Evaluation of hydrophilic matrix tablets based on Carbopol® 971P and low-viscosity sodium alginate for pH-independent controlled drug release

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Introduction

Recently, there is an increased interest in using ionizable polymers in controlled release matrix formulations in order to achieve pH independent drug release.

In this work, polymer mixtures comprised of Carbopol® 971P (CP) and low-viscosity sodium alginate (SA) were evaluated as hydrophilic matrix formers for pH independent controlled release. Paracetamol, salicylic acid and verapamil HCl were selected as model drugs of neutral, acidic and basic properties, respectively.

Experimental methods

- **Materials**

The polymers used were Carbopol® 971P (from Noveon, USA) and sodium alginate (from BDH, UK). Model drugs used were: 1) paracetamol, from Midpharma, Amman, Jordan, 2) verapamil HCl, from Medex, UK, and 3) salicylic acid from Gainland Chemical Company (GCC), UK.

- **Preparation of matrix-tablets**

Matrix tablets were prepared by direct compression of physical mixtures in a 13-mm diameter die using manual hydraulic press. Physical mixtures were composed of equal amounts of drug (paracetamol, salicylic acid or verapamil HCl) and matrix former. The matrix former was composed of CP and SA at five different ratios (0:100, 25:75, 50:50, 75:25 and 100:0). The drug was mixed with the polymers using a spatula for 15 min. Then, 480 mg of the powder mixture was compressed at pressure 20 MPa for 30 seconds.

- **In vitro drug release**

The release study was performed in a USP II paddle system at 100 rpm using 900 ml of dissolution medium (0.1 N HCl, pH = 1.2, and Phosphate buffer, pH = 6.8). Three tablets were tested for each batch and samples were analyzed by UV spectroscopy. The release results were fitted to power law model of Peppas in order to characterize release rate and mechanism. Similarity factor (f_2) was calculated to compare the release profiles in two media, in order to elucidate the suitable CP:SA ratio for pH-independent controlled release for each model drug (neutral, acidic or basic).

Results and Discussion

The release profiles in two dissolution media (0.1 N HCl, pH = 1.2, or phosphate buffer, pH = 6.8) for compacts containing CP and SA at different ratios, as a matrix former, and paracetamol, salicylic acid, and verapamil HCl, as model drugs, are shown in Fig. 1(A-C), respectively. The results of fitting the release data to power law model are shown in Table 1 as release rate constant (K_p) and release exponent (n).

From Table 1, It can be seen that the release rate constant (K_p) increased generally by decreasing CP:SA ratio for the three model drugs and both

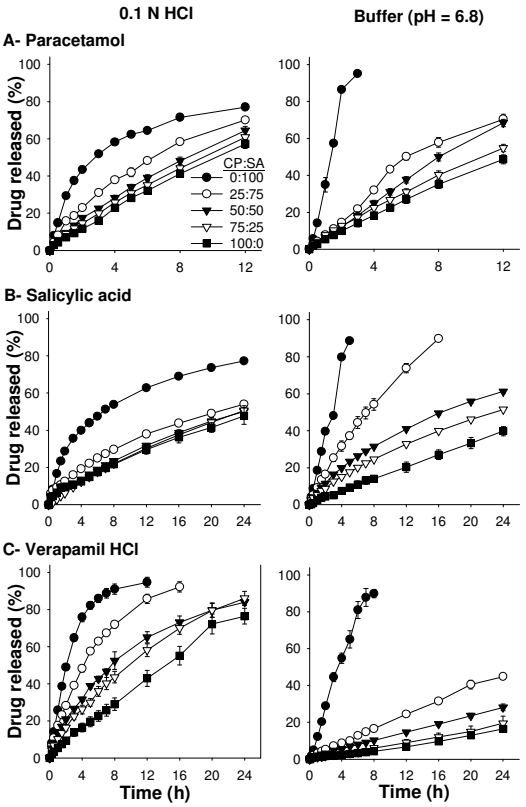

Fig. 1. Release profiles of paracetamol (A), salicylic acid (B) and verapamil HCl (C) from matrices containing Carbopol® 971P, CP, and sodium alginate, SA, at different ratios in 0.1 N HCl (left) and phosphate buffer, pH = 6.8 (right). Symbols are according to paracetamol profiles in 0.1 N HCl.

