to their enolizable keto group (Shapiro et al., 1960), they possess specific interaction tendencies. Phenindione was shown (Mortada and Khalil, 1977) to undergo complex formation with polyvinylpyrrolidone. The interaction was found to be pH-dependent and apparently involved the unionized form of the drug. Moreover, being carbon acids [1] (Stella and Gish, 1979a, and b) phenindione and diphenadione undergo non-instantaneous [2] ionization kinetics which may lead to non-classical behaviour in phase transport studies (Stella, 1975). Interaction of coumarin anticoagulants with various substances was the subject of many reports. For example, solid–solid surface interactions between dicoumarol and some excipients were shown to occur in vitro (Lach and Bighley, 1970). Dicoumarol was also reported (Cho et al., 1971b) to form a soluble complex with polyvinylpyrrolidone.

In vivo studies performed by measuring plasma levels of dicoumarol in dogs and in vitro dissolution rate tests indicated that significant differences in the bioavailability of dicoumarol from commercial products do exist (Akers et al., 1973b). Reports dealing with the effect of selected antacids and excipients on the in vivo absorption of warfarin and dicoumarol also appeared in the literature (Robinson et al., 1971; Ambre and Fisher, 1973). Concomitant administration of dicoumarol with some of these antacids inhibited or potentiated the anticoagulant effect depending on their type and amount (Akers et al., 1973a; Ambre and Fisher, 1973).

The prevention and therapy of thromboembolic vascular diseases may be extended over long periods of time. Lack of data concerning interaction of oral anticoagulants in solution with concomitantly administered antacids and antidiarrhoeals, initiated the present in vitro study. In vitro experiments are usually simple, easy to interpret and should with careful consideration of the results help to predict interactions that might take place in the GIT. The detection and evaluation of such potential interactions, through the performance of adsorption–elution experiments is the aim of the present study. Effects of antacids or adsorbents on the dissolution of some drugs was also tested.

[1] Carbon acids are acids in which the dissociating proton is bound to a carbon atom instead of a heteroatom such as oxygen or nitrogen.

[2] The conversion of the acid to its basic component and vice versa take place slower than the residence times in the diffusion layer.

Experimental

Materials

The anticoagulants tested were phenindione [3] powder or tablets [4], diphenadione [5], dicoumarol [6], warfarin [7], nicoumalone [8], phenprocoumon [9], and ethyl biscoumacetate [8]. The antacids and antidiarrhoeals employed were: aluminium hydroxide (B.P.), aluminium glycinate (B.P.), bismuth carbonate (B.P.C.), bismuth salicylate (B.P. 1953), bismuth subgallate and subnitrate, both of the B.P.C. grade, calcium carbonate (B.P.), dihydroxyaluminium sodium carbonate (U.S.N.F.), kaolin (B.P.C.), magaldrate [10] (U.S.P.), light magnesium carbonate (B.P.), light magnesium oxide (B.P.) and magnesium trisilicate (B.P.) Charcoal (B.P.C.), a model adsorbent, was used for comparative reasons.

Glycine, polysorbate 80, ethanol, sodium bicarbonate, sodium hydroxide, hydrochloric acid and glacial acetic acid of pharmaceutical grade, were also used.

Methods

(a) Adsorption–elution study

Solutions of the drugs ranging in concentration from 0.7 to 50 mg/100 ml were freshly prepared, either in 0.014 N sodium bicarbonate or in 0.01 N hydrochloric acid. In each case, the medium contained 3% v/v ethanol to increase drug solubility. 20 ml of each drug solution was added to 100 ml stoppered conical flasks containing 1 g of antacid or adsorbent except in case of magaldrate [11]. A blank for the adsorbing materials was also prepared in the same way but without drug. A flask containing drug solution of known concentration without the adsorbent was also prepared and treated in the same manner. This solution was used as a control to check for any change in drug stability. The effect of 5% w/v glycine on the adsorption of dicoumarol by some antacids was also tested. A control flask containing dicoumarol solution with 5% w/v glycine was also prepared. The flasks were dipped in a thermostatically controlled water bath at 37 °C and shaken (45 cycles per minute). A period of 18 h was found sufficient to attain equilibration. At the end of this time, the content of each flask was filtered firstly through a Whatman no. 1 filter paper then through a Millipore filter (0.45 μm). The concentration of diphenadione in the filtrate was determined spectrophotometrically [12] in an ethanol–0.1 N sodium hydroxide mixture (19 : 1) at 284 nm, while phenindione, warfarin,

[3] Courtesy of the Nile Co. for Pharmaceuticals and Chemical Industries, Cairo, A.R.E.
[4] Dindevan 50 mg; The Nile Co. for Pharmaceuticals and Chemical Industries, Cairo, A.R.E. Produced under licence of Evans Medical, U.K.
[5] Courtesy of the Upjohn Co. U.K., Kalamazoo, MI, U.S.A.
[6] Nutritional Biochemicals Corporation, U.S.A.
[7] Sigma Chemicals, U.S.A.
[8] Ciba-Geigy, Basle, Switzerland.
[9] Hoffman La Roche, Basle, Switzerland.
[10] Riopan suspension, Ayerst Laboratories; Montreal, Canada.
[11] 5 ml of Riopan suspension (containing 400 mg magaldrate) was used.
[12] Unicam SP 1800 Spectrophotometer.

