Vol. 15 (2012) 10-17

An *in vitro* Study of the Effect of Some Commonly Used Antacids on the Release Profile of Paracetamol and Metronidazole Tablets

E.O. AWOLARU AND L.G. BAKRE*

Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, Olabisi Onabanjo University, P. O. Box 22613, Ibadan, Oyo State, Nigeria.

This study reports on the effect of magnesium oxide, magnesium trisilicate, aluminium hydroxide and bentonite antacids on the disintegration and dissolution characteristics of commercial paracetamol and metronidazole tablets. The effect of salt on the interaction between the drugs and the antacids was also studied. The disintegration times of the tablets were determined in the different antacid solutions while the effect of antacids on dissolution was studied by adding various amounts of the antacid powders to the dissolution medium. The presence of magnesium trisilicate, magnesium oxide and bentonite delayed disintegration of paracetamol tablets. Generally, the introduction of 7.5% w/w sodium chloride into each of the antacid resulted in a reduction in disintegration time of paracetamol tablets. Combination of the antacids resulted in a greater retardation of dissolution of the paracetamol and metronidazole tablets. The retardation of dissolution of metronidazole from the tablets followed the rank order: bentonite > magnesium trisilicate > magnesium oxide > aluminium hydroxide. The addition of salt to magnesium trisilicate and bentonite dissolution medium decreased T_{50} and T_{70} with 7.5% w/w sodium chloride causing a greater reduction than 5.0% w/w. The results suggest that concomitant administration of magnesium oxide, magnessium trisilicate, aluminium hydroxide and bentonite with paracetamol and metronidazole should be discouraged since the bioavailability of these drugs may be compromised.

Keywords: Antacids, disintegration and dissolution times, paracetamol, metronidazole

INTRODUCTION

A drug interaction has been described as a situation in which a substance affects the activity of a drug, i.e. the effects are increased or decreased, or they produce a new effect that neither produces on its own. Typically, interaction between drugs comes to mind (drug-drug interaction) but interactions may also exist between drugs and foods (drug-food interactions), as well as drugs and herbs (drug-herb interactions). Generally speaking, drug interactions are to be avoided due to the possibility of poor or unexpected outcomes. However, drug interactions have been deliberately used, such as co-administering probenecid with penicillin prior to mass production of penicillin. Drug interactions may be the result of various processes. These processes may include alterations in the pharmacokinetics of the drug, such as alterations in the absorption, distribution, metabolism, and excretion of a drug. Alternatively, drug interactions may be the result of the pharmacodynamic properties of the drug.

Antacids are commonly used self-prescribed medications. They consist of calcium carbonate and magnesium and aluminum salts in various combinations. The effect of antacids on the stomach is due to partial neutralisation of gastric hydrochloric acid and inhibition of the proteolytic enzyme, pepsin. Each cation salt has its own pharmacological characteristics that are important for determination of which product can be used for certain indications. Antacids have been used for duodenal and gastric ulcers, stress gastritis, gastro-oesophageal reflux disease, pancreatic insufficiency, non-ulcer dyspepsia, bile acid mediated diarrhoea, biliary reflux, constipation, osteoporosis, urinary alkalinisation and chronic renal failure as a

*Author to whom correspondence may be addressed.

dietary phosphate binder [1]. Concomitant use of antacid preparations with other medications is common. The potential for antacid-drug interactions is dependent upon the chemistry and physical properties of the antacid preparation. The intragastric release of free aluminum and magnesium ions has potent effects on gastrointestinal function and on drug pharmacokinetics. All antacids can produce drug interactions by changing gastric pH, thus altering drug dissolution of dosage forms, reduction of gastric acid hydrolysis of drugs, or alter drug elimination by changing urinary pH. Most antacids, except sodium bicarbonate, may decrease drug absorption by adsorption or chelation of other drugs [2].

