

# Adjusting the Release Rate of Mesalazine from Matrix Formulations by Addition of various Excipients

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## INTRODUCTION

Mesalazine is widely used drug compound to treat inflammations within the gastrointestinal tract (GIT). The APIs is mostly supplied as very fine powder with extremely poor flowability and wet granulation is most often used to meet the challenge. However, mesalazine is prone to degradation by several pathways (e.g. oxidation to oxidation and forms quinoneimine), especially if brought into contact with water [1]. Therefore, dry granulation by roll compaction seems to be a viable alternative. Very often a prolonged release profile or targeting to the large intestine is desired for the delivery profile of this API. To achieve the desired release profile matrix systems containing HPMC (hydroxypropylmethyl cellulose) are often formulated. The release profile is then governed by several factors such as the viscosity grade of the polymer as well as the porosity of the dosage form and the solubility of the drug and other formulation components [2].

Meaningful testing of the API release from such matrix formulations can be challenging. Simulating the pH gradient within the GIT and the use of various compositions of simulated intestinal fluids has been well established [3]. It remains a challenge to reproduce the mechanical stress that a dosage form is exposed to during the passage through the GIT. Garbacz et al. [4] investigated the effect of mechanical stress on a 8 commercially available dosage forms containing mesalazine and found that the release profiles obtained while putting the dosage forms under mechanical stress differ significantly from those obtained under commonly used dissolution methods described in the pharmacopoeias.

In the presented study it is shown that poorly flowing mesalazine can be formulated into a prolonged release dosage form by roll compaction of the mixture containing a matrix former, such as HPMC and direct compression fillers. Moreover, the influence of several fillers on the drug release profiles in standard dissolution methods is compared to that in bio-relevant, mechanical stress simulating dissolution tests.

Roll compaction proved to be a versatile technique to obtain granules suitable for tableting purposes. It is shown that the addition of insoluble fillers (e.g. calcium hydrogen phosphate) does not only help to adjust the release profile but also provides an easy route to improve the mechanical robustness of the dosage form when exposed to mechanical stress encountered in the GIT.

## MATERIALS

The composition of each formulation is provided in Table 1. Mesalazine (MZN) was obtained from Merck Chemicals Ltd (Beeston; UK). Lactose (LAC) of the type Flowlac 100 was obtained from Meggle Group (Wasserburg, Germany). Calcium hydrogen phosphate (DCP), DI-CAFOS A60, was produced by Chemische Fabrik Budenheim KG (Budenheim, Germany) and magnesium stearate (Mg-St) of the type Ligamed MF-2-V by Peter Greven (Bad Münstereifel, Germany). HPMC of the type Bonucel D4000 H2208 was obtained at from Bioground GmbH (Huenstetten, Germany). All materials were used as delivered without further conditioning. Tablets

were coated with the methacrylate Eudragit L30 55D (Evonik, Darmstadt, Germany).

Form. No.	DCP	LAC	MZN	HPMC	Mg-St
N1	27	27	35	10	1
N2	22	22	35	20	1
N3	0	54	35	10	1
N4	0	44	35	20	1
N5	12.25	36.75	35	15	1
N6	12.25	36.75	35	15	1

Table 1: Percentages of composition of mesalazine formulations

## METHODS

The API, the filler and the matrix polymer were blended on a Turbula blender (Willy A. Bachofen AG, Muttenz, Switzerland) for seven minutes followed by addition of the Mg-St and additional blending for three minutes. Roller compaction was carried out using a Freund-Vector TFC 220 pilot scale roll compactor at 13 kN/cm and 4,5 rpm to obtain a ribbon thickness of 2 mm. The ribbons were milled subsequently milled on an oscillating sieve mill with 2.25 mm and 1.0 mm mesh widths. The obtained granules were compressed into tablets of 714 mg weight containing 250 mg of API on a Fette 102i rotary press (Fette Compacting GmbH, Schwarzenbek, Germany) using 18mm x 8 mm oblong shaped punches. The compaction force was varied between 280 MPa and 310 MPa so as to obtain a consistent tablet porosity of 12 %. Tablets were coated with an aqueous dispersion to obtain a coating of 9 % of the tablet mass.

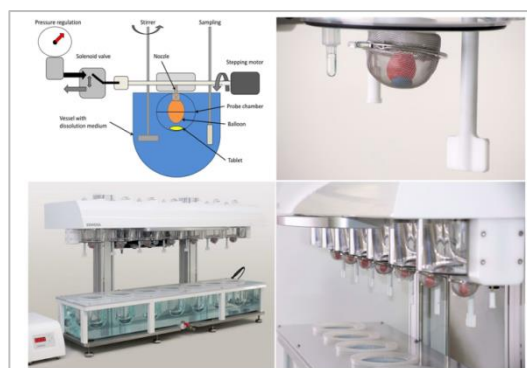


Figure 1: Dissolution stress test device. (a) Schematic representation of the apparatus. (b) Photograph of one opened chamber with the paddle

Standard dissolution tests (USP Apparatus 2) of the coated and un-coated tablets were carried out on a PTWS 820D system (Pharmatest, Hainburg, Germany) at 100 rpm. Biorelevant stress tests were carried out on the device shown in Figure 1 whereas the tablets are positioned in a rotating cage with a balloon simulating gastric pressure waves that act on the dosage forms. Dissolution media were 0.1 N HCl for two hours, pH 6.0 phosphate buffer for one

hours followed by a pH change to 7.2 according to the monograph for mesalazine delayed release tablets. The second buffer stage run time was extended from 1.5 h to 24 h for this study.