nicoumalone, phenprocoumon and ethyl biscoumacetate, in 0.014 N sodium bicarbonate were measured at 278, 308, 304, 310 and 310 nm, respectively. Dicoumarol was read in 0.1 N sodium at 312 nm. Some bismuth salts interfered with the assay of the drugs at their λ_{max}. The position of the λ_{max} of phenindione equilibrated with bismuth subnitrate was found to shift to 269 nm. Spectrophotometric reading was then done at this wavelength for this system. Bismuth salicylate also interfered with the assay of the drugs. The wavelength of minimum absorption (260 nm) for bismuth salicylate was therefore used to measure phenindione concentration and the wavelength of 328 nm was used in case of the coumarin derivatives. No interference from the other adsorbents or from glycine on the assay of the various drugs was observed. When glycine was used in conjunction with magnesium oxide and dicoumarol, 0.014 N sodium bicarbonate instead of 0.1 N sodium hydroxide was used as the diluting medium to prevent the slight precipitation of magnesium hydroxide which occurs on using sodium hydroxide. The filtrate from the antacid suspensions without drug was similarly analyzed and appropriate blank corrections were done. Under the experimental conditions used, no change in the colour of the control solutions nor in their absorbing properties was observed. The pH of drug solutions and of some selected filtrates was measured.

The possibility of desorption of the drugs from the antacids or adsorbents was also investigated using 0.014 N sodium bicarbonate as eluent. The residue of the filtration process was dried at room temperature and shaken for 3 h in 100 ml eluent at 37°C. The quantity of the drug desorbed in the filtrate was then determined as previously mentioned.

(b) Dissolution study

The dissolution rate of phenindione tablets (50 mg) was determined using the U.S.P. XIX dissolution apparatus. The dissolution medium consisted of 500 ml (at 37°C) of either 0.01 N hydrochloric acid or 0.014 N sodium bicarbonate with or without 5 g antacid or adsorbent. The basket was rotated at 100 rpm. In the case of dicoumarol, the U.S.P. paddle stirrer apparatus was used (U.S.P. XX, NF XV), as the drug was in powdered form. 50 mg of powdered dicoumarol were sprinkled over 500 ml of the dissolution medium in absence and presence of 5 g magnesium oxide. Sodium bicarbonate (0.014 N) containing 0.02% w/v polysorbate 80 kept at 37°C was the dissolution medium. The inclusion of a surfactant in the dissolution medium served to reduce surface tension to simulate in vivo conditions and to decrease the tendency of drug particles to float or accumulate at the surface. The paddle rotated at 50 rpm. A 5 ml sample was removed at various time intervals and carefully replaced by 5 ml fresh medium. Samples were properly filtered, diluted and their drug content assayed as previously mentioned. A blank antacid suspension was also prepared and its pH measured.

Results and Discussion

Tables 1 and 2 show the amount (percent) of the anticoagulants adsorbed per gram adsorbent. Bismuth salicylate, bismuth subnitrate and charcoal adsorbed all

TABLE 1

PERCENT DRUG ADSORBED PER GRAM ADSORBENT AND PERCENT ELUTION [a]

Drug (mg/100 ml)	Adsorbent											
	Al glycinate	Al hydroxide	Bi carbonate	Bi subnitrate	Bi salicylate	Ca carbonate	Dihydroxy-Al Na carbonate	Magaldrate	Mg carbonate	Mg oxide	Mg trisilicate	Charcoal
pH [b]	7.9	7.8	8	3	5.1	9.5	9.3	8.3	10	9.9	8.4	8.3
pH [c]		6.5	2.6			7.7			8	8.1	7.6	4
Phenindione [b] 50	34.0	43.6 (7)	62.0 (5)	68.2 (3)	54.0 (14)	2.4	16.0	26.0	2.0	87.8 (4)	14.4 (5)	99.9
Phenindione [b] 30	15.0	23.0	21	48.0 (1)	55.0 (12)	–	15.0	18.2	–	84	–	99.2 (0)
Phenindione [b] 7	0.0	2.1	0.0	69.5	74.6	–	0.0	0.0	–	75.8	–	99.3
Phenindione [b] 3.5	0.0	1.0	0.0	–	–	–	0.0	0.0	–	79.5	–	98.7
Phenindione [c] 2	43.6	23.5	95.0	65.6	–	–	–	–	–	43.6	–	100
Diphenadione [b] 7	41.7	32.0	38.0	100 (3)	–	25.0	–	–	94.4 (6)	44.4 (21)	70.8	100 (0)

Kaolin and bismuth subgallate (pH of suspensions 8.1 and 7.9, respectively) did not adsorb phenindione in any of the concentration ranges tested.

[a] Figures between brackets represent elution.

[b] 0.014 N sodium bicarboate/3% v/v ethanol (pH = 7.3).[c] 0.01 N hydrochloric acid/3% v/v ethanol (pH = 2.5).

