Effect of Alcohol on Drug Release Kinetics from HPMC-Based Matrix Tablets Using Model Drugs

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ABSTRACT

Drug dissolution testing is routinely used to provide in vitro drug release information for both quality control purposes and drug development. For extended-release (ER) formulations, the dissolution test can serve not only as a quality control tool for the manufacturing process but also as an indicator of how the formulation will perform in vivo to establish an in vitro–in vivo correlation. Hydrophilic matrices are a robust ER formulation technology in which the formation of a viscous hydrated polymer layer at the surface provides a diffusion barrier that retards drug release. Hydroxypropyl methylcellulose (HPMC) is the most widely used polymer for this application.

The purpose of this study was to investigate the effect of various proportions of alcohol on in vitro drug release from HPMC-based matrix tablets using three model drugs having different physicochemical properties. The percent drug release increased with increasing levels of alcohol for all three model drugs. It was observed that dose-dumping did not occur for drugs that had low solubility; however, for highly soluble drugs, dumping occurred even at low concentrations of alcohol in the media. The impact of alcohol was prominently observed in terms of initial rapid release for all drugs in the first hour irrespective of the concentration of alcohol. Relative swelling studies of HPMC matrix tablets with and without drug suggest that alcohol retarded hydration and swelling of the polymer. The findings also suggest that the release mechanism changes with an increase in the concentration of alcohol.

KEYWORDS: HPMC matrices, alcohol, dissolution media, extended release, diclofenac potassium, tramadol HCl, venlafaxine HCl.

INTRODUCTION

The potential impact of concomitant alcohol consumption on the in vivo release of drugs from modified-release oral dosage forms is currently evincing interest. This is a consequence of the finding that co-consumption of significant quantities of alcoholic beverages can result in potentially serious dose-dumping of a drug such as the opioid analgesic hydromorphone from a controlled-release capsule dosage form (1). As studies in human volunteers involving coadministration of drug and significant amounts of alcohol pose ethical and operational challenges, it is appropriate to consider in vitro studies to provide insight on release mechanisms in media containing alcohol, thereby channeling formulation strategies especially for extended-release (ER) dosage forms and assessing the potential for alcohol-related dose-dumping. Matrix tablets, in particular hydrophilic matrices, are the most popular system used for ER as they provide efficient and long-lasting effects, are easy to formulate, and can be manufactured at a relatively low cost (2). Hydroxypropyl methylcellulose (HPMC) is the most extensively used cellulose derivative for oral matrix formulation. This polymer is resistant to enzymes, is stable over the pH range of 3–11, is nonionic, and swells to form a gel that controls drug release (3).

A United Kingdom National Health Service survey (4) indicated that 73% of men and 57% of women aged 16 and over had alcoholic drinks on at least one day per week.

In another report (5), United States statistical data showed that around 50% of the American population also routinely consumes alcoholic beverages. The potential effect of alcoholic drinks in significantly accelerating drug release from ER oral formulations has been of some concern in the recent past (6). It is known that alcohol has an influence on the absorption, metabolism, and excretion of drugs, which can potentially lead to adverse side effects. Toxicity is most often associated with acute intake rather than long-term consumption of alcohol, but both patterns can impact the toxicokinetics of concomitantly administered medicines (7).

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 essential that retardation properties be tightly controlled to ensure that a rapid release of the drug, or dose-dumping, cannot occur.

In 2005, FDA issued an alert to healthcare professionals regarding an alcohol–Palladone interaction (1). This alert cited an increase in the peak plasma concentration of the drug hydromorphone to potentially lethal levels because of the breakdown of the dosage form when ingested with significant amounts of alcohol. A pharmacokinetic study of healthy volunteers showed that co-ingestion of a Palladone capsule with 240 mL of 40% alcohol caused an average peak drug concentration that was approximately six times greater than when taken with water; one subject experiencing 16-fold increase. In some volunteers, 240 mL of 4% alcohol (equivalent to two thirds of a typical serving

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of beer) resulted in almost twice the peak drug plasma concentration relative to when it was ingested with water (1, 8). In the present study concentrations of ethanol in the range of 0–40% v/v were studied; 0% was the control, and 40% the maximum. The ER formulation contained two types of diluent: MCC, which is an insoluble diluent, and lactose, a soluble one, to check the effect of diluent solubility on drug release in the presence of alcohol in media.