Paracetamol (acetaminophen) is a pain reliever and a fever reducer. The exact mechanism of action is not known but it is used to treat many conditions such as headache, muscle aches, arthritis, backache, toothaches, colds, and fevers. Metronidazole, on the other hand is an antibiotic effective against anaerobic bacteria and certain parasites; and it is used to treat parasitic infections including giardia infections of the small intestine, amoebic liver abscess, and amoebic dysentery. The literature is replete with reports of drug-drug interactions involving adsorbents used as antacids and antidiarrhoeals [3,4,6]. Such interaction may decrease the bioavailabilty of drugs [5].

This study is aimed at investigating the possible interaction of paracetamol and metronidazole with magnesium oxide, magnesium trisilicate, aluminium hydroxide and bentonite which are sometimes prescribed and taken concomitantly. The effect of salt (from salty food) on the interaction between the drugs and the antacids was also studied.

MATERIALS

Magnessium trisilicate and sodium hydroxide crystals (analytical grade) were obtained from BDH chemicals, U. K. Aluminium hydroxide, magnesium hydroxide and bentonite (all from Merck, Germany) were used as supplied. Paracetamol tablets 500 mg and metronidazole 200 mg (Unique Pharmaceuticals Limited, Nigeria) were purchased from a local pharmacy. All the other chemicals used were of analytical grade. Water was double distilled.

METHODS

Disintegration time testing

Control test

The disintegration time of the tablets were determined in distilled water and in the different antacid solutions at 37±0.5 °C using a BP Manesty disintegration test unit (Poole, U.K.) and an ultrasonic bath sonicator (Grant, U.K.) to ensure even distribution of the antacids. Six tablets of each drug were placed on the wire mesh just above the surface of the distilled water in the tube and the apparatus was started simultaneously. The tablets were kept in contact with the distilled water contained in the tube. The time taken for all the tablets to disintegrate and go through the wire mesh was recorded. Determinations were made in triplicate.

Dissolution test

The rate of dissolution of paracetamol from the tablets was studied in a USP apparatus operated at 100 rpm using a Logan Dissolution tester, UDT-804 (Logan, U.S.A.). The dissolution medium was 900 ml of distilled water at 37±0.5 °C. The effect of antacids on dissolution was studied by adding various amounts of the antacid powders to the dissolution medium. At various time intervals, 5 ml samples were withdrawn, filtered and the filtrate suitably diluted (where necessary). The amount of paracetamol in each sample was analysed spectrophotometrically at 245 nm on a SP6-450 UV/VIS spectrophotometer (Pye Unicam, Middlesex, England). After a sample was withdrawn for analysis, a fresh aliquot of the dissolution medium containing the antacid was added to maintain a constant volume and concentration of the antacid at the same temperature. Determinations were made in triplicate. The same procedure was repeated for metronidazole using 0.1N hydrochloric acid as the dissolution medium and 275 nm as the wavelength of absorption.

RESULTS AND DISCUSSION

The paracetamol and metronidazole tablets disintegrated within the BP 15 min time limit for uncoated tablets despite delayed disintegration in the presence of some of the antacids. Table 1 shows that the presence of magnesium trisilicate, magnesium oxide and bentonite delayed disintegration of paracetamol tablets while aluminium hydroxide had no effect on the disintegration time. It should be noted that the presence of bentonite caused almost a two-fold increase in disintegration time of paracetamol tablets. The delayed disintegration of the paracetamol tablets may be due to the antacids particles which may have been attracted onto the pores on the tablet surface thereby blocking the capillary pathways within the tablets through which liquid is drawn in to rupture the interparticulate bond of the drug molecules. Bentonite, a native colloidal hydrated silicate absorbs about twelve times its own volume of water to produce a gel which is thixotropic in nature hence blocks the pores more than the other antacids (i.e., a two-fold increase in disintegration time) [8].

With the introduction of 5% w/w sodium chloride to the dissolution medium containing bentonite, there was faster disintegration of the tablets. The disintegration time of paracetamol tablets in the presence of bentonite was 4.31 which decreased to 1.46 on adding 5.0% w/w sodium chloride indicating a two-fold reduction effect on the disintegration time of paracetamol tablets.

