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The influence of hydro-alcoholic media on drug release

From polyethylene oxide extended-release matrix tablets

Dasha Palmer, Marina Levina, Thomas P. Farrell and Ali R. Rajabi-Siahboomi

Hydrophilic matrices are widely used for extended release (ER) drug delivery, and polyethylene oxide (PEO) has recently been studied as a matrix-forming polymer. Concomitant alcoholic beverage ingestion may modify the release characteristics of ER formulations, causing dose dumping, which may threaten patient safety. The FDA recommends that ER medicinal products should be tested during development to ensure dosage form robustness in hydro-alcoholic media. The authors investigate the influence of hydro-alcoholic media on hydration and drug release from PEO ER matrices using two model APIs with different solubilities in water. No matrix failure was recorded for either formulation when exposed to ethanol–water solutions. In addition, pure PEO compacts made of three viscosity grades of polymer showed consistent swelling upon exposure to hydro-alcoholic media.

Marina Levina, PhD,* is senior manager, product development at Colorcon Limited, Dartford, England. mlevina@colorcon.com, +44 (1) 322-627321.

Dasha Palmer is product development scientist, **Thomas P. Farrell, PhD,** is director, product development, and **Ali R. Rajabi-Siahboomi, PhD,** is director of scientific affairs, all at Colorcon.

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Hydrophilic matrices are a popular and extensively used strategy for oral extended-release (ER) drug delivery. Hypromellose (hydroxypropyl methylcellulose, HPMC) is the polymer of choice as the rate-controlling carrier (1). In addition to HPMC, polyethylene oxide (PEO) has been used as a matrix-forming polymer (2, 3). These excipients are nontoxic and have pH-independent hydration and swelling, good compressibility and lubricity, and versatility due to a wide range of molecular weights. PEO polymers have global regulatory acceptance and can be utilised for modulating the release of drugs at various solubilities and doses (1-13).

PEO polymers are white, free-flowing hydrophilic powders commercially available as Polyox, water soluble resins (WSRs), with molecular weight ranging from 100000 Da to 7000000 Da (14). A list of Polyox grades suitable for ER hydrophilic matrix applications is shown in **Table I**.

When in contact with water, PEO hydrates rapidly, swells to a large extent and forms a gelatinous barrier layer around the tablet (15). Drug release from the PEO matrices is generally controlled by diffusion of the drug through the swollen gel at the surface of the tablet and/or gel erosion (9, 16). The rates of wetting, swelling and erosion are controlled by polymer molecular weight and other ingredients within the matrix (17).

Rapid polymer hydration and uniform gel formation are critical to the performance of hydrophilic matrix systems (18). It is also crucial to take into account the type of dissolution media the tablets are exposed to, because it may affect polymer hydration and gel formation.

Alcoholic beverages have been consumed for thousands of years, and a UK National Health Service survey indicated that 73% of men and 57% of women (aged 16 and over) had alcoholic drinks on at least one day per week (19). In another report, US statistical data showed that around 50% of the American population routinely consumed alcoholic beverages (20).

The potential effect of alcoholic drinks in significantly accelerating drug release from ER oral formulations has been of some concern (21). It is known that alcohol has an influence on the absorption, metabolism and excretion of drugs, which can potentially lead to adverse side effects (22). Toxicity is most often associated with acute intake rather than longer-term consumption of alcohol, but both patterns can impact the toxico-kinetics of concomitantly administered medicines (23).

ER formulations, which are intended for once or twice daily administration, are designed with a higher unit dose of the drug than

conventional formulations. Therefore, it is imperative that retardation properties are tightly controlled to ensure that a rapid release of the drug, or dose dumping, cannot occur.

In July 2005, the FDA published an alert for healthcare professionals regarding the negative effect of alcoholic drinks on drug release from Palladone (hydromorphone). Alcohol breaks down the ER formulation, and, as a result, increases peak plasma concentration causing potentially lethal dose dumping (24). Several publications have outlined the influence of hydro-alcoholic media on the performance of solid oral ER systems in the years since the FDA alert.

