

Modified-release oral delivery systems with the active ingredients of herbal origin: a mini-review

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Introduction

Owing to modifying the release of the active pharmaceutical ingredient(s) (API(s)) in the human body efficacy of oral drugs can be significantly enhanced. Modified release (MR) oral formulations providing sustained, delayed, or targeted release have been developed for plenty of synthetic APIs. However, when it comes to the APIs of herbal origin, such as extracts consisting of a complex of biologically active substances (BAS), the task of the synchronous release modification of all compounds, or even a group of them, becomes much more challenging. Nevertheless, MR delivery systems (DS) for herbal-origin APIs are also described in the literature, so our aim was to summarize the existing experience in this field.

Materials and methods

The Pubmed, ScienceDirect, and SpringerLink databases were used for selecting the articles on the formulation development and/or evaluation of the MR delivery systems incorporating herbal-derived APIs.

Results and discussion

The steady ratio of the BAS of herbal-derived drugs greatly contributes to their therapeutic action and thus should be kept when releasing from MR formulations. Because of that, approaches such as diffusion-driven DS are often inapplicable for herbal APIs, as constituents may differ in their structure, solubility, and diffusion rates. Therefore, the goal is a so-called synchronous release of all therapeutic markers. This problem was attempted to be solved with silymarin as a model API by formulating an

erodible matrix prepared as a solid dispersion with two excipients – highly hydrophobic glyceryl monostearate and hydrophilic PEG 6000 or poloxamer 188 (Lu et al., 2007). The matrix gradually eroded releasing all embedded BAS simultaneously and irrespectively of their physicochemical properties and resulted in better therapeutic efficacy than the non-synchronous swellable hypromellose matrix. In another study with silymarin (Xie et al., 2013) an osmotic system consisting of a PVP-based solid dispersion mixed with an osmotic agent in the core and perforated shell was developed. The synchronous release of main constituents was suggested to be achieved also due to the API solubilized state in solid dispersion. Self-microemulsifying system was chosen for the sustained release of Ginkgo biloba extract that allowed not only prolonging the release time but also increasing the cumulative release (determined by three main flavonoids of the extract). In turn, solubility increase was linked to more gastrointestinal absorption after single oral administration in dogs (Gu et al., 2017). Wang and coauthors (2019) evaluated the capsules composed of four kinds of sustained-release pellets, each with a different formulation design and incorporating one of four main BAS of Chinese herbal medicine, and all four therapeutic markers had similar dissolution and pharmacokinetic profiles. The gastroretentive DS of Gentiana lutea root extract was obtained in the form of tablets directly compressed from the powder of the solid lipid microparticles (Mudrić et al., 2021) which, in turn, were produced by freeze-drying from double emulsion (W/O/W). In vitro dissolution test has shown that the biphasic release from formulated tablets with a burst in the first 45 min and a slower release until 6 h was achieved, although the release profile was characterized by only one marker compound. MR delivery systems described for the herbal-derived APIs are summarized in Table 1.

Table 1. MR delivery systems of the herbal-derived APIs

API	MR delivery system	Ref.
Silymarin (an extract from <i>Silybum marianum</i>)	Erodible matrix based on combination of highly hydrophobic (glyceryl monostearate) and hydrophilic (PEG 6000 or poloxamer 188) agents	Lu et al., 2007
Silymarin	Monolithic osmotic tablets consisting of a core and semi-permeable coating of cellulose acetate with laser perforated release orifices	Xie et al., 2013
Ginkgo biloba extract	Self-microemulsifying sustained-release pellets consisting of oil, surfactant, cosurfactant and the API	Gu et al., 2017
Danshen (Chinese medicine derived from <i>Salvia miltiorrhiza</i> Bunge)	Hard gelatin capsules with sustained release of four main BAS separately incorporated different type pellets which are based on: phospholipid complex, proliposomes, solid dispersion, and pellets with absorption enhancer	Wang et al., 2019
Gentiana lutea root extract	Gastroretentive tablets obtained from solid lipid microparticles prepared by freeze-drying double (W/O/W) emulsions with the extract as the inner water phase, Gelucire® 43/01 as a solid lipid component, and porous silica (Sylysia® 350) in the outer water phase	Mudrić et al., 2021
Bixa orellana (annatto) seed extract	Alginate microcapsules obtained by ionotropic gelation method with the largest release of polyphenols at pH of 6.5	Naranjo-Durán et al., 2021

Conclusion

MR systems for herbal-derived APIs should maintain a steady ratio of the therapeutic marker compounds. The most promising approaches, described in the literature so far, include erosion-driven sustained release formulations, osmotic DS, capsules filled with different design pellets separately incorporating each marker BAS, and self-microemulsifying DS. Also, it should be noted that all

mentioned techniques led to the solubilization of herbal APIs (by means of solid dispersion matrices, and emulsifying systems), otherwise, the isochronous release of all BAS into the release medium would not be possible.

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