Table 1: Disintegration times of paracetamol and metronidazole tablets in various media at 37±0.5°C

S/N	Disintegration medium	Disintegration time (min)	
		Paracetamol	Metronidazole
1.	Distilled water	1.58	6.35
2.	1% w/v Magnesium trisilicate	2.33	6.19
	1% w/v Magnesium trisilicate + 7.5% w/w sodium chloride	1.44	6.21
	1% w/v Magnesium trisilicate + 5.0% w/w sodium chloride	1.58	5.44
	1% w/v Magnesium trisilicate + 1% w/v aluminium hydroxide	1.54	6.43
	1% w/v Magnesium trisilicate + 1% w/v bentonite	2.17	7.20
3.	1% w/v Aluminium hydroxide	1.58	7.48
	1% w/v Aluminium hydroxide + 7.5% w/w sodium chloride	1.43	8.40
	1% w/v Aluminium hydroxide + 5.0% w/w sodium chloride	1.59	7.38
	1% w/v Aluminium hydroxide + 1% w/v magnesium trisilicate	1.54	6.43
4.	1% w/v Magnesium oxide	2.16	6.30
	1% w/v Magnesium oxide + 7.5% w/w sodium chloride	1.43	6.47
	1% w/v Magnesium oxide + 5.0% w/w sodium chloride	2.17	5.47
5.	1% w/v Bentonite	4.31	9.56
	1% w/v Bentonite + 7.5% w/w sodium chloride	2.16	6.55
	1% w/v Bentonite + 5.0% w/w sodium chloride	1.46	6.47
	1% w/v Bentonite + 1% w/v magnesium trisilicate	2.17	7.20

The introduction of 7.5% w/w sodium chloride to each of the antacid resulted in a reduction in disintegration time of paracetamol tablets except that of bentonite. The presence of 7.5% w/w sodium chloride caused a greater reduction of the disintegration time of the tablets compared to 5.0% w/w sodium chloride. The reduction in the disintegration time of the paracetamol tablets in the presence of sodium chloride could be due to the fact that when dissolved, sodium chloride is present in greater concentration in the bulk solution than at the interface. The sodium and chloride ions form strong attractive bonds with the antacid molecules by ion dipole attractions thereby preventing the antacids molecules from migrating into the pores of the tablets. This allows for water to penetrate the pores of the tablets easily to break up the tablets. For the metronidazole tablets, there was delayed disintegration of the tablets in the presence of aluminium hydroxide and bentonite. The delay was highest with bentonite (9.56 min). On the other hand, the presence of magnesium trisilicate and magnesium oxide caused a reduction in disintegration time of the metronidazole tablets. The introduction of 5% and 7.5% w/w sodium chloride into magnesium trisilicate disintegration medium caused a reduction in the disintegration times of the tablets. While the presence 7.5% w/w sodium chloride in the antacid medium caused a greater decrease in disintegration time of paracetamol tablets than 5.0% w/w sodium chloride, it resulted in increase in disintegration time of metronidazole tablets.

The mixture of magnesium trisilicate and aluminum hydroxide; and magnesium trisilicate and bentonite resulted in a delay in disintegration time of paracetamol and metronidazole tablets. This may be as a result of increased concentration of the antacids present to block the pores of the tablets.

Figure 1 illustrates the dissolution profile of paracetamol tablets in the presence of magnesium trisilicate. All the antacids used in this study retarded the dissolution of paracetamol from the tablets.

The retardation of dissolution of paracetamol from the tablets followed the rank order: magnesium trisilicate > magnesium trisilicate + bentonite > magnesium trisilicate + aluminium hydroxide > magnesium trisilicate + 7.5% w/w sodium chloride > magnesium trisilicate + 5.0% w/w sodium chloride.

