ORIGINAL ARTICLE

IN VITRO SCREENING OF ALCOHOL-INDUCED DOSE DUMPING PHENOMENA FOR CONTROLLED RELEASE TRAMADOL TABLETS

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Abstract

The aim of the study was to evaluate the influence of ethanol content in acidic media on the *in vitro* release of tramadol hydrochloride from controlled release tablets. The selected products represented both hydrophilic and lipid-based monolithic systems, covering a wide range of dose strengths with various similarity degrees of the qualitative composition. The results confirmed the inhibition of release by gradually increasing the ethanol proportion up to 40% (v/v). The reduced hydration of the macromolecular agents and consequent increased diffusional resistance were suggested as the leading causes of this phenomenon. *In vitro* release similarity was observed between the different strengths of the same product, as well as between reference listed drug and generics, for the same media. The critical conditions simulated by the upper level of alcohol content minimized the impact of composition and manufacturing variables. Irrespective of media composition, strength and hydro-lipophilic nature of the matrix, the kinetic model adequately describing the experimental data was preserved.

Rezumat

Scopul studiului a fost evaluarea influenţei conţinutului de etanol din mediul acid gastric simulat asupra cedării *in vitro* a tramadolului clorhidrat din comprimate cu cedare controlată. Produsele selectate au reprezentat sisteme monolitice hidrofile şi lipidice, acoperind un interval larg de doze şi având diferite grade de similaritate a compoziţiei calitative. Rezultatele au confirmat inhibiţia cedării prin creşterea graduală a proporţiei de etanol până la 40% (v/v). Reducerea hidratării agentului macromolecular şi creşterea consecutivă a rezistenţei difuzionale au fost sugerate ca fiind cauzele principale ale acestui fenomen. Similaritatea cedării *in vitro* a fost observată între doze diferite ale aceluiaşi produs, dar şi între referinţă şi generice, pentru acelaşi mediu. Condiţiile critice simulate prin nivelul superior de concentraţie a alcoolului a minimizat impactul variabilelor de compoziţie şi de proces de fabricaţie. Independent de compoziţia mediului, doză şi natura hidro-lipofilă a matricei, s-a păstrat modelul cinetic, descriind adecvat datele obţinute experimental.

Keywords: tramadol hydrochloride, controlled release, alcohol, dose-dumping, *in vitro* release

Introduction

The *in vitro* drug release studies are generally recognized as powerful quality control and performance screening tools. Lately, their role has been extended to the assessment of release profiles in conditions that simulate the impact of manipulation procedures applied to individual dosage units, according to the information provided in the summary of product characteristics, e.g. splitting of functionally scored tablets [1]. Another key application is part of the evaluation of safety profiles, especially considering the physicochemical interaction with dietary components prior to the absorption processes [2]. One of the most significant interactions is related to the influence of alcohol on the release of psychotropic drugs from modified release oral solid dosage forms. Despite the fact that product labelling clearly states that no alcohol intake is allowed during the therapy with this type

of drugs and drug products, in several instances patients search for a potentiation of specific effects such as analgesia [3]. For the *in vivo* product performance, the presence of alcohol in the media surrounding the dosage unit is able to change not only the solubility of the active pharmaceutical ingredient and, consequently, the concentration gradient that controls the diffusional release, but also the kinetic mechanism. There is a direct and significant interaction between the coating films or the matrix of the drug formulation and ethanol, potentially leading to rapid and sometimes complete release of the active entity, phenomenon described as *dose-dumping* [4]. Obviously, the impact is strongly dependent on the quantity of ingested alcoholic beverage, its ethanol content [5], as well as on the lag time between consumption and drug intake [6]. It should be considered that physiological factors may also be changed, for example the gastric emptying rate is decreased by alcoholic beverages depending on the percentage of ethanol, but also on the caloric content and presence of various ingredients [5]. Moreover, the direct interactions between alcohol and the dosage forms usually occurs at the gastric level, due to the fact that the absorption of ethanol is rapid and takes place in the proximal segments of the digestive tract [6]. Based on the available reports on hydromorphone once-a-day extended release products, including clinical reviews or conclusions of the advisory committees meetings of Food and Drug Administration [7], specific comparative *in vitro* performance studies have been designed and officially adopted [8]. The selection of appropriate formulation factors is mandatory for the development of abuse deterrent generics [9]. The robustness of release mechanism in the presence of various quantities of ethanol is tested using compendial dissolution apparatus and hydro-alcoholic media. The vulnerability of the dosage unit is assessed during 2 hours, a period relevant for the gastric emptying [10]. Despite the fact that an agreement on the alcohol content of the release media was apparently reached (0 to 40% ethanol, v/v), there is still a considerable variability in terms of parameters selection, including the composition of the aqueous fluid to be used as reference system, as well as on the type of apparatus and hydrodynamic conditions.