TABLE 2

PERCENT DRUG ADSORBED PER GRAM ADSORBENT AND PERCENT ELUTION [a]

Drug (mg/100 ml)	Molecular weight	Adsorbent									
		Al glycinate	Al hydroxide	Bi carbonate	Bi salicylate	Bi subgallate	Bi subnitrate	Charcoal	Magaldrate	Mg oxide	Mg trisilicate
	pH	7.9	7.8	8.0	5.1	7.9	3.0	8.3	8.3	9.9	8.4
Dicoumarol ~10	336.3	35.0	11.5	70.0	100.0 (30)	11.0	99.0 (0.6)	99.0	24.5	77.0	–
Dicoumarol ~30	336.3	–	4.1	68.1	–	–	–	–	–	80.0 (12)	7.9 (1)
Ethylbiscoumacetate ~30	408.4	0.0	–	–	80.0	5.5	14.7	80.9	0.0	–	–
Ethylbiscoumacetate ~40	408.4	–	1.2	2.5	–	–		–	–	9.1	0.0
Nicoumalone ~40	353.3	0.0	0.0	0.0	100.0 (22)	–	98.6 (2)	100.0	0.0	3.6	14.5
Phenprocoumon ~40	280.3	–	0.0	0.0	100.0	–	97.4 (3)	98.2 (0)	0.0	0.0	0.0
Warfarin ~40	307.3	–	0.0	0.0	100.0	–	96.4 (7)	99.3 (0)	0.0	0.0	0.0

[a] Figures between brackets represent elution.

Calcium carbonate, dihydroxyaluminium sodium carbonate and magnesium carbonate showed bo adsorption to any of the drugs tested.

the drugs tested. With the exception of diphenadione, calcium and magnesium carbonate as well as dihydroxyaluminium sodium carbonate did not adsorb the drugs. The adsorbing power of the other substances was variable according to the type of drug tested. For example, phenindione and dicoumarol were highly adsorbed onto magnesium oxide and bismuth carbonate, while the adsorption of ethyl biscoumacetate, warfarin, nicoumalone and phenprocoumon on the same substances was low or even zero.

The degree of interaction with the adsorbents can be modified by changes in the size, shape and polarity of the interacting drug molecule (Blaug and Gross, 1965; Khalil and Iwuagwu, 1978). Charcoal adsorbed all anticoagulants tested. Drugs are known to penetrate or diffuse into fissures, pores or channels present in the charcoal particles, (Sorby, 1965). Ethyl biscoumacetate showed a relatively low adsorption value on charcoal, compared to either dicoumarol or to the single ring derivatives, probably due to its high molecular weight (Sorby, 1965). The adsorption of the anticoagulants on bismuth salicylate and subnitrate (pH of suspensions ~ 5.1 and 3.0, respectively) was quite high. The pH solubility effect may be partly responsible for the observed decrease in the concentration of the drug in solution. The low results of elution from bismuth subnitrate in sodium bicarbonate solution suggest a strong binding between the drugs and bismuth subnitrate.

The adsorption isotherms of phenindione as an example of an indandione derivative and of dicoumarol as an example of a coumarin derivative, on the various adsorbents, obtained by plotting x/m [13] (mg drug adsorbed per gram adsorbent) versus Ce (concentration of drug in mg/100 ml at equilibrium) are shown in Figs. 1 and 2. The adsorption of phenindione and dicoumarol on most adsorbents used obeyed the Freundlich adsorption isotherm (Fig. 3):

$$x/m = KC_e^n$$

The Freundlich constant K represents the amount of drug adsorbed per unit weight of adsorbent at a unit drug concentration. The constant n represents the amount of drug adsorbed for a given concentration change, i.e. the relative strength of the bond between the drug and the binding site (Gangian et al., 1980). The slopes and intercepts (Table 3) of the various adsorption isotherms were calculated using the least-squares method.

Adsorption of phenindione on magnesium oxide from alkaline solution was fairly high ($K = 0.746$) (Table 3). Magnesium oxide was previously shown (Haines and Martin, 1961a) to give in sodium bicarbonate solution a cement-like crystalline substance ($Mg_2(OH)_2CO_3$) as a result of chemical bonding due to hydration effects. This crystalline structure may provide new adsorption sites on the surface (Giles et al., 1960). The adsorption isotherm of phenindione on magnesium oxide (Fig. 1) was of the S-type. This implies a side-by-side association between adsorbed molecules helping to hold them to the surface in a vertical position (Giles et al., 1960).

[13] x/m values represent in some cases apparent values because the pH of the adsorbent suspension may decrease the amount of drug in solution or the adsorbent may react with the medium.

Fig. 1.

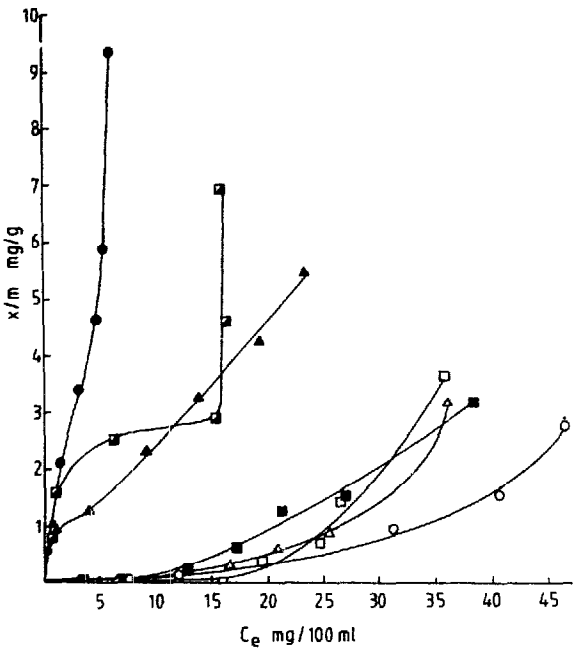

Fig. 2.

