

Development of gastroretentive floating granules with gentian root extract by hot-melt granulation

JELENA MUDRIĆ^{1*}, MIRJANA PAJIĆ², DUBRAVKA BIGOVIĆ¹, AND JELENA ĐURIŠ²

¹Institute for Medicinal Plants Research „Dr. Josif Pančić“, Tadeuša Koščuška 1, 11000 Belgrade, Serbia

²University of Belgrade, Faculty of Pharmacy, Department of Pharmaceutical Technology and Cosmetology, Vojvode Stepe 450, 11221 Belgrade, Serbia

*Corresponding author: jmudric@mocbilja.rs

Received: April 3, 2020

Accepted: May 19, 2020

Published on-line: September 14, 2020

Published: December 25, 2020

The roots of yellow gentian, *Gentiana lutea* L. (Gentianaceae) are used in traditional medicine for the treatment of gastrointestinal disorders, with the literature data indicate a local gastric effect of gentian root extract (GRE) and support the use of the solid pharmaceutical forms. Gentiopicroside, as a dominant secoiridoid in the GRE, has a short elimination half-life and low bioavailability and, consequently, its bioactivity is limited. The aim of the study was to develop gastroretentive floating delivery system with GRE, and to provide prolonged release of gentiopicroside. Floating granules with dry GRE (DGRE) were prepared by the hot-melt granulation technique, while formulations included effervescent components (citric acid and sodium bicarbonate), hydroxypropyl methylcellulose (HPMC) and meltable binders (Compritrol[®] 888 ATO and Gelucire[®] 50/13). The flowability of the DGRE and prepared formulations was determined by calculating the Carr index and Hausner ratio. Floating properties and *in vitro* dissolution rate of gentiopicroside from investigated formulations were examined. Floating granules were characterized with improved flowability (Carr index 14-22 %; Hausner ratio 1.16-1.28) in comparison to the DGRE (Carr index 28.99 %; Hausner ratio of 1.41). Furthermore, the floating granules exhibited immediate and long-lasting buoyancy and prolonged-release of gentiopicroside (over 8 h). Compritrol[®] 888 ATO has provided sustained release of gentiopicroside from floating granules, while HPMC has decreased release rate additionally. On the other hand, Gelucire[®] 50/13 has increased gentiopicroside release rate. The results have shown that hot-melt granulation technique, as a green granulation method was successfully employed for obtaining gastroretentive floating granules with DGRE.

Key words: *Gentiana lutea*; gentiopicroside; prolonged release; Compritrol[®] 888 ATO; HPMC; Gelucire[®] 50/13.

<http://dx.doi.org/10.5937/leksir2040040M>

1. INTRODUCTION

Underground parts of yellow gentian, *Gentiana lutea* L. (Gentianaceae) are used in traditional medicine for the treatment of gastrointestinal disorders, such as dyspepsia, liver dysfunction, loss of appetite, while it is official in the European and many national Pharmacopoeias (Šavikin et al., 2015; Ph. Eur. 10.0, 2020). Previous studies have shown choleric (Öztürk et al., 2002), anti-inflammatory (Mathew et al., 2004), antitumorogenic (Niiho et al., 2006), radioprotective (Menković et al., 2010), analgesic (Öztürk et al., 2002) and antimicrobial (Pontus et al., 2006) activity of gentian root extract. Beneficial health effects of gentian root extract are associated with the presence of bitter-tasting secoiridoids (gentiopicroside, sweroside, swertiamarin, loganic acid) and biphenyl derivatives (amarogentin, amaropanaxin and amaroswerin), as well as phenolics i.e. xanthones (isogentisin, gentioside, gentisin), and flavonoids

(isovitexin, isoorientin) (Šavikin et al., 2015; Živković et al., 2019). Gentiopicroside is the dominant bioactive compound in the gentian root extract with choleric, hepatoprotective, adaptogenic and anti-inflammatory activities (Wu et al., 2017). However, there are obstacles, due to suboptimal pharmacokinetic properties of gentiopicroside, such as short elimination half-life (2.8 h) and low bioavailability (39.6 %), reported after animal studies (Wang et al., 2004) that limit its bioactive potential. Therefore, there is a need to formulate delivery systems with prolonged release of gentian root extract. Furthermore, the literature data indicate a local gastric effect of gentian root extract and support the use of the solid pharmaceutical forms (EMA, 2018).

