Many diseases of the digestive tracts, including oesophageal reflux, require polypragmasy i.e., simultaneous administration of several drugs. Such therapeutic modality increases the efficacy of treatment, but on the other hand, exposes the patient to the risk of drugs interaction. Drugs interaction may cause increase or decrease of their activity (1–2). Taking into account multifactorial pathogenesis of oesophageal reflux disease, the use of combination of drugs inhibiting the secretion of hydrochloric acid and cytoprotective agents (sucralfate) with prokinetic drugs (metoclopramide and cisaprid) seems highly justified (3–4).

Preliminary investigations of the physical and chemical properties of sucralfate demonstrated its capability of polymerization, forming complexes and chelates. The substance reveals strong adsorption potentials which largely depend on pH of the environment. This may result in delayed or decreased absorption of simultaneously administered drugs. In our previous studies (5–7), we have demonstrated adsorption properties of sucralfate in relation to sulfasalazine, certain inhibitors of H2 receptors as well as selected spasmylytics. In the present study, we have decided to investigate the character of the interactions between sucralfate and certain prokinetic agents used in the treatment of oesophageal reflux disease, taking into account certain physicochemical factors.

EXPERIMENTAL

Substances
Metoclopramide, analytically pure, Kraków Pharmaceutical Factory „Polfarma” Cracow, Poland; cisaprid, analytically pure, Kutno Pharmaceutical Factory „Polfa” Kutno; sucralfate, analytically pure (KRKA), Slovenia; Venter tabl. (KRKA), Poland; hydrochloric acid, analytically pure, (POCH) Gliwice, Poland; sodium hydroxide, analytically pure, (Chemical Works Oświęcim); potassium dihydrogenphosphate, analytically pure, (POCH), Gliwice, Poland.

Preparation of standard solutions of the investigated prokinetic agents
0.006 g samples of analytically pure cisaprid were weighed on an analytical balance and subsequently transferred to 100 cm³ volumetric flasks, diluted and supplemented with Clark-Lubs buffer at pH = 1.5, Walpole’s acetate buffer at pH = 3.6, Sörensen’s buffer at pH = 5.0 (8). Cisaprid solution from tablets was prepared in a similar way. For this purpose, 0.108 g portions of powdered tablets were weighed and the obtained solution was filtered. 0.04 g portions of analytically pure metoclopramide were weighed on the analytical balance and transferred to volumetric flasks, diluted and buffer solution
at specific pH was added to the volume of 100 cm³. Metoclopramide solution from tablets was prepared in a similar way, using 0.44 g weighed portions of powdered tablets. The obtained solution was filtered.

Quantitative analysis of the investigated prokinetic drugs

Cisaprid was assessed spectrophotometrically following prior dissolution of the investigated samples in methanol (10) at λ wavelength = 275 nm. Metoclopramide was assessed spectrophotometrically after dissolving the samples in 0.1 M HCl solution (11) at λ = 309 nm.

The levels of the investigated active agents were obtained from standard plots described by the equation for cisaprid $y = 0.4727x - 0.0074$, and for metoclopramide $y = 3.4205x - 0.002$.

Preparation of sucralfate in the form of adhesive paste

Determination of adsorption isotherms for the tested prokinetic drugs

The methods of sucralfate preparation in the form of adhesive paste as well as the determination of adsorption isotherm lines of the investigated therapeutic agents was presented in previously published reports (6–7).

Research

Adsorbance of the investigated prokinetic drugs was measured by means of a statistical method in the concentration range from 0.6 mg/10 cm³ to 0.06 mg/10 cm³ for cisaprid and from 4 mg/10 cm³ to 0.4 mg/10 cm³ for metoclopramide, using various buffer solutions at pH from 1.5 to pH = 5.0.

Adsorbance was determined for selected prokinetic drugs in the form of powder and tablets.

Sucralfate occurs in various forms depending of pH of the environment. At pH below 3, it forms polymers in the form of adhesive paste. At pH = 3.0 – 6.5 sucralfate has the form of suspension. At pH above 6.5 and higher, it undergoes hydrolysis (12). Thus the adsorbance of the selected active agents was measured on sucralfate in the form of paste and suspension.

The levels of the investigated drugs corresponded to the average single doses of the drugs used in therapy and pH of the buffers was the same as pH in individual parts of the digestive system.

The measurements of the bound amounts of substances stimulating peristalsis were used to determine Freundlich adsorbance isotherms (Figures 1–2), to determine the parameters of adsorbance isotherm equation (Table 1) and to calculate mean percentage of the adsorbed dose of the drug (Table 2).

Standard deviations of mean adsorbance levels were within the limits from 0.12 mg/cm³ to 0.94 mg/cm³ and variation coefficients were from 2.21% to 9.78%.

