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# A study of the *in vitro* adsorption of the anti-amoebic drugs: metronidazole and chloroquine phosphate on magnesium trisilicate, maize and *Tacca involucrata* starches

CHUKWU, K.I.*[1], OFOKANSI, K.C[2], OGBONNA, O[1] and IBEZIM, E.C.[2]
[1] Department of Pharmaceutical Technology & Industrial Paharmacy,
[2] Department of Pharmaceutics
University of Nigeria, Nsukka.

* Correspondence

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The *in vitro* adsorption of the amoebicides: chloroquine phosphate and metronidazole unto the antacid magnesium trisilicate and the excipients maize starch and *Tacca involucrata* starch was investigated. The effects of various experimental conditions on the adsorptive process were studied. Results revealed that the extent of adsorption was dependent on drug type generally, and specifically on the pH and ionic strength. The high adsorptive capacity of magnesium trisilicate to chloroquine phosphate and metronidazole could have serious bioavailability implications when magnesium trisilicate is co-administered with either of the two amoebicides. The extent of adsorption was generally low with the two excipients even though the adsorptive affinity of tacca starch to metronidazole was high at neutral pH. On the whole maize starch exhibited the least adsorptive capacity and could serve as good formulation excipients for chloroquine phosphate and metronidazole tablets.

**Key words**: In vitro adsorption, Metronidazole, Chloroquine phosphate. Magnesium trisilicate, Maize starch, *Tacca involucrata* starch.

## INTRODUCTION

Metronidazole (2-mthyl 5-nitroimidazole -1-ethanol) is an anti-amoebic drug that has also found use in infections caused by anaerobic bacteria, while chloroquine phosphate (7-chloro-4 [4-diethylamino- 1-methybutylamino] is an anti-amoebic drug though it is widely used as an antimalarial drug [1-2].

The possibility of adsorption of medicaments onto formulation excipients should be considered in drug formulation in order to forestall problems in bioavailability that could result from drug adsorption. This was the case in the suspected '*in vivo*' interaction between para-aminosalicylic acid (containing bentonite) and rifampicin [3]. Similar problems may also occur in solid dosage forms: the case with talc, and cyanocobalamin in tablet formulation [4] is a typical example. Significant adsorption interactions have been shown to exist between magnesium or magnesium oxide and some antichlolinergics, transquilizers carthatics and mild sedatives [4]. Extensive studies on the adsorption of atropine, chlorpromazine, oxyphenonium and dicoumaral unto magnesium trisilicate revealed that these drugs were adsorbed significantly [5] hence any formulation containing magnesium trisilicate and any of these drugs may experience compromised bioavailability

Adsorption of drugs to solid adsorbents has valuable applications in the management of accidental intoxication [6]. Common drugs employed in the treatment of endemic diseases are often kept in various households and may be accidentally or incidentally ingested in toxic doses. Metronidazole is employed extensively in the treatment of amoebic infections and other intestinal disorders while chloroquine phosphate is commonly used as an antimalaria agent. The presence of these drugs in the stock of various households makes their misuse and possible intoxication likely, especially given the high incidence of self-medication in our society.

The present work reports on the extent of adsorption of chloroquine phosphate and metronidazole onto magnesium trisilicate, tacca involucrata and maize starches and comments on the therapeutic and

toxicological implications of these forms of interactions.

## EXPERIMENTAL

### Materials and Reagents

Metronidazole powder, choroquine phosphate (May and Baker, Nigeria); Magnesium trisilicate (BDH. England), Maize starch and *Tacca involucrata* starch were obtained from batches processed in our laboratory. All other reagents were of analytical grade and were used such.

### Adsorption study

A 10 mg quantity of metronidazole was weighed out and dissolved in 100 ml of distilled water to form a 10mg % stock solution. Serial concentrations of the drug ranging from 0.2 to 1.2mg % in 0.2mg% increments were prepared in triplicate and placed in conical flasks. Similar concentrations of chloroquine phosphate were also prepared. Ten 5 g portions each of magnesium trisilicate, maize starch and tacca starch were also weighed out and transferred into different conical flasks that contain 50 ml of the drug solutions. The mixtures were corked and stirred with a mechanical shaker (GallenKamp England) for 10 h. This time period is longer than the time usually employed for such adsorption study (4,9) but was considered sufficient to allow complete adsorption even under very slow process. The mixtures were centrifuged at 2,500 rpm for 1 h, the supernatant solutions were collected and the concentrations of free drug determined spectrophotometrically by reference to a standard Beer's plot using a suitable spectrophotometer (Unico UV 2102 United Product Inc USA). In order to determine the effect of acidic environment and ionic strength on the adsorption process, the whole experiment was similarly repeated in solutions of 0.1N hydrochloric acid and 0.25 mol/L sodium chloride solution respectively.