The aim of this paper was to evaluate the *in vitro* release behaviour of the marketed controlled-release formulations containing tramadol hydrochloride in a wide range of strengths and with considerable differences in terms of qualitative composition. The goal was to comparatively assess their *in vitro* robustness concerning both the cumulative fraction released and kinetics during the gastric level, by adopting various concentrations of ethanol and using mild stirring conditions.

Materials and Methods

The tested products were purchased from commercial sources and were used as received. The reference listed drug and several generic products available in two or three dose strengths were included in this study. Details on the qualitative composition for the core tablets and coating film, together with batch identification and assigned codes are provided in Table I.

Table I

The qualitative composition of the controlled release tablets and identification of product batches

Code	R	**K100**	**K150**	**K200**	**L150**	**L200**	**Z100**	**Z150**
Tramadol hydrochloride (mg)	200	100	150	200	150	200	100	150
Core tablet								
(Hydroxypropyl)-methyl cellulose	✓[a]	✓[b]	✓[b]	✓[b]	✓[c]	✓[c]	- - -	- - -
Microcrystalline cellulose	✓	✓	✓	✓	✓	✓	- - -	- - -
Glyceryl dibehenate	- - -	- - -	- - -	- - -	- - -	- - -	✓	✓
Povidone	- - -	✓	✓	✓	✓	✓	✓[d]	✓[d]
Calcium hydrogen phosphate dihydrate	- - -	- - -	- - -	- - -	- - -	- - -	✓	✓
Anhydrous colloidal silicon dioxide	✓	✓	✓	✓	✓	✓	✓	✓
Magnesium stearate	✓	✓	✓	✓	✓	✓	- - -	- - -
Lactose monohydrate	✓	✓	✓	✓	- - -	- - -	- - -	- - -
Coating film								
Propylene-glycol 6000	✓	✓	✓	✓	✓	✓	- - -	- - -
(Hydroxypropyl)-methyl cellulose	✓[e]	✓[f]	✓[f]	✓[f]	✓[g]	✓[g]	- - -	- - -
Propylene glycol	✓	- - -	- - -	- - -	- - -	- - -	- - -	- - -
Tartrazine (E102)	- - -	- - -	- - -	- - -	✓	✓	- - -	- - -
Titanium dioxide (E171)	✓	✓	✓	✓	✓	✓	- - -	- - -
Talcum	✓	✓	✓	✓	✓	✓	- - -	- - -
Polyacrylate dispersion 30%	- - -	- - -	- - -	- - -	✓	✓	- - -	- - -
Sicopharm Rot 30 pigment	- - -	- - -	✓	✓	- - -	- - -	- - -	- - -
Sicopharm Gelb 10 pigment	- - -	- - -	✓	✓	- - -	- - -	- - -	- - -
Batch	9320932E06	TB5335	T93830	TA9527	3G022A	2L003A	3060713	2021013

[a]100000 mPa·s; [b]4000 and 100000 cPa·s; [c]15.000 Pa·s; [d]Kollidone K25; [e]6 mPa·s; [f]6 cPa·s; [g]5 mPa·s.