Combination of the antacids resulted in a greater retardation of dissolution with the combination of 1% bentonite and 1% magnesium trisilicate producing the greatest effect. Table 2 shows that the presence of salts improves the dissolution of paracetamol from the tablets with the lower concentration of 5.0% w/w enhancing better dissolution than 7.5% w/w. For example, the addition of 5% w/w sodium chloride to magnesium trisilicate resulted in the time taken for 50% (T_{50}) and 70% (T_{70}) dissolution of the drugs to decrease from well over 1 h to 5.0 and 8.0 min respectively; and to 4.6 and 39.2 min respectively when the salt was added to magnesium oxide. However as the concentration of the salt increases there is an increase in T_{50} and T_{70}. The T_{50} of paracetamol tablets in the presence of aluminium hydroxide and bentonite increases when 1% w/w magnesium trisilicate was added to either of the antacids.

Figure 2 shows the effect of antacid on the dissolution profile of metronidazole from the assay tablets. All the antacids retarded the dissolution of metronidazole from the tablets. There was a decrease in T_{50} and T_{70} of metronidazole tablets in the presence of a mixture of magnesium trisilicate and aluminium hydroxide compared to when either were used alone. The implication of the result of this dissolution study in relation to bioavailability of paracetamol and metronidazole when administered concomitantly with any of these antacids needs to be confirmed by in vivo studies. For metronidazole tablet, the addition of salt to magnesium trisilicate and bentonite dissolution medium decreased T_{50} and T_{70} with 7.5% w/w sodium chloride causing a greater reduction than 5.0% w/w sodium chloride. The reverse is however the case for magnesium trisilicate and aluminium hydroxide.