According to Fadda et al., vulnerable formulations are likely to cause adverse pharmacokinetic and therapeutic outcomes in patients on exposure to alcoholic solutions. The extent of the adverse reaction depends on the drug, polymer, and excipients in the formulation (25, 26). Some oral ER dosage forms contain drugs and excipients that exhibit a higher solubility in aqueous solutions containing ethanol. Accordingly, such products may be expected to exhibit more rapid drug dissolution and release in the presence of ingested ethanol (27).

Koziara et al. reported an increased permeability, elasticity, and swelling of cellulose acetate semipermeable membranes used for osmotic drug delivery in 0-60% ethanol solutions (28). Although drug release from the analysed osmotic-controlled release oral deilvery systems increased slightly, it was fully controlled, and no morphological changes to the dosage form occurred. The system maintained its functionality, and no potential for dose dumping was reported.

Roberts et al. studied the influence of alcohol on the release of aspirin from HPMC matrix tablets (29). They found that ethanol retarded hydration of the polymer and produced a more rapid initial drug dissolution but overall did not result in dose-dumping.

The influence of ethanol on the *in vitro* release of opioid drugs from various ER formulations (e.g., tablets, capsules, and suspensions) was examined by Walden et al. An extrapolation of the findings to the likely outcome *in vivo* indicated no risk of dose dumping (27).

Traynor et al. studied the potential for dose dumping in hydro-alcoholic media from three commercially available opioid analgesic (tramadol) formulations. The formulations provided 24-h dissolution using release-controlling coatings (30). The authors found that for two products (Ultram ER tablets and T-long capsules), the release of tramadol significantly increased in the presence of alcohol.

Table I: Polyox WSR NF polymers for ER matrix applications. Data adapted with permission from The Dow Chemical Company.

Polyox NF Products	Approximate molecular weight (Da)	Viscosity range in water at 25°C (mPa·s)		
		5% solution	2% solution	1% solution
WSR N-1105 LEO	900,000	8,800 – 17,600		
WSR N-12K	1,000,000		400 – 800	
WSR N-60K	2,000,000		2,000 – 4,000	
WSR-301 LEO	4,000,000			1,650 – 5,500
WSR Coagulant	5,000,000			5,500 – 7,500
WSR-303 LEO	7,000,000			7,500 – 10,000

Note: WSR is water soluble resin. LEO is low ethylene oxide.

Conversely, a decrease in the rate of drug release in hydro-alcoholic media was recorded for Tridural ER tablets.

Skalsky et al. analysed the effect of alcoholic beverage concentrations up to 40% (v/v) on model highly water-soluble drugs, diltiazem HCl and metoprolol succinate, using both methacrylic copolymers and HPMC in matrix formulations (22). Drug release behavior was unchanged in all media. However, the authors suggested a significant difficulty in correlating *in vitro* data to potential *in vivo* results due to the unpredictable effect of alcohol on absorption, metabolism, and excretion from the human body.

Levina et al. investigated the effect of hydro-alcoholic solutions on hydration, gel formation, and drug release from HPMC ER tablets and reported that hydro-alcoholic media containing up to 40% ethanol did not affect the performance of the matrices (18). Investigation of the effect of hydro-alcoholic solutions on textural and rheological properties of various controlled-release grades of hypromellose was also described by Missaghi et al. (31).

According to Ager et al., the effect of ethanol on pseudoephedrine HCl from HPMC ER matrix systems depended on the qualitative and quantitative composition of the tablets (32). The authors claimed that the drug release may be affected when using a filler with decreased solubility in ethanol (e.g., lactose or starch) and formulations containing fillers that have both poor aqueous and ethanol solubility (e.g., microcrystalline cellulose) might have no effect on drug release.

The influence of hydro-alcoholic media on PEO ER matrices has not yet been investigated. This research studies the influence of hydro-alcoholic media on the hydration and swelling properties of pure PEO compacts manufactured using different viscosity grade of Polyox, and drug release from ER matrices using two model drugs with different aqueous solubilities.

Materials and methods

Formulation and preparation of PEO ER matrices

The influence of hydro-alcoholic media on formulations of practically water insoluble gliclazide and freely water soluble metformin HCl

Table II: Polyethylene oxide extended-release formulations used in the study.