Gastroretentive delivery systems are designed to provide prolonged residence time in the stomach as well as controlled release of active compounds. Such systems are suitable for active compounds with the local effect in the stomach, short

elimination half-life, higher absorption in the upper part of the gastrointestinal tract or in the case of active compounds instability in the intestine at higher pH (Lopes et al., 2016; Tripathi et al., 2019). Shah et al. (2009) have reviewed gastroretentive floating delivery systems for *Helicobacter pylori* eradication with herbal drugs. In addition, Prasanthi (2019) has presented gastroretentive tablets of *Coccinia grandis* leaf extract for treating *H. pylori* infection. Zhang et al. (2018) have demonstrated enhanced gastric therapeutic effects of *Brucea javanica* oil formulated in a gastroretentive delivery system, compared to the commercial products. Kim et al. (2017) have demonstrated, in *in vivo* studies, the gastroprotective effects of *Artemisia princeps* gastroretentive floating tablets. Efficient antiulcer gastroretentive systems have been developed for *Boswellia oleogum* resin (Yusif et al., 2016) and aspen bark dry extract (Krylova et al., 2018).

Floating drug delivery systems are gastroretentive delivery systems with lower density compared to the gastric fluid (1.004 g/cm³) (Tripathi et al., 2019). Therefore, these systems float on the surface of the gastric fluid and remain in the stomach longer, while the active principles are released from the system at the desired, modified rate. Multiple-unit gastroretentive delivery systems, such as floating granules have been proposed to overcome the risk of losing effect too early due to “all-or-none” emptying from the stomach related to single-unit dosage forms (Mishra and Dhole, 2019; Zhai et al., 2014). The hot-melt granulation technique is recognized as an environmentally-friendly solvent-free green method that can be utilized for the preparation of gastroretentive floating delivery systems (Aoki et al., 2015; Khaled et al., 2020; Shimpi et al., 2004; Zhai et al., 2014). Furthermore, meltable binders that enable the hot-melt granulation, may also sustain the active ingredients release rate and provide floating due to the hydrophobic nature (Patel et al., 2018).

There is an unmet need in developing formulations with gentian root extract that could stay in the stomach, as the targeted site of action, for prolonged periods of time. The development of gastroretentive formulations is considered as a viable approach that could lead to an increase in the therapeutic efficacy and reduction in the dosing frequency. Therefore, the aim of the presented study was to develop gastroretentive floating delivery system, by using the hot-melt granulation technique, and to provide prolonged release of active compounds from gentian root extract. Gentiopicroside, selected as a marker compound, is expected to be released in a continuous manner. The effect of lipid excipients (Compritol[®] 888 ATO and Gelucire[®] 50/13) and hydrophilic polymer (hydroxypropyl methylcellulose) on flowability, floating time and gentiopicroside release rate was investigated.

2. MATERIALS AND METHODS

2.1. Plant material and chemicals

Excipients used for formulation were hydroxypropyl methylcellulose (HPMC, Methocel[®] E5 LV, Dow[®], USA), hydrophilic polymer used as a matrix forming excipient, lactose monohydrate was used as a diluent, citric acid and sodium bicarbonate as an effervescent components, while glyceryl behenate (Compritol[®] 888 ATO, Gattefrosse, Saint-priest, Cedex, France) and stearyl macrogol-32 glycerides (Gelucire[®] 50/13, Gattefrosse, Saint-priest, Cedex, France) were used as meltable binders. Ethanol 96 % (v/v) (Honeywell Riedel de Haën, Seelze, Germany), orthophosphoric acid (Sigma-Aldrich Chemie GmbH, München, Germany), acetonitrile (Merck, Germany) was HPLC grade and ultra-pure water was prepared using a Milli-Q purification system (Millipore, France). Gentiopicroside (ChromaDex, USA) standard was used. All excipients, reagents and standards used were of analytical grade.

2.2. Preparation of dry extract

Plant material, *Gentiana lutea* roots, was purchased from the Institute for Medicinal Plants Research “Dr. Josif Pančić” (Belgrade, Serbia). Liquid gentian root extract was obtained by heat-assisted extraction under the optimal conditions described by Mudrić et al. (2020). Extraction in a thermostated water bath (Grant, model LSB 18, United Kingdom) lasted 129 minutes, at a temperature of 65 °C, ethanol concentration was 49 % and the solid-to-solvent ratio was 1:40. After filtration, the liquid extract was dried in a laboratory spray dryer. The inlet temperature was 95 °C, the outlet temperatures varied between 50-70 °C, the feed flow rate of the extract was 22 rpm. Obtained dry gentian root extract was used in all prepared formulations.