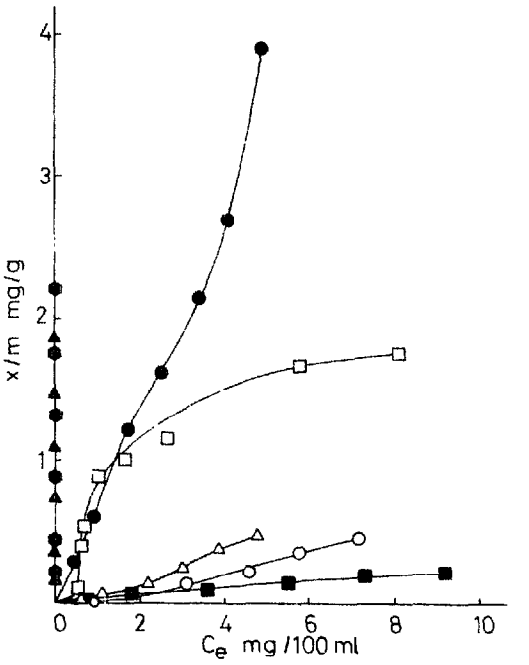

Fig. 1. Adsorption isotherms of phenindione on magnesium oxide (●———●); bismuth carbonate (□———□); bismuth salicylate (▲———▲); bismuth subnitrate (◪———◪); aluminium glycinate (△———△); aluminium hydroxide (■———■); and dihydroxyaluminium sodium carbonate (○———○).

Fig. 2. Adsorption isotherms of dicoumarol on bismuth carbonate (□———□); bismuth salicylate (▲———▲); bismuth subnitrate (●———●); magnesium oxide (●———●); aluminium glycinate (△———△); aluminium hydroxide (■———■); and dihydroxyaluminium sodium carbonate (○———○).

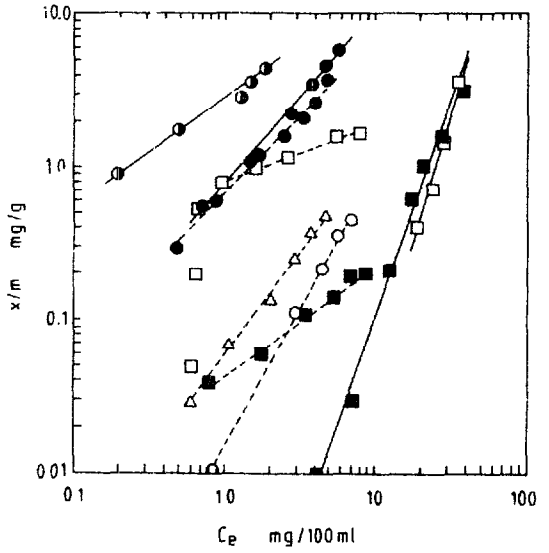

Fig. 3. Freundlich adsorption isotherms of: (a) phenindione on charcoal (◑———◑) (C_e values presented in the figure are ×10); magnesium oxide (●———●); bismuth carbonate (□———□); and aluminium hydroxide (■———■). (b) dicoumarol (dotted lines) on bismuth carbonate (□———□); magnesium oxide (●———●); magaldrate (○———○); aluminium glycinate (△———△); and aluminium hydroxide (□———□).

TABLE 3

FREUNDLICH ADSORPTION ISOTHERM CONSTANTS FOR ANTICOAGULANTS–ANTACIDS [a] INTERACTIONS

Adsorbent	Phenindione		Dicoumarol	
	n [b]	$K \times 10^{2}$ [c]	n [b]	$K \times 10^{2}$ [c]
Aluminium glycinate	3.1	0.004	1.3	5.8
Aluminium hydroxide	3.1	0.008	0.7	4.3
Bismuth carbonate	3.3 [d]	0.003 [d]	0.4 [e]	80.0 [e]
Bismuth salicylate	0.7	59.600	–	–
Charcoal	0.7	1487.000	–	–
Dihydroxyaluminium sodium carbonate	2.5	0.100	–	–
Magaldrate	–	–	1.5	2.6
Magnesium oxide	1.1	74.600	1.0	65.0

[a] Drug dissolved in 0.014 N sodium bicarbonate in 3% v/v ethanol.
[b] The amount of drug adsorbed per unit weight of adsorbent for a given concentration change.
[c] The amount of drug adsorbed per unit weight of adsorbent at a unit drug concentration.
[d] Calculated from the linear part of the Freundlich adsorption isotherm.
[e] For $0.6 < Ce < 2$ mg/100 ml.

Phenindione, a weak acid ($pk_a \sim 4.6$) will be mainly ionized at the pH of magnesium oxide suspension (pH ~ 9.9). Moreover, having a fairly large hydrophobic residue ($> C_5$), it is expected to exhibit a marked localization of the forces of attraction for the polar substrate over a short section of its periphery (Giles et al., 1960). Low elution of drug from the surface of magnesium oxide was consistent with its relatively high n value (Table 3). Suspending magnesium oxide in acidic medium increased the pH to ~ 8.7. Adsorption of phenindione on magnesium oxide from this medium was also high (Table 1) and probably involved as well the ionized form of the drug.