Three drugs having distinct properties with respect to solubility and salt form were selected as model drugs to correlate the drug release profile from HPMC-based matrices in dissolution media containing alcohol to the drug properties. Diclofenac potassium (DICP) is sparingly soluble in water, while tramadol HCl (TRAH) and venlafaxine HCl (VENH) are freely soluble in water. The solubilities of DICP and TRAH are pH-dependent and change with a change in pH. VENH shows pH-independent solubility, with no effect on solubility as the pH changes.

The aim of this investigation was to assess the effect of various concentrations of alcohol on the dissolution kinetics and release mechanisms of DICP, TRAH, and VENH from HPMC hydrophilic matrices.

MATERIALS AND METHODS
Materials
Diclofenac potassium, tramadol hydrochloride, and venlafaxine hydrochloride were gifted by Lupin Research Park (Pune, India). Hydroxypropyl methylcellulose (HPMC K4M) and MCC 102 were obtained as gift samples from Colorcon Asia Ltd. (Goa). Lactose monohydrate, magnesium stearate, and talc were procured from Loba Chemie Pvt. Ltd. (Mumbai). Other reagents were of analytical grade and were used as received.

Formulation and Preparation of HPMC Matrix Tablets
Tablets comprising different concentrations of HPMC K4M, 100 mg of drug (DICP, TRAH or VENH), and fixed concentrations of magnesium stearate, talc, and diluents (lactose or MCC 102) were prepared by direct compression on a six-station rotary tablet compression machine (Model JM-6, General Machinery Company, Mumbai) using 9-mm concave punches. The composition of various formulations is given in Table 1.

Preparation of HPMC Compacts (without drug)
Compacts of HPMC without drug containing only excipients were made using direct compression. All materials were passed through 40# sieve separately and mixed uniformly in a polybag. This powder blend was then directly compressed into HPMC compacts (tablets) with a target weight of 300 mg as described above.

Evaluation of Tablets
Tablets of each formulation (F1–F6) were evaluated for routine parameters such as thickness, weight variation, drug content, hardness, and friability. Hardness of tablets was measured using a Pfizer hardness tester (Polyscience, Mumbai, India) and friability by Roche friability tester (Electrolab, Mumbai, India).

Drug Release Studies and Effect of Alcohol on Release Patterns
Drug release was monitored for all tablets using USP Apparatus 2 (Electrolab Model- TDT-08L, India) at a speed of 50 rpm, in 900 mL of medium at 37 °C. Various media were evaluated: phosphate buffer (pH 6.8) and phosphate buffer with 10%, 20%, 30%, and 40% (v/v) alcohol (ethanol). Aliquots (10 mL) were withdrawn at specific time intervals and filtered through Whatman filter paper (45 µm). For each medium, drug release was monitored spectrophotometrically (Shimadzu UV-1800, Japan) at 276 nm, 271nm, and 225 nm for DICP, TRAH, and VENH, respectively. At each time of withdrawal, 10 mL of fresh dissolution medium was replaced into the dissolution flask.

Swelling Study
The effect of dissolution medium composition on the swelling properties of HPMC compacts (without drug)

Table 1. Composition of Formulations

Ingredient	F1	F2	F3	F4	F5	F6
	Amount (mg)					
Diclofenac potassium	100	100				
Tramadol HCl			100	100		
Venlafaxine HCl					100	100
HPMC K4M	48	48	120	120	120	120
Lactose		144		72		72
MCC 102	144		72		72	
Talc	5	5	5	5	5	5
Magnesium stearate	3	3	3	3	3	3
Total weight	300	300	300	300	300	300

and HPMC matrix tablets (with drug) in first hour and fifth hour were determined using a modified version of the method described by Tahara et al. (9) and Kavanagh and Corrigan (10). In this method, the wet weight of the hydrated HPMC compacts (without drug) and HPMC matrix tablets (with drug) were measured. Testing ($n = 6$) was conducted in Apparatus 2 (paddle method) in 900 mL of dissolution medium at 50 rpm. The dissolution media were phosphate buffer (pH 6.8) with 0%, 10%, 20%, 30%, and 40% (v/v) ethanol at 37.0 ± 0.5 °C. The relative swelling, calculated as the ratio of the wet weight (W_w) to the initial weight (W_i), was determined as an indication of the extent of matrix swelling. Swelling studies were only done for DICP.

$$\text{Relative swelling} = W_w / W_i \qquad (1)$$

Kinetic Modeling of Dissolution Profiles

Various mathematical models like zero-order, first-order, Higuchi (matrix), Hixson–Crowell (cube-root equation), and Korsmeyer–Peppas were evaluated with respect to the dissolution profiles of all formulations in the presence of different concentrations of alcohol in the dissolution media. PCP-Disso-V 2.08 software was used to fit models to the dissolution profiles. The correlation coefficient (R^2) was used as an indicator of the best fit for each of the models.

