Development of lipid-based gastroretentive capsules and influence of digestion process

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INTRODUCTION

Gastroretentive delivery systems are retained in the stomach for a prolonged period of time, during which they release the bioactive compounds in a controlled manner (1). Lipid-based floating systems with Gelucire® 43/01 are promising due to their triglyceride-based nature that promotes contact with the intestinal membranes and increases the solubilization, while at the same time, the prolonged release is enabled and thus the absorption of bioactive compounds is improved. However, lipid-based formulations are substrates for digestive lipases and digestion can significantly influence their properties, i.e. release of bioactive compounds. Furthermore, it is generally supposed that pancreatic lipase is the main enzyme involved in lipolysis, and consequently, the gastric step is omitted in most *in vitro* digestion models. However, it is known that 10–30 % of the triglyceride lipolysis is catalyzed by gastric lipase (2) and therefore this step could be important in the case of lipid-based gastroretentive formulations. Gentian (*Gentiana lutea* L., Gentianaceae) root extract is chosen as the model active compound since it has a local effect in the stomach. Moreover, gentiopicroside, a dominant bioactive compound in gentian extract has low bioavailability and short elimination half-life, thus it was reported that there is a need for formulation with prolonged release (3).

Therefore, the aim of this study was to develop lipid-based gastroretentive capsules with prolonged release of gentiopicroside, as well as to elucidate the influence of gastric and intestinal enzymes on the dissolution of gentiopicroside from developed formulation.

MATERIALS AND METHODS

Gentian root extract preparation

Gentian extract was obtained by using ethanol (50 %, v/v) as a solvent, while the solid-to-solvent ratio was 1:2 (g/ml). Ethanol was evaporated from the filtrated extract.

Double emulsion preparation

Double emulsions ($W_1/O/W_2$) were fabricated according to the multiple (double) emulsion–melt dispersion technique according to the previously described method (4). The composition of the double emulsion is presented in Table 1.

Preparation of gastroretentive capsules

The double emulsion was freeze-dried and obtained powder was filled in hard gelatin capsules No. 1 using a semi-automatic capsule filling machine. Gentian extract powder was obtained by freeze-drying of liquid gentian extract, under the same conditions as emulsion.

		Emulsion (%)	Powder (%)
W_1	Gentian extract	13.13	19.35
	Sodium chloride	0.06	0.25
	Sodium alginate	0.26	1.12
O	Gelucire® 43/01	5.32	22.73
	Polyglycerol polyricinoleate	0.98	4.21
W_2	Purified water	68.00	0
	Sodium chloride	0.23	0.99
	Sodium alginate	1.58	6.73
	Trehalose	7.88	33.66
	Lecithin	1.58	6.73
	Sylysia 350	1.00	4.23

Table 1. Composition of double emulsion and gastroretentive capsules.

Powder characterization

Powder yield and encapsulation efficiency were calculated according to the reported procedure (4). Also, the flowability of powder was assessed by calculating the Carr index and Hausner ratio according to the European Pharmacopoeia 11.0 (2023).

Capsules evaluation

The floating lag time and floating duration of capsules and dry gentian extract were determined in the water bath at 50 rpm at 37 °C. Samples were placed in glass beakers, containing 200 ml of 0.1 M HCl and 0.2 % methylcellulose. Capsules, as well as dry gentian extract, were tested using the USP IV apparatus to evaluate the release kinetics of gentiopicroside, according to the previously reported method (4). Furthermore, during *in vitro* release testing of investigated formulation, the average size of the dispersed nanostructures was measured after 15 min and after 6 h, by using photon correlation spectroscopy. *In vitro* digestion of powder obtained after freeze-drying of emulsion and

capsules with the same powder was conducted according to the INFOGEST protocol (5).

