The Influence of Hydro-Alcoholic Media on Drug Release from Polyethylene Oxide Extended Release Matrix Tablets

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Purpose

Hydrophilic matrices (HM) are popular and widely used formulation options for oral extended release (ER) drug delivery. Polyethylene oxide (PEO) is one of the polymers that can be used as a matrix former.[1, 2] While HMs have been proven to be safe and efficacious in numerous drug products globally, it is important for formulation scientists to continue to demonstrate this in view of new published information. In July 2005, the FDA issued an alert for healthcare professionals regarding dissolution media effects on drug release from an ER dosage form not involving a hydrophilic matrix, ie, alcohol-Palladone interaction.[3] When ingested with alcohol, the peak plasma concentration of the drug, hydromorphone, increased to potentially lethal levels due to breakdown of the ER formulation. Therefore, the aim of this study was to investigate the influence of hydro-alcoholic media on the release rate of two model APIs with various aqueous solubility (gliclazide and metformin HCl) from PEO ER matrices. The effect of alcohol containing media on hydration properties of compacts made of pure PEO with different molecular weights was also investigated.

Methods

Preparation and Testing of PEO ER Matrices

Two formulations containing either a practically water insoluble drug, gliclazide, or a freely water soluble drug, metformin HCl, were used in the study (**Table 1**). Microcrystalline cellulose (MCC) and fumed silica were screened through a 500 µm sieve. All ingredients except for the lubricant were blended in a 1L Turbula mixer at 64 rpm for 10 minutes. Magnesium stearate was then added, and the formulation was blended for an additional one minute. Metformin HCl (7x18 mm convex, 1000 mg) and gliclazide (7 mm standard concave, 200 mg) tablets were produced at 20 kN compression force using an instrumented 10-station rotary press (Piccola, Riva).

Dissolution tests were conducted in a AT7 Sotax dissolution bath using a USP Apparatus II (paddles) with 8-mesh (2.38 mm) quadrangular baskets[4] (Quality Lab Accessories) in 1000 mL water, 5% or 40% w/v aqueous ethanol solutions at 100 rpm. Tablets were subjected to the hydro-alcoholic media for duration of either 24 hours or 1 hour followed by 23-hour dissolution in water. Absorbance was measured using a dual-beam UV/Vis spectrophotometer (PerkinElmer) using 5 mm quartz cells at 228 nm and 0.1 mm cells at 233 nm for gliclazide and metformin HCl, respectively.

Table 1. Formulations of Metformin HCl and Gliclazide Matrices

	Gliclazide formulation		Metformin HCl formulation	
	% w/w	mg/tablet	% w/w	mg/tablet
Gliclazide (Kemprotec)	15.0	30.0		
Metformin HCl (Ferico Labs)			50.0	500.0
PEO (POLYOX™ WSR 1105, Dow)	35.0	70.0		
PEO (POLYOX WSR 301, Dow)			30.0	300.0
MCC (Microcel 102, Blanver)	49.0	98.0	19.0	190.0
Fumed silica (Aerosil 200, Degussa)	0.5	1.0	0.5	5.0
Magnesium stearate (Peter Greven)	0.5	1.0	0.5	5.0
Total	100.0	200.0	100.0	1000.0

Methods (cont'd)

Drug release profiles in different media were compared to that in water using the f_2 factor.[5, 6] An f_2 value between 50 and 100 indicates that the two dissolution profiles are similar.

Preparation and Testing of Pure PEO Compacts

Two viscosity grades of PEO were tested, POLYOX™, water soluble resins, WSR-1105 (900,000 Da) and POLYOX WSR-301 (4,000,000 Da). PEO compacts with a target weight of 300 mg were manufactured using a semi-automated hand press (T8, Atlas, Specac) fitted with 10 mm flat-faced tooling at a compression force of 20 kN. Compacts were tested in a AT7 Sotax dissolution bath using Apparatus II and 15x31 mm sinkers (Sotax), in 900 mL of 0:100, 25:75 and 50:50 w/v ethanol:purified water mixtures at 100 rpm. The swelling properties of the compacts in various media were determined using a modified version of the method described by Tahara et al.[7] and Kavanagh & Corrigan[8] by measuring the wet weight of the hydrated PEO compacts over time (15, 30, 60, 120 minutes). The wet weight at each time point was determined in triplicate, and the averages and standard deviations were calculated. The ratio of the wet weight (W_w) to the initial weight (W_i) of the compacts was determined as an indication of the extent of matrix swelling similar to the Panomsuk et al. approach.[9]

Relative compact swelling = W_w/W_i

Results

Robust matrices with high mechanical strength of 13.9 kp (2.5 MPa) and 18.9 kp (0.9 MPa) were produced, for gliclazide and metformin HCl formulations respectively. For both formulations, reproducible drug release profiles were obtained in all tested media.