## RESULTS AND DISCUSSION

The adsorption isotherms of the interaction of metronidazole and chloroquine phosphate with the excipients are shown in Figs. 1 to 4. The adsorption isotherms fall under class 1 or s-curve isotherm and these were well described by the Freundlich's equation [8]. The extents of adsorption of the drugs to the excipients seem to increase as the equilibrium concentrations increase. The 'S' curve is characteristic of systems in which the solute molecule has a single point of strong attachment to the adsorbent with sequential mono to multi-layer adsorption of the solute to the adsorbent. This implies that there may be intermolecular interaction with the adsorbed layer. It may also be indicative of strong competition by the solvent or other species present in the system for the adsorption sites. Figure 2 suggests that chloroquine phosphate has strong monolayer adsorption to both magnesium trisilicate and maize starch at neutral pH, while in acidic pH and in the presence of sodium chloride both drugs experienced only minimal adsorptions to magnesium trisilicate.

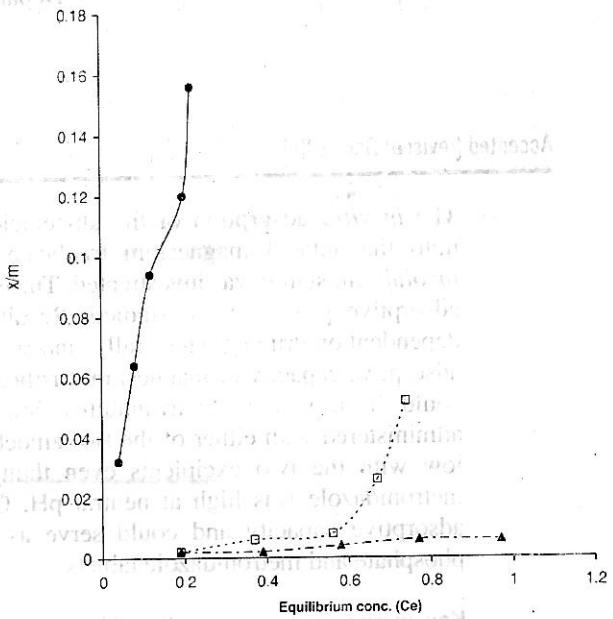


**Fig 1: Adsorption isotherm of the interaction between metronidazole and the adsorbents at neutral pH**

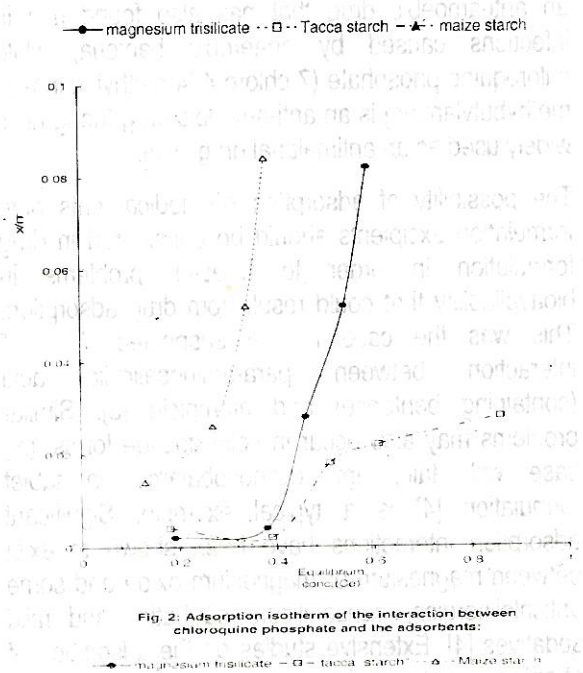


**Fig. 2: Adsorption isotherm of the interaction between chloroquine phosphate and the adsorbents:**

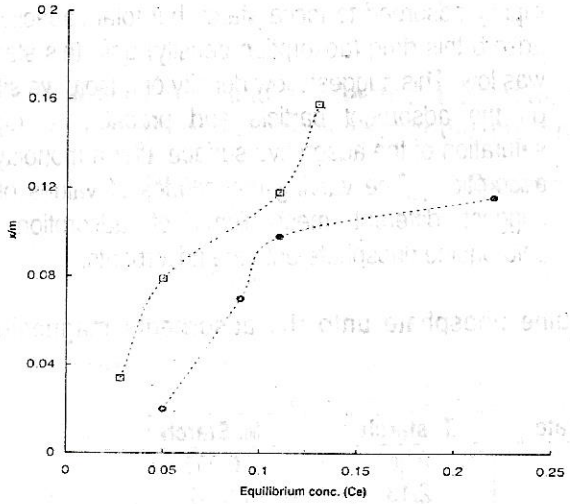


Fig. 3: Adsorption isotherm of the interaction of magnesium trisilicate metronidazole and chloroquine phosphate with in acidic pH

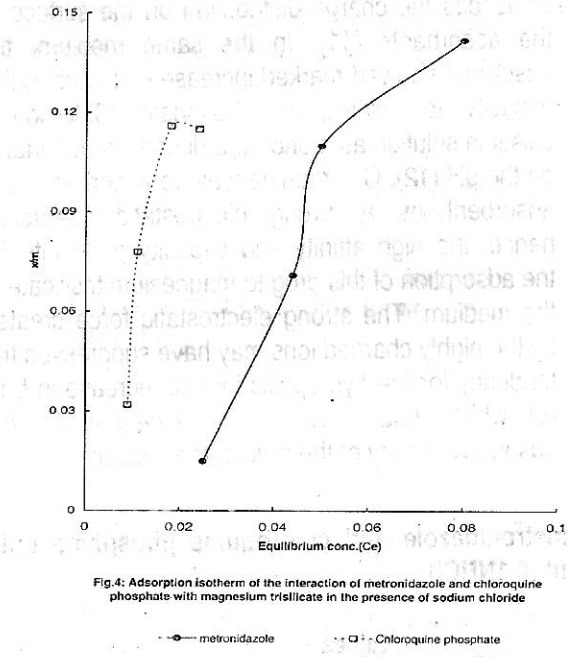


Fig.4: Adsorption isotherm of the interaction of metronidazole and chloroquine phosphate with magnesium trisilicate in the presence of sodium chloride

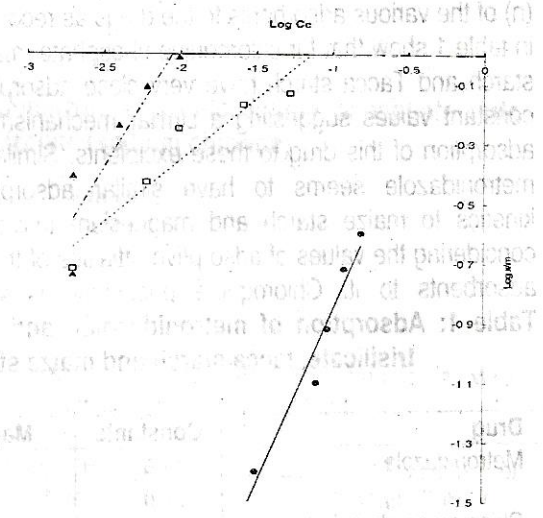


Fig.5: Logarithmic plots of the interactions of metronidazole and magnesium trisilicate, tacca starch with maize starch at neutral pH

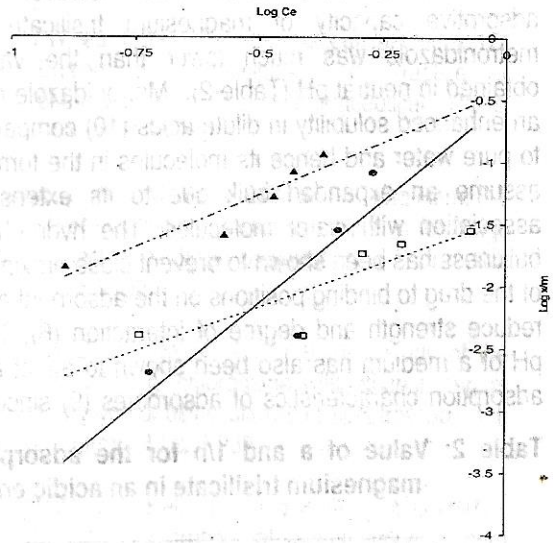


Fig.6: Logarithmic plots of the interaction of chloroquine phosphate and magnesium trisilicate, tacca starch and maize starch at neutral pH

