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Granfiller-D® & Hisorad® As New Co-processed Excipients For Orall Disintegrating Tablets Produced by Direct Compression

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INTRODUCTION

Tablets are still the most widely used dosage form for oral application due to their simple administration and relatively low manufacturing costs. One main disadvantage of tablets is the difficulty in swallowing or chewing. This is especially relevant for special patient groups, e.g. pediatric and geriatric patients [1]. To avoid this problem and still enable oral tablet drug therapy, orodispersible tablets (ODTs) can be used. Orodispersible tablets rapidly disintegrate after their administration to the mouth without chewing or intake of water. With the help of ODTs easy application of liquid dosage forms can be combined with the high physical and chemical stability of solid drug dosage forms [2]. Our investigations focused on the direct compression of co-processed excipients (CPE) together with enalapril maleate, ibuprofen and paracetamol as model APIs. Ideally, the co-processing leads to multifunctional excipients, which offer a better balance between sufficient strength and required disintegration time [3]. The aim of this study was the comparison of two new co-processed excipients with already commercially available ones. For this purpose, the dependence of disintegration time on achieved tablet strength was analysed for seven CPEs including each of the three APIs.

MATERIALS AND METHODS

The CPEs investigated in this study were Granfiller-D® 211 (Daicel, Japan), Hisorad® (Daicel, Japan), SmartEx® QD-50 (Shin-Etsu, Japan), Ludiflash® (BASF, Germany), Prosolv® ODT (JRS Pharma, Germany), Pearlitol® Flash (Roquette, France) and Parteck® ODT (Merck, Germany). Each of the CPEs to be tested was blended with 3 model APIs separately for 15 minutes. In a second mixing step 1 % magnesium stearate was added as lubricant and mixed for 3 more minutes. Each batch of the powder blends containing paracetamol and ibuprofen (both 50 %) as model APIs was directly compressed on the compaction simulator Styl´One Evolution (Medel´Pharm, France). To thoroughly evaluate in how far the CPEs can impact content uniformity (not shown) for low dosed formulations, the blends containing enalapril maleate (4 %) were directly compressed on a rotary tablet press Korsch XM 12 (Korsch, Germany). Six different compression pressures were applied (50-250 MPa). Flat faced, facetted punches with a diameter of 9 mm were used. Tablet properties were measured by Smart Test ST 50 (Sotax, Switzerland). The tensile strength was calculated according to Fell and Newton [4]. Disintegration studies were performed in a disintegration test apparatus (Z32 Erweka GmbH, Germany) according to Ph.Eur. 10.

RESULTS AND DISCUSSION

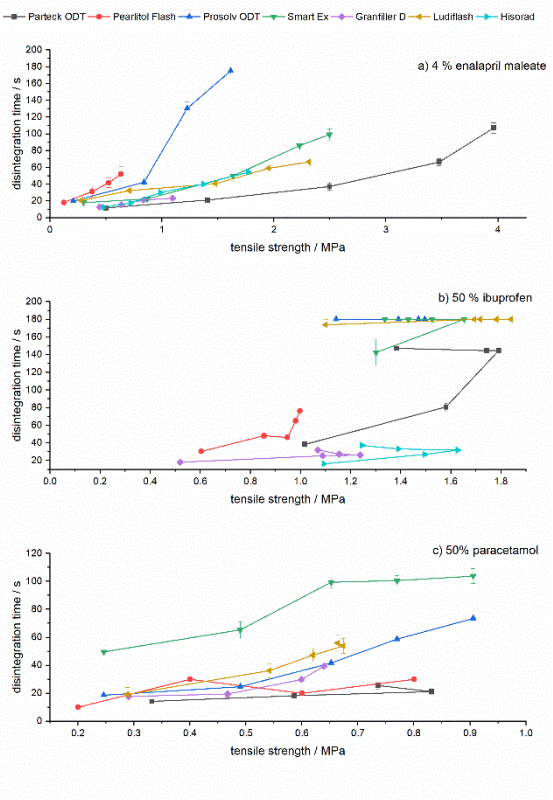

fig 1: Effect of tensile strength on disintegration time; n=6; mean ± CI (α=0.05)

For the adequate evaluation of the CPEs for direct compression of orodispersible tablets, the disintegration time seems to be the most important quality aspect. Nevertheless, it is often not very reliable to use the disintegration time as the only criterion, but rather it should be considered in correlation with the mechanical strength of the tablets expressed as tensile strength (TS). For this reason, the relation between mechanical strength and disintegration time was investigated. The disintegration profiles for the tested CPEs correlating to their TS are presented in figure 1 (a-c), where each diagram represents another API.

As expected, in most cases the disintegration time increased with higher TS for the formulations containing enalapril maleate (figure 1a). Prosolv® ODT exhibited a disintegration behaviour which showed the strongest dependence on increased TS. A sharp increase in disintegration time was observed even in the lower range of mechanical strength (0.7-1.2 MPa), up to disintegration times of 180 s, thus exceeding the requirements set by Ph.Eur. For the other CPEs, the requirements of Ph.Eur. were fulfilled over the whole tested range. Due to the low drug load (4 %) this specific behaviour can be mainly attributed to the properties of the CPEs.

The corresponding results for 50 % ibuprofen (figure 1b), show the effects of an added API, which is widely known to cause a poor disintegration, due to the hydrophobicity and predominantly plastic deformation. Here, distinct differences in the performance became clearly visible. The profiles for several CPEs, especially for Ludiflash®, Smart Ex® and Prosolv® ODT, changed significantly. Regardless of TS, none of these tablets showed disintegration times below 180 s and could not be declared as orodispersible tablets anymore. A sufficient compensation of ibuprofens challenging properties could not be achieved. The disintegration time showed strong dependence on the tensile strength. Interestingly, this relation could not be observed for Hisorad® und Granfiller-D®. Their profiles were only slightly influenced by the addition of ibuprofen and the tablets seemed to disintegrate independent of tablet strength and corresponding porosity. Ibuprofen containing ODTs manufactured with Granfiller-D® and Hisorad® even fulfilled the requirements of FDA (30 s) for orally disintegrating tablets.

Figure 1c displays the profiles for the tablets composed of 50 % paracetamol. All of them met the set requirements, thus can be declared as orodispersible tablets. Nevertheless, this statement should be considered critically, because none of these compacts exhibited TS above 1 MPa, which most likely explains the short disintegration time.

CONCLUSION

This study reveals that the directly compressed tablets made from Granfiller-D® and Hisorad®, prove to be a promising alternative in the formulation of orodispersible tablets. This is especially the case when hydrophobic APIs, which often lead to adverse disintegration performance, should be incorporated. For ibuprofen, which was selected as a model drug with said characteristics, it could be observed that the disintegration predominantly took place independent from porosity and tensile strength. For low dosed APIs all CPEs tested except for Pearlitol® Flash and Prosolv® ODT showed satisfying results. Efficient formulation of orodispersible tablets containing high loads of poorly compressible drugs like paracetamol, remains however an unmet challenge.

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