Influence of ethanol on swelling and release behaviors of carbomer-based tablets

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Introduction

Recently, there has been an increasing research attention regarding the impact of concomitant intake of ethanol on the release from oral controlled release (CR) dosage forms and the associated risk of dose dumping.

The aim of this study was to investigate the effect of ethanol on the *in vitro* swelling and release behavior of carbomer-based tablets.

Experimental methods

- **Materials**

Carbopol® (CP) 971P NF and 974P NF were obtained from Lubrizol, USA. Theophylline (THEO), caffeine (CAF) and metformin HCl (MH) were obtained from Sigma-Aldrich (USA), Fluka (USA) and JPM (Jordan), respectively.

- **Hydro-ethanolic media**

Six media comprising hydrochloric acid (0.1N, pH = 1.2) and phosphate buffer (pH = 6.8), each with 0, 20 and 40% (v/v) ethanol were used in swelling and release studies.

- **Determination of solubility of model drugs in the hydro-ethanolic media**

The solubility test was performed by adding excess amounts of the model drugs to the hydro-ethanolic media (at 37 °C). The concentration of dissolved drug was determined spectrophotometrically.

- **Preparation of CP drug-free compacts and matrix tablets**

Drug-free CP compacts (200 mg, 13-mm diameter) were prepared by directly compressing (300 $kg.cm^{-2}$) powder from each grade. Matrix tablets (151.5 mg, 7-mm diameter) were prepared by direct compression (100 $kg.cm^{-2}$) of physical mixtures of CP with the model drug at a 1:4 polymer:drug ratio adding 1% Mg stearate as a lubricant.

- ***In vitro* swelling studies**

Swelling experiments were performed for drug-free CP tablets in a paddle dissolution system at 100 rpm using 500 ml of the hydro-ethanolic medium. Each tablet was fixed on a pin at the bottom of the dissolution vessel to avoid sticking to the vessel. At 1, 4 and 8 hours, tablets were gently withdrawn from the media and a filter paper was used to remove excess liquid from around the swollen tablets. The tablets were then weighed and dried at 105 °C to a constant weight. Medium uptake and mass loss were calculated according to Al-Zoubi et al. [1].

- ***In vitro* drug release testing**

The release studies were performed in a basket dissolution system at 100 rpm using 900 ml of the hydro-ethanolic dissolution medium. Samples were analyzed by UV spectroscopy. The release data were fitted to Higuchi and Peppas models in order to characterize release rate and mechanism, respectively. Similarity factor (f_2) was used to compare the release profiles of each model drug in media containing 20 and 40% ethanol with the corresponding in medium with 0% ethanol.

Results and discussion

- **Solubility of model drugs**

Fig. 1 shows that MH has the highest solubility and THEO has the lowest solubility in all of the tested media. Furthermore, by increasing the percentage of ethanol in both acidic and buffered media, the solubility of MH is decreased, due to suppression of salt dissociation, while the solubility of THEO and CAF is remarkably increased.

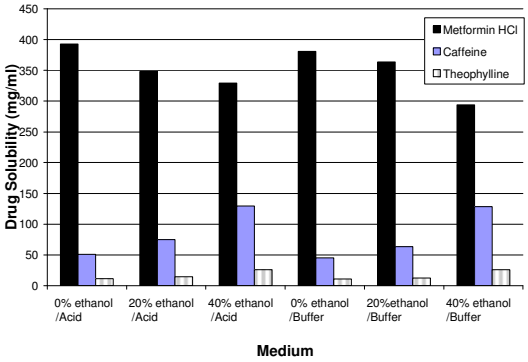

Fig. 1. Effect of ethanol concentration on the solubility of MH, CAF and THEO in acidic and buffered media.

- ***In vitro* swelling behavior**

Fig. 2 shows that increasing ethanol concentration in buffer causes a decrease in dissolution medium uptake and mass loss of CP drug-free compacts. On the other hand, the swelling and erosion of the compacts in acidic solution, were less clearly affected (for CP 971) or slightly increased (for CP 974P) by increasing ethanol concentration.

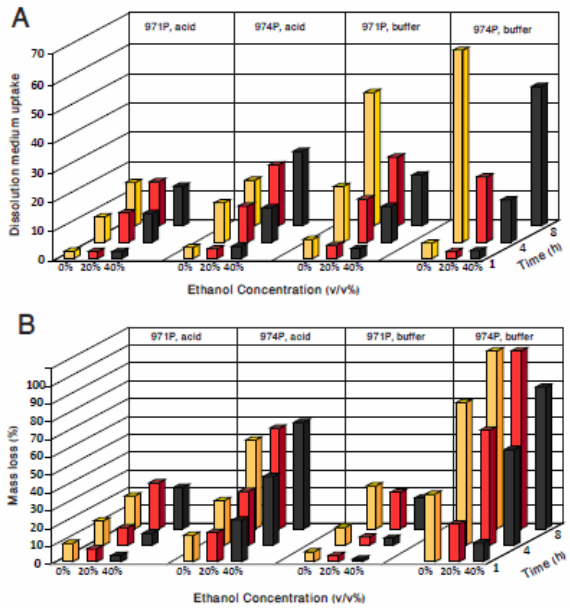

Fig. 2. Dissolution medium uptake (A) and mass loss (B) for CP 971P and 974P compacts in hydro-ethanolic acidic and buffered media.