2.3. Preparation of formulations

Five formulations were prepared according to the Table 1. Physical mixture of powders (formulation A) was prepared by mixing of dry gentian root extract, lactose monohydrate, HPMC, effervescent components (citric acid and sodium bicarbonate) according to the principle of compound powder production. Formulations B, C, D and E and were prepared by the hot-melt granulation. Powder mixture was added to melted binder (Compritol[®] or mixture of Compritol[®] and Gelucire[®] 50/13) at a temperature of 75 °C ± 2 °C, with continuous stirring. After cooling, obtained mass was crushed, with a mortar and pestle and granulate was sieved through a 250 µm sieve.

2.4. Micromeritic properties

Bulk density was determined by measuring the mass of a known volume of powder in a beaker. Tapped density was determined in a vibrating volumeter (Stampfvolumeter STAV 2003, Jel, Germany). Based on the data on bulk and tapped density, it is possible to define the flowability of granules by calculating Carr index and Hausner ratio as follows:

$$\text{Carr index (\%)} = \frac{\text{tapped density} - \text{bulk density}}{\text{tapped density}} \times 100$$

$$\text{Hausner ratio} = \frac{\text{tapped density}}{\text{bulk density}}$$

The powder/granules flow classification was performed according to the European Pharmacopoeia 10.0 (Ph. Eur. 10.0, 2020).

2.5. Floating investigation

Formulations A, B, C, D and E were placed in 500 mL (37 °C ± 0.5 °C) of 0.1 M HCl (pH=1.2) in the type II dissolution apparatus (apparatus with rotating paddle, Erweka DT600, Germany). The medium was agitated by paddle at 50 rpm. The time taken by the powers/granules (8 g of each formulation) to rise over the surface of the medium (floating lag time) and total floating time was measured visually (Mishra and Dhole, 2019).

2.6. *In vitro* dissolution rate of gentiopicroside and floating properties of the formulations

The dissolution tests were performed in triplicate using apparatus type II (apparatus with rotating paddle, Erweka DT600, Germany) with a paddle rotation speed of 50 rpm. Dissolution medium consisted of 500 mL of 0.1 M HCl (pH=1.2) heated to 37 °C ± 0.5 °C. The weight of the powder/granules used for the test was 8 g. The sample (4 mL) was taken after certain time intervals and the medium was replenished after each sampling. After filtration, the amount of dissolved gentiopicroside was analyzed by high pressure liquid chromatography (HPLC).

2.7. Determining the content of gentiopicroside by HPLC

Analyses were carried out on an Agilent 1200 RP HPLC instrument, with diode array detector (DAD) and a reverse phase Zorbax SB-C₁₈ analytical column (150 mm × 4.6 mm; 5 μm particle size) at a temperature of 25 °C according to the previously described method (Balijagić et al., 2012). The mobile phase consisted of solvent A (1 % v/v, solution of orthophosphoric acid in water) and solvent B (acetonitrile) using a gradient elution as follows: 0-5 min, 98-90 % A; 5-15 min, 90 % A; 15-20 min, 90-85 % A; 20-25 min, 85-70 % A; 25-30 min, 70-40 % A; 30-34 min, 40-0 % A. The injection volume was 5 μL. Detection wavelengths were set at 260 nm and the flow rate was 1 mL/min. The amounts of the dissolved gentiopicroside was calculated using calibration curve.

Table 1. Composition of prepared formulations

Ingredients	Formulation codes				
	A	B	C	D	E
	[%]	[%]	[%]	[%]	[%]
DGRE ^a	25	25	25	25	25
HPMC ^b	15	15	15	15	-
Lactose, monohydrate	45	25	15	13	30
Effervescent components ^c	15	15	15	15	15
Compritol [®] 888 ATO	-	20	30	30	30
Gelucire [®] 50/13	-	-	-	2	-

^a DGRE - dry gentian root extract

^b HPMC- hydroxypropyl methylcellulose

^c Citric acid and sodium bicarbonate in the ratio of 0.76:1

3. RESULTS AND DISCUSSION

The flowability of the dry gentian root extract, and prepared formulations, was determined by calculating Carr index and Hausner ratio (Table 2). Dry gentian root extract has exhibited poor flowability with Carr index of 28.99 % and Hausner ratio of 1.41, which could be attributed to the sticky nature of the extract. Furthermore, poor flowability of formulation A has indicated that the addition of HPMC, lactose, and effervescent compounds (sodium hydrogen carbonate and citric acid) to gentian root extract has not enhanced flowability. Granules with gentian root extract obtained by the hot-melt granulation (formulations B, C, D and E) were characterized by improved flowability (Carr index 14-22 %; Hausner ratio 1.16-1.28) in comparison to the gentian root extract and formulation A.