The adsorption of phenindione on aluminium containing antacids (aluminium hydroxide, aluminium glycinate and dihydroxyaluminium sodium carbonate) suspended in sodium bicarbonate solution gave S-type isotherms (Fig. 1) similar to magnesium oxide. However, relatively low K values (Table 3) were obtained indicating low capacity of these antacids for the drug. Evidence of covalent interaction between carbonate anions and aluminium hydroxide was previously shown (Feldkamp et al., 1981). Thus, a competition for the antacid surface between the drug and bicarbonate ions may exist. The pH of aluminium hydroxide suspension in sodium bicarbonate solution is 7.8 (Table 1). This pH is quite near the isoelectric point or zero point charge (~ 8.5) of aluminium hydroxide Vanderlaan et al., 1979). Aluminium hydroxide will thus possess a slight net positive charge. Therefore, it can

be assumed that phenindione anions are attached more or less vertically to surface sites by ion–ion attraction. The high n value of the Freundlich adsorption isotherm of phenindione on aluminium hydroxide (Table 3) and the relatively low drug elution (Table 1) confirm the previous assumption. The adsorption of phenindione on aluminium hydroxide from acidic medium (pH of suspension ~ 6.5), on the other hand, was greater than that from alkaline medium (Table 1). This may be due to the decreased solubility of the drug in acid medium, associated with a reduction in charge density on phenindione molecules, leading to lower repulsion of like charges during the process of adsorption. In acid medium, the aluminium hydroxide surface itself will also carry a positive charge of somewhat higher density than in alkaline medium, thus favouring ion–ion attraction. Similarly to aluminium hydroxide, adsorption of phenindione on aluminium glycinate was much more evident from acidic than from alkaline medium (Table 1).

The first part of the adsorption isotherm of phenindione on bismuth subnitrate, from alkaline medium, was slightly convex (Fig. 1). This indicates that as more sites in the substrate are filled, it becomes more difficult for a solute molecule to find a vacant site. However, further increase in solute concentration overcame this energy barrier and resulted in a sharp rise of the isotherm indicating the formation of a new layer (Giles et al., 1960). The pH of bismuth subnitrate suspension in sodium bicarbonate solution was ~ 3. Adsorption of pheninindione on bismuth subnitrate is not mainly a pH solubility effect since similar adsorption occurred when the drug was initially dissolved in acidic medium (Table 1). Bismuth subnitrate was previously reported (Haines and Martin, 1961b; Blaug and Gross, 1965) to possess strong adsorbing properties. Attachment of phenindione molecules through their keto function to water tightly held on surface sites of bismuth subnitrate (Haines and Martin, 1961b) could take place. The small portion of ionized molecules would get attached by ion–ion attraction to the positive bismuth surface atoms (Schott, 1976). Low elution results (Table 1) confirmed the strong binding between phenindione molecules and the bismuth subnitrate surface.

The adsorption isotherm of phenindione on bismuth carbonate (Fig. 1) suspended in alkaline medium was of the S-type similar to that of magnesium oxide and aluminium containing antacids. However, adsorption of phenindione on bismuth carbonate appeared to be highly concentration-dependent. Low x/m values approximating zero at Ce up to ~ 8 mg/100 ml were observed indicating a possible strong competition from the solvent for the substrate (Nogami et al., 1968). As concentration increased, adsorption became easier. The n value (Table 3), as calculated from the linear part of the isotherm (Fig. 1), was high for this adsorbent. This possibly indicates that while the number of sites available on bismuth carbonate is somewhat low, (as reflected in a small K value) (Table 3), the strength of binding is high. This observation can be supported by the low elution results (Table 1). In acid medium (pH of suspension ~ 2.8), the adsorption isotherm of the drug on bismuth carbonate was of the H-type or high affinity type (Giles et al., 1960). Here, the values of x/m are coincident with the y-axis.

The isotherm of phenindione on bismuth salicylate from alkaline medium (Fig. 1) was a borderline case intermediate between the S- and L-types. The slightly convex

part of the isotherm suggests that the adsorbed drug molecules lie more or less flat on the adsorbent surface. The very short inflection, arising in the adsorption isotherm at higher drug concentrations, may indicate that the adsorbed molecules expose a surface that has the same affinity for more solute as the original surface had. The isotherm beyond the inflection rises steadily representing a multilayer adsorption (Giles et al., 1960).

Diphenadione was adsorbed on most antacids tested (Table 1). The low solubility of the drug even in alkaline medium (Shapiro, 1960) may account for its general tendency to get adsorbed even in the low concentration used. Elution results were also fairly low (Table 1), an observation that again confirms the strong adsorption.