Material (Grade, Supplier)	Gliclazide formulation		Metformin HCl formulation	
	% w/w	mg/tablet	% w/w	mg/tablet
Gliclazide (Kemprotec)	15.0	30		
Metformin HCl (Ferico Labs)			50.0	500
PEO (Polyox WSR 1105, Dow)	35.0	70		
PEO (Polyox WSR 301, Dow)			30.0	300
MCC (Microcel 102, Blanver)	49.0	98	19.0	190
Fumed silica (Aerosil 200, Degussa)	0.5	1	0.5	5
Magnesium stearate (Peter Greven)	0.5	1	0.5	5
Total	100.0	200	100.0	1000

Note: MCC is microcrystalline cellulose. PEO is polyethylene oxide.

was investigated. Two 12-h release PEO matrix formulations were developed containing gliclazide or metformin HCl, PEO (i.e., Polyox 1105 or 301) as a matrix former, microcrystalline cellulose (MCC) as a filler, fumed silica as a flow aid, and magnesium stearate as a lubricant (see **Table II**). **Table III** shows the solubility of the drugs, polymer, and filler in water and alcohol.

Both formulations, batch size 400 g, were blended in a shaker-mixer (Turbula, Bachofen). Microcrystalline cellulose and fumed silica were first screened through a 500 µm (35 mesh) sieve to homogenise the powder. The rest of the ingredients, except the lubricant, were added and blended for 10 min at 64 rpm. Magnesium stearate was then added and the formulations were mixed for an additional one minute.

Tablets were manufactured using an instrumented 10-station rotary tablet press (Piccola, Riva) operating at 20 rpm. Gliclazide tablets with a target weight of 200 mg were produced using 7 mm normal concave tooling at 20 kN (255 MPa). Metformin HCl matrices with a target weight of 1000 mg were manufactured using 7 × 18 mm concave caplet tooling at 20 kN (79 MPa).

Dissolution studies

Dissolution tests were conducted in a *USP* compliant dissolution bath (Sotax) using Apparatus II (i.e., paddles) with 8-mesh (2.38 mm) quadrangular baskets (QLA) in 1000 mL purified water, 5% or 40% w/v ethanol (USP/BP Hayman) solutions at 100 rpm and 37.0 ± 0.5 °C. Tablets were subjected to the hydro-alcoholic media for duration of 12 h, or 1 h followed by 11-h dissolution in water.

Absorbance was measured with a dual-beam UV–vis spectrophotometer (PerkinElmer) using 5 mm quartz cells at a wavelength of 228 nm and 0.1 mm cells at 233 nm for gliclazide and metformin HCl, respectively. Tablets were analysed in triplicates using an automated sampling device, and mean with standard deviation values were reported.

The drug release profiles in hydro-alcoholic media were compared to those in purified water using the f_2 factor. An f_2 value between 50 and 100 indicates that the two dissolution profiles are similar (7, 38).

Table III: Solubility of the drugs, polymer and filler used in the study, in water and alcohol (14, 33-37).

Material	Solubility in water	Solubility in alcohol
Gliclazide	Practically insoluble (<0.1 mg/mL)	Slightly soluble (1-10 mg/mL)
Metformin HCl	Freely soluble (500 mg/mL)	Slightly soluble (10 mg/mL)
PEO	Soluble (33-100 mg/mL)	Insoluble (<0.1 mg/mL)
MCC	Practically insoluble (<0.1 mg/mL)	Practically insoluble (<0.1 mg/mL)

Note: HCL IS define here.

Table IV: f_2 values for drug release profiles from polyethylene oxide matrices in hydro-alcoholic media compared with non-exposure to ethanol solutions.

Duration of exposure to alcohol containing media (h)	5% w/v ethanol		40% w/v ethanol	
	1	12	1	12
Gliclazide formulation	62	91	74	59
Metformin HCl formulation	96	75	58	42

To investigate the mechanism of drug release in various media, the release data between 5 and 60% were fitted to the following equation (16, 39–40):

$$Q = kt^n$$

where Q is the percentage drug released at time t, k is a kinetic constant incorporating structural and geometric characteristics of the tablet and n is the diffusion exponent that indicates the drug release mechanism (39–40).

For matrix tablets, an n value close to 0.5 indicates predominantly diffusion control of drug release. An n value around 1.0 indicates erosion or relaxation control mechanism of drug release (41–42). Intermediate values suggest that both diffusion and erosion contribute to the overall release mechanism (18).

