

The effect of excipients on oral lyophilizates quality attributes

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Introduction

Pharmaceutical industry is constantly focused on researching patient-centered dosage forms that can maximize the therapeutic potential of an active pharmaceutical ingredient, as for example orodispersible form. The main advantage of orodispersible dosage forms is that they are suitable for patients with swallowing problems, children, geriatric, and psychiatric patients, leading to improvement in patient compliance. Orodispersible drug formulations include orodispersible tablets, oral lyophilizates, orodispersible granules, mini-tablets, orodispersible films, and some less common. Oral lyophilizates are solid forms, intended either to be placed in the mouth or to be dispersed (or dissolved) in water before administration. The composition of oral lyophilizates determines their quality attributes, and generally includes binders, fillers, taste modifiers, sweeteners, and preservatives (Bjelošević Žiberna et al., 2023; Slavkova & Breitreutz, 2015).

Our aim was to design formulations for preparation of oral lyophilizates by implementation of aggressive primary drying conditions, contributing to a smaller financial and environmental burden. The objectives were: (i) to examine the influence of glycine, and croscarmellose on the quality attributes of lyophilizates based on mannitol, gelatin, and polyvinylpyrrolidone K25; and (ii) to discover the potential of hydrolyzed gelatin in oral lyophilizates.

Materials and methods

Gelatin, hydrolyzed gelatin, polyvinylpyrrolidone (PVP) K25, were from Sigma-Aldrich, Germany, and glycine, mannitol, and croscarmellose were purchased from Merck, Germany.

Sample preparation: First, a half amount of water was weighed in a beaker and then the excipients were gradually added during mixing. In the case of gelatin, the water was heated to 70 °C. At the end, the rest of the water was added.

Lyophilization: The process was conducted in a laboratory freeze-dryer (Epsilon 2-6D; Christ, Germany). In freezing step, the shelf temperature was -45 °C. During primary drying, the shelf temperature was raised to 20 °C with chamber pressure of 0.10 mbar, while in secondary drying temperature was set to 40 °C.

Disintegration time: Oral lyophilizates with acceptable appearance were placed in 200 mL of water (22 °C), and time needed to complete disintegration was determined. According to European Pharmacopoeia oral lyophilizates have to disintegrate within 3 min.

Scanning electron microscopy: The small amount of lyophilizates in a thin layer were fixed with double-sided adhesive tape onto the stubs for scanning electron microscopy (SEM; Supra 35 VP, Carl Zeiss, Germany) and analyzed with a secondary detector (voltage of 1 kV).

The Brunauer–Emmett–Teller method: To measure the specific surface area (SSA), a Nova 2000 analyzer (Quantachrome, Germany) together with NovaWin software 11.05 was utilized. SSA was determined based on five data points, in the P/P₀ range from 0.050 to 0.300.

Results and discussion

Previously obtained results revealed that considering disintegration time and visual appearance, lyophilizates with a mixture of gelatin, PVP K25, and mannitol (1:2:5) formed from liquid formulations with 6 % (w/w) excipients are the most suitable. Thus, the said composition was starting point for a further study, where four-component formulations were prepared. As seen in Table 1, disintegration time of the lyophilizates with either glycine

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or croscarmellose depended on the gelatin concentration. While croscarmellose provided lyophilizates with shorter disintegration time and also appropriate visual appearance, glycine only had a positive effect on the elegant appearance of lyophilizate cake (Figure 1). However, when the gelatin content exceeds 12.5 %, its binding property outweighs the disintegration ability of croscarmellose, and the disintegration time of such lyophilizates exceeds 3 min.

Table 1. The composition, disintegration times and evaluated visual appearance of lyophilizates.

ratio of excipients					disintegration time (s)	appearance
gelatin	PVP K25	glycine	croscarmell	mannitol		
0	2	0.5	0	4.5	22	✓
0.5	2	0.5	0	4.5	50	✓
0	2	0	0.5	4.5	10	✓
0.5	2	0	0.5	4.5	12	✓
1	2	0	0.5	4.5	15	✓



Fig. 1. Lyophilizates with gelatin: PVP K25: glycine/ croscarmellose: mannitol = 0.5: 2: 0.5: 4.5 (glycine left, croscarmellose right).

Chemical or enzymatic modification can alter the protein-based composition of gelatin and thus affect its solubility and gelling properties. Therefore, we tested the effect of hydrolyzed gelatin on the disintegration time and visual appearance of oral lyophilizates that did not disintegrate in previous parts of the study. Hydrolyzed gelatin significantly shortened the disintegration time of the oral lyophilizates. All lyophilizates obtained from a liquid formulation with 6 % (w/w) of excipients, disintegrated completely within 5 s, but in case of low concentrations of hydrolyzed gelatin the lyophilizates were extremely fragile. Consequently, the concentration of excipients in the pre-lyophilized liquid formulation was increased to 15 % (w/w). Lyophilizates obtained from the liquid formulation with 15 % (w/w) excipients in hydrolyzed gelatin: PVP K25: mannitol ratio of 4: 2: 5 disintegrated in 50 s and did not exhibit friability. Addition of croscarmellose as a superdisintegrant or glycine resulted

in much shorter disintegration times: 8 and 10 s, respectively. Also, oral lyophilizates containing hydrolyzed gelatin have higher SSA (glycine: 5.3 m²/g; croscarmellose: 3.4 m²/g) than lyophilizates with non-hydrolyzed gelatin (glycine: 3.1 m²/g; croscarmellose: 1.6 m²/g). Lyophilizate containing hydrolyzed gelatin and glycine has the highest SSA, because of mannitol and glycine crystals forming a grainy structure, whereas the structure of the lyophilizates without glycine consists of smooth plates (Figure 2). However, incorporation of croscarmellose outweighed the impact of SSA, namely, despite the lower SSA in comparison to lyophilizates with glycine, both showed the same disintegration time of 10 s.

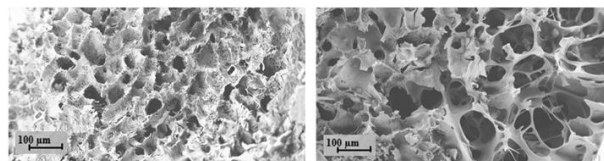


Fig. 2. SEM micrographs of lyophilizates with hydrolyzed gelatin: PVP K25: glycine (left)/ croscarmellose (right): mannitol ratio of 4: 2: 0.5: 4.5.

Conclusion

The study demonstrates that selection of excipients has a great importance to obtain oral lyophilizates with appropriate disintegration time and appearance. Considering disintegration time and visual appearance, lyophilizates with hydrolyzed gelatin: PVP K25: glycine/ croscarmellose: mannitol ratio of 4: 2: 0.5: 4.5 show the highest potential for incorporation of poorly soluble and low-dose drugs.

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