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Mebeverine HCl and Aluminium/Magnesium Antacid Interactions: A Potential Impact on Electrolyte Replacement Therapy

Fadilah Sfouq Aleanizy[1*], Eram El Tahir[1], Fulwah Yahya Alqahtani[1], Omaimah Al Gohary[1], Rania Al Shalabi[2]

[1]*Department of Pharmaceutics, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia*
[2]*Pharmacy Department, King Faisal Specialist Hospital, Riyadh, Saudi Arabia*

e-mail: faleanizy@ksu.edu.sa

ABSTRACT

When antacids are administered with other drugs, they can alter the absorption, bioavailability, and/or excretion of concomitantly administered drugs. This study aims to characterize the in vitro interaction between different formulations of mebeverine HCl and magnesium trisilicate antacids and salts used for electrolyte-replacement therapy. The dissolution profiles of different formulations of mebeverine alone and in the presence of aluminium/magnesium-containing antacids and salts were studied. The release profiles of the drugs and the model and mechanisms of drug release were determined using differential scanning calorimetry and infrared techniques. Polyethylene glycol laxative (Movicol) combined with aluminium/magnesium hydroxide (Rialox, three tablets) [225 mg $Al(OH)_3$, 200 mg $Mg(OH)_2$] resulted in 59.2%, 55.7%, and 30% loss of mebeverine HCl in 135 mg film-coated tablets (Mebagen), 135 mg sugar-coated tablets (Colospasmin forte), and 200 mg retard capsules (Duspatalin), respectively. Three tablets of Rialox, three tablets of Moxal [405 mg $Al(OH)_3$, 100 mg $Mg(OH)_2$], and Movicol resulted in 50.7%, 27.7%, and 35.18% loss, respectively, of mebeverine HCl in Duspatalin capsules. Moxal suspension combined with Movicol led to 41.8% loss of mebeverine HCl in Duspatalin capsules. The loss of mebeverine HCl in each case appeared to be caused by absorption. The calorimetry and infrared results suggest that mebeverine HCl interacts with the antacids and with Movicol. These results should be added to the in vitro drug-drug interaction chart. It is advisable to administer other drugs at least 0.5-1.0 h before antacid ingestion to ensure consistent absorption and effect and to avoid potential interactions.

KEYWORDS: Mebeverine, electrolyte replacement therapy, film-coated mebeverine tablets, sugar-coated mebeverine tablets, retard mebeverine capsule, antacids, dissolution

INTRODUCTION

Irritable bowel syndrome might be associated with gastric and duodenal ulcers and inflammation of the gastrointestinal tract (*1, 2*). Antacids are the most widely recommended drugs for treatment of the gastrointestinal tract (*3*). Antacids are often co-administered with other drugs, including mebeverine HCl, an effective spasmolytic drug with direct action on the smooth muscle of the gastrointestinal tract (*4*). Patients suffering from irritable bowel syndrome often complain of constipation, which is usually treated by polyethylene glycol 3350 plus electrolytes (*5*). Although the efficacy of many drugs may not be affected by concomitant administration with antacids, many studies of clinically important interactions between antacids and other drugs have shown that antacids reduce the dissolution, inhibit the absorption, and reduce the efficacy of some drugs including tetracyclines, digoxin, phenytoin, and certain psychotherapeutic agents (*6*).

Aluminium hydroxide was found to delay gastric emptying and absorption and to lower the blood levels of some drugs (*6*). Antacids were found to cause the accelerated excretion of acidic drugs like salicylate and, per contra, might cause the retention of basic drugs like quinidine or amphetamine by elevating the urine pH (*6*). In addition, antacid fexofenadine interaction has been shown and revealed significant affinity to form charge transfer complexes as determined by both ultraviolet (UV) spectrophotometry and high-performance liquid chromatography (HPLC) (*7*).