The *in vitro* studies were performed on an Agilent 708-DS Dissolution Apparatus (Agilent Technologies, United States), using the standard paddle method at 50 rpm. The evaluations were conducted in triplicate, using four media consisting of hydrochloric acid 0.1 N pH = 1.2 with or without absolute ethanol (coded 0%, 5%, 20% and 40%, according to the percentage of alcoholic component, v/v). The media was filtered at ambient temperature under vacuum (800 mBar) on cellulose acetate membranes (0.45 μm, Sartorius Stedim Biotech, Sartorius GmbH, Germany), in order to prevent significant losses of the volatile component. Supplementary, after transferring the media into individual vessels, the low-loss evaporation covers were sealed with vapour-tight Parafilm® M laboratory film (Science Services, Germany). When the temperature of the media reached 37 ± 0.5°C, the controlled release tablets were dropped and the dedicated space was resealed. Samples of 5 mL were collected using resident cannula with immersed polypropylene filters (mean pore diameter of 10 μm, PharmaTest GmbH, Germany), every 15 minutes for 2 hours after introduction of dosage units and initiation of stirring. Their content of tramadol hydrochloride was analysed spectrophotometrically (Agilent 8453 spectrophotometer, Agilent Instruments Germany), using quantification methods based on calibration probes prepared and processed according to the same protocol as the samples (λ_{max} = 271 nm, respectively 272 nm for 40% ethanol absolute, v/v). The *in vitro* profiles were analysed for variability, as well as for alteration of cumulative fraction released at each sampling time point and for changes of the kinetic model. The evaluation of release similarity was performed both within formulations (different strengths of the same product) and between formulations (same strength of different products), for a given media.

The hydrochloric acid 37% and absolute ethanol (Chromasolv®) were purchased from Sigma-Aldrich and were of analytical grade. The purified water was generated on an Ultra Clear™ TWF system (SG Wasseraufbereitung und Regenerierstation GmbH, Germany).

Results and Discussion

The mean *in vitro* release profiles of tramadol hydrochloride are presented in Figures 1 and 2. The variability of the generated data was below 10% throughout the test duration, with only two exceptions for the first sampling point (but still lower than 15%). No dose-dumping phenomena were reported. As general observation, all the evaluated products displayed decreases in the cumulative fraction recovered in the media, for the gradual increase in the ethanol content. This corresponded to negative values of the $D_{A/N}$ parameter proposed by Smith *et al* (defined as "*differential % dissolved in alcohol relative to % dissolved in <<non-alcoholic>> media*", [11]), irrespective of the considered time point.

The most significant alterations were observed for products sharing the hydrophilic macromolecular agent, the fraction release dropping by 11.11 to 13.47% in the media containing 40% ethanol, compared to the reference acidic conditions. The lipid-based matrix of product Z was less sensitive to the changes in the alcoholic content, the mean profiles being essentially similar (the lowest value of the calculated similarity factor, f_2, being 50.65, corresponding to release from product Z100 in the extreme conditions). Notably, the marked non-similarity of the qualitative composition between Z product and the reference listed drug induced a constant difference in released fractions, independent on the composition of media (f_2 values between 56.13 and 60.17, not correlated with ethanol percentage). For monolithic matrix systems, there was an obvious similarity within the same product, as well as between each formulation and the reference. This confirms that the differences in nature or quantity of excipients are gradually levelled by the increase in the quantity of alcohol in the media. Considering also that the theoretic solubility of the active pharmaceutical ingredient is progressively increased, it may be assumed that inhibition of the release may be due to the changes in gel barrier structure. The dose dumping phenomena has been linked to solubility of some macromolecular agents in the hydro-alcoholic mixtures [6]. Nevertheless, we observed that in these conditions the hydration of (hydroxypropyl)-methyl cellulose-based matrix is reduced, with no significant alterations of the initial disintegration of the coating film. At the end of the study, the oblong tablets were gently removed from the bottom of the vessel, transferred to filter paper and divided both longitudinally and transversely. From 0 to 40% absolute ethanol, the thickness of superficial gel layer decreased, whereas its consistency was considerably higher. Therefore, it may be assumed that the increase in diffusional resistance is one of the main factors leading to the apparent inhibition of release.