The values of n and k are inversely related, such that a decrease in n value results in a k value increase. A very high k value may suggest a burst drug release from the matrix (43–44).

Preparation and testing of PEO compacts

Three viscosity grades of PEO were tested (i.e., Polyox 1105, 301, and Coagulant). PEO compacts with a target weight of 300 mg were manufactured using hydraulic automatic press (Auto T8, Atlas, Specac) and 10 mm flat-faced tooling at a compression force of 20 kN (255 MPa).

Compacts were tested in a *USP*-compliant AT7 Sotax dissolution bath using Apparatus II (i.e., paddles) with large (15 × 31 mm) sinkers (Sotax), in 900 mL of 0:100, 25:75 and 50:50 w/v ethanol:purified water mixtures at 100 rpm and 37 ± 0.5 °C.

The swelling properties of the compacts in various media were determined using a modified version of the method described by Tahara et al. and Kavanagh and Corrigan by measuring the wet weight of the hydrated PEO compacts at 15, 30, 60 and 120 min (45, 46). Each compact was placed into a preweighed plastic container; the excess media was drained and blotted from around the tablet without touching it. The compact and the container were weighed, and the wet weight of each tablet was established. Every determination at each time point was performed in triplicate, and average and standard deviation values were calculated.

The ratio of the wet weight (W_w) to the initial weight (W_i) of the compacts was calculated, as an indication of the extent of matrix relative swelling, similar to the Panomsuk et al. approach, as described in the following equation (47):

$$\text{Relative compact swelling} = W_w \div W_i$$

Table V: Values of the kinetic constant (k), diffusion exponent (n) derived from Equation 1, and correlation coefficients (R^2) for PEO ER matrices in various media.

	Dissolution testing conditions	k	n	R^2
Gliclazide formulation	No exposure to alcohol	9.095	1.2932	0.9991
	1 h in 5% v/v ethanol	8.743	1.3177	0.9888
	1 h in 40% v/v ethanol	7.676	1.3691	0.9945
Metformin HCl formulation	No exposure to alcohol	32.964	0.6084	0.9988
	1 h in 5% v/v ethanol	33.498	0.6284	0.9964
	1 h in 40% v/v ethanol	24.240	0.7431	0.9939

Results and discussion

The effect of hydro-alcoholic media on drug release from PEO ER matrices

Robust PEO ER matrices with strength values of 2.32 MPa (13.0 ± 0.2 kp) for gliclazide and 0.70 MPa (14.0 ± 0.5 kp) for metformin HCl were produced. Reproducible drug release profiles were obtained for both formulations in all tested media. No dose dumping from the PEO matrices was observed even after 12-h exposure to the hydro-alcoholic media.

Figure 1 and **Table IV** show that gliclazide release was not significantly affected by either 1- or 12-h exposure to 5% or 40% w/v ethanol solutions. The differences observed in the dissolution profiles can be attributed to the different solubility of the drug in ethanol (see **Table III**).

Metformin HCl release from PEO ER matrices in hydro-alcoholic media was similar to the dissolution results in water in all the tests (f_2 > 50), with the exception of the 12-h exposure to 40% w/v ethanol (f_2 = 42), where drug release was significantly slower (see **Figure 2** and **Table IV**). This result can be explained by a reduction in metformin HCl solubility from 450 mg/mL in water to 295 mg/mL in 40% v/v ethanol (18). However, such extreme conditions (i.e., high concentration of ethanol during a prolonged period of time) are unlikely for *in vivo* conditions. In the human body, tablets taken with alcohol are unlikely to be exposed to a 40% v/v hydro-alcoholic medium for a 12-h period because of the rapid absorption of ethanol from the gastro-intestinal tract (18, 33). This study did not reveal any effect on dissolution after 1-h exposure of PEO ER tablets to hydro-alcoholic media for either active.

Drug-release variability, in particular with gliclazide, increased when matrices were tested in alcohol. The standard deviation for gliclazide tablets subjected to hydro-alcoholic media increased from 2.3% (no exposure to alcohol) up to 3.6% (exposure to 5% w/v alcohol) and up to 5.6% (exposure to 40% w/v alcohol), respectively (see **Figure 1**). This result may be due to the influence of ethanol on hydration of the polymer and erosion of the gel structure on the surface of the matrix.