The logarithmic form of the Freundlich's equation is given as: $\text{Log}\frac{x}{m} = \text{Log a} + \frac{1}{n}\text{Log C}_e$

Where x/m represents the amount of drug adsorbed per unit weight of the adsorbent, Ce is the equilibrium drug concentration, a is the relative adsorbent capacity for a given solid, and 1/n reflects the affinity of the adsorbent for a particular solute. A plot of Log x/m against Log Ce is linear with Log a as the intercept and 1/n as the slope. The logarithmic plots of the adsorption isotherms of metronidazole and chloroquine phosphate with the adsorbents are shown in Figs. 5 and 6 respectively.

It is evident from these figures that in neutral aqueous solutions, metronidazole has higher adsorption capacities/density (a) to magnesium trisilicate than maize starch and tacca starches. Specifically, the adsorption capacity of magnesium trisilicate to metronidazole is ten times greater than that of tacca starch and about 100 times greater than that of maize starch (Table 1). Adsorption of chloroquine phosphate to these adsorbents has similar variations in the magnitude of their adsorption capacities to metronidazole with maize starch still having the least capacity for the former. Adsorptive affinity is the measure of the readiness of a solute's adsorption to the adsorbent. The values of the adsorptive affinities

(n) of the various adsorbents to the drugs as recorded in table 1 show that for chloroquine phosphate, maize starch and Tacca starch have very close adsorption constant values suggesting a similar mechanism of adsorption of this drug to these excipients. Similarly, metronidazole seems to have similar adsorption kinetics to maize starch and magnesium trisilicate considering the values of adsorptive affinities of these adsorbents to it. Chloroquine phosphate is very rapidly adsorbed to tacca starch but total capacity to adsorb this drug (adsorption density) unto this starch was low. This suggests low density of adsorptive sites on the adsorbent particle and probably, a rapid saturation of the adsorptive surface after a monolayer adsorption. The varying magnitudes of values of n suggest different mechanisms of adsorption of chloroquine phosphate unto the adsorbents.

**Table 1: Adsorption of metronidazoloe and chloroquine phosphate unto the adsorbents magnesium trisilicate, tacca starch and maize starch**

| Drug | Constants | Mag. Trisilicate | T. starch | M. Starch |
|---|---|---|---|---|
| Metronidazole | a | 0.56 | 0.06 | 0.006 |
| | n | 0.87 | 2.13 | 0.79 |
| Chloroquine phosphate | a | 0.32 | 0.38 | 0.035 |
| | n | 3.29 | 1.69 | 1.45 |

The adsorption characteristics of the drugs to maize and tacca starches in acidic pH did not vary widely from what was observed in water. However, the adsorptive capacity of magnesium trisilicate to metronidazole was much lower than the value obtained in neutral pH (Table 2). Metronidazole has an enhanced solubility in dilute acids (10) compared to pure water and hence its molecules in the former assume an expanded bulk due to its extensive association with water molecules. The hydrophilic bulkiness has been shown to prevent close proximity of the drug to binding positions on the adsorbent and reduce strength and degree of interaction (6). The pH of a medium has also been shown to affect the adsorption characteristics of adsorbates (9) since it influences the charge distribution on the surface of the adsorbents (11). In the same medium, the adsorbent showed marked increase in its adsorptive capacity to chloroquine phosphate. Chloroquine exists in solution as mono- and di-cations depending on the pH (12). Chloroquine may be adsorbed to the adsorbent by a strong electrostatic interaction hence, the high affinity and capacity constants for the adsorption of this drug to magnesium trisilicate in the medium. The strong electrostatic force created by the highly charged ions may have suppressed the tendency for the hydrophilic ions to increase in bulk (6), which should have caused a decrease in the adsorptive affinity of the drug in the medium.