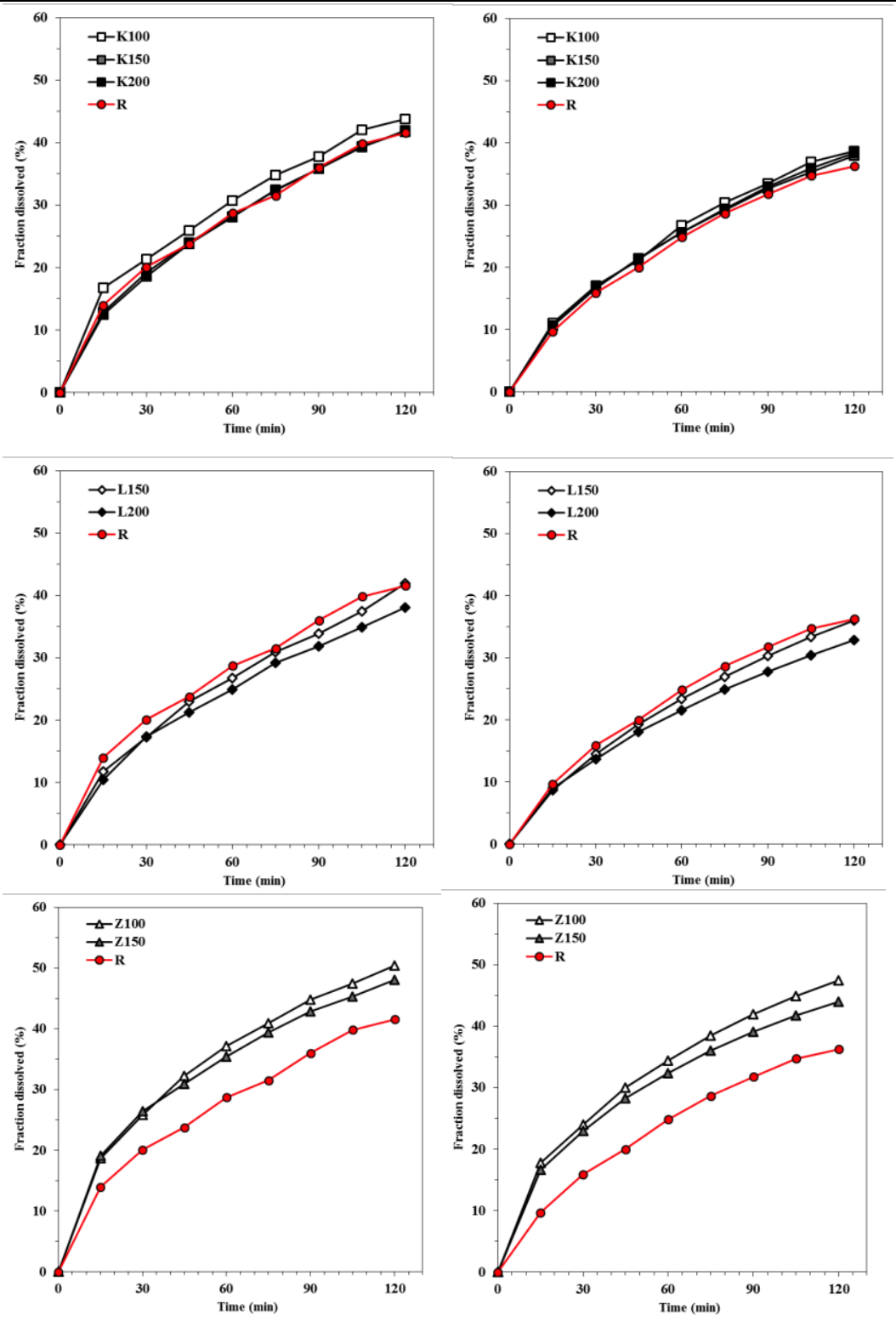

Figure 1.

Mean *in vitro* dissolution profiles of tramadol hydrochloride from prolonged release tablets in hydrochloric acid 0.1 N, pH = 1.2 without (left) or with addition of absolute ethanol 5% v/v (right)
(n = 3, standard deviation not displayed for improved clarity of graphs)