RESULTS AND DISCUSSION

The yellow and homogenous powder was obtained after freeze-drying of prepared double emulsion. Powder yield (92.64 ± 1.94) was high, as well as gentiopicroside encapsulation efficiency (97.34 ± 0.29). Hausner ratio (1.15 ± 0.02) and Carr index (13.35 ± 0.34) indicated that powder with good flowability was developed. Capsules floated immediately after contact with the medium and the floating time was longer than 6 hours. This result indicated that gastroretentive capsules were developed and the floating of capsules was attributed to low density of lipid material (Gelucire® 43/01). On the other hand, gentian extract powder was dissolved immediately after the contact with medium under simulated gastric conditions. The dissolution profile of gentiopicroside from dry gentian extract, as well as from capsules is presented in Figure 1. It is evident that prolonged release of gentiopicroside from capsules was achieved. On the other hand, gentiopicroside was dissolved from dry gentian extract powder rapidly (94.02 % for 45 min). Furthermore, it was shown that nanoassociates dispersed in the medium during the examination of *in vitro* release of gentiopicroside from capsules had uniform size, since the PDI was less than 250 after 15 min (0.231 ± 0.009), as well as after 6 hours (0.179 ± 0.061).

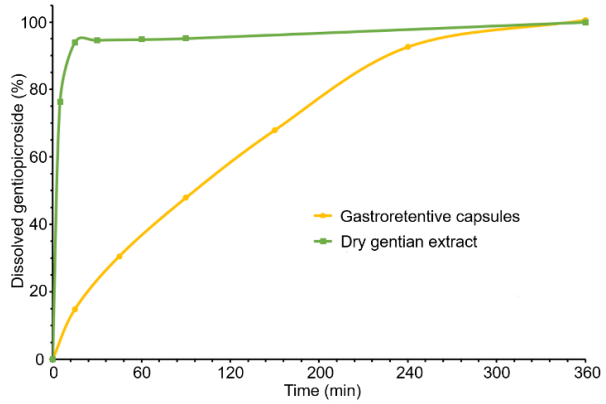

Figure 1. Dissolution profile of gentiopicroside from dry gentian extract and gastroretentive capsules.

The results of *in vitro* digestion presented in Figure 2 indicated that the enzymes of both the gastric and intestinal phases did not affect the dissolution of gentiopicroside from capsules, since difference was not observed in the dissolution profile of gentiopicroside from the control sample (without enzyme) and the digested sample. In order to determine whether the presence of the gelatin capsule affected the digestion process, powder used for capsules preparation was tested under the same conditions. It was shown that powder was a substrate for gastric lipase, while the influence of pancreatic lipase was not observed, most likely due to the release of the maximum amount of gentiopicroside, which was available after 240 minutes. This result indicated that developed powder was substrate for gastric lipase. Furthermore, gelatin present in the capsule shell influenced the dissolution profile of gentiopicroside during *in vitro* digestion.

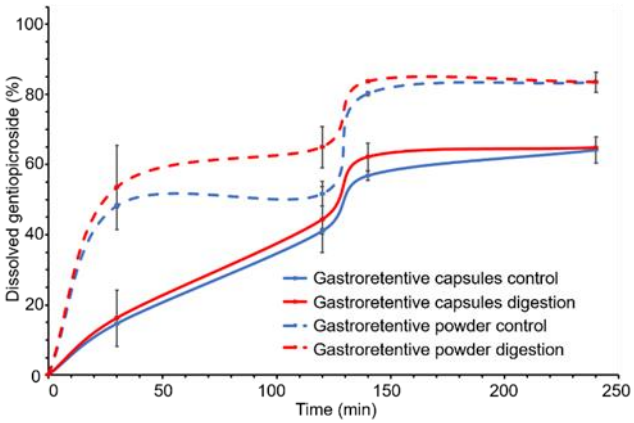

Figure 2. Dissolution profile of gentiopicroside during *in vitro* digestion testing.

CONCLUSION

Gastroretentive capsules were prepared with powder developed by freeze-drying of double emulsions obtained by double emulsion–melt dispersion technique. It is shown that gastric enzymes are involved in the digestion of investigated lipid-based formulation. Therefore, *in vitro* digestion test could be important during the development of lipid-based gastroretentive formulations.

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