## RESULTS

Dry granulation of the powder mixtures increased the flowability from very poor (AOR around 62 °) to a passable flow (AOR around 40 °) for all mixtures while the bulk density was increased 2.6 fold. Tableting yielded compacts that had porosities between 11.5 % and 12.3 %, showing a breaking force between 73 N and 100 N and friability values between 0.2 % and 0.3 %.

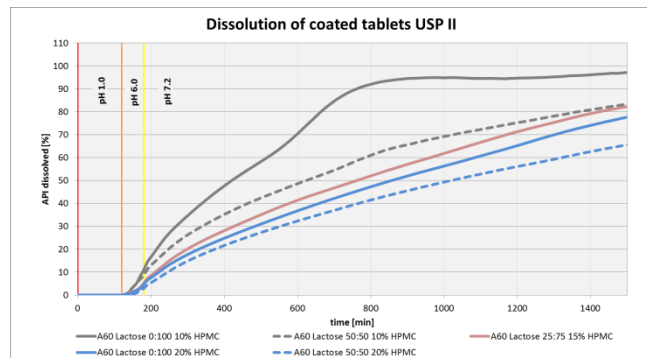


Figure 2: Dissolution profiles of coated tablets from USP II apparatus

Figure 2 and Figure 3 show the drug release from coated tablets and it can be observed that no drug is released in gastric fluid. A slow onset of drug release can be observed if the pH is elevated from 1.0 to 6.0. In the USP II apparatus only the formulation containing only lactose as filler releases the whole amount of drug within 24 hours. Elevated levels of HPMC as well as the addition of insoluble calcium phosphate delay API release. Switching the conditions to the stressed test it can be observed that all formulations containing a lower HPMC concentration show a significant effect of the enacted pressure waves. Even at higher HPMC concentration of 20 % the formulations containing only lactose as filler are prone to show a burst release upon being affected by the simulated pressure wave. In contrast to that the formulation containing a mixture of lactose and calcium hydrogen phosphate (1:1 ratio) and 20% HPMC shows more robustness and a continued linear drug release.

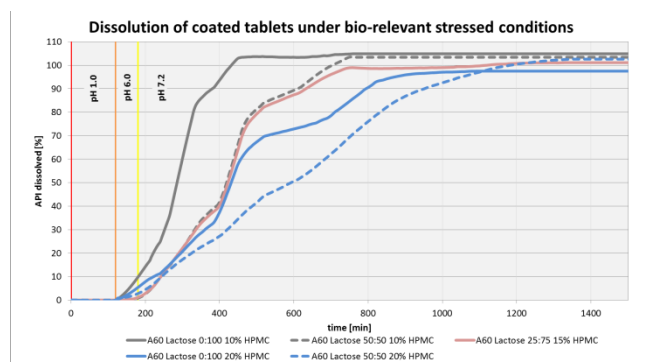


Figure 3: Dissolution profiles of coated tablets under stressed conditions

Figure 4 shows the release profile from un-coated tablets to evaluate the effect of the acid solubility of the filler in gastric media. It can be observed that the burst release under acidic conditions is not only correlated to the concentration of matrix forming polymer but also on the acid solubility of the filler incorporated into the matrix. At a low concentration of HPMC especially the formulation containing calcium hydrogen phosphate shows a significant burst in drug release. At the higher concentration of HPMC the difference between the formulations with and without calcium phosphate is diminished.

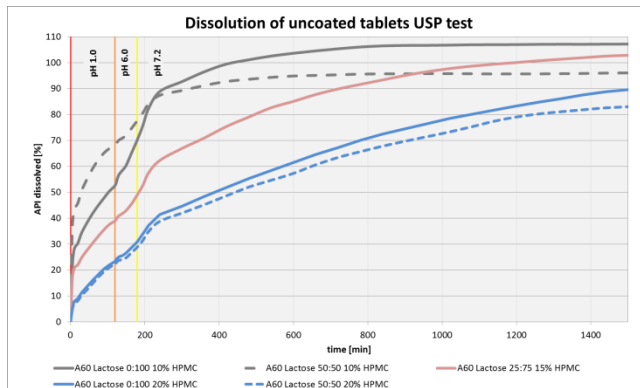


Figure 4: Dissolution profiles of un-coated tablets from USP II apparatus

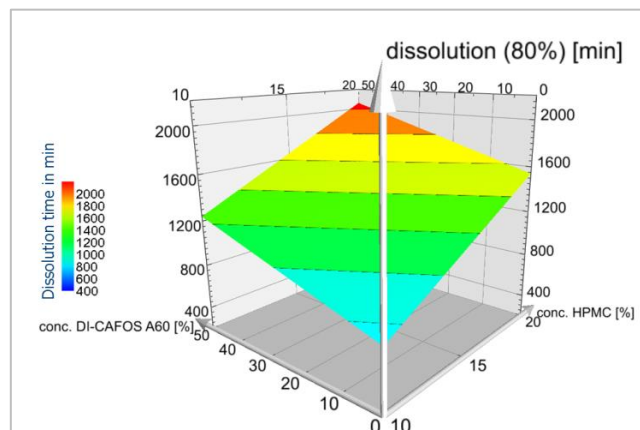


Figure 5: Drug release within USP II apparatus in correlation to the HPMC and calcium hydrogen phosphate content

Figure 5 gives an example of the correlations between the contents of the matrix former as well as the calcium phosphate component and the release time for 80% of the API. An increased HPMC level retards the liberation of the drug and so does the addition of the phosphate filler.

## CONCLUSION

Roll compaction was found to be a suitable technique to prepare granules with the very poorly flowing API mesalazine. Release profiles from standard USP dissolution tests and biorelevant stressed dissolution tests differ significantly. Addition of an insoluble filler, anhydrous calcium hydrogen phosphate, helps to retard the drug release while also providing the formulation with more mechanical strength.

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