The values of the kinetic constant (k), the release exponent (n), and correlation coefficient (R^2) determined from the drug release data are presented in **Table V**.

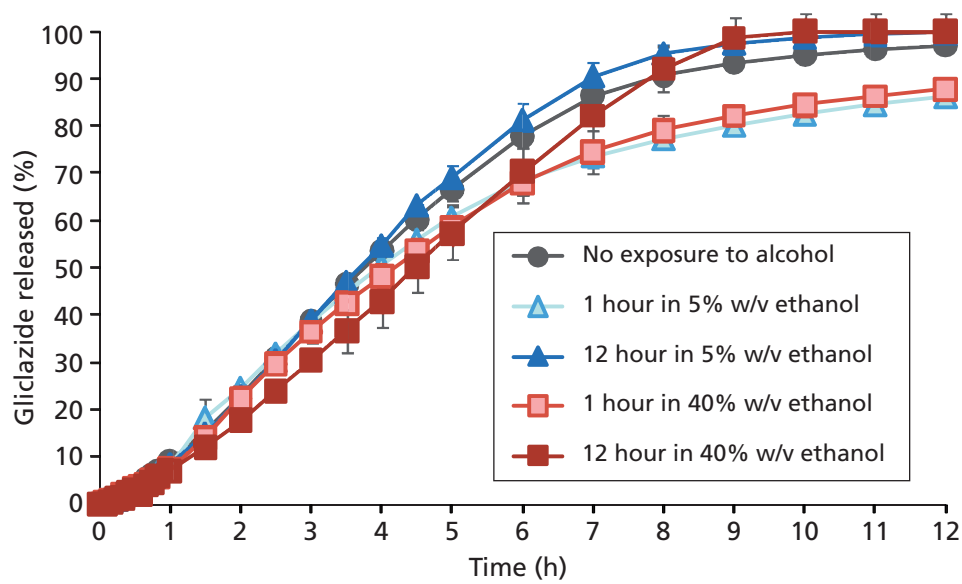
As gliclazide is practically insoluble in water and slightly soluble in alcohol (see **Table III**), its release from ER hydrophilic matrices was expected to occur predominantly by gel erosion. This was confirmed by high n values (1.3–1.4) suggesting that erosion was the main mechanism of gliclazide release from PEO matrices in all studied dissolution media.

On the other hand, a combination of diffusion and erosion (n = 0.6-0.7) was observed with metformin HCl (see **Table V**), which was anticipated due to its high aqueous drug solubility. Metformin HCl solubility changes from freely soluble in water to slightly soluble in

Table VI: Effect of hydro-alcoholic media on wet weight of Polyox compacts (n = 3).

Time (min)	Weight (mg) Polyox 1105						Weight (mg) Polyox Coagulant		
	Water	25% w/v ethanol	50% w/v ethanol	Water	25% w/v ethanol	50% w/v ethanol	Water	25% w/v ethanol	50% w/v ethanol
0	307±11	309±6	308±81	315±1	315±10	314±4	317±5	308±2	316±4
15$_s$	635±56	601±6	589±31	688±25	634±34	616±45	714±19	630±18	620±17
30	760±49	744±9	718±26	893±13	807±40	778±39	942±18	823±34	797±17
60	858±40	846±23	847±22	1183±20	1075±28	1031±38	1217±5	1056±21	1022±17
120	996±44	989±49	994±25	1453±15	1376±44	1331±49	1548±36	1383±34	1337±17

Figure 1: Gliclazide 30 mg release profile from polyethylene oxide extended-release matrices in different media containing 0, 5 or 40% w/v ethanol (n = 3).



alcohol (see **Table III**), resulting in a greater erosion contribution to the drug release from the tested PEO matrices. This was reflected by an increase in n value from 0.61 in water to 0.63 and to 0.74 in 5 and 40% w/v ethanol solutions, respectively. These findings agree with the Roberts data showing that ethanol affects the kinetics and mechanism of drug release from hydrophilic matrix tablets, but does not result in dose dumping (29).

Because the values of n and k are inversely related, k values changed slightly from 32.96 in water to 33.50 and 24.24 for metformin HCl tablets exposed to 5% and 40% w/v ethanol solutions, respectively. These results imply that the rate of drug release is slightly slower in 40% w/v ethanol solution than in water.