A case report study demonstrated treatment failure for supraventricular tachycardia in newborns as a result of interaction among anti-arrhythmia (amiodarone), esomeprazole, and calcium carbonate/sodium bicarbonate/sodium alginate antacid (Gaviscon) (*8*). Al^{3+}- and Mg^{2+}-containing antacids were found to markedly decrease the absorption of nemonoxacin in healthy

*Corresponding author

Chinese males (*9*). Another study indicated that there was unfavorable pharmacological interaction between low doses of magnesia laxative and antacid in cancer patients (*10*). A recent study revealed that the use of antacids shortened overall survival duration in epidermal growth factor receptor (EGFR)-mutant non-small-cell lung cancer (NSCLC) patients treated with first-line, first-generation EGFR tyrosine kinase inhibitors (TKIs), especially in patients with de novo brain metastasis (*11*). Moreover, an in vitro study showed significant adsorption of zidovudine by the antacids, which is thought to reduce the amount of active ingredient available for absorption and subsequently drug resistance and therapeutic failure (*12–14*).

In vivo drug interaction can be potentially predicted by several in vitro techniques, including dissolution. In addition, in vitro studies can be used as a screening tool for further in vivo assessment and can provide the basis for design of subsequent in vivo drug interaction studies.

Since antacids have the capacity to adsorb many drugs, it was warranted to investigate such interaction between several dosage forms of mebeverine HCl and aluminum/magnesium-containing antacids (*15*). Additionally, interaction with electrolyte-replacement therapy was conducted. This issue was studied using different techniques such as in vitro dissolution test, differential scanning calorimetry, and infrared spectrophotometry.

METHODS AND MATERIALS

Materials

Mebeverine HCl was obtained as pure powder and film-coated tablets (Mebagen 135 mg) from Riyadh Pharma Medical and Cosmetic Products Co. Ltd. (Riyadh, Saudi Arabia), as sugar-coated tablets (Colospasmin forte 135 mg) from Egyptian International Pharmaceuticals Industries Co. (10th of Ramadan City, Egypt), and as retard capsules (Duspatalin 200 mg) from Abbott Healthcare SAS (Lieu-Dit Maillard, France). Rialox antacid tablets and suspension (each tablet and 5 mL of suspension contained 225 mg aluminum hydroxide and 200 mg magnesium hydroxide) were obtained from Riyadh Pharma Medical and Cosmetic Products Co. Ltd. Moxal antacid tablets and suspension (each tablet and 5 mL of suspension contained 405 mg aluminum hydroxide and 100 mg magnesium hydroxide) were obtained from Julphar-Gulf Pharmaceutical Industries (Ras al-Khaimah, UAE). Movicol salt (13.8 g; one sachet contains 65 mmol/L sodium, 53 mmol/L chloride, 17 mmol/L bicarbonate, and 5.4 mmol/L potassium) was obtained from Norgine Limited (UK). Aluminum hydroxide and magnesium hydroxide pure powders were obtained from Riyadh Pharma Medical and Cosmetic Products Co. Ltd. All other reagents were of pure grade and were used as supplied.

Dissolution Tests

In vitro release studies of the different formulations of mebeverine HCl were performed at 100 rpm and 37 °C using a USP dissolution apparatus-I (Pharma Test DT 70, Germany). The dissolution medium for the tablets was 900 mL 0.1 M HCl with or without different concentrations of antacid and with or without Movicol salt (1 sachet). Aliquots were withdrawn periodically every 8 min over a 2 h period, appropriately diluted, and measured spectrophotometrically at 264 nm. For the retard capsules, the test was performed in 900 mL 0.1 M HCl for the first 2 h, after which the dissolution medium was adjusted with a known amount of sodium hydroxide to pH 6.8, and samples were withdrawn every 20 min over a period of 3 h, then the amount of drug released was determined.

Differential Scanning Calorimetry Determinations

Differential scanning calorimetry (DSC) thermograms were recorded on an Auto Q20 DSC (TA Instruments, USA) calibrated with indium (99.9%). An aliquot (2 mg) of the sample was heated at a rate of 10 °C/min over a temperature range of 30–350 °C in closed aluminum pans under an argon purge. At least three determinations were used to calculate the mean value and standard deviation for each sample.

Infrared Spectroscopy Determinations

Infrared (IR) spectra were taken from potassium bromide (KBr) pellets on a Nicolet 6700 FT-IR (Thermo Scientific, USA). For the samples, the KBr ratio was 1:300 mg, and a pressure of 15 tons was used. The spectrum was scanned at a resolution of 2 cm^{-2} over a frequency range of 400–4000 cm^{-1} with a scan speed of 300 cm^{-1}/min.