Data Analysis

Drug release data were analyzed using a modified power-law equation (eq 2) proposed by Ford et al. (11):

$$M = k\,(t - l)^n \qquad (2)$$

where M is the percentage of drug released at time t, k is a constant incorporating structural and geometric properties of the devices, l the lag time, and n the release exponent, indicative of the drug release mechanism.

Statistical Analysis

To compare the drug release profiles in the presence and absence of alcohol in the dissolution media (pH 6.8), a two-way analysis of variance (ANOVA) was carried out using GraphPad Prism Software Version 5.01. A statistically significant difference was indicated when $p < 0.05$.

Similarity Factor (f_2) Studies in the Presence of Alcohol

A model-independent comparison of the formulations was done by determining the similarity factor (f_2 value) between dissolution profiles in media containing different concentrations of alcohol and plain media (devoid of alcohol) using PCP-Disso software. The FDA and the European Agency for the Evaluation of Medicinal Products suggest that two dissolution profiles are declared similar if f_2 is between 50 and 100.

RESULTS AND DISCUSSION

Evaluation of Tablets

The tablets of all the drugs were compressed on a six-station rotary tablet compression machine. The tablets were in compliance with all the evaluation parameters. The average drug content was in the range of 99.1–99.9% showing uniform distribution of drug in matrix. Average tablet weights were 300 ± 4 mg for all formulations. Percentage weight loss (friability) of the tablets of each formulation was measured and was less than 1%. The diameter was 9 ± 0.05 mm, and thickness was 5 ± 0.2 mm for all the formulations.

Drug Release Studies

The release profiles of diclofenac potassium from HPMC matrices are shown in Figure 1A,B, and those of tramadol HCl and venlafaxine HCl are depicted in Figures 2 and 3, respectively. In the case of all formulations, drug release increased with an increase in alcohol content in the dissolution medium. Drug release followed the rank order 40% > 30% > 20% > 10%. Interestingly, dose-
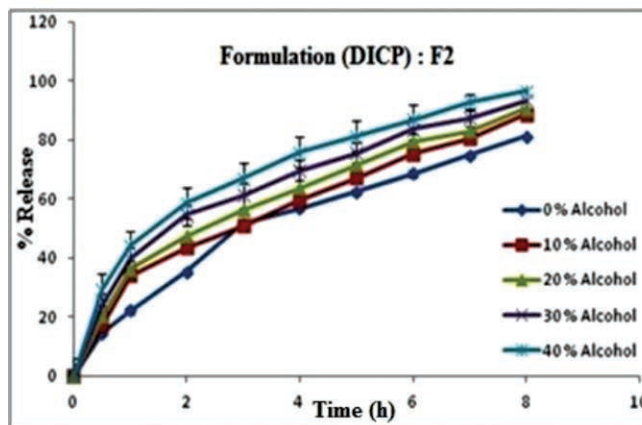
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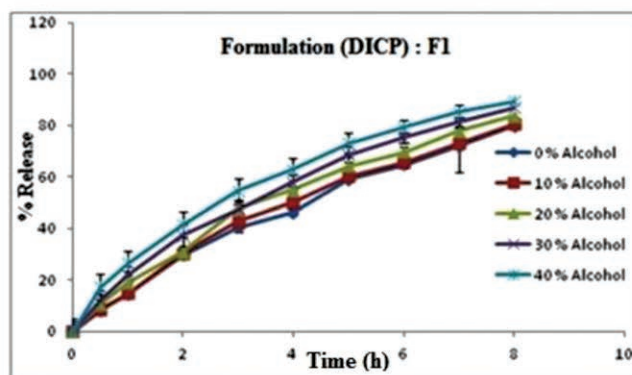
B