Flowability of granules with the highest content of lipid excipients (formulation D) was superior to the flowability of granules with lower content of lipid excipients. This result has indicated that the hot-melt granulation has a positive influence on the flowability of gentian root extract and that the addition of lipid excipients is related to the improved flowability. This finding is in accordance with a previous study where the influence of hot-melt granulation on the flowability of divalproex was investigated (Khaled et al., 2020).

Furthermore, lipid-based floating multiparticulate delivery systems with berberine hydrochloride as active compound and lipid carrier Gelucire[®] 43/01 as release retardant, HPMC K4M as matrix polymer and sodium bicarbonate as a gas former were characterized with fair to good flowability (Mishra and Dhole, 2019).

Table 2. Carr index and Hausner ratio of prepared formulations and gentian root extract

	Carr index	Hausner ratio	Flowability
	[%]		
DGRE ^a	29	1.41	Poor
A	30	1.43	Poor
B	20	1.25	Fair
C	20	1.25	Fair
D	14	1.16	Good
E	16	1.19	Fair

^a DGRE - dry gentian root extract

3.1. *In vitro* characterization of formulations

All investigated formulations have floated all the time during the dissolution test. There was no floating lag time for any formulations. This feature could be due to the lipophilic nature and low density (0.46 g/mL) of Compritol[®]. The same finding was reported when Compritol[®] was used to formulate a self-emulsifying floating drug delivery system with tetrahydrocurcumin (Setthacheewakul et al., 2011). Furthermore, gas (CO₂) was formed by the reaction of a base (sodium bicarbonate) and acidic component (citric acid) of the formulation in the presence of dissolution medium, while the density of dosage forms decreased due to incorporation of generated gas in HPMC matrix.

The influence of Compritol[®], Gelucire[®] 50/13 and HPMC on the gentiopicroside release behavior from the obtained floating granules (formulations B,C,D and E) and powder (formulation A) was investigated. Release of gentiopicroside from formulation A was rapid and more than 37.23 % of gentiopicroside was dissolved in 1 h. On the other hand, a significant decrease in the release rate of gentiopicroside was observed in the case of granules obtained by the hot-melt granulation (formulations B, C, D and E). It can be noticed that after the burst release of gentiopicroside (21.98 %) in the first 30 min from formulation A, in the second phase gentiopicroside release was slower. It was reported previously that release from HPMC based gastric floating drug delivery system appear to be bi-phasic with initial burst effect (less than 30 min) followed by a polymer-controlled slower release in the second phase (Li et al., 2003), while both diffusion and erosion mechanisms contribute to the controlled release of active substances (Zhai et al., 2014). By comparing the dissolution rates of formulations A and B after 60 minutes, it is clear that the addition of Compritol[®] (20 %) has prevented the initial burst effect, and dissolution rate of gentiopicroside was significantly decreased, due to the pronounced hydrophobic nature of Compritol[®], that facilitates the sustained release of active compounds (Figure 1).

Khaled et al. (2020) have reported that Compritol[®] 888 ATO (glyceryl behenate) has enabled prolonged release of divalproex and release was slower than in the case of meltable binders such as Geleol[®] (glyceryl monostearate), Precirol[®] ATO5 (glyceryl palmitostearate), and Gelucire[®] 50/13 (Stearoyl macrogol-32 glycerides). By comparing gentiopicroside release from formulation B (28.61 %) and C (23.71 %) minor changes are noticed after 240 min, indicating that the increase in the amount of Compritol[®] (from 20 % to 30 %) has a negligible effect on dissolution rate. Formulation D with a mixture of meltable binders (Gelucire[®] 50/13 and Compritol[®]) was characterized with increased gentiopicroside release rate in comparison to formulation C with Compritol[®], as meltable

