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INTERACTION OF WEAK BASE DRUG TRIMETAZIDINE AND CARBOPOL AS FURTHER RETARDATION IN THE MATRIX TABLET

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Abstract: Hydrophilic polymers using as matrix former in matrix tablets is a common approach and well-known excipient Carbopol is widely used for this reason too. In common case polymer doesn't interact with drug but Carbopol is a weak polyacrylic acid and obviously can interact at physiological enteric conditions with weak base drugs like trimetazidine dihydrochloride. During matrix tablet dissolution at enteric conditions, the microenvironment pH inside tablet changes from surface to center. It was found that hydrated matrix has unusual structured in microenvironment pH diapason of possible trimetazidine-Carbopol interactions. This matrix structuration resulted in significant matrix behavior changing and increasing trimetazidine release retardation in comparison with release data at gastric conditions. Thus, the example of trimetazidine-Carbopol interactions demonstrate additional mechanism of drug retardation that could be used for another appropriate weak base drugs.

Keywords: Carbopol, trimetazidine, matrix tablet, release retardation

In case of soluble matrices, a hydrogel formed after contact of matrix with medium and drug release occurs either *via* drug diffusion through a network of capillaries formed between compacted matrix former or/and erosion of the matrix. Dependent on the aqueous drug solubility, one of the mechanisms could dominate or combination of both takes place (1). Despite that Carbopol 71G is crosslinked polyacrylic acid and in principle is insoluble, the drug release occurs similarly to the water soluble matrices including erosion (2). Being a weak acid, Carbopol 71G can interact with weak bases at pH about pKa = 6.1. Trimetazidine dihydrochloride as a week base (pKa_1 4.45, pKa_2 9.14 (4)) can interact with Carbopol 71G. Therefore, the aim of this work was to investigate the trimetazidine-Carbopol interactions and their effect on drug release from matrix tablet.

EXPERIMENTAL

Materials

API: Trimetazidine dihydrochloride (TMZ × 2HCl, Sochinaz SA, Switzerland); matrix former: crosslinked polyacrylic acid (Carbopol 71G, Lubrizol Corp., USA); filler: lactose monohydrate (Granulac 200, Meggle AG, Germany); glidant: colloidal silicon dioxide (Aerosil 200 Ph, Evonik AG, Germany), lubricant: sodium stearyl fumarate (Pruv, JRS Pharma, Germany).

Tablets preparation

Direct compression method was applied to obtain 200 mg biconvex tablets with 8 mm diameter according to the formulation presented in Table 1 using a mixer (Turbula T2F, Willy A. Bachofen AG, Switzerland) and eccentric tablet press (Korsch EKO, Korsch AG, Germany).

Dissolution test

The drug release from tablets was investigated in a paddle apparatus (Vankel VK 300, Vankel Industries, Edison., NJ, USA) at following conditions: 900 mL of 0.1 M HCl or PBS pH 6.8, 100 rpm, 37°C; (n = 3). Samples were withdrawn at predetermined time points, filtered through 0.35 μm filters and measured UV-spectrophotometrically at λ = 269 nm (pH 1: $y = 0.0022x$, $R^2 = 0.9999$; pH 6.8: $y = 0.0022x + 0.0276$, $R^2 = 0.9993$).

Aqueous solubility determination

The shake-flask method was used for TMZ × 2HCl and Granulac 200 solubility determination.

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Table 1. Tablet composition (% per 200 mg tablet)

Formulation	F1	F2
TMZ × 2HCl	17.5	—
Granulac 200	31.3	48.8
Carbopol 71G	50	
Aerosil 200 Ph. and Pruv	0.2 and 1.0	

Table 2. Aqueous solubility of TMZ × 2HCl and Granulac 200 (n = 3, SD ≤ 5%)

Compounds	Solubility (mg/mL) at pH corresponding to	
	Stomach	Small intestine
TMZ × 2HCl	620 (pH 0.6)	340 (pH 6.7)
Granulac 200	210 (pH 0.9)	210 (pH 6.5)

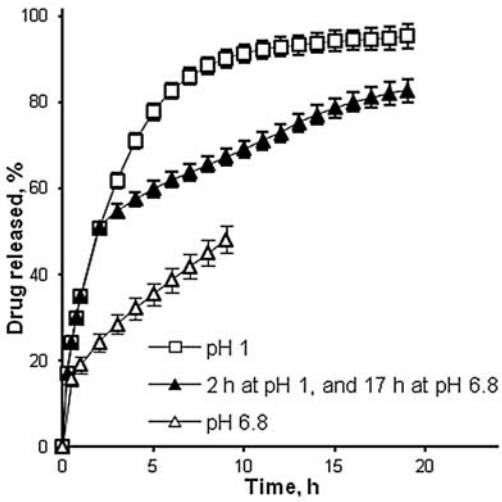


Figure 1. Effect of medium pH on drug release

The excess of tested substance was added to 50 mL of medium (0.1 M HCl or PBS pH 6.8). The equilibrium concentration was achieved in three days. The substance solubility was calculated after drying of known quantity of aliquot to constant weight at 105°C.