Figure 1. DICP release profiles of (A) formulation F1 and (B) formulation F2 as a function of different concentrations of alcohol in the dissolution media.
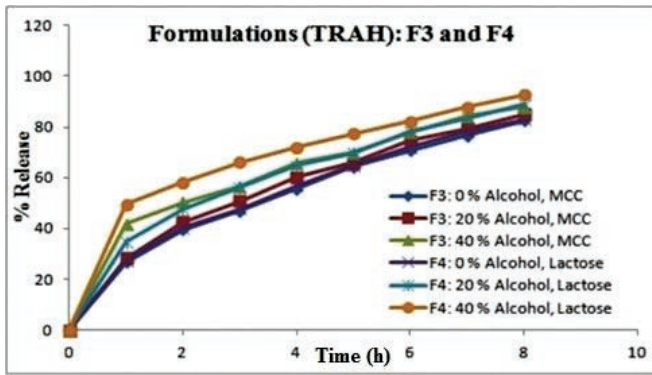
Figure 2. TRAH release profiles of formulations F3 and F4 as a function of different concentrations of alcohol in the dissolution media.
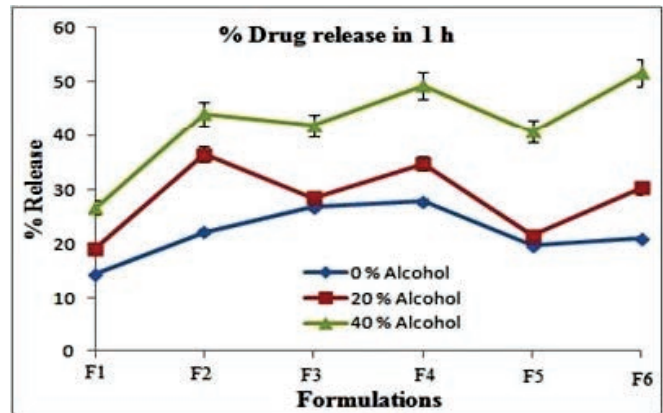

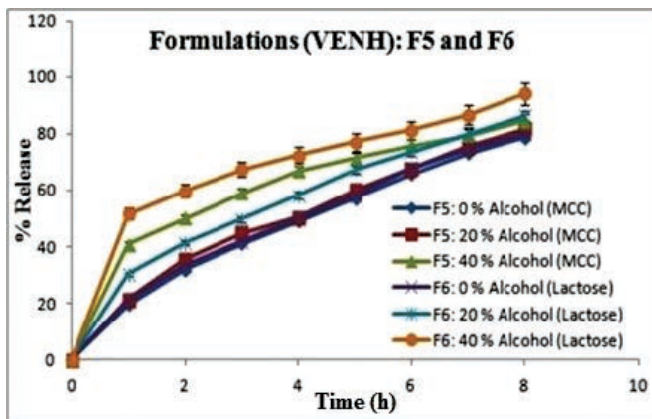Figure 4. Percentage drug release during the first hour from all formulations.

Figure 3. VENH release profiles of formulations F5 and F6 as a function of different concentrations of alcohol in the dissolution media.
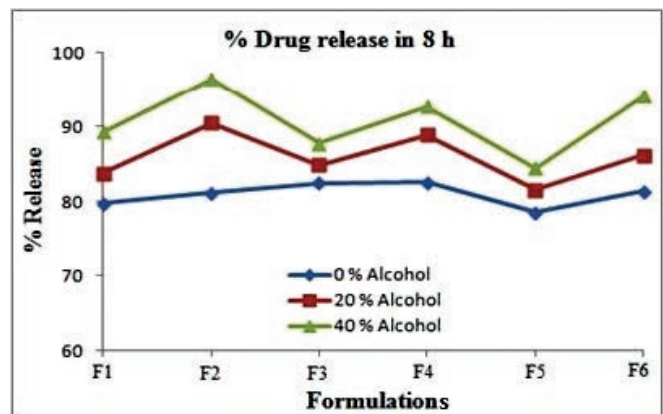

Figure 5. Percentage drug release in 8 h from all formulations.

dumping was seen in TRAH and VENH, which are soluble drugs, but not in DICP, which has low solubility. All three drugs have different physicochemical properties and showed increased drug release in the presence of alcohol, which indicates that an increase in drug release is not only because of inherent drug properties, but that the retardant property of the polymer is also reduced by the presence of alcohol in the dissolution medium. The high standard deviation observed for dissolution, as shown in Figures 1–3 for 40% alcohol, could be indicative of nonuniform gel layer generation, causing inconsistency in release.

