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In Vitro Investigation on Interaction of Ranitidine Hydrochloride in the Presence of Cross-Linked Carboxymethyl Cellulose Sodium.

B. Grimling, J. Pluta

Summary: The adsorbance of ranitidine hydrochloride – drug selective H_2 histamine receptor inhibitor used In the treatment of gastric and duodenal ulcer was investigated in the presence of croscarmellose, a cross- linked polymer of polysaccharide character used as a swelling additive in oral pharmaceutical formulations – capsules, tablets and granules.

The evaluation of adsorbance capability was carried out by means of a statistical method in *in vitro* conditions, taking into account environmental pH, concentration of the investigated drug as well as the properties of the polymer. Obtained results prove that the analyzed active agent is adsorbed on polymer at all the investigated pH ranges and the capability of polymer binding depends on environmental pH. The highest binding capability was revealed in samples with pH of 7.6, (adsorbance capacity $k = 0.6958$) while the lowest binding capability was observed at pH 1.5 (adsorbance capacity $k = 0.0005$) in the presence of croscarmellose sodium. Level of adsorption depends on the analyzed drug concentration and adsorption on polymer in increasing concentration and pH environment.

Keywords: croscarmelose sodium; drug-excipient interaction; Freundlich adsorption isotherm; ranitidine hydrochloride

Introduction

Drug excipient interactions are among the most important factors that should be considered in any preformulation study. Many reports in the last few decades showed that excipients can physically or chemically interact with drug substances either in the solid state or liquid state. These interactions can affect the stability,[1] dissolution[2] and possibly the bioavailability of drug.[3] Most drug-excipient interactions that have been identified affect the processes of disintergration and/or dissolution. Effects on physiological factors or processes such as the pH of the microenvironment, the stability of a drug substance in the gastrointenstinal tract and the permeability of gastrointestinal membranes to the drug can also alter the bioavailability of a drug.

Adsorption is one of most important mechanisms of interaction between drugs and excipients.

The adsorption of drug molecules onto the surface of excipients can reduce drug particle size and increase the surface area of the drug available to the dissolution medium.[4] Both of these effects might increase dissolution and, as a result, bioavailability. Adsorption of drug molecules can render the drug unavailable for dissolution and diffusion and this might, in turn, reduce bioavailability.[5] Adsorption can be reversible and might not affect the bioavailability of the drug. The forces involved in this type of interaction can be physical or chemical in nature, or a combination of both.

Physical interaction occurs to some extent in all systems and is primarily due

Departament of Drug Form Technology, Wrocław Medical University, 38 Szewska Str,.50-139 Wrocław, Poland
E-mail: bamag@interia.pl

to weak van der Waals' attraction forces. In some systems, however, stronger electrostatic attractions can be involved. Chemical interaction is more specific and is primarily attributed to covalent bond formation and occurs only when chemical interaction between the drug and excipent is possible.

Croscarmellose sodium is a cross-linked polymer of carboxymethylcellulose sodium. It is insoluble in aqueous solution, but can swell to two to four times of the original volume in water solutions.[6] Ranitidine hydrochloride is the active compound of the pharmaceutical formulation. It competitively inhibits the action of histamine on the H_2-receptors of parietal cells, and reduces gastric acid secretion under daytime and nocturnal basal conditions. The drug is used for the short-treatment of active duodenal ulcer, active and benign gastric ulcer, treatment of pathogenic gastrointestinal hypersecretory conditions such as Zollinger-Ellison Syndrome, it also gives short-term symptomatic relief of gastroesophaegal reflux.[7]

Preliminary investigations of the physical and chemical properties of crosscarmellose sodium demonstrate its capability of 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 the present study we have decided to investigate the character of the interactions between croscarmellose sodium-excipient and ranitidine hydrochloride used in the treatment of peptic ulcers and related disorders, taking into account certain physicochemical factors.