Gliclazide release from PEO ER matrices was not significantly affected by a 24-hour (f_2 = 91, 59) or by a 1-hour exposure to 5% or 40% w/v ethanol/water solutions followed by 23 hours in water (f_2 = 82, 74) (**Figure 1**). Metformin HCl release in hydro-alcoholic media was similar to the dissolution results in water in all the tests (f_2 > 50) with an exception of the 24-hour extreme exposure to 40% w/v ethanol (f_2 = 42) where drug release was slower (**Figure 2**). This could be explained by a reduction in metformin HCl solubility in alcohol compared to water. The results are in agreement with the previously published data where similar resistance to hydro-alcoholic media was reported for hypromellose ER matrices.[10]

To support the finding that the hydrophilic matrix structures appeared to remain intact when the model drug products of this study were exposed to hydro-alcoholic media, the media uptake and swelling behavior of pure PEO compacts were examined in hydro-alcoholic media as well. **Figure 3** shows that in water and hydro-alcoholic solutions, all PEO compacts underwent swelling and gelation without any disruption to the matrix integrity. Correspondingly, progressive weight gains by the PEO compacts in water and hydro-alcoholic media occurred with time (**Figure 4**). **Table 2** shows that the extent of relative swelling increased with increasing molecular weight of PEO from 900,000 Da (POLYOX 1105) to 4,000,000 Da (POLYOX 301).

Results (cont'd)

Figure 1. Gliclazide Release in Different Dissolution Media

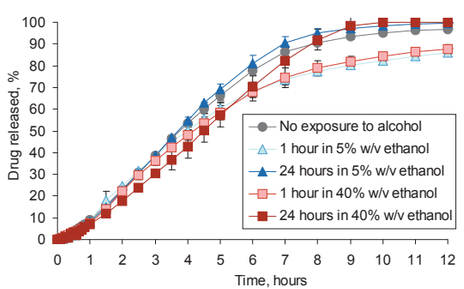

Figure 2. Metformin HCl Release in Different Dissolution Media

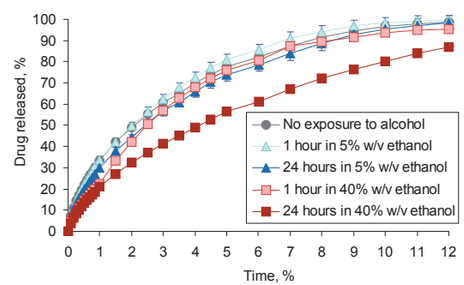

Figure 3. Swelling of Pure PEO Compacts in (a) water, (b) 25% w/v ethanol and (c) 50% w/v ethanol

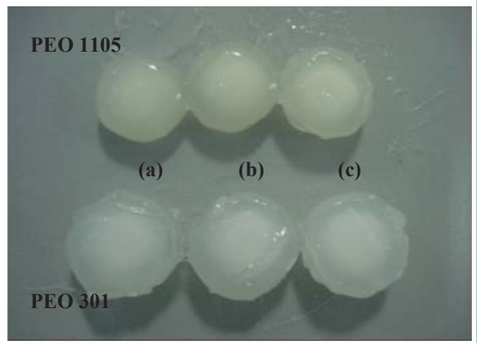

Figure 4. Wet Weight of PEO Compacts in Different Dissolution Media

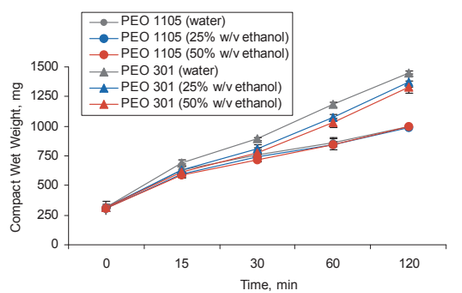

Table 2. Effect of Media on Relative Swelling (W_w/W_i) of PEO Compacts

	PEO 1105			PEO 301		
Time (min)	Water	25% Ethanol	50% Ethanol	Water	25% Ethanol	50% Ethanol
15	2.07	1.94	1.91	2.19	2.01	1.96
30	2.47	2.41	2.33	2.84	2.56	2.48
60	2.79	2.74	2.75	3.76	3.41	3.28
120	3.24	3.20	3.23	4.62	4.36	4.24

Conclusions

- Robust POLYOX ER matrix tablets were produced using a practically water insoluble drug gliclazide and freely water soluble metformin HCl.
- The extended release dissolution performance of both formulations was not adversely influenced by their exposure to the 5% w/v hydro-alcoholic media. Although gliclazide release was not affected by 40% w/v ethanol solution, metformin HCl release was slower as compared to the results obtained in water. No dose dumping was observed with any of the formulations in any of the media.
- For both grades of PEO, compact relative swelling was slightly slower in hydro-alcoholic media compared to water. Higher relative swelling was recorded for POLYOX 301, the polymer with higher molecular weight as compared to POLYOX 1105.

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