Table 1. Results of model fitting to power law (release rate constant, K_p, and exponent, n) for CP-SA matrices (R > 0.98)

Drug	CP:SA ratio	0.1 N HCl		Buffer	
		K_p (h^{-n})	n	K_p (h^{-n})	n
Para-cetamol	0:100	0.272	0.584	0.345	1.259
	25:75	0.147	0.670	0.086	0.940
	50:50	0.092	0.766	0.071	0.829
	75:25	0.088	0.776	0.058	1.058
	100:0	0.069	0.853	0.053	0.906
Salicylic acid	0:100	0.180	0.547	0.194	0.874
	25:75	0.092	0.561	0.098	0.832
	50:50	0.049	0.740	0.078	0.665
	75:25	0.040	0.800	0.058	0.691
	100:0	0.054	0.683	0.021	0.927
Verapamil HCl	0:100	0.264	0.896	0.134	1.041
	25:75	0.173	0.744	0.026	0.907
	50:50	0.129	0.670	0.016	0.894
	75:25	0.101	0.704	0.006	1.000
	100:0	0.049	0.869	0.005	1.114

dissolution media, which indicates lower release sustaining capability of SA than that of CP in both media.

The release rate coefficient (K_p) for paracetamol matrices was higher in 0.1 N HCl than in buffer for all CP:SA ratio levels except the minimum (i.e. 100 % SA), while for salicylic acid matrices it was lower in 0.1 N HCl than in buffer for all CP:SA ratio levels except the maximum (100 % CP). In case of verapamil HCl matrices K_p was higher in 0.1 N HCl than in buffer for all CP:SA ratios.

The faster paracetamol release in buffer than in 0.1 N HCl for SA matrices (low CP:SA level) and the slower release in buffer for higher CP:SA levels is explained by the opposite release retarding capability change of the two polymers with changing pH of the medium [1-4]. In case of acidic and basic drugs, another important factor that affects the release rate, in addition to the abovementioned effect of the medium on the two polymers, is the higher solubility of the acidic drug in buffer and of the basic drug in acidic medium.

The release exponent (n) was generally higher in phosphate buffer than in 0.1 N HCl except for two cases corresponding to salicylic acid matrices with CP:SA ratios of 50:50 and 75:25. The higher n values in phosphate buffer than in 0.1 N HCl indicates shift in the release mechanism from Fickian diffusion towards polymer swelling and relaxation by increasing pH of the dissolution medium, which is due to pH dependent swelling of both polymers and lower solubility, in case of verapamil HCl, in buffer [1,4]. The unclear trend noticed for salicylic acid matrices is probably due to combined effect of changes in: 1) matrix swelling and erosion, 2) drug solubility and 3) the acidic microenvironment inside the matrix caused by drug dissolution.

Table 2. Similarity factor (f_2) comparing the release profiles in 0.1 N HCl and phosphate buffer for three drugs from matrices with different CP:SA ratios

CP:SA ratio	Similarity factor (f_2)		
	Paracetamol	Salicylic acid	Verapamil HCl
0:100	29.6	32.8	40.1
25:75	62.2	34.5	20.5
50:50	70.3	56.8	22.4
75:25	59.1	78.7	21.1
100:0	93.4	59.1	26.8

The results of f_2 comparing the release profiles in two dissolution media are presented in Table 2. It can be seen that for paracetamol matrices the value of f_2 is higher than 50, indicating pH-independent release, for all CP:SA ratio levels except the minimum (100 % SA). The pH-dependent release of paracetamol at 100 % SA is explained by the known pH-dependent swelling and erosion of SA [1] and the nearly pH-independent solubility of paracetamol.

In case of salicylic acid, pH-independent release ($f_2 > 50$) was found for matrices with CP:SA ratios ≥ 50:50. The f_2 and K_p results indicate the possibility of manipulating the drug release rate, being at the same time pH-independent, by changing the CP:SA ratio within the ranges 25:75 - 100:0 and 50:50 - 100:0 for paracetamol and salicylic acid, respectively.

In case of verapamil HCl matrices, the results of f_2 for all CP:SA levels were lower than 50, indicating pH-dependent release, with least pH dependence (f_2 = 40.1) found at lowest CP:SA level (100 % SA). The pH-dependence of verapamil HCl release is explained by the higher solubility of drug, due to higher degree of ionization, in 0.1 N HCl than in buffer. This property has been opposed by the lower swelling and erosion, and more constrained release from SA at low pH. However, even at lowest CP:SA level (100 % SA), this opponent effect was not sufficient to achieve pH-independent release of verapamil HCl, and in order to achieve that, higher SA:verapamil HCl ratio might be needed.

Conclusion

Matrices containing different proportions of Carbopol® 971P (CP) and low viscosity sodium alginate (SA) form a promising versatile system for pH-independent controlled release. By adjusting the CP:SA ratio in the matrices, it is possible to control the release rate and enhance pH-independence.

References

[1] A. Hodsdon, J. Mitchell, M. Davies, C. Melia, J. Control. Release **33**, 143–152 (1995).

[2] M. Efentakis, G. Buckton, Pharm. Dev. Technol. **7**, 69–77 (2002).

[3] J. Parojcic, Z. Duric, M. Jovanovic, S. Ibric, D. Jovanovic, J. Pharm. Pharmacol. **56**, 735-741 (2004).

[4] Lubrizol, Pharmaceutical bulletin No. **31** (2008).