RESULTS AND DISCUSSION

The present study focused on the possibility of interaction between mebeverine HCl and antacids or salts when those compounds are concomitantly administered orally, either as prescribed by a physician or as over-the-counter drugs. The dissolution of different formulations of mebeverine HCl alone and in the presence of different formulations of aluminum/magnesium-containing antacids and salts was studied. The release profiles of the drugs and the model and mechanisms of drug release were determined using dissolution tests. In addition, the mechanisms of interaction between different formulations of mebeverine HCl and magnesium trisilicate antacids and salts used for electrolyte-replacement therapy were characterized based on DSC analysis and IR spectroscopy.

Dissolution Studies

As shown in Figure 1, it is not recommended to co-administer Colospasmin forte with three tablets of Rialox and one sachet of Movicol, because the combination resulted in an approximately 55.7% decreased release of mebeverine HCl. Also, the combination of Colospasmin forte with one sachet of Movicol or three tablets of Rialox resulted in weak interactions because those combinations resulted in a decrease of 25.4% and 24.1%, respectively, in the release of mebeverine HCl. The co-administration of Colospasmin forte with 15 mL Rialox suspension alone or in combination with one sachet of Movicol did not result in any significant interactions, as the release of mebeverine HCl was 101.82–102.14%; therefore, it would be acceptable to administer those drugs together.

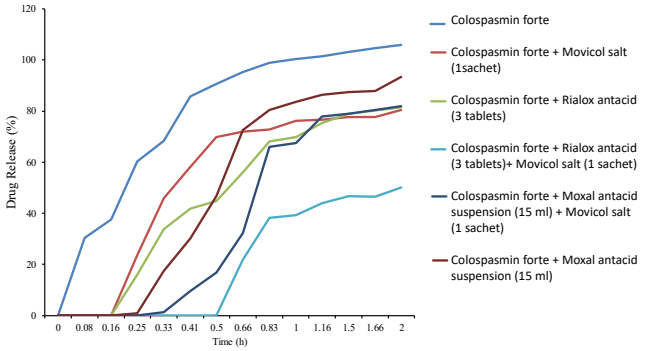

Figure 1. In vitro release profile of Colospasmin forte with Rialox and Moxal antacids and Movicol salt (n = 6).

The combination of Colospasmin forte with 15 mL Moxal suspension alone or in combination with one sachet of Movicol resulted in a weak interaction, due to a decrease of 18.1% and 24%, respectively, in the release of mebeverine HCl (Table 1). The co-administration of Colospasmin forte with three tablets of Moxal in combination with one sachet of Movicol did not result in any significant interaction, as the release of mebeverine HCl was 93.4–102.11% (Table 1); therefore, it would be acceptable to administer those drugs together.

The in vitro release studies of Colospasmin forte revealed that the Higuchi model produced the highest R^2 value (Table 1). The highest rate constants (K values) were exhibited when Colospasmin forte was mixed with 15 mL Rialox suspension or with three Moxal tablets, without Movicol, as the in vitro environment was still acidic (pH 1.95 and 1.99, respectively; Table 1). The acidic environment increased the drug solubility and the dissolution rate. Colospasmin forte alone or mixed with Rialox and Movicol had n values less than 0.45, indicating that the drug release follows Fickian diffusion, which describes the diffusion flux through a surface barrier according to the concentration. When Colospasmin forte was mixed with Movicol or with antacid suspensions or tablets, the n value was between 0.45 and 0.89, indicating anomalous diffusion or non-Fickian diffusion, which refer to combinations of diffusion-controlled and erosion-controlled release.

Figure 2 shows the release profile of Mebagen in the presence of Rialox and Moxal antacids and Movicol salt. It is not recommended to co-administer Mebagen with three tablets of Rialox in combination with one sachet of Movicol salt, because the combination resulted in a decrease in the release of mebeverine HCl of approximately 59.2%. Also, the combination of Mebagen with 15 mL Rialox suspension alone or in combination with one sachet of Movicol resulted in a weak interaction, as there was a decrease of about 16.5–20% in the release of mebeverine HCl. The co-administration of Mebagen with one sachet of Movicol or three tablets of Rialox did not result in any significant interactions, as the release of mebeverine HCl was 93.66–101.23%. Therefore, it would be acceptable to administer those drugs together.

