

# Influence of mannitol and sorbitol on the in vitro dissolution of a model poorly water-soluble drug

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## Introduction

Mannitol and sorbitol as well as other polyols are widely used as diluents in chewable tablet formulations. The reason behind this is their great taste masking ability and pleasant mouth feel. Even though they both belong to the same group of organic compounds, there are several differences between them that have to be considered during pharmaceutical development. Mannitol has an advantage over sorbitol in terms of chemical inertness and low hygroscopicity, which make it compatible with moisture sensitive drugs.

This paper is intended to investigate the effect of different forms of mannitol and a combination of mannitol and sorbitol on the in vitro dissolution of a model poorly water-soluble drug. The drug of choice is a leukotriene receptor antagonist with anti-inflammatory and bronchodilating activity. It is characterized with high lipophilicity and low dissolution rate.

## Materials and methods

### Materials

Excipients: mannitol (Pearlitol® DC (PDC) from Roquette Freres, mannitol powder (MP) from Fluka Analytical, Parateck® Delta M (PDM) from Merck, sorbitol (Parateck® SI (PSI) from Merck), croscarmellose sodium (JRS Pharma), hydroxypropyl cellulose (Shin-Etsu), iron oxide red (Venator Pigments), microcrystalline cellulose (JRS Pharma), aroma cherry (Curt Georgi), sodium cyclamate (Rainbow Rich Industrial) and magnesium stearate (Mosselman).

Active pharmaceutical ingredient (API): model poorly water-soluble drug

### Preparation of chewable tablets

Chewable tablets were previously prepared by wet granulation and subsequently compressed into a round tablet, 8 mm in diameter on a tablet press (MINI PRESS II B, PHARMAG, Germany). The concentration of the diluent(s) in these chewable tablets was approximately 65%. Other excipients were used in concentrations in accordance with recommended concentrations from Handbook of Pharmaceutical Excipients.

In order to evaluate the effect of polyols, different chewable tablet formulations were prepared: only PDC as a diluent, only MP as a diluent, only PDM as a diluent, PDC and PSI (30:70) as diluents, and PDM and PSI (30:70) as diluents.

In this study only two critical parameters were observed: hardness and dissolution.

### Hardness

The tablet hardness was determined using a hardness tester (PTB 311E, PHARMATEST, Germany).

### Dissolution

The dissolution rate of the API from the chewable tablets was measured using apparatus II (paddle type) at 50 rpm. The drug concentration was measured by an HPLC method.

## Results and discussion

### Hardness

Hardness is a critical quality attribute for chewable tablets. Chewable tablets should be such that they

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withstand manufacturing, packaging and distribution as well as be easily chewed by patients.<sup>3</sup>

Mannitol in powdered form (MP) as expected produced tablets with lowest hardness (average 50.01N). Due to smaller particles this type of mannitol has worse flowability, as well as compactability.<sup>2</sup> These values are within the target limits, but might pose a risk of tablet damaging during scale up. PDC due to its larger particle size showed better compressibility and produced tablets with satisfactory hardness (average 57.86N). As expected and consistent with previous findings<sup>4</sup>, PDM produced tablets with highest hardness (average 60.55N).

In an effort to improve the dissolution, PSI was added as a second diluent to formulations with PDC and PDM. Chewable tablets with both sorbitol and mannitol showed no significant change in tablet hardness (62.96N - PDC and PSI combination vs. 64.72N - PDM and PSI combination).

### Dissolution

Mannitol is the diluent of choice due to its chemical inertness and low hygroscopicity. Additionally, taking into consideration that the API is a poorly water-soluble drug, there is a potential for dissolution enhancement by incorporating mannitol. Because of its good water solubility, mannitol attracts water when in contact with the dissolution medium and could improve the dissolution rate. Here, a comparison between mannitol with different particle sizes and polymorph forms (beta and delta) was made.

MP is a crystalline powder, while PDC is a granulated form of mannitol in its beta polymorph form. Previous findings claim that larger particle size grades give tablets with longer disintegration time<sup>1</sup>, while differences in disintegration times may influence dissolution rates. In this case, chewable tablets with MP compared to those with PDC showed better dissolution (95.98% vs. 92.72%). However, the difference is insignificant and both formulations satisfy the set specification requirements (min. 80% dissolved API).

The most used and stable form of mannitol is its beta polymorph. However, other polymorphs can also be used as diluents, such as the delta polymorph which during wet granulation undergoes transition to the more stable beta polymorph. This transition is accompanied by an increase in surface area and better compressibility<sup>4</sup>. Having this in mind, chewable tablets with delta mannitol (PDM) were prepared. The average dissolution rate was 95.12%, with values from 94.07% to 97.31%. This uniformity in dissolution rates might indicate a uniform distribution of the API on the surface of mannitol.

Sorbitol, an isomer of mannitol, has similar characteristics as mannitol with few differences. It is more hygroscopic, which makes it less suitable for

moisture sensitive APIs, but on the other hand it has better water solubility than mannitol. This could mean that it is a better dissolution enhancer. In order to investigate this, the two formulations that showed best results were modified by adding sorbitol as a second diluent. The results were the following: combination of PSI and PDC in ratio 70:30 (from 93.28% to 97.39%, average 94.69%), and combination of PSI and PDM in ratio 70:30 (from 93.78% to 105.12%, average 98.48%). As can be seen from the results, incorporating sorbitol resulted with an improvement of the dissolution rate.

### Conclusion

The obtained results for these chewable tablets are only preliminary and their stability studies are in progress. However, it can be clearly seen that tablet hardness and dissolution of the API is dependent on the particle size of mannitol. Granulated mannitol with larger particle size produces chewable tablets with higher tablet hardness, but slightly lower dissolution rate than powdered mannitol. On the other hand, the delta polymorph produced tablets with excellent hardness and dissolution rate, maybe due to the greater porosity of these tablets. Including sorbitol as a diluent didn't seem to have an effect on tablet hardness, but dissolution was improved.

### References

- Kosugi, A., Leong, K.H., Tsuji, H., Hayashi, Y., Kumada, S., Okada, K., Onuki, Y., 2020a. Characterization of powder and tablet properties of different direct compaction grades of mannitol using a Kohonen self-organizing map and a Lasso regression model. *J. Pharm. Sci.* 109(8), 2585-2593. <https://doi.org/10.1016/j.xphs.2020.05.010>
- Kosugi, A., Leong, K.H., Urata E., Hayashi, Y., Kumada, S., Okada, K., Onuki, Y., 2020b. Effect of different direct compaction grades of mannitol on the storage stability of tablet properties investigated using a Kohonen self-organizing map and elastic net regression model. *Pharmaceutics* 12(9), 886. <https://doi.org/10.3390/pharmaceutics12090886>
- U.S. Food and Drug Administration, 2008. Quality attribute considerations for chewable tablets, Guidance for industry.
- Yoshinari, T., Forbes, R.T., York, P., Kawashima, Y., 2003. The improved compaction properties of mannitol after a moisture-induced polymorphic transition. *Int J Pharm.* 258(1-2), 121-31. [https://doi.org/10.1016/s0378-5173\(03\)00157-1](https://doi.org/10.1016/s0378-5173(03)00157-1).