For both formulations, greater erosion contribution to the drug release from the tested matrices was observed in ethanol solutions compared with aqueous media. The results of this study identified similar trends to the previously published data for HPMC ER matrix systems (18). This finding is interesting in light of gastrointestinal tract motility. According to Bode and Bode, alcohol may interfere with the activity of the muscles surrounding the stomach and the small intestine and thus alter the transit time of food through

Figure 2: Metformin HCl 500 mg release profile from PEO ER matrices in different media containing 0, 5 or 40% w/v ethanol (n = 3).

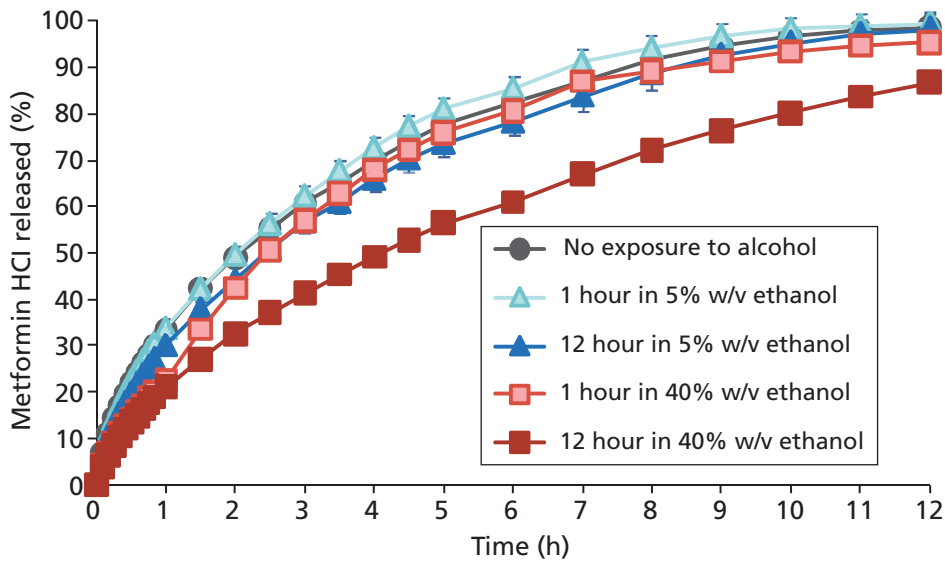
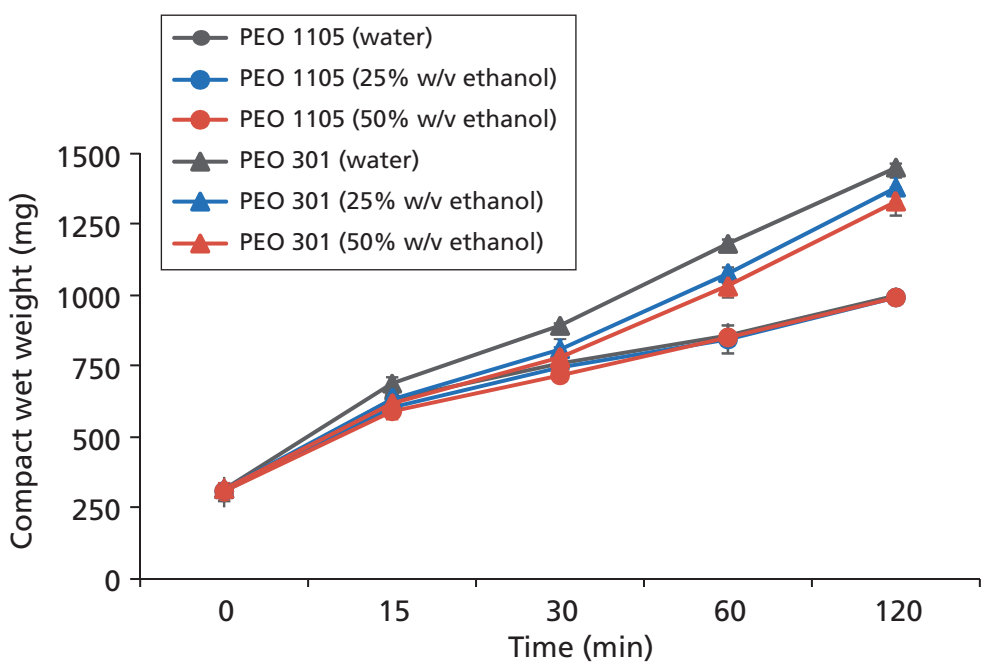