Research

Adsorbance of the investigated drug was measured by means of a statistical method at concentration ranges from 0.03 mg/10cm^3 to 3 mg/10cm^3, using various buffet solutions at pH from 1.5 to pH 7.6. Concentration of active substances was corresponding to average single doses used in the treatment, pH of the buffers corresponded to pH in successive segments of the digestive tract, temperature of the medium corresponded to physiological and dietary conditions. 0,2 g portions of powdered croscarmellose sodium (Avebe, Vendam, The Netherlands) were placed in six 50 cm^3 Erlenmayer flasks to which 1 cm^3, 2 cm^3, 4 cm^3, 6 cm^3, 8 cm^3, 10 cm^3 of ranitidine hydrochloride (Polpharma SA, Poland) stock solution was added. The volumes were made up to 10 cm^3 with buffer solution

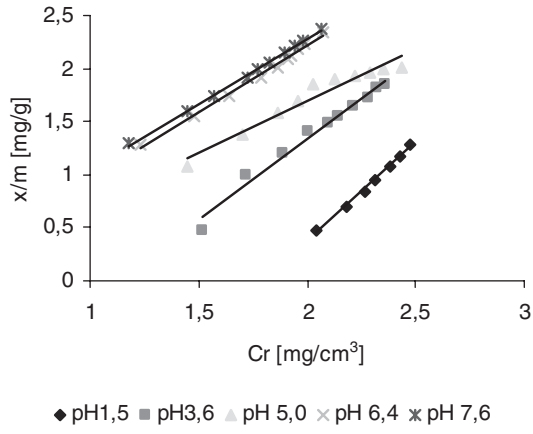

Figure 1.
Freundlich Adsorption isotherms of ranitidine hydrochloride from buffer solutions on croscarmellose sodium; Cr- concentration of adsorbent in equilibrium solution (mg/cm^3)x/m- amount of adsorbed substance (mg/g).

Table 1.
The effect of environment pH on the adsorption of Ranitidine hydrochloride in the presence croscarmellose sodium.

C[a)]	pH 1.5	pH 3.6	pH 5.0	pH 6.4	pH 7.6
[mg/cm^3]	X[b)] [%]	X[b)] [%]	X[b)] [%]	X[b)] [%]	X[b)] [%]
0.003	2.31	15.59	29.81	52.73	58.02
0.006	2.49	16.83	33.15	54.72	59.00
0.009	2.68	17.79	34.76	55.83	60.12
0.012	2.80	18.83	38.48	57.12	61.20
0.015	3.32	20.06	41.61	58.63	62.03
0.018	3.76	20.69	47.32	60.14	63.15
0.021	4.28	21.28	51.28	61.17	64.05
0.024	4.79	21.69	56.02	62.61	65.10
0.027	5.30	23.59	60.06	63.69	66.00
0.030	5.80	24.19	62.80	64.62	66.76

a) C – Concentration of Ranitidine hydrochloride;
b) X% - mean percentage adsorbance;

of a relevant pH. The flasks were agitated on a rotary shaker at 80 cycles/minute at 36 °C for 180 minutes. Next the mixtures were allowed to stand for 30 minutes to enable decanting the solutions, centrifuged and the supernatants were used for the determination of levels of the investigated therapeutic agent. Ranitidine hydrochloride level was determined spectrophotometrically following prior dissolution of the investigated samples in 0.1 M solution hydrochloric acid at $\lambda = 227$ nm. The levels of the investigated active agent was found from standard plots described by the equation $y = 5.4763x\text{-}0.0561$. The correlation coefficient was 0.9995 and regression standard deviation – 0.037169.

The amount of the drug adsorbed on croscarmellose sodium was calculated from the difference between the amounts of the investigated drugs determined prior to and after sorption.

The measurements of the bound amounts of substance stimulating peristalsis were used to determine Freundlich adsorbance isotherms (Figure 1), to determine the parameters of adsorbance isotherm equation (Table 2) and to calculate mean percentage of the adsorbed dose of the drug (Table 1). Standard deviations of mean adsorbance levels were in the limits from 0.012 mg/cm^3 to 0.094 mg/cm^3 and variation coefficients were from 2,21% to 4,78%.

Results and Discussion

The observed delayed absorption of the drug in the presence of croscamellose sodium can be explained by formation of complexes, chelates and adsorption.[8]

Moreover, obtained results prove that the investigated active agent is adsorbed on croscarmellose sodium at all the inves-

Table 2.
Parameters of Freundlicha isotherm equation of Ranitidine hydrochloride sorption from buffer solutions on croscarmellose sodium.

pH of investigated solution	$1/n^{a)} \pm \Delta 1/n^{b)}$	$k^{a)} \pm \Delta\ k^{b)}$	r[c)]	Rg. b. std.[d)]
pH 1.5	0.9684 ± 0.054	0.00049 ± 0.00001	0.9906	0.0215
pH 3.6	1.2167 ± 0.029	0.0674 ± 0.0002	0.9976	0.0891
pH 5.0	1.2639 ± 0.056	0.4886 ± 0.009	0.9941	0.0432
pH 6.4	1.5237 ± 0.018	0.5757 ± 0.001	0.9911	0.0112
pH 7.6	1.8843 ± 0.056	0.6958 ± 0.002	0.9974	0.1231

a) 1/n. k – Freundlich adsorption isotherm equation constants;
b) Δ1/n. Δk - 1/n. k parameters errors in Freundlicha isotherm equation;
c) r – correlation coefficient;
d) Rg. b. std – regression standard deviation.

tigated pH ranges, and the capability of croscarmellose sodium binding depends on its form, i.e. indirectly on pH of the environment.