The coumarin anticoagulants tested in the present study were either single- or double-ring structures. The adsorption behaviour of the 3 single-ring coumarin derivatives: warfarin, nicoumalone and phenprocoumon was quite similar. This is possibly due to the minor variations in their structure. Nicoumalone differs from warfarin only by the presence of a nitro group, while warfarin differs from phenprocoumon by the presence of a dimethyl ketone side-chain instead of an ethyl chain. Dicoumarol and ethyl biscoumacetate are double-ring coumarin derivatives. However, they did not exhibit a similar adsorption tendency for the adsorbents tested. The presence of an acetyl side-chain in ethyl biscoumacetate imparted some hydrophilic character to the molecule. In addition, the side-chain in ethyl biscoumacetate may have prevented adsorption through a steric hindrance effect (Blaug and Gross, 1965). On the other hand, the presence of intramolecular hydrogen bonding in the dicoumarol molecule as well as the absence of hydrogen bonding with water have been previously reported (Cho et al., 1971a). This may have decreased the solubility of dicoumarol and increased its adsorption tendency. Moreover, dicoumarol has its active group exposed for direct interaction with the adsorbent, while the presence of the side-chain in ethyl biscoumacetate may shield such group from close contact with the adsorbent surface.

The strong interacting tendency of dicoumarol with bismuth compounds may be due to the following fact. Dicoumarol is a weak acid (pk_a for the first ionization ~ 4.4 and for the second ~ 8) (Cho et al., 1971a). The negative charge produced by the first ionization is expected to increase the electronegativity of the oxygen atom in the carbonyl group and consequently its ability for hydrogen bonding (Cho et al., 1971a) and is also expected to increase its tendency for bonding to the positive sites on bismuth subnitrate surface (Schott, 1976). At the pH of bismuth carbonate, (~ 8), dicoumarol starts to undergo the second ionization (80% of dicoumarol will exist as the mono-ionized species and 20% as the di-ionized species). Di-ionized dicoumarol can undergo ion ion, ion dipole or hydrogen bonding (Cho et al., 1971a). The amount of dicoumarol adsorbed on bismuth subnitrate and salicylate was higher than that on bismuth carbonate (Table 2). At the higher pH of bismuth carbonate, dicoumarol is more ionized and more soluble, so we can postulate that there is a competition between the alkaline medium and the adsorbent surface for the drug. At the lower pH of bismuth subnitrate and salicylate we have a shift of the equilibrium to the undissociated form and adsorption increases.

The adsorption isotherms of dicoumarol on the various adsorbents tested are

shown in Fig. 2. No adsorption studies were done from acid medium because of the limited solubility of dicoumarol in acid (0.5 mg/l or 1.5×10^{-6} mol/l) (Cho et al., 1971a). From Fig. 2, it is obvious that unlike the plot of the adsorption of dicoumarol on bismuth carbonate, the adsorption behaviour of dicoumarol on bismuth salicylate and subnitrate followed the H-type isotherm (Giles et al., 1960). This is a special case of the L-type in which the solute in dilute solution is completely adsorbed or at least there is no measurable amount remaining in solution. The relatively higher elution value (Table 2) obtained with bismuth salicylate compared to bismuth subnitrate may be attributed to the presence of weaker attraction forces as a result of its hydrophobic part.

Magnesium oxide exhibited relatively low adsorption properties to most coumarin derivatives except dicoumarol. Magnesium oxide–dicoumarol residue, after filtration, was coloured yellow orange suggesting the formation of a dicoumarol–magnesium chelate. Previous studies using diffuse reflectance spectroscopy revealed a solid–solid interaction between dicoumarol and magnesium oxide (Lach and Bighley, 1970). Dicoumarol was also shown (Bighley and Spivey, 1977) to form a soluble chelate with magnesium oxide under certain conditions favouring its solubility.

Magnesium carbonate contains magnesium atoms and gives nearly the same pH as magnesium oxide; however, it did not adsorb dicoumarol from solution (Table 2). The availability of the metal portion may differ due to satisfied valency requirements by binding to adjacent atoms (Lach and Bighley, 1970).

Aluminium glycinate and magaldrate had a rather strong affinity for the drug (high n value) but a low capacity (low K value) (Table 3).

Dicoumarol showed relatively low adsorption properties on either magnesium trisilicate or aluminium hydroxide in the concentration range studied (Table 2 and Fig. 2). These results are contrary to those reported using diffuse reflectance spectroscopy which indicated the presence of a solid–solid interaction between dicoumarol and these antacids (Lach and Bighley, 1970). Aluminium hydroxide was also shown (Akers et al., 1973a) to decrease the bioavailability of dicoumarol when given in certain amounts to dogs. Adsorption of the drug from solution probably is not the only factor responsible for such reported decrease at least at the pH and in the concentration range used. It is suggested that the effect observed in vivo is also the result of the influence of aluminium hydroxide on the gastric emptying rate (Hurwitz and Sheehan, 1971).

Addition of glycine (5% w/v) to the solution of dicoumarol resulted in a decrease in the amount of drug adsorbed on bismuth carbonate, bismuth subnitrate and magnesium oxide ($\sim$ 37, 4.5 and 12% decrease, respectively, using an initial concentration of $\sim$ 7 mg/100 ml). Glycine was shown to get adsorbed on some surfaces and to decrease the adsorption of bovine serum albumin on porous glass (Mizutani and Mizutani, 1978). Glycine is expected to compete with the drug for positive adsorption sites on bismuth carbonate since the amino acid will bear mainly a negative sign in the alkaline medium of the antacid. On the other hand, in acidic medium in presence of bismuth subnitrate, glycine will bear a positive charge resulting in reduction of its adsorption on the positive bismuth sites of bismuth subnitrate. In case of magnesium oxide, glycine increased the amount of magnesium

ions leached from magnesium oxide surface probably through formation of magnesium glycinate in solution. Thus, magnesium ions will be less available to chelate with dicoumarol on the surface of the antacid.