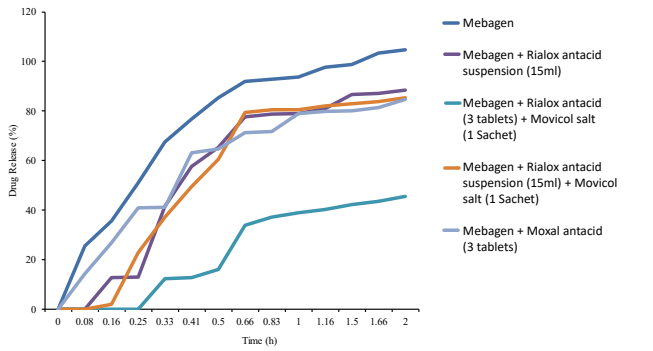

Figure 2. In vitro release profile of Mebagen with Rialox and Moxal antacids and Movicol salt (n = 6).

The combination of Mebagen with three tablets of Moxal resulted in a weak interaction, as there was a decrease of about 20% in the release of mebeverine HCl (Figure 2). The co-administration of Mebagen with one sachet of Movicol, 15 mL Moxal suspension, three tablets of Moxal in combination with one sachet of Movicol, or 15 mL Moxal suspension in combination with one sachet of Movicol did not result in any significant interactions, as the release of mebeverine HCl was 93.7–108.86%; therefore, it would be acceptable to administer those drugs together.

The in vitro release studies of Mebagen revealed that the Higuchi model produced the highest R^2 value (Table 1). The highest K values were exhibited when Mebagen was mixed with Rialox suspension alone (not tablets), Rialox

Table 1. Comparative Values of Correlation Coefficient (R^2) and Rate Constant (K) of In Vitro Release Profiles at 37 + 0.5 °C in Different Models of Drug Release

Drug			Zero-Order Model		First-Order Model		Higuchi Model		Korsmeyer-Peppas Model		Estimated *n* value*
			R^2	*K*	R^2	*K*	R^2	*K*	R^2	*K*	
Colospasmin forte alone			0.792	33.39	0.732	0.502	0.886	64.99	0.651	1.903	0.181
Mebagen alone			0.8245	35.18	0.7471	0.546	0.9091	67.54	0.6218	1.877	0.184
Duspatalin alone			0.7820	7.455	0.728	0.119	0.597	0.872	0.306	1.737	0.0033
Colospasmin forte + Movicol salt (1 sachet)			0.760	36.57	0.649	1.837	0.8572	71.76	0.650	1.513	0.743
Mebagen + Movicol salt (1 sachet)			0.9202	39.55	0.6788	1.358	0.9572	71.64	0.6294	1.561	0.512
Duspatalin + Movicol salt (1 sachet)			0.861	5.157	0.596	0.223	0.715	0.655	0.210	1.377	0.00468
Colospasmin forte +		Rialox antacid (3 tablets)	0.890	43.07	0.678	1.718	0.953	80.36	0.621	1.515	0.640
Mebagen +			0.8239	34.46	0.7465	0.553	0.91	66.27	0.6075	1.859	0.183
Duspatalin +			0.827	3.888	0.580	0.206	0.757	0.545	0.213	1.312	0.00448
Colospasmin forte +		Moxal antacid (3 tablets)	0.929	60.15	0.740	2.023	0.972	109.61	0.611	1.524	0.679
Mebagen +			0.7699	34.7	0.6713	0.559	0.8649	67.89	0.6328	1.891	0.214
Duspatalin +			0.861	5.621	0.673	0.147	0.894	27.36	0.293	39.29	0.0037
Colospasmin forte +		Rialox antacid suspension (15 mL)	0.957	62.08	0.811	2.109	0.968	109.37	0.556	1.431	0.587
Mebagen +			0.821	42.39	0.6458	1.36	0.9031	81.2	0.63	1.646	0.54
Duspatalin +			0.806	6.651	0.726	0.151	0.603	0.762	0.271	1.638	0.00335
Colospasmin forte +		Moxal antacid suspension (15 mL)	0.878	54.27	0.735	2.256	0.935	100.65	0.599	1.432	0.747
Mebagen +			0.7699	34.7	0.6713	0.559	0.8649	67.89	0.6328	1.891	0.214
Duspatalin +			0.773	3.819	0.711	0.328	0.869	18.55	0.253	12.42	0.00691
Colospasmin forte +	Movicol salt (1 sachet) +	Rialox antacid (3 tablets)	0.920	33.27	0.856	2.662	0.931	58.64	0.288	0.891	0.363
Mebagen +			0.9015	26.6	0.7662	1.914	0.9492	48.83	0.5719	1.17	0.581
Duspatalin +			0.871	5.203	0.602	0.225	0.706	0.646	0.209	1.370	0.00464
Colospasmin forte +		Moxal antacid (3 tablets)	0.85	55.27	0.672	1.821	0.925	104.77	0.608	1.615	0.669
Mebagen +			0.764	43.2	0.5614	1.178	0.8655	85.17	0.5947	1.775	0.507
Duspatalin +			0.751	4.723	0.6288	0.1671	0.8782	23.23	0.2594	30.38	0.00413
Colospasmin forte +	Movicol salt (1 sachet) +	Rialox antacid suspension (15 mL)	0.959	58.28	0.924	1.332	0.958	101.44	0.458	1.6314	0.268
Mebagen +			0.8133	42.33	0.648	1.569	0.9001	81.58	0.6143	1.597	0.605
Duspatalin +			0.793	6.528	0.704	0.152	0.623	0.785	0.290	1.631	0.00370
Colospasmin forte +		Moxal antacid suspension (15 mL)	0.926	54.21	0.8427	2.613	0.947	96.55	0.535	1.218	0.675
Mebagen +			0.8254	34.08	0.5421	0.6	0.9046	65.04	0.6437	1.823	0.509
Duspatalin +			0.7234	6.171	0.6665	0.1787	0.8466	30.41	0.2678	36.39	0.00424