Figure 3: Effect of hydro-alcoholic media containing 0, 25 or 50% w/v ethanol on wet weight of PEO (Polyox 1105, 301 and Coagulant) compacts (n = 3)



these organs (48–49). In humans, alcohol's effect on gastric motility depends on the alcohol concentration and accompanying meals. In general, beverages with alcohol concentrations above 15% appear to inhibit gastric motility and thus delay the emptying of the stomach. In the small intestine, alcohol decreases the muscle movements that help retain the food for further digestion (i.e., the impeding wave motility). However, alcohol does not affect the movements that propel food through the intestine (i.e., the propulsive wave motility) in either alcoholics or healthy subjects.

It is also important to take into account the solubility of additional excipients (e.g., fillers, bulking agents, and surfactants) used in the formulation. The most popular fillers used in hydrophilic matrix systems can be ranked in ascending order according to their solubility in ethanol: MCC and dicalcium phosphate dehydrate, pregelatinised starch, and lactose (18). Practically insoluble in both water and aqueous alcoholic solutions, MCC was the filler least likely to be affected by the dissolution media choice in this study.

The effect of hydro-alcoholic media on swelling of pure PEO compacts

Mechanically strong compacts (i.e., >21 ±0.5 kp, > 3.3 MPa) were produced for all three grades of PEO tested in this study. In water and hydro-alcoholic solutions all PEO tablets underwent swelling and gelation without any disruption to the matrix integrity. A similar progressive weight gain by compacts made of various viscosity grades of PEO was observed in water and hydro-alcoholic media (see **Figure 3** and **Table VI**). For high viscosity grades of PEO (e.g., Polyox 301 and Coagulant), a slightly lower swelling and gel formation in the presence of ethanol was recorded. This result can be attributed to a decrease in polymer solubility in alcohol compared with water (see **Table III**), retarded hydration of the polymer, and the resulting change in gel viscosity (29, 31, 50–51).

Table VII shows that the extent of swelling increased with increasing molecular weight (MW) of PEO from 900000 Da (Polyox 1105) to 4000000 Da (Polyox 301). However, no significant difference in compact relative swelling was observed when MW was further increased from 4000000 Da (Polyox 301) to 5000000 Da (Polyox Coagulant).

Conclusion

Extended-release PEO tablets of the practically water insoluble drug gliclazide (30 mg) and freely soluble metformin HCl (500 mg) retained their hydrated structural integrity when exposed to 5% and 40% w/v ethanol solutions for up to 12 h. The matrices did not fail in hydro-alcoholic media. Small differences in drug release profiles were explained in terms of drug solubility in various media. The results of this study identified trends similar to those in previously published data for HPMC ER matrix systems.

Exposure of compacts of three different viscosity grades of PEO (Polyox 1105, 301, and Coagulant) to water or hydro-alcoholic solutions had shown gradual swelling and gelation without any disruption to the tablet integrity. The compact wet weight appeared to be only slightly lower in hydro-alcoholic solutions compared to water. The extent of their relative swelling was found to increase with increasing molecular weight of PEO from 900000 Da to 5000000 Da. No significant difference in compact relative swelling was observed when MW increased further from 4000000 Da (Polyox 301) to 5000000 Da (Polyox Coagulant).

This study clearly indicates that PEO matrices produces consistent drug release in water and in hydro-alcoholic media with no signs of a potential dose dumping. **PTE**

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Table VII: Effect of various media on relative swelling of Polyox compacts (n = 3).