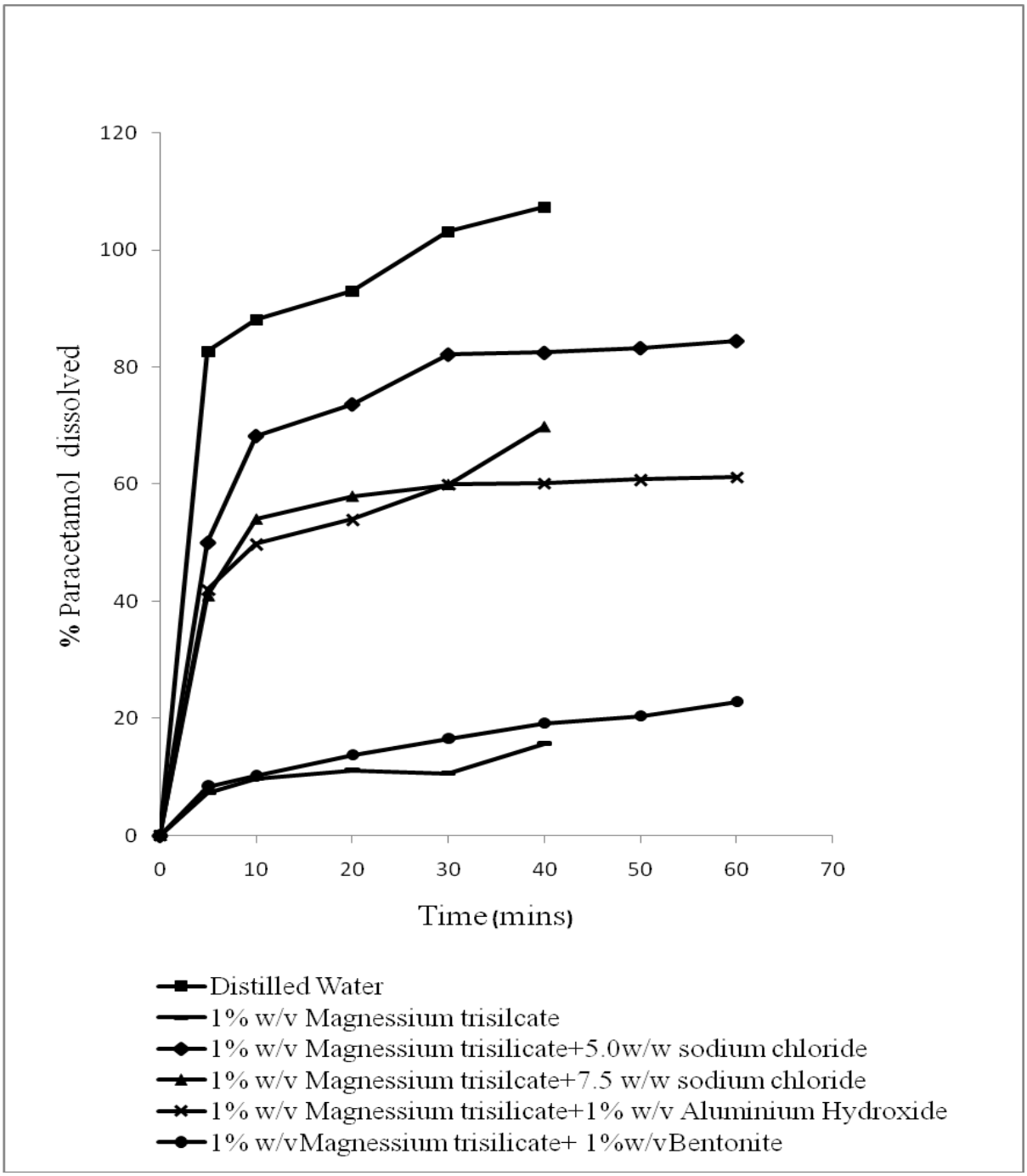

Figure 1. The effect of antacid on the dissolution profile of paracetamol from tablets in various media at 37±0.5 °C.

Table 2: Dissolution parameters of paracetamol and metronidazole tablets in various media at 37±0.5 °C

S/N	Dissolution medium	Dissolution parameters			
		Paracetamol		Metronidazole	
		T_{50} (min)	T_{70} (min)	T_{50} (min)	T_{70} (min)
1.	Distilled water	3.6	4.4	3.8	5.6
2.	1% w/v Magnesium trisilicate	>60	>60	9.0	10.2
	1% w/v Magnesium trisilicate + 7.5 g sodium chloride	10.2	38.2	9.0	13.0
	1% w/v Magnesium trisilicate + 5.0 g sodium chloride	5.0	8.2	9.2	24.0
	1% w/v Magnesium trisilicate + 1% w/v aluminium hydroxide	15.0	>60	8.5	17.5
	1% w/v Magnesium trisilicate + 1% w/v bentonite	>60	>60	15.0	19.4
3.	1% w/v Aluminium hydroxide	7.2	>60	4.0	6.0
	1% w/v Aluminium hydroxide + 7.5 g sodium chloride	3.5	4.5	5.0	7.0
	1% w/v Aluminium hydroxide + 5.0 g sodium chloride	>60	>60	5.2	7.6
	1% w/v Aluminium hydroxide + 1% w/v magnesium trisilicate	15.0	>60	8.5	17.5
4.	1% w/v Magnesium oxide	>60	>60	7.5	12.0
	1% w/v Magnesium oxide + 7.5 g sodium chloride	40.0	52.3	3.8	7.0
	1% w/v Magnesium oxide + 5.0 g sodium chloride	4.6	39.2	6.0	9.0
5.	1% w/v Bentonite	3.6	4.5	25.3	30.4
	1% w/v Bentonite + 7.5 g sodium chloride	5.0	7.0	7.0	10.3
	1% w/v Bentonite + 5.0 g sodium chloride	3.2	5.0	7.6	14.2
	1% w/v Bentonite + 1% w/v magnesium trisilicate	>60	>60	15.0	19.4