The results of the dissolution study are shown in Fig. 4. The effect of antacids on the dissolution rate of phenindione tablets in alkaline medium, was in general slight. In acidic medium, however (Fig. 4), the aluminium and to a lesser extent the bismuth compounds, had a decreasing effect on the dissolution of the drug. Magnesium trisilicate, on the other hand, enhanced markedly the dissolution rate of the drug. This effect may be associated with lack of drug adsorption on the antacid in addition to the alkalinity imparting effect of magnesium trisilicate. Reduction in the dissolution rate of phenindione in the presence of aluminium and bismuth containing compounds may partially be due to the obvious adsorption of the drug on these antacids in acidic medium (Table 1).

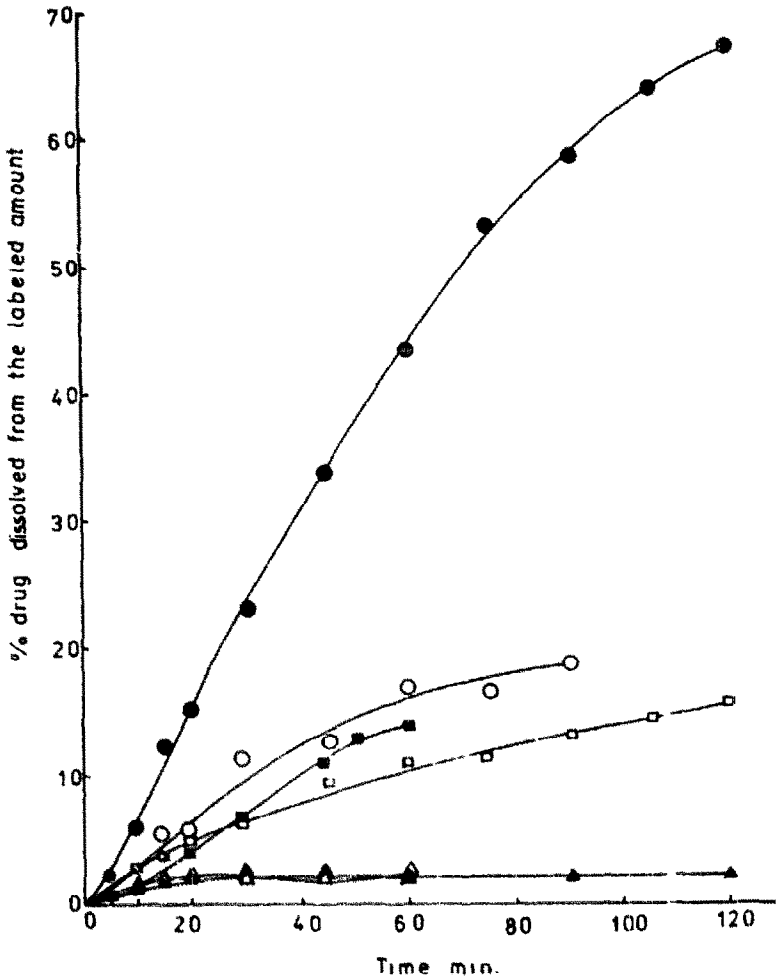

Fig. 4. Dissolution rate of phenindione in 0.01 N hydrochloric acid in absence (○———○); and in presence of aluminium glycinate (△———△); aluminium hydroxide (▲———▲); bismuth carbonate (□———□); bismuth subnitrate (■———■); and magnesium trisilicate (●———●).

The relative increase in the viscosity of the dissolution medium due to the presence of the colloidal aluminium compounds, may also affect the dissolution of phenindione. The gel structure and viscosity of aluminium hydroxide may be affected by changes of pH and ions present in the medium (Feldkamp et al., 1981).

In the acidic pH of the stomach, slow dissolution rate of phenindione in presence of these antacids and its subsequent adsorption on their surface prior to its passage to the duodenum (where absorption is expected to be optimum), may become important factors in decreasing its bioavailability.

On the other hand, magnesium oxide was found to decrease the dissolution rate of dicoumarol (~ 46 and 53% decrease after 10 and 30 min, respectively) in spite of its alkalinity-imparting effect (pH of dissolution medium ~ 10). The decrease in the dissolution rate is probably due to adsorption of the drug on the antacid which may have outweighed the expected increase in dissolution resulting from the formation of a soluble dicoumarol–magnesium chelate. The present in vitro results are contrary to in vivo reports (Akers et al., 1973a; Amber and Fisher, 1973) which indicated a promoting effect of magnesium oxide on the availability of dicoumarol. This discrepancy may be in part due to the complexity of the biological system affecting the solubility of the chelate as well as the release of magnesium ions from the antacid surface.

The observed in vitro results may not exactly mimic in vivo conditions. However, the concomitant administration of anticoagulants with antacids or antidiarrhoeals should only be made under rigid drug monitoring especially for drugs of little solubility with a slow and erratic absorption like dicoumarol. Further in vivo studies on human subjects are still needed to determine the exact consequence of the co-administration of antacids and antidiarrhoeals with oral anticoagulants.