RESULTS AND DISCUSSION

Observed delayed absorption of the drug in the presence of sucralfate can be explained by the formation of complexes, chelates and adsorption (11).

Moreover, obtained results prove that the investigated active agents are adsorbed on sucralfate in all the investigated pH ranges, and the capability of sucralfate binding depends on its form i.e., indirectly on pH of the environment.

Figure 1. Adsorption isotherms of metoclopramide (substance) from buffer solutions on sucralfate.

Figure 2. Adsorption isotherms of cisapride (substance) from buffer solutions on sucralfate.
At pH corresponding to fasting pH in gastric environment, the mean sorption rate in relation to the levels of cisaprid was observed to range from 12.8% to 59.2%, while for metoclopramide it was from 1.4% to 4.7% and it was the lowest of all the analyzed samples (Table 2).

At pH = 3.6 and 5.0, corresponding to pH in a full stomach, the mean sorption rate for the highest dose of cisaprid on sucralfate suspension was 81.7% and 72% respectively and for metoclopramide – 18% and 12%, respectively.

This proves the observation that sorption on

<table>
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<tr>
<th>Form of sucralfate</th>
<th>Concentration of cisaprid [mg/10 cm³]</th>
<th>pH</th>
<th>pH</th>
<th>pH</th>
<th>Concentration of metoclopramide [mg/10 cm³]</th>
<th>pH</th>
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<td>3.6</td>
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<td>X%</td>
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<td>5.57</td>
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</table>

X% – mean percentage adsorbance

Table 2. Parameters of the Freundlich isotherm equation of prokinetic drugs sorption from buffer solutions on sucralfate

<table>
<thead>
<tr>
<th>Active agent</th>
<th>pH of investigated solutions</th>
<th>l/n± D1/ n</th>
<th>k ± D k</th>
<th>r</th>
<th>Rg. b. std.</th>
<th>l/n± D1/ n</th>
<th>k ± D k</th>
<th>r</th>
<th>Rg. b. std.</th>
</tr>
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<td>Cisaprid</td>
<td>pH 1.5</td>
<td>0.2698 ± 0.054</td>
<td>4.5814 ± 0.01</td>
<td>0.9892</td>
<td>0.0215</td>
<td>1.0146 ± 0.060</td>
<td>0.2036 ± 0.092</td>
<td>0.9648</td>
<td>0.1432</td>
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<tr>
<td></td>
<td>pH 3.6</td>
<td>0.3069 ± 0.029</td>
<td>8.4839 ± 0.02</td>
<td>0.9976</td>
<td>0.089</td>
<td>1.6545 ± 0.058</td>
<td>0.6685 ± 0.012</td>
<td>0.9944</td>
<td>0.0600</td>
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<tr>
<td></td>
<td>pH 5.0</td>
<td>0.2738 ± 0.056</td>
<td>6.8454± 0.095</td>
<td>0.9826</td>
<td>0.0432</td>
<td>1.0583 ± 0.086</td>
<td>0.4333 ± 0.092</td>
<td>0.0059</td>
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<tr>
<td>Metoclopramide</td>
<td>pH 1.5</td>
<td>0.2658 ± 0.018</td>
<td>1.0048 ± 0.028</td>
<td>0.9914</td>
<td>0.1112</td>
<td>0.4697 ± 0.094</td>
<td>0.1175 ± 1.27</td>
<td>0.9802</td>
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<td>pH 3.6</td>
<td>0.8995 ± 0.056</td>
<td>1.5563 ± 0.002</td>
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<td>0.1231</td>
<td>1.4768 ± 0.091</td>
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<td>0.9991</td>
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<tr>
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<td>pH 5.0</td>
<td>0.8807 ± 0.055</td>
<td>1.2277 ± 0.001</td>
<td>0.9938</td>
<td>0.0121</td>
<td>1.0871 ± 0.089</td>
<td>0.0735 ± 0.098</td>
<td>0.9826</td>
<td>0.0741</td>
</tr>
</tbody>
</table>

l/n, k – Freundlich adsorption isotherm equation constants;

r – correlation coefficient;

D1/n, Dk – l/n, k parameters errors in the Freundlich isotherm equation;

Rg. b. std – regression standard deviation
sucralfate in the form of adhesive paste is significantly decreased in relation to at on sucralfate suspension. This results from a strong dissociation of sucralfate at pH = 1.5, which takes the form of adhesive paste.