** = Represents diffusion or release exponent of in vitro release profile of the drug.*

suspension and one sachet of Movicol, or Moxal tablets and one sachet of Movicol, as the in vitro environment was still acidic (pH = 1.47, 1.52, and 2, respectively). The acidic environment enhanced the drug solubility and increased the rate of dissolution. Mebagen alone or combined with Rialox tablets or Moxal tablets or suspension had n values less than 0.45 (Table 1), indicating that the drug release follows the Fickian diffusion. When the Mebagen was mixed with one sachet of Movicol, Rialox suspension, Rialox suspension or tablets in combination with one sachet of Movicol, or one sachet of Movicol salt in combination with Moxal suspension or tablets, the *n* value was between 0.45 and 0.89, indicating anomalous diffusion or non-Fickian diffusion.

It is not recommended to co-administer Duspatalin with one sachet of Movicol salt alone or with three tablets of Rialox alone or in combination with one sachet of Movicol, because those combinations resulted in a decrease in the release of mebeverine HCl of 35.2%, 50.7%, and 29.7%, respectively (Figure 3). Also, the combination of Duspatalin with 15 mL Rialox suspension in combination with one sachet of Movicol resulted in a weak interaction, as there was a decrease of about 16.8% in the release of mebeverine HCl. The co-administration of Duspatalin with 15 mL Rialox suspension did not result in any significant interactions, as the release of mebeverine HCl was 91.36%; therefore, it would be acceptable to administer those drugs together.

It is not recommended to co-administer Duspatalin with three tablets of Moxal alone or in combination with one sachet of Movicol or with 15 mL Moxal suspension alone, because those combinations resulted in a decrease in the release of mebeverine HCl of 27.7%, 42%, and 15.34%, respectively (Figure 3). Also, the combination of Duspatalin with 15 mL Moxal suspension alone or in combination with one sachet of Movicol resulted in weak interactions, as there was a decrease of 15.34% and 25%, respectively, in the release of mebeverine HCl .