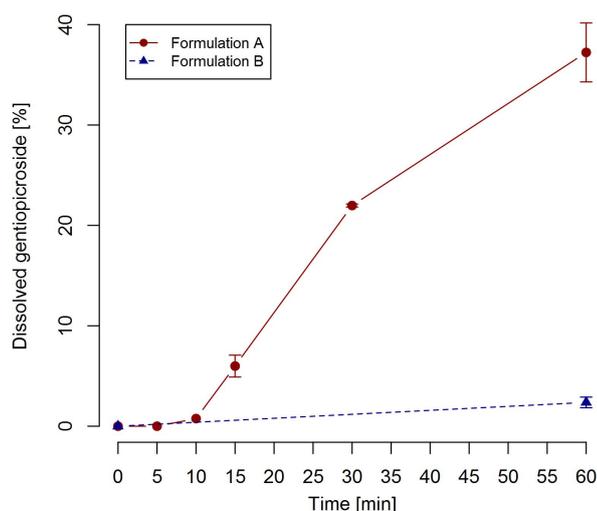


Fig. 1. Gentiopicroside release profile from formulation A and B

binder (Figure 2). This result is in accordance with the study of Zhai et al. (2014) where it was noticed that metronidazole release rate was increased, after the addition of Gelucire[®] 50/13 (2-4 %), as a bioavailability and solubility enhancer, to the formulation of gastroretentive extended-release floating granules, while addition of higher concentration (10-15 %) Gelucire[®] 50/13 resulted in loss of sustained release. The effect of HPMC on the release was evident when the percentage of dissolved gentiopicroside from formulation C (50.95 %) and E (100.46 %) after 8 h were compared. Gentiopicroside release from formulation E was characterized as bi-phasic with initial slower release and faster release in the second phase. The increased release rate in the second phase could be a consequence of increased diffusion of dissolution medium in floating granules without HPMC, due to the absence of gelatinous layer formed in contact of hydrophilic polymer and dissolution medium. A control over gentiopicroside release rate is necessary, in order to avoid incomplete release that can occur in the case of lipid-based delivery systems (Knežević et al., 2009).

CONCLUSION

In this study, the hot-melt granulation technique, as a green granulation method was successfully employed for obtaining gastroretentive floating granules with gentian root extract. The obtained floating granules were characterized with improved flowability, immediate and long-lasting floating and prolonged-release (over 8 h) of gentiopicroside, as a marker compound in the gentian root extract. Compritol[®] 888 ATO (20-30 %) used as a meltable binder has provided sustained release of gentiopicroside from floating granules, while HPMC (15 %) as a hydrophilic polymer has decreased release rate additionally. On the other hand, Gelucire[®] 50/13 (2 %) has increased release rate of gentiopicroside. Therefore, gastroretentive floating granules with Compritol[®] 888 ATO and addition of Gelucire[®] 50/13 and HPMC could be used for targeted and sustained release of gentian root extract in the stomach. Further development, optimization and *in vitro* and *in vivo* evaluation of prepared floating systems could contribute to gentian root extract efficiency, in terms of reduced dosing frequency and ease of formulated product administration.

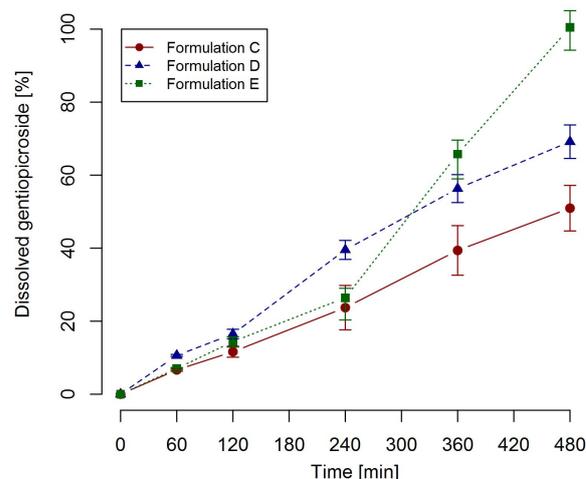


Fig. 2. Gentiopicroside release profile from formulations C, D and E

ACKNOWLEDGMENTS

This research was supported by the Ministry of Education, Science and Technological Development of Republic of Serbia, contract number 451-03-68/2020-14/ 200003 and 451-03-68/2020-14/200161.