RESULTS AND DISCUSSION

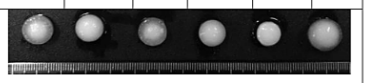
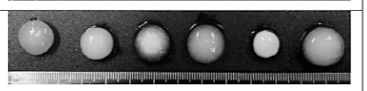
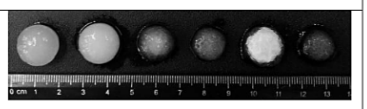
TMZ × 2HCl release from matrix tablets at pH 1 was much faster than at pH 6.8 (Fig. 1) or slowed down upon medium change from pH 1 to pH 6.8 after 2 h.

Since the solubility of Granulac 200 and TMZ × 2HCl is relatively pH independent in the range 1-6.8 (Tab. 2), the ionic interaction between positively charged TMZ and negatively charged Carbopol 71G could be a reason for slower drug release.

The swelling/erosion behavior of acidic dissolution medium (e.g., pH 1) of Carbopol 71G containing tablets was not affected by the presence of TMZ × 2HCl (Fig. 2). In this medium, Carbopol 71G was not ionized and no interaction with TMZ × 2HCl occurred. The release of freely soluble drug from swollen tablets was driven by diffusion and was relatively fast (Fig. 1).

In the medium with pH 6.8, approx. 80 % of carboxyl groups of Carbopol 71G and almost all tertiary amine groups of TMZ were ionized (according to pKa_1) and can interact with each other forming salt in a form of erodible gel layer (Fig. 3) on the surface of the tablet. Tablets containing TMZ (F1) did not swell in this medium in contrast to drug free (F2) tablets (Fig. 2).

The increased swelling and viscosity of ionized Carbopol 71G in the dissolution medium with pH 6.8 is well known phenomenon (3). However, due to interaction with ionized TMZ, drug containing tablets did not swell but rather eroded (Fig. 2). pH measurement of different regions of tablet cross-section after 5 h of dissolution test in phosphate buffer pH 6.8 showed a pH gradient inside of tablets (Fig. 3 D). Cone-shaped rolled strips of indicator paper which allows inserting the paper into a point was used to pH determination. The pH decreased from approx. 7 on the surface to 2-3 in the centre of the tablet. A thin erodible surface layer which contacts with PBS pH 6.8 organoleptically looks like mucus (Fig. 3 A). The pH 5-7 in outer layer corresponds to ionized state of Carbopol 71G and TMZ × 2HCl, where the interaction was possible. This outer layer has rubber-like structure with elastic properties (Fig.

	pH 1		2 h at pH 1 and 17 h at pH 6.8		pH 6.8	
Time, h	F1	F2	F1	F2	F1	F2
2						
5						
19						
Dry residue* after 19 h, mg (n = 3; SD < 5%)	112.0	100.8	57.8	28.1	107.2	22.4

* Dry residue was determined after drying to constant weight at 105°C

Figure 2. Matrix tablets behavior during dissolution test

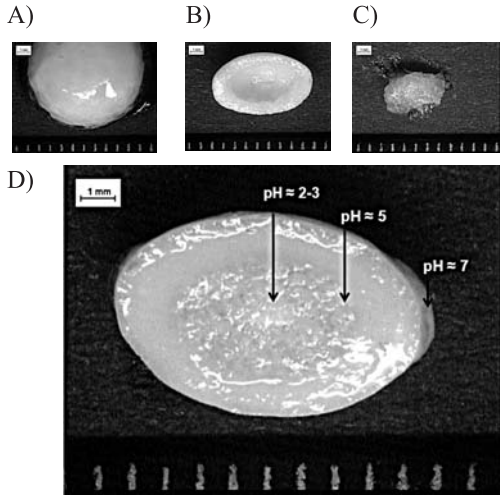


Figure 3. TMZ × 2HCl containing matrix tablet after 5 h of dissolution test at pH 6.8: A) whole tablet, B) separated rubber-like layer, C) separated gel core, D) cross-section

3 B). The central part of tablet cross-section, which corresponds to pH 2-5, has a form of plastic gel (Fig. 3 C) easy separable from outer layer. In contrast to TMZ tablets (F1), the drug free tablet (F2) in PBS pH 6.8 swelled without formation of internal structure and different way eroded (Fig. 3). After 19 h of dissolution test in PBS pH 6.8 (Fig. 2), the solid residue of drug free tablet (F2) was lower than solid residue of TMZ contain tablet (F1) in spite of lower solubility of Granulac 200 than TMZ × 2HCl.

The different behavior of TMZ containing tablet during dissolution test in 0.1 M HCl solution in contrast to PBS pH 6.8, the behavior difference of TMZ containing tablet in PBS pH 6.8 in contrast to drug free tablet, the internal structure formation of TMZ containing tablet in PBS pH 6.8 in contrast to drug free tablet allow us to ascertain the presence of TMZ-Carbopol 71G interaction. It seems that found interaction of Carbopol 71G and TMZ in the outer layer could be used for retardation of drug release.

CONCLUSION

Slowdown of release in the release medium with pH 6.8 was due to the interaction of TMZ × 2HCl and Carbopol 71G with rubber-like layer formation. This interaction could be used for further retardation. Different release rate and mechanical properties of tablet in different physiological pH could provide problems for *in vitro*/*in vivo* correlation because of unpredictable tablet presence in the stomach. Therefore, one of the approaches to achieve this retardation in pH independent manner would be an enteric coating.

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