The in vitro release studies of Duspatalin with Rialox and Movicol showed that the zero-order model, in which the drug release rate is independent of the concentration of the dissolved substance, produced the highest R^2 value (Table 1). On the other hand, in vitro release studies of Duspatalin with Moxal and Movicol showed that the Higuchi model produced the highest R^2 value (Table 1). The highest *K* values were exhibited when Duspatalin was alone or in the presence of Movicol during dissolution. Duspatalin alone or mixed with an antacid or Movicol had *n* values less than 0.45, indicating that the drug release follows Fickian diffusion (Table 1).

For the Rialox antacid, the results can be summarized as follows: (a) 59.2% of mebeverine HCl in the Mebagen film-coated tablet was lost when combined with three tablets of Rialox and one sachet of Movicol; (b) 55.7% of mebeverine HCl in the Colospasmin forte sugar-coated tablet was lost when combined with three tablets of Rialox and one sachet of Movicol; (c) 50.7% of mebeverine HCl in the Duspatalin retard capsule was lost when combined with three tablets of Rialox; (d) 35.2% of mebeverine HCl in the Duspatalin retard capsule was lost when combined with one sachet of Movicol; and (e) 30% of mebeverine HCl in the Duspatalin retard capsule was lost when combined with three tablets of Rialox and one sachet of Movicol; therefore, the following order was concluded: a (59.2%) > b (55.7%) > c (50.7%) > d (35.2%) > e (30%).

For the Moxal antacid, the results can be summarized as follows: (a) 41.8% of mebeverine HCl in the Duspatalin retard capsule was lost when combined with three tablets of Moxal and one sachet of Movicol; (b) 27.7% of mebeverine HCl in the Duspatalin retard capsule was lost when mixed with three tablets of Moxal; (c) 25% of mebeverine HCl in the Duspatalin retard capsule was lost when combined with 15 mL Moxal suspension and one sachet of Movicol; and (d) 15.34% of mebeverine HCl in the Duspatalin retard capsule was lost when combined with 15 mL Moxal suspension; therefore, the following order was concluded: a (41.8%) > b (27.7%) > c (25%) > d (15.34%).

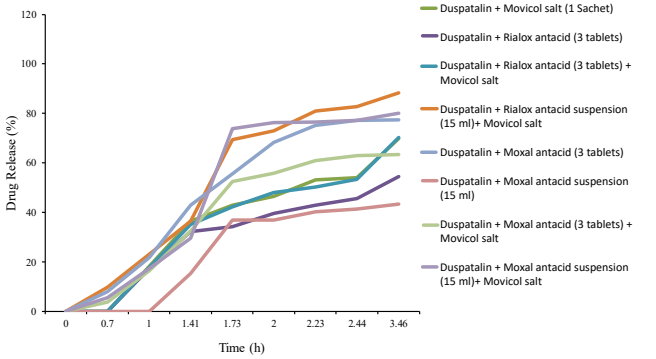

Figure 3. In vitro release profile of Duspatalin with Rialox and Moxal antacids and Movicol salt (n = 6).

Differential Scanning Calorimetry Analysis

The DSC data are presented in Figure 4. The curve for pure mebeverine HCl showed a sharp endothermic response corresponding to the melting of the mebeverine HCl at 133 °C. The DSC thermograms of mebeverine HCl

combined with Rialox or Moxal were suggestive of a possible interaction between mebeverine HCl and Rialox or Moxal and Movicol (Figure 4).

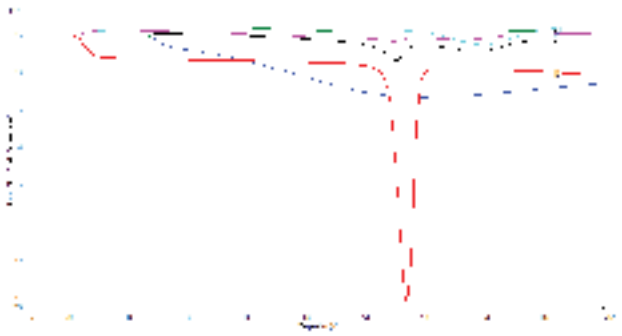

Figure 4. Differential scanning calorimetry analysis of mebeverine HCl interactions with Rialox and Moxal antacids and Movicol salt. A: Rialox; B: mebeverine; C: mebeverine + Rialox + Movicol; D: mebeverine + Moxal + Movicol; E: Moxal; F: Movicol.