At pH 1.5 corresponding to fasting pH in gastric environment, the mean sorption rate in relation to the levels of ranitidine hydrochloride was observed to range from 2.3% to 5.8% and it was the lowest of all the analyzed samples in the acidic medium (Table 1).

The lowest adsorbance at pH 1.5 may be explained by chemical properties of croscarmellose sodium, which assumes negative charge only at pH > 2 and then it can reveal electrostatic adsorbance in relation to the actions of the active substance of a slightly alkaline character.[9]

At pH 3.6 and 5.0 corresponding to pH in a full stomach, the mean sorption rate for the highest concentration of the drug on croscarmellose was 24.2% and at pH 5.0 it was up to 62.8% respectively. At pH 6.4 described as duodenal environment, the average sorption value on the polymer increased to 64.6% and at pH 7.6 corresponding to this of the small intestine, it was 66.8% and was the highest of all the examined ranges. Croscarmellose sodium is a cross linked polymer of carboxymethylcellulose sodium and insoluble in aqueous solution, but can swell to two to four times of original volume in water solutions.[6] Because of carboxylic groups, the surface of crosscarmellose sodium is ionizable in an aqueous solution and carries a negatively charged ion (–COO–).[2] The increase of ranitidine hydrochloride adsorption on a polymer with pH increasing from 1.5 to pH 7.6 may be explained by swelling properties of croscarmellose sodium, which increase with increasing pH of the environment toward alkaline pH. Thus the proper surface of the polymer as well as its sorption capability increase.

Mathematic interpretation of the adsorbance findings of the examined drug 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/cm^3)

x- amount of adsorbed substance (mg/)

k, 1/n – isotherm equation constants

The magnitude of 1/n parameter in Freundlich equation allows to evaluate the rate of adsorbance of a given substance. The magnitude of k constant determines the adsorption capability of croscarmellose sodium. The trial to describe ranitidine hydrochloride adsorption on the investigated polymer by means of Langmuir's curve failed, what may prove lack of chemisorption.

Thus it may be presumed that the adsorbance on croscarmellose sadium may result mainly from the effect of physical forces (intermolecular, electrostatic).

Freundlich adsorption isotherms presented in Figure 1 demonstrated enhancement of the sorption with increase of concentration of the investigated drug. Mean sorption obtained at the highest concentration of the investigated drug was 0.5 to 4.0 higher than this obtained at the lowest concentrations of the investigated substances.

The parameters and the analysis of the course of isotherms of the investigated drug from buffer solutions (Table 2, Figure 1) demonstrated differences in the affinity of the compounds to polymer at various pH of the environment.

Statistical analysis was carried out by means of a uni-factorial Anova/Manova analysis, post hoc Nir test, confirmed statistically significant differences in the percentage of value adsorption of drug on polymer. Value $p < 0.05$ was assumed as statistically significant.

The adsorbance capability of croscarmelose (k) at pH 7.6 is the highest of all the investigated pH ranges. Adsorbance capability of polymer (k) at pH 7,6 is the highest in case of ranitidine hydrochloride ($k = 0{,}6958$).

The highest, 1000-fold increase of adsorption capability of polymer (k) was observed

at pH changing from 1.5 to pH 7.6. Obtained values of 1/n parameter of Freundlich equation describing adsorbance capability of ranitidine hydrochloride demonstrated that there were slight differences in the adsorbance rate on the investigated polymer.

Conclusions

The above considerations lead to a conclusion that the investigated drug interacts with the polymer. The interaction has an antagonistic character and consists in adsorption of the investigated substance on excipient.

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

The rate of adsorbance largely depends on pH. The highest adsorbance capability was found in samples at pH 7.6 at pH corresponding to that in the small intestine juice. Adsorbance capability of the investigated drug also depends on this concentration and on the physicochemical properties of croscarmellose sodium.

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