Preliminary studies of formulation development of an oral lyophilisate

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Introduction

Oral lyophilisates are solid preparations intended either to be placed in the mouth or to be dispersed (or dissolved) in water before administration. They are obtained by freeze-drying (lyophilisation).
The presence of metastable state and the glass transition temperature (Tg' ºC) are two important aspects when formulating a freeze drying product. The metastable state indicates the presence of polymorphism, which can alter the stability of the system. The Tg' ºC can helps us design a lyophilisation cycle.
Therefore, thermal analysis studies (differential scanning calorimetry, DSC) were performed in order to determine Tg' ºC and the presence/absence of metastable state forms for each excipient separately, and for the active substance used as model, plus nine combinations among them.
We have studied two common excipients used in freeze drying formulations: mannitol - in concentrations from 2-7% (w/V) - and polyvynilpirrolidone K30 (PVP) - in concentrations from 1-5 %(w/V).
Mannitol is one of the most common excipients used in oral lyophilisate formulations. It presents a good redispersability and provides crystalinity to the oral lyophilisate -desired for giving a robust aspect. However, it can present polymorphism, which can compromise the stability of the oral lyophilisate. PVP, on the other hand, is an amorphous excipient used in lyophilisation formulas to maintain the structure of the substances during the freezing process, and also helps to increase Tg' ºC, which can diminish the lyophilisation cycle time.

Materials and Methods

• Materials

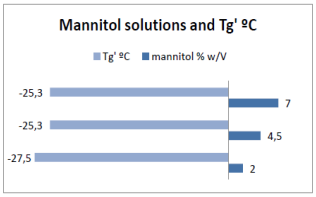
Active substance supplied by Reig Jofre Group, mannitol Ph.Eur. and polyvinylpyrrolidone (povidone K30) Ph. Eur. (Fagron Ibérica, SAU, Terrassa). Purified water.

• Methods

Differential scanning calorimetry (DSC)
DSC 821^{e} Mettler Toledo (Toledo, USA), with software STAR^{e} SW 9.30.
DSC cycle:
- 25 ºC to - 80 ºC (- 10ºC/min)
- - 80 ºC 1.0 min
- - 80 ºC to 25 ºC (10 ºC/ min).

Results

By DSC it was possible to recognize that all mannitol solutions presented metastable state forms, whereas none of the PVP solutions presented (Fig. 1), and so the active substance (with Tg' ºC of – 23).
Plus, three out of nine formulas studied (with the active substance, A, D and E) did not presented metastable state forms, all presenting a Tg' ºC ranging from -27 to -32ºC. Also, it was observed that increased concentration of PVP slightly decreased Tg' ºC in the non metastable formula E (Fig. 2).



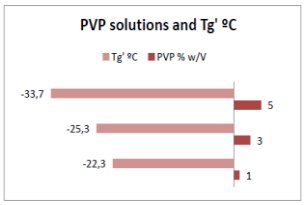
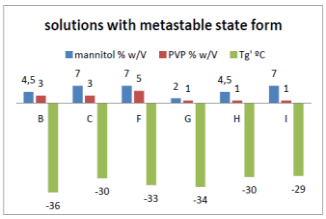


Fig. 1



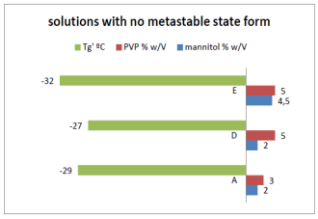


Fig. 2

Discussion and summary

• PVP inhibited mannitol polymorphism in solutions A, D and E only when added in higher concentration that mannitol, and almost with the same proportion among excipients as in solution E, with 5% PVP (w/V) and 4,5% mannitol (w/V)
• Tg' ºC was decreased for solutions A, D and E (Fig. 2) in comparison to the results found for each mannitol's concentration studied at 2 and 4,5 w/V % (Fig. 1), showing that the addition of PVP in higher concentration (3 and 5 w/V %) than mannitol did not increase Tg' ºC as it would have been expected
• A freeze drying viability test for solutions, A, D and E will be carried out in order to determine if the solutions are able to form a robust oral lyophilisate, with a rapid disintegration time and absence of cracking on the surface

Acknowledgments

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