Infrared Spectroscopy Determinations

The IR spectra are shown in Figure 5. The spectrum of mebeverine HCl displayed characteristic bands at 2945, 1717, 1265, and 1221 cm^{-1} assigned to νCH (aliphatic), νC=O (ester), and νC-O (ether; for the last two peaks), respectively. The spectra of mebeverine HCl combined with Rialox or Moxal and Movicol were suggestive of possible interaction between mebeverine HCl and Rialox or Moxal and Movicol. The intensity of the C=O peak around 2945 cm^{-1} was reduced for physical mixtures of mebeverine HCl and Rialox or Moxal at a 1:1 ratio, and the peak disappeared for those physical mixtures at a ratio of 1:2.

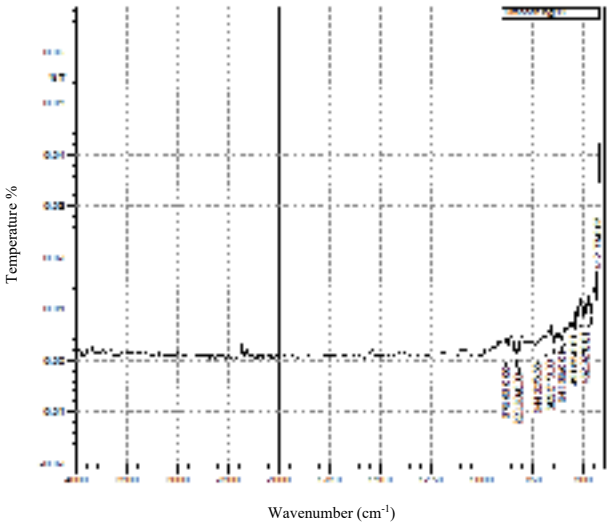

Figure 5. Infrared spectrum determinations of mebeverine HCl with Rialox and Moxal antacids and Movicol salt.

The previous study showed that mebeverine HCl was absorbed by the magnesium antacid, which likely caused some of the observed decrease in the release of mebeverine HCl in the current study from the various formulations (sugar, film, and retard release tablets) in the presence of the antacids. Antacids can alter drug absorption due to physical adsorption; however, the potential effect of antacids and Movicol on mebeverine HCl absorption could not be assessed in this in vitro study (*16, 17*). Despite that, it had been previously suggested that antacids increase the pH of the medium leading to decrease in the dissolution of many antibiotics and the dissolution rate is markedly reduced at high pH values; however, there was no significant increase in pH by the addition of these antacids in the dissolution medium in the current study (*17, 18*). Furthermore, differences in the aluminium/magnesium ratios in the tested antacid tablets and suspensions could affect the release of the mebeverine HCl. The types and amounts of excipients or suspending agents added to the antacids and the types and grades of polymers used in the preparation of the suspensions might also affect the viscosity and sedimentation rate in the suspension system.

On the other hand, differences in the form of delivery (sugar-coated tablet, film-coated tablet, or retard release capsule) could account for the observed differences in the release of mebeverine HCl in the system. Clearly, the different dosage forms of a drug can play a role in determining in vitro availability of the drug alone or in combination with other drugs such as antacids. The results (Tables 1) showed that the presence of the salts (Movicol) used to treat constipation, either alone or in combination with the antacids, affected the release rate of the antispasmodic drug (mebeverine HCl). Those results might be due to the effect of sodium chloride on the electrical layer as previously reported and the presence of sodium bicarbonate, which alters the pH. In addition, polyethylene glycol 3350 in the formula of Movicol might affect viscosity (*19*).

CONCLUSION

In the present study, the release rate of mebeverine HCl from different formulations was reduced when mebeverine HCl formulations were combined with different antacids and/or Movicol salt. In addition, the results of DSC and IR were also suggestive for interactions between different formulations of mebeverine HCl and antacids and/or Movicol salt. Hence, these interactions

might lead to an alteration in the clinical efficacy of mebeverine HCl; therefore, further in vivo studies should be conducted to assess the effect of such interactions on drug absorption and bioavailability.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest related to this article.

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