- **In vitro drug release**

It can be seen from K_H values in Table 1 that the effect of ethanol on release was different for model drugs according to their solubility change with ethanol concentration. No dose dumping was manifested. The release rate of MH was decreased with increasing ethanol concentration for both CP grades, probably due to the decrease of matrix erosion in buffer and of drug solubility, in acidic and buffered media, with increasing ethanol concentration.

For CAF and THEO, the release rate (K_H results, Table1) in acidic and buffered media decreased by increasing ethanol concentration from 0 to 20%, while increased by increasing ethanol concentration from 20 to 40% (i.e. release was slowest at 20% ethanol concentration). This trend can be explained in buffered media by the contradicting effects of increasing ethanol concentration through decreased matrix erosion and increased drug solubility, which are expected to slow and hasten the release, respectively. However, in acid, the release rate was expected to increase persistently with increasing ethanol concentration because erosion results do not oppose the increase of drug solubility. Thus, the swelling and erosion results of drug-free polymer tablets were not in good consistence with the release results and this suggests that the effect of ethanol on swelling and erosion of both CP polymers might be different in the presence of model drugs.

Regarding release mechanism, the n values in buffer were decreasing with increasing ethanol concentration for CAF and THEO because of increased drug solubility and decreased polymer swelling and erosion, but this trend is not found in the case of MH probably because of the contradicting effects of ethanol on release mechanism through decreasing both the solubility of MH and tablet swelling/erosion. For the three drugs in acid, the trend for the changing of release exponent (n) with ethanol concentration was less obvious.

Table 1. Exponent (n) of the Peppas model and Higuchi constant of the square root model for release data of CP matrix-tablets in hydro-ethanolic media.

Drug	CP grade	Eth. Conc. (v/v %)	Acid		Buffer	
			n	K_H ($h^{-0.5}$)	n	K_H ($h^{-0.5}$)
MH	971P	0	0.41	70.02	0.46	66.41
	971P	20	0.40	51.64	0.56	47.91
	971P	40	0.45	48.07	0.50	44.69
	974P	0	0.40	71.90	0.44	50.25
	974P	20	0.37	58.54	0.56	48.97
	974P	40	0.53	48.63	0.53	42.71
CAF	971P	0	0.65	27.65	0.84	22.55
	971P	20	0.70	26.08	0.75	22.43
	971P	40	0.65	26.73	0.64	24.73
	974P	0	0.80	32.55	1.10	35.28
	974P	20	0.95	30.43	0.97	29.19
	974P	40	0.85	36.26	0.84	33.04
THEO	971P	0	0.70	18.61	0.96	17.16
	971P	20	0.71	17.02	0.74	12.57
	971P	40	0.68	18.20	0.64	16.98
	974P	0	0.92	23.93	1.15	31.47
	974P	20	0.88	22.16	0.86	17.75
	974P	40	0.83	23.76	0.78	21.58

The results of similarity factor (f_2) are shown in Table 2. According to these results, ethanol led to different release profiles ($f_2 < 50$) in 7 of 8 cases for matrices containing MH and in 3 of 8 cases for matrices containing CAF and THEO.

Table 2. Similarity factor (f_2) comparing the release profiles for CP matrices in dissolution media containing ethanol (test) with those in media with 0% ethanol (reference).

Drug	CP grade	Similarity factor			
		20% ethanol		40% ethanol	
		Acid	Buffer	Acid	Buffer
MH	971P	43.4	41.0	37.6	41.4
	974P	46.2	60.3	33.1	42.1
CAF	971P	68.5	65.3	72.3	60.8
	974P	42.7	34.5	48.2	51.1
THEO	971P	70.7	48.1	81.6	59.0
	974P	62.0	28.1	59.1	35.6

Conclusion

From this study, it was found that the presence of ethanol in dissolution media at concentrations relevant to alcoholic beverages affected the *in vitro* drug release from CP matrices, although no dose dumping was manifested and release was slowed in most cases. The influence of ethanol on release can be explained to a high extent by its combined effects on the solubility of model drugs and the swelling/erosion behavior of polymers

References

[1] N. Al-Zoubi, H. AlKhatib, W. Obeidat. *Drug Dev. Ind. Pharm.* 37: 798–808 (2011)