REFERENCES

- Aoki, H., Iwao, Y., Mizoguchi, M., Noguchi, S. and Itai, S. (2015). Clarithromycin highly-loaded gastro-floating fine granules prepared by high-shear melt granulation can enhance the efficacy of *Helicobacter pylori* eradication, *European Journal of Pharmaceutics and Biopharmaceutics* **92**: 22–27.
- Balijagić, J., Janković, T., Zdunić, G., Bošković, J., Šavikin, K., Gođevac, D., Stanojković, T., Jovančević, M. and Menković, N. (2012). Chemical profile, radical scavenging and cytotoxic activity of yellow gentian leaves (*Genitaneae luteae folium*) grown in northern regions of Montenegro, *Natural Product Communications* **7**(11): 1934578X1200701.
- EMA (2018). European medicines agency, assessment report on *Gentiana lutea* L., radix. Ref.: EMA/HMPC/607863/2017.
- Khaled, A., Abdel-Hamid, S., Nasr, M. and Sammour, O. A. (2020). Fabrication of extended-dissolution divalproex tablets: a green solvent-free granulation technique, *Drug Development and Industrial Pharmacy* **46**(6): 975–987.
- Kim, J.-I., Park, S.-W., Lim, J.-J., Sohn, S.-I., Shin, J.-S., Park, S. C., Jang, Y. P., Chung, E. K., Lee, H.-W. and Lee, K.-T. (2017). Gastroprotective effects of the isopropanol extract of *Artemisia princeps* and its gastroretentive floating tablets on gastric mucosal injury, *Acta Pharmaceutica* **67**(4): 479–494.
- Knežević, Z., Gosak, D., Hraste, M., Rausl, D. and Khan, M. I. (2009). Application of hot-melt coating process for designing a lipid based controlled release drug delivery system for highly aqueous soluble drugs., *Chemical and pharmaceutical bulletin*, **57**(5): 464–471.
- Krylova, S. G., Turetskova, V. F., Makarova, O. G. and Zueva, E. P. (2018). Technology development and antiulcer activity of gastroretentive tablets with aspen bark dry extract, *Pharmaceutical Chemistry Journal* **52**(2): 133–138.