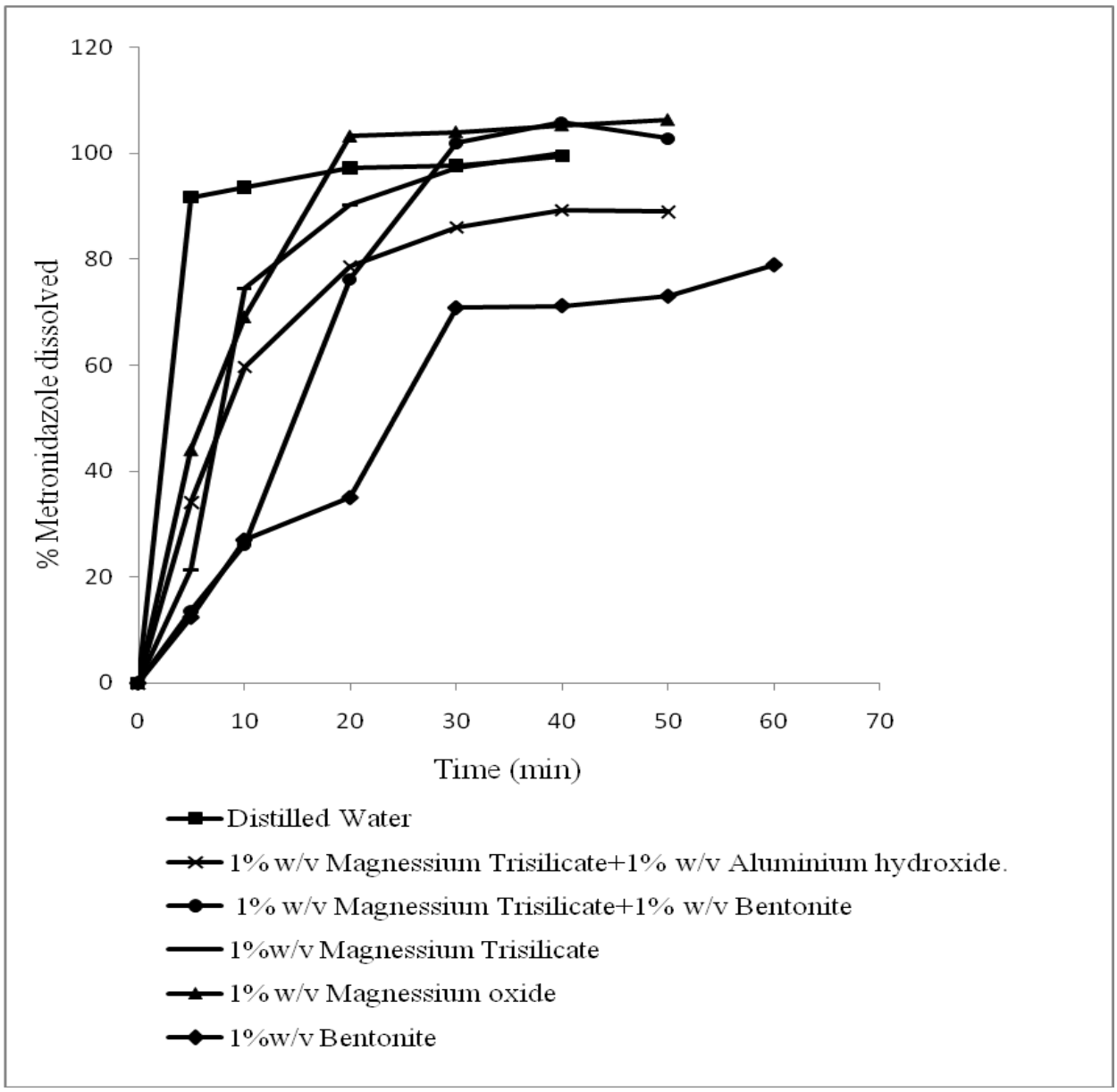

Figure 2. The effect of antacid on the dissolution profile of metronidazole from tablets in various media at 37±0.5 °C.

CONCLUSION

This study has demonstrated that the disintegration and dissolution of paracetamol and metronidazole tablets were retarded by all the antacids studied and that the presence of sodium chloride improves the dissolution of the drugs from the tablets. The clinical implications of these interactions should be further investigated by in vivo studies. It is however suggested that concomitant administration of magnesium oxide, magnessium trisilicate, aluminium hydroxide and bentonite with paracetamol and metronidazole should be discouraged since the bioavailability of these drugs may be impaired.

ACKNOWLEDGEMENT

The authors acknowledge the National Agency for Food, Drug and Administrative Control (NAFDAC) for the use of its laboratory.

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