Mathematic interpretation of the adsorbance findings of certain prokinetic drugs allowed to plot Freundlich adsorbance isotherms as logarithmic functions of the amount of the drug adsorbed by sucralfate mass unit by equilibrium concentration of adsorbents in buffer solutions.

\[ \log \frac{x}{m} = \frac{1}{n} \log c + \log k \]

\( c \) – concentration of adsorbent in equilibrium solution (mg/cm³)
\( x \) – amount of adsorbed substance (mg)
\( k, 1/n \) – isotherm equation constants

The magnitude of \( 1/n \) parameter in the Freundlich equation allows to evaluate the rate of adsorbance of a given substance. The magnitude of \( k \) constant determines the adsorption capability of sucralfate.

Thus it may be presumed that metoclopramide and cisaprid adsorbance on sucralfate may result mainly from the effect of physical forces (intermolecular, electrostatic).

Freundlich adsorption isotherms presented in Figures 1–2 demonstrated the enhancement of the sorption with increasing concentration of the investigated drugs. Mean sorption obtained at the highest concentration of the investigated drugs was 1.5 to 4.5 higher than that obtained at the lowest concentrations of the investigated substances.

The parameters and the analysis of the course of isotherms of the investigated prokinetic drugs from buffer solutions (Table 1, Figures 1–2) demonstrated differences in the affinity of the compounds to sucralfate at various pH of the environment.

Statistical analysis was carried out by means of the Student test. Value \( p<0.05 \) was assumed as statistically significant.

The adsorbance capability of sucralfate (k) at pH = 3.6 is the highest of all the investigated pH ranges. Adsorbance capability of sucralfate (k) at pH = 3.6 is the highest in case of cisaprid (k=8.48), while for metoclopramide, it was found to be seven times lower (k=1.56). Thus the findings have demonstrated that cisaprid is the best adsorbed drug of all the investigated prokinetic agents.

The highest, twofold increase of adsorption capability of sucralfate (k) at pH changing from 1.5 to pH = 3.6 was observed for cisaprid. Metoclopramide revealed lower dynamic increase of the adsorbance capability in the same conditions. The differences in \( k \) parameter for cisaprid and metoclopramide were statistically significant for \( p = 0.05 \).

Obtained values of \( 1/n \) parameter of the Freundlich equation describing adsorbance capability of prokinetic drugs demonstrated that there were slight differences in the adsorbance rate on sucralfate.

Analysing sorption findings, adsorbance on sucralfate from tablets was found to be decreased in relation to sucralfate suspension at all investigated pH ranges. Adsorption capability of substances coming from tablets was found to be 2–8% lower. This phenomenon can be explained by the affect of adjuvant substances which slightly decreased adsorption due to their powerful hydrophobic properties.

CONCLUSIONS

The above considerations lead to the conclusion that the investigated prokinetic drugs interact with sucralfate. The interaction has an antagonistic character and consists in adsorption of the investigated drugs on sucralfate.

Mathematical interpretation of the findings was applied to plot the Freundlich adsorption isotherms. Thus, we can presume that adsorption has a physical character.

Cisaprid was found to be the best adsorbed drug of the investigated digestive tract motility stimulants, while the adsorbance capability of metoclopramide was much lower.

Investigations carried out so far on the character and the degree of mutual interactions of gastroenterological agents (H₂ histamine receptors inhibitors, spasmyotics, prokinetic drugs) in the presence of sucralfate confirm an antagonistic interaction consisting in adsorption.

The adsorption capability of sucralfate depend largely on the reaction of the environment. At pH below 3, it dissociates according to the formula:

\[ 4H^+ + 4Cl^- + Al(OH)_3SO_R = [Al(OH)]^+ + RSO_3^- + 4Cl^- \]

in which we can observe an increased solubility of aluminum ions, what leads to the formation of sucralfate polymers of the consistency of adhesive paste with a relatively small specific surface and weakly developed adsorption surface. Thus adsorption of the investigated agents on sucralfate at pH = 1.5 i.e., administered in fasting conditions, is lower in comparison to the remaining pH of the environment. H₂ histamine receptor inhibitors reveal medium capability of adsorption at the level of 20.4%–49.5%.
spasmolytic drugs are adsorbed in 7%–17%, while prokinetic agents in 4.7%–59% (6,7).

At pH = 3.0–6.5, an increased solubility of sucrose sulphate in relation to that of aluminium is observed in a sucralfate particle, which assumes a form of suspension with much more potent adsorption capability. The investigated H₂ histamine receptor inhibitors administered together with sucralfate postprandially reveal mean adsorption rates at the level of 49%–83.1%, spasmolytic agents – at 12.4%–27.8%, while the investigated prokinetic drugs – at 18%–81.7% (6,7).

Moreover, adsorption of the investigated drugs on sucralfate depends on their concentration, adsorption of the administered drug on sucralfate increases with dose.

The above analysis of the results of our studies confirms the significance of the problem and allows to complete the biopharmaceutical information concerning the investigated preparations as well as enables control of the efficiency of polypragmasy.

REFERENCES

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