- Li, S., Lin, S., Daggy, B. P., Mirchandani, H. L. and Chien, Y. W. (2003). Effect of HPMC and Carbopol on the release and floating properties of Gastric Floating Drug Delivery System using factorial design, *International Journal of Pharmaceutics* **253**(1-2): 13–22.
- Lopes, C. M., Bettencourt, C., Rossi, A., Buttini, F. and Barata, P. (2016). Overview on gastroretentive drug delivery systems for improving drug bioavailability, *International Journal of Pharmaceutics* **510**(1): 144–158.
- Mathew, A., Taranalli, A. D. and Torgal, S. S. (2004). Evaluation of anti-inflammatory and wound healing activity of *Gentiana lutea* rhizome extracts in animals, *Pharmaceutical Biology* **42**(1): 8–12.
- Menković, N., Juranić, Z., Stanojković, T., Raonić-Stevanović, T., Šavikin, K., Zdunić, G. and Borojević, N. (2010). Radioprotective activity of *Gentiana lutea* extract and mangiferin, *Phytotherapy Research* **24**(11): 1693–1696.
- Mishra, R. and Dhole, S. (2019). Lipid-based floating multiparticulate delivery system for bioavailability enhancement of berberine hydrochloride, *Journal of Applied Pharmaceutical Science*, **9**(11): 036–047.
- Mudrić, J., Janković, T., Šavikin, K., Bigović, D., Đukić Ćosić, D., Ibrić, S. and Đuriš, J. (2020). Optimization and modelling of gentiopicroside, isogentisin and total phenolics extraction from *Gentiana lutea* L. roots, *Industrial Crops and Products* **155**: 112767.
- Niiho, Y., Yamazaki, T., Nakajima, Y., Yamamoto, T., Ando, H., Hirai, Y., Toriizuka, K. and Ida, Y. (2006). Gastroprotective effects of bitter principles isolated from gentian root and swertia herb on experimentally-induced gastric lesions in rats, *Journal of Natural Medicines* **60**(1): 82–88.
- Öztürk, N., Başer, K. H. C., Aydin, S., Oztürk, Y. and Caliş, I. (2002). Effects of *Gentiana lutea* ssp. *symphyandra* on the central nervous system in mice, *Phytotherapy research: PTR* **16**(7): 627–631.
- Patel, A. U., Caudhari, D. V., Shah, P. J. and Shah, S. A. (2018). Hot melt granulation method for the preparation of floating matrix tablets of tolperison hydrochloride, *Future Journal of Pharmaceutical Sciences* **4**(2): 139–149.
- Ph. Eur. 10.0 (2020). European Pharmacopoeia, Council of Europe, Strasbourg.
- Pontus, S., A.P., M. and Chaim, I. (2006). Use of *Gentiana lutea* extracts as an antimicrobial agent., European Patent EP1663271.
- Prasanthi, D. N. L. (2019). Design and development of gastroretentive tablets of *Coccinia grandis* leaf extract for treating *Helicobacter pylori* infection, *Asian Journal of Pharmaceutics* **13**(3): 184–191.
- Šavikin, K., Aljančić, I., Vajs, V., Milosavljević, S., Jadranin, M., Đorđević, I. and Menković, N. (2015). Bioactive secondary metabolites in several genera of *Gentianaceae* species from the central regions of the Balkan Peninsula, in J. J. Rybczyński, M. R. Davey and A. Mikula (eds), *The Gentianaceae - Volume 2: Biotechnology and Applications*, Springer, Berlin, Heidelberg, pp. 319–347.
- Setthacheewakul, S., Kedjinda, W., Maneenuan, D. and Wiwatapanapatee, R. (2011). Controlled release of oral tetrahydrocurcumin from a novel self-emulsifying floating drug delivery system (SEFDDS), *AAPS PharmSciTech* **12**(1): 152–164.
- Shah, S. H., Patel, J. K. and Patel, N. V. (2009). Gastroretentive floating drug delivery systems with potential herbal drugs for *Helicobacter pylori* eradication: a review, *Zhong Xi Yi Jie He Xue Bao = Journal of Chinese Integrative Medicine* **7**(10): 976–982.
- Shimpi, S., Chauhan, B., Mahadik, K. R. and Paradkar, A. (2004). Preparation and evaluation of diltiazem hydrochloride-gelucire 43/01 floating granules prepared by melt granulation, *AAPS PharmSciTech* **5**(3): 51–56.
- Tripathi, J., Thapa, P., Maharjan, R. and Jeong, S. H. (2019). Current state and future perspectives on gastroretentive drug delivery systems, *Pharmaceutics* **11**(193): 1–22.
- Wang, C.-H., Wang, Z.-T., Annie Bligh, W. W., White, K. N. and White, C. J. B. (2004). Pharmacokinetics and tissue distribution of gentiopicroside following oral and intravenous administration in mice, *European Journal of Drug Metabolism and Pharmacokinetics* **29**(3): 199–203.
- Wu, S., Yang, L., Sun, W., Si, L., Xiao, S., Wang, Q., Dechoux, L., Thorimbert, S., Sollogoub, M., Zhou, D. and Zhang, Y. (2017). Design, synthesis and biological evaluation of gentiopicroside derivatives as potential antiviral inhibitors, *European Journal of Medicinal Chemistry* **130**: 308–319.
- Yusif, R. M., Abu Hashim, I. I., Mohamed, E. A. and Badria, F. A.-E. (2016). Gastroretentive matrix tablets of *Boswellia oleogum* resin: preparation, optimization, *in vitro* evaluation, and cytoprotective effect on indomethacin-induced gastric ulcer in rabbits, *AAPS PharmSciTech* **17**(2): 328–338.
- Zhai, H., Jones, D. S., McCoy, C. P., Madi, A. M., Tian, Y. and Andrews, G. P. (2014). Gastroretentive extended-release floating granules prepared using a novel fluidized hot melt granulation (FHMG) technique, *Molecular Pharmaceutics* **11**(10): 3471–3483.
- Zhang, Y., Zhang, L., Zhang, Q., Zhang, X., Zhang, T. and Wang, B. (2018). Enhanced gastric therapeutic effects of Brucea javanica oil and its gastroretentive drug delivery system compared to commercial products in pharmacokinetics study, *Drug Design, Development and Therapy* **12**: 535–544.
- Živković, J., Janković, T., Menković, N. and Šavikin, K. (2019). Optimization of ultrasound-assisted extraction of isogentisin, gentiopicroside and total polyphenols from gentian root using response-surface methodology, *Industrial Crops and Products* **139**: 111567.