Figures 1–3 show that diluents having different solubilities affect drug release kinetics in the presence of different concentrations of alcohol. Drug release was faster from the matrix containing lactose as a diluent than from the matrix containing MCC 102 as a diluent. This substantial change can be ascribed to differences in diluent solubility. Alderman (12) proposed that lactose accelerates drug release by increasing the gel layer porosity as it dissolves, which is enhanced with increasing alcohol

concentration, whereas MCC remains as inclusions in the gel layer (13). Lactose may therefore facilitate drug transport through the gel layer, whereas MCC provides an additional barrier by increasing the tortuosity of the diffusion path, indicating that diluents do not change their inherent property even in presence of alcohol (12, 14–16). All three drug formulations containing lactose as diluent (i.e., F2, F4, and F6) showed faster drug release than formulations containing MCC 102 as a diluent (i.e., F1, F3, and F4). Thus, it can be inferred that with the use of insoluble diluents in the formulation, accelerated drug release in the presence of alcohol in the dissolution medium can be reduced, and matrix tablets with improved resistant properties to alcohol can be prepared. Thus, dose-dumping can be avoided by proper selection of polymer and diluent.

Release profiles in media containing alcohol were characterized by an initial rapid release (first hour), with the rate of drug release decreasing progressively over time, suggesting that a diffusion-controlled release mechanism predominated in the latter stage (Figures 4 and 5). Initial rapid drug release may be due to the reduced

hydration and swelling of polymer in the first hour. After rapid release during the first hour, drug release was not different over the period of 2–8 h (Figures 4 and 5), which may be due to the competitive affinity between alcohol and polymer for water. The initial interaction between the polymer and water is reduced in presence of alcohol, causing an increase in drug release, but over a period of time, the interaction between polymer and alcohol decreases, and hydration of polymer takes place to cause retarded release.
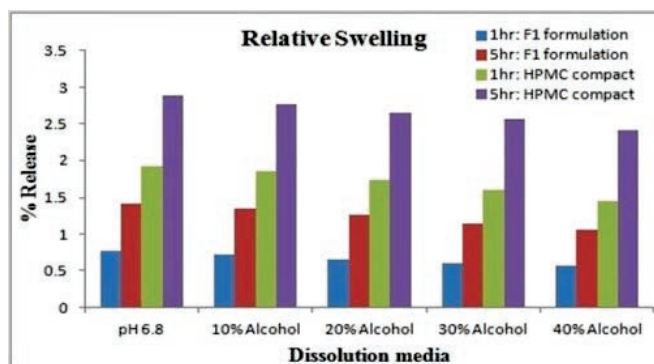

Figure 6. Relative swelling of F1 formulation of DICP and HPMC compacts (without drug).

Table 2. Effect of Alcohol Concentration on the Release Exponent and Regression Coefficient of Formulations

Diclofenac potassium (DICP) formulations				
% Alcohol	F1		F2	
	n	R^2	n	R^2
0	0.83	0.986	0.68	0.948
10	0.80	0.975	0.57	0.935
20	0.76	0.963	0.50	0.906
30	0.69	0.964	0.46	0.884
40	0.65	0.941	0.44	0.852
Tramadol HCl (TRAH) formulations				
% Alcohol	F3		F4	
	n	R^2	n	R^2
0	0.56	0.938	0.51	0.917
20	0.54	0.924	0.41	0.898
40	0.39	0.856	0.33	0.784
Venlafaxine HCl (VENH) formulations				
% Alcohol	F5		F6	
	n	R^2	n	R^2
0	0.68	0.975	0.57	0.941
20	0.63	0.963	0.52	0.924
40	0.36	0.825	0.30	0.766

Relative Swelling

Relative swelling studies were carried out to determine if the effect of increasing alcohol concentration on release was due to the polymer or due to the inherent properties of the drug. Results of a relative swelling study of the F1 formulation of DICP and HPMC compacts (without drug) in the first and fifth hours are shown in Figure 6. The relative swelling of drug-containing matrix tablets and HPMC compacts was greater in plain medium (phosphate buffer, pH 6.8), which was devoid of alcohol, than in media containing alcohol. Swelling was greater in HPMC compacts than in matrix tablets, which is obviously due to the higher concentration of HPMC in the compacts as compared with the drug-containing formulations. Relative swelling decreased with an increase in alcohol content in dissolution media. In media containing 40% alcohol, both matrix tablets and HPMC compacts demonstrated a lower degree of swelling. This indicates that at a high concentration of alcohol, hydration of the polymer is reduced and swelling cannot take place; a gel barrier is not formed properly, resulting in faster drug release.