**Table 2: Value of a and 1/n for the adsorption of metronidazole and chloroquine phosphate onto magnesium trisilicate in an acidic environment (0.1NHCl)**

| Drug | Constants | Values |
|---|---|---|
| Metronidazole | a | 0.074 |
| | n | 0.64 |
| Chloroquine | a | 30.11 |
| | n | 2.00 |

Changes in ionic strength and pH have been shown to affect the solubility and ionization of drugs [13]. These also affect the surface charges on the adsorbent and the dielectric constant of drug solutions [14]. Results obtained using 0.25 mol/L NaCl as the adsorption medium reveal that the adsorptive capacity of magnesium trisilicate to metronidazole increased but decreased for chloroquine phosphate in this medium. The effects of ionic environment on this adsorption characteristic observed with tacca and maize starches (Table 3) for the two drugs were only marginal. This seems to suggest that the adsorption of chloroquine phosphate to magnesium trisilicate occurs by ion-exchange mechanisms, while metronidazole adsorbs to it possibly through other mechanisms, such as non-polar interaction. Sodium chloride may be exerting its action on chloroquine phosphate in this phenomenon through competitive anion interaction on the adsorptive sites of the adsorbent (15).

**Table 3: Values of a and 1/n for the adsorption of metronidazole and chloroquine phosphate unto magnesium trisilicate under the effect of an electrolyte (sodium chloride)**

| Drug | Constants | Values |
|---|---|---|
| Metronidazole | a | 1.12 |
| | n | 0.96 |
| Chloroquine | a | 0.64 |
| | n | 1.14 |

## CONCLUSIONS

It is evident from this study that chloroquine phosphate showed a high adsorption to the antacid, magnesium trisilicate especially in acidic pH; a typical state of the gastric environment. This interaction may lead to inadequate absorption of chloroquine when administered orally. The two drugs studied were more strongly adsorbed to tacca starch than maize starch, suggesting that maize starch could be a better formulation excipient for the drugs.

## REFERENCES


1. Goodmann. L.S. and Gilman. A. (1970). The Pharmacological Basis of Therapeutics. 4th ed. Macmillan Pub. Co. New York. Pp. 1101

2. Levine. R.R. (1973). Pharmacology of Drug Actions and Reactions. 1st ed. Little Brown and Co. Boston. P.284.

3. Bonman. D.S. (1975). In vivo interaction between p-aminosalicylic acid and rifampicin. J. Pharm. Sci. 64, 756-758.

4. Dony. A.N. (1973). In viro adsorption of cyanocobolamin onto talc in tablet formulation. J. Pharm. Sci. 62, 1131-1135.

5. Ferguson. R.I (1977). Drug Interactions of Clinical significance. I.M.S, New Zealand. Pp. 11-23.

6. Johns, W.H. and Bates T.R. (1970). Quantification of the binding tendencies of cholestramine II: Mechanism of interaction with the salts and fatty acids. J. Pharm. Sci. 59:329-333.

7. Bailey, D. N., Coffee, J. J., Andreson. B., and Manoguerra, A. S. (1992) Interaction of tricyclic antidepressants with cholestramine in vitro. Ther. Drug Monitor 14: 339-342.

8. Davis. H. (1961). In: Bently's Textbook of Pharmaceutics. 7th ed. Macmillan Pub. Co. London P. 115.

9. Adikwu. M.U. (1994). Adsorption of some salycylates onto the sclerotium of pleurotus: implication in food-drug interactions. J of Univ. of Sci. and Tech. 14, 24-27

10. Lund W. ed. (1994) The Pharmaceutical Codex 12th Edition. The Principles and Practice of pharmaceutics. The Pharmaceutical Press. London. P.95-960.

11. Hermosin. M.C. Cornejo. J White J. L. and Hem. S.L (1981). Sepiolite, potential excipients for drugs subject to oxidative degradation. J Pharm. Sci. 70,189-192.

12. Tarla. P.G and Dakas. C.J. (1988) A study of the interaction of chloroquine with ethanol, sugars and glycerol using ultraviolet spectroscopy. Int. J. Pharm., 43:225-232

13. Bambride. C.A. Kelly, E.L and Walking W.D (1977). In vitro adsorption of acetaminophen onto activated charcoal. J. Pharm. Sci. 66, 480-482.

14. Nasipuri. R.N. and Khalil. S.A. (1974). Effect of citrate ion and pH on adsorption of Benzoic acid by sulphamerazine. J Pharm. Sci. 63, 956-959).

15. Probcan. L.S., Serna. C.J. White. J. L. and Hem. S.L. (1978). Adsorption of clindamycine and tetracycline onto moutmorillonite. J. Pharm. Sci. 67, 1081-1087.