References

Akers, M.J., Lach, J.L. and Fisher, L.J., Alterations in absorption of dicoumarol by various excipient materials. J. Pharm. Sci., 62 (1973a) 391–395.

Akers, M.J., Lach, J.L. and Fisher, L.J., Bioavailability of dicoumarol from different commercial tablets in dogs. J. Pharm. Sci., 62 (1973b) 1192–1193.

Ambre, J.J. and Fisher, L.J., Effect of coadministration of aluminium and magnesium hydroxides on absorption of anticoagulants in man. Clin. Pharmacol. Ther., 14 (1973) 231–237.

Bighley, L.D. and Spivey, R.J., Chelates of dicoumarol I: preparation and structure identification of magnesium chelate. J. Pharm. Sci., 66 (1977) 1124–1127.

Blaug, S.M. and Gross, M.R., In vitro adsorption of some anticholinergic drugs by various antacids. J. Pharm. Sci., 54 (1965) 289–294.

Cho, M.J., Mitchell, A.G. and Pernarowski, M., Interaction of bishydroxycoumarin with human serum albumin. J. Pharm. Sci., 60 (1971a) 196–200.

Cho, M.J., Mitchell, A.G. and Pernarowski, M., Interaction of bishydroxycoumarin with polyvinylpyrrolidone. J. Pharm. Sci., 60 (1971b) 720–724.

Feldkamp, J.R., Shah, D.N., Meyer, S.L., White, J.L. and Hem, S.L. Surface charge characteristics and physical properties of aluminium hydroxide gel. J. Pharm. Sci., 70 (1981) 638–640.

Ganjian, F., Cutie, A.J. and Jochsberger, T., In vitro adsorption studies of cimetidine. J. Pharm. Sci., 69 (1980) 352–353.

Giles, C.H., MacEwan, T.H., Nakhwa, S.N. and Smith, D., Studies in adsorption. Part XI; A system of classification of solution adsorption isotherms, and its use in diagnosis of adsorption mechanisms and in measurements of specific surface areas of solids. J. Chem. Soc., (1960) 3973–3993.

Haines, B.A., Jr. and Martin, A.N., Interfacial properties of powdered materials; caking in liquid dispersions I: Caking and flocculation studies. J. Pharm. Sci., 50 (1961a) 228–232.

Haines, B.A., Jr. and Martin, A.N., Interfacial properties of powdered materials; caking in liquid dispersions III: Adsorption studies. J. Pharm. Sci., 50 (1961b) 756–759.

Hurwitz, A. and Sheehan, M.B., The effect of antacids on the absorption of orally administered pentobarbital in the rat. J. Pharmacol. Exp. Ther. 179 (1971) 124–131.

Khalil, S.A.H. and Iwuagwu, M., In vitro uptake of oral contraceptive steroids by magnesium trisilicate. J. Pharm. Sci., 67 (1978) 287–289.

Lach, J.L. and Bighley, L.D., Diffuse reflectance studies of solid–solid interactions. J. Pharm. Sci., 59 (1970) 1261–1264.

Mizutani, T. and Mizutani, A., Estimation of adsorption of drugs and proteins on glass surfaces with controlled pore glass as a reference. J. Pharm. Sci., 67 (1978) 1102–1105.

Mortada, L.M. and Khalil, S.A.H., The interaction of phenindione with polyvinylpyrrolidone. Indian J. Pharm., 39 (1977) 33–35.

Nogami, H., Nagai, T., Fuknoka, E. and Uchida, H., Physicochemical approach to biopharmaceutical phenomena I: Adsorption of tryptophan from aqueous solution. Chem. Pharm. Bull., 16 (1968) 2248–2256.

Robinson, D.S., Benjamin, D.M. and McCormack, J.J., Interaction of warfarin and nonsystemic gastrointestinal drugs. Clin. Pharmacol. Ther., 12 (1971) 491–495.

Schott, H., Controlled flocculation of coarse suspensions by colloidally dispersed solids I: Interaction of bismuth subnitrate with bentonite. J. Pharm. Sci., 65 (1976) 855–861.

Shapiro, S.L., Geiger, K. and Freedman, L., Indanedione anticoagulants. J. Org. Chem., 25 (1960) 1860–1865.

Sorby, D.L., Effect of adsorbents on drug absorption I: Modification of promazine absorption by activated attapulite and activated charcoal. J. Pharm. Sci., 54 (1965) 677–683.

Stella, V.J. and Gish, R., Ionization kinetics of the carbon acid phenindione. J. Pharm. Sci., 68 (1979a) 1042–1047.

Stella, V.J. and Gish, R., Kinetics and mechanism of ionization of the carbon acids 4-substituted-2-phenyl-1,3-indanediones. J. Pharm. Sci., 68 (1979b) 1047–1049.

Stella, V.J., Nonclassical phase transfer behaviour of phenylbutazone. J. Pharm. Sci., 64 (1975) 706–708.

Vanderlaan, R.K., White, J.L. and Hem, S.L., Effect of interaction of aluminium hydroxycarbonate gel and magnesium hydroxide gel on acid neutralization. J. Pharm. Sci., 68 (1979) 1498–1501.