Best-Fit Model for Formulations (Release Kinetics Studies)

From modeling studies of drug release kinetics, the matrix (Higuchi) model was the best fit in plain medium (0% alcohol), and the Peppas model was best fit in media containing alcohol for DICP formulations. TRAH formulation (F3) followed the Peppas release kinetics model in media containing 0% and 20% alcohol, while in 40% alcohol it followed the Higuchi model. Formulation F4 data best fit the Higuchi model in media containing 0% and 20% alcohol, and the Peppas model in 40% alcohol. In the case of VENH formulations F5 and F6, the Peppas model was the best fit for the F5 formulation in the presence and absence of alcohol in the media. However, for the F6 formulation in media containing 0% and 20% alcohol, data followed the Higuchi model, and in media containing 40% alcohol, the Peppas model. From drug release kinetics studies, the alcohol content in the dissolution medium changes the drug release kinetics of drugs.

The analysis of the release data using eq 2 is shown in Table 2. Data confirm the previous impression that release in media containing 40% ethanol was different from release in media containing a lower percentage of alcohol. All formulations except F1 show lower n values in the presence of 40% alcohol. In addition, the value of the regression coefficient decreased with an increase in the dissolution medium alcohol content in the case of all three drugs. The release mechanism in 40% alcohol, denoted by the lower n value (<0.5), appears to be dependent on diffusion, while in all other media, the higher n values (>0.5) indicate that a diffusion and erosion mechanism is dominant.

Statistical Evaluation of Formulations

Table 3 shows the *p* values for DICP, TRAH, and VENH formulations. Significant differences in release rates

Table 3. p Values (Significant Difference) of Formulations in the Presence of Different Concentrations of Alcohol in the Dissolution Medium

Diclofenac potassium (DICP) formulations		
% Alcohol in media	F1	F2
10	$p > 0.05$	$p < 0.05$
20	$p > 0.05$	$p < 0.01$
30	$p > 0.05$	$p < 0.001$
40	$p < 0.01$	$p < 0.001$
Tramadol HCl (TRAH) formulations		
% Alcohol in media	F3	F4
20	$p > 0.05$	$p > 0.05$
40	$p < 0.01$	$p < 0.001$
Venlafaxine HCl (VENH) formulations		
% Alcohol in media	F5	F6
20	$p > 0.05$	$p > 0.05$
40	$p < 0.05$	$p < 0.001$

Table 4. f_2 Values for Formulations in the Presence of Alcohol

Diclofenac potassium (DICP) formulations		
% Alcohol in media	F1	F2
10	84	63
20	66	49
30	50	41
40	39	32
Tramadol HCl (TRAH) formulations		
% Alcohol in media	F3	F4
20	76	64
40	47	39
Venlafaxine HCl (HCl) formulations		
% Alcohol in media	F5	F6
20	72	65
40	48	34

were observed for the F2 formulation in all media containing alcohol (10–40%), but in the case of the F1 formulation, a significant difference was observed only in media containing 40% alcohol. Significant differences were observed for the F3, F4, F5, and F6 formulations in media containing 40% alcohol, and no significant difference was observed in media containing 20% alcohol.

Similarity Factor Studies for DICP, TRAH, and VENH Formulations

Values of f_2 for formulations of DICP, TRAH, and VENH in the presence and absence of alcohol in dissolution media were determined using PCP-Disso software (Table 4). All DICP formulations showed similar dissolution profiles in media containing 10% alcohol, while in media containing 20–40% alcohol, dissolution profiles were dissimilar (except for F1) from those in media devoid of alcohol. For TRAH and VENH formulations, similar dissolution profiles were observed in media containing 20% alcohol, while in media containing 40% alcohol, dissolution profiles were dissimilar from those in media devoid of alcohol. Based on the f_2 values for all drugs, alcohol plays a significant role above a 20% concentration in the case of DICP and above 40% for TRAH and VENH. This indicates that drug solubility plays an important role in dose-dumping or increasing the drug release rate in the presence of alcohol in vitro.

CONCLUSION

These studies have shown that alcoholic media can affect the kinetics and mechanism of drug release from HPMC-based matrix extended-release formulations in

a manner related to the alcohol content. Drug release rates increase with an increase in alcohol concentration, and the initial burst release observed in the first hour may be due to polymer–alcohol interaction. On the basis of the dissolution profiles of all drugs, in vitro release of ER tablets in the presence of alcohol in media would also depend on the aqueous drug solubility. A relative swelling study shows that swelling decreases with an increase in alcohol content, which may be due to decreased hydration of the polymer by alcohol. Decreased swelling led to decreased hydration and therefore increased drug release, but as time progressed, hydration increased and swelling dominated the process, bringing about a reduction in release. This study also demonstrates that through the judicious choice of diluents, HPMC matrices can be designed for a slower drug release in the presence of alcohol to avoid dose-dumping.

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