Time (min)	Relative swelling Polyox 1105			Relative swelling Polyox 301			Relative swelling Polyox Coagulant		
	Water	25% w/v ethanol	50% w/v ethanol	Water	25% w/v ethanol	50% w/v ethanol	Water	25% w/v ethanol	50% w/v ethanol
15	2.07	1.94	1.91	2.19	2.01	1.96	2.25	2.05	1.96
30	2.47	2.41	2.33	2.84	2.56	2.48	2.97	2.67	2.53
60	2.79	2.74	2.75	3.76	3.41	3.28	3.84	3.43	3.24
120	3.24	3.20	3.23	4.62	4.36	4.24	4.89	4.49	4.24

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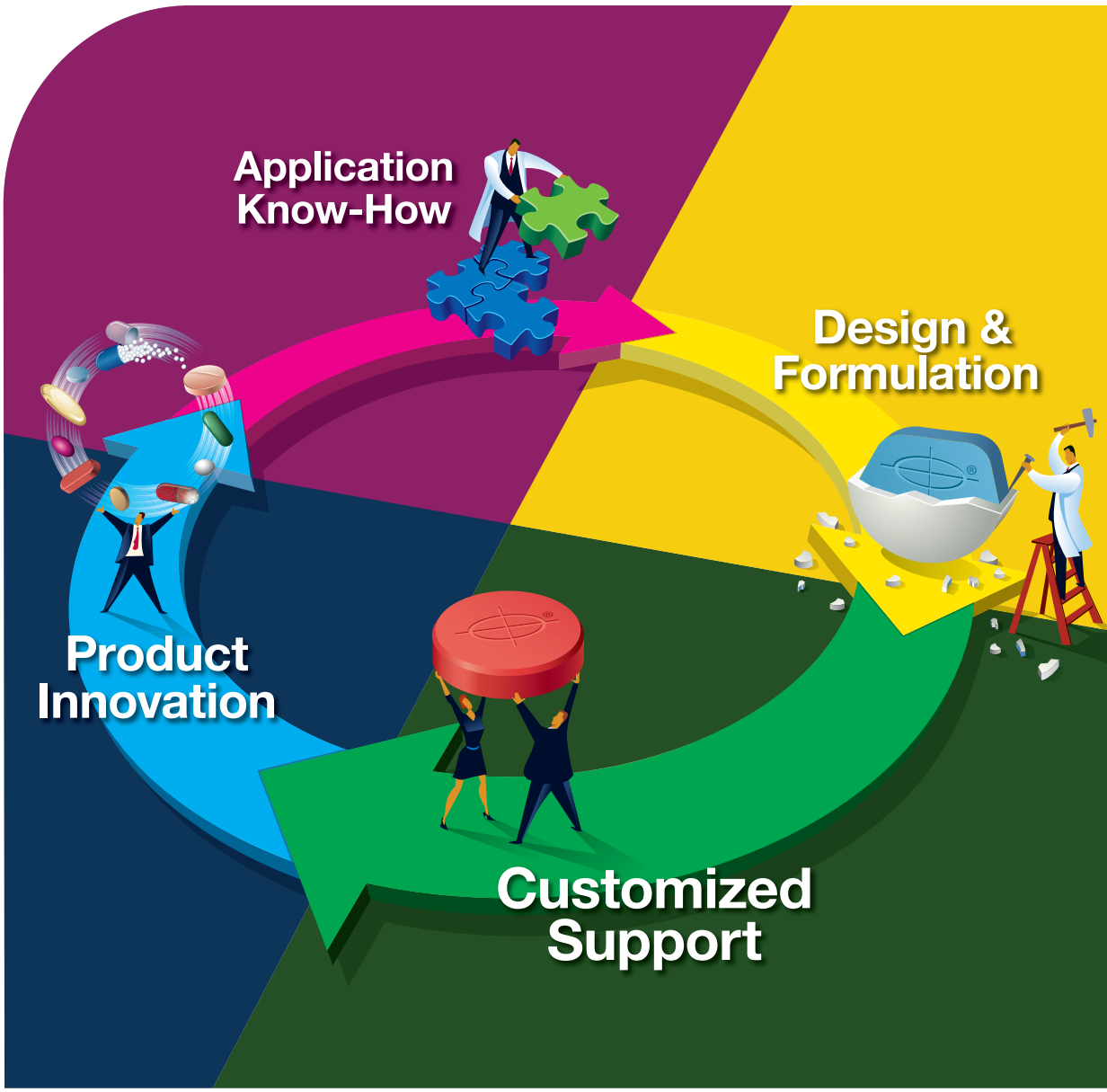

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