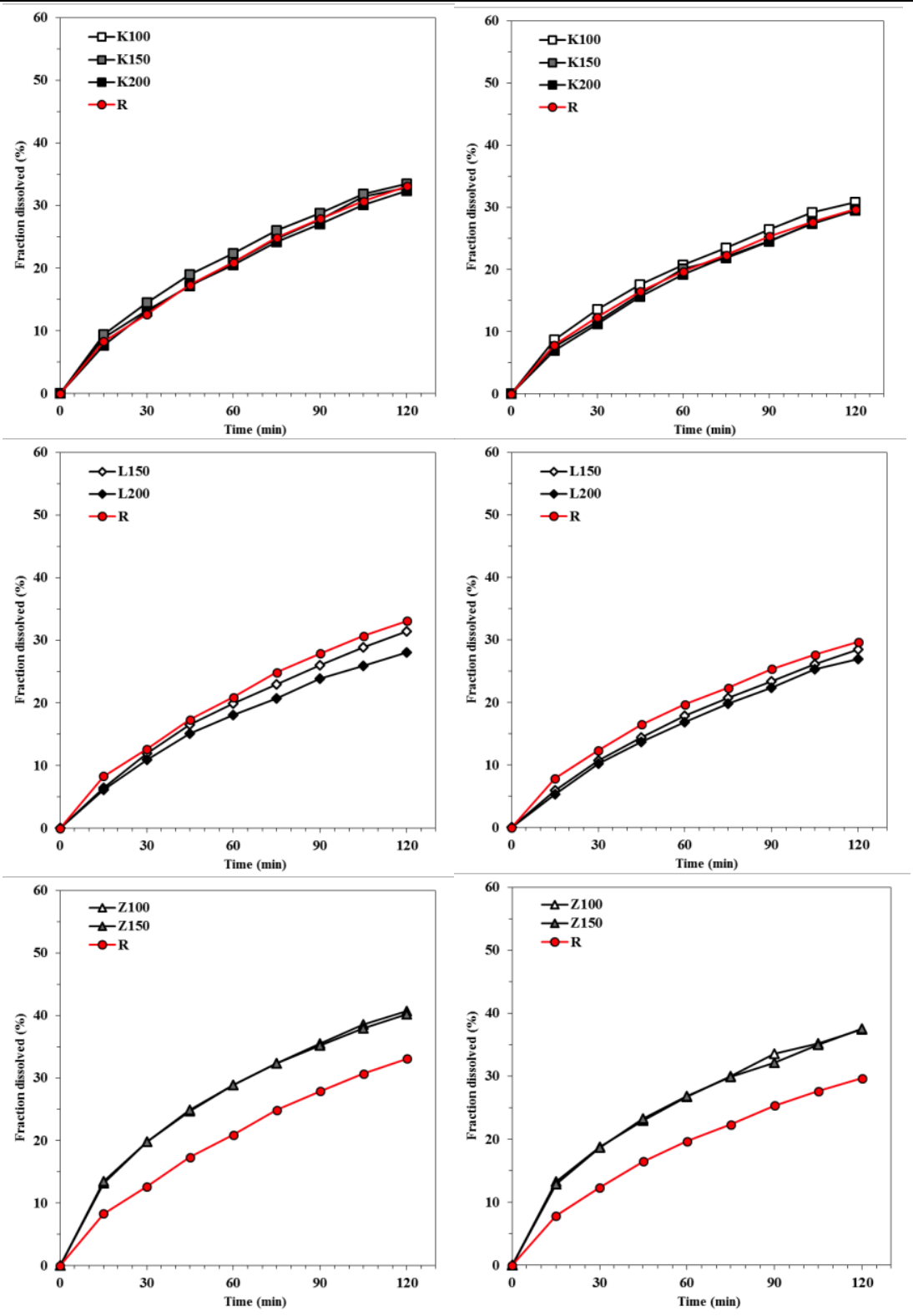

Figure 2.

Mean *in vitro* dissolution profiles of tramadol hydrochloride from prolonged release tablets in hydrochloric acid 0.1 N, pH = 1.2 with addition of 20 % v/v (left) or 40% v/v (right) absolute ethanol (n = 3, standard deviation not displayed for improved clarity of graphs)

In fact, when the mean profiles were subjected to modelling procedures, it was concluded that Korsmeyer-Peppas kinetic model adequately described the release process (Figure 3, fitting parameters not shown), independent on the product or media. The values of the n parameter were higher than 0.5, confirming the similar reports of anomalous transport [12, 13]. Relaxation pattern of

the macromolecular matrix-forming agent is contributing to the previously described, diffusion controlled mechanism. For the lipid-based product Z, the kinetics corresponding to the highest concentration of absolute ethanol in media were described by the square root law (Higuchi model, n = 0.504, correlation coefficient of 0.9992). It was previously suggested that glyceryl behenate may be used for manufacturing of modified release formulation robust in terms of ethanol interaction up to 20% [14]. Higher alcohol concentration increases the wetting of lipidic matrix and promotes the penetration of the media within the pores of the dosage unit. But the presence of calcium hydrogen phosphate was previously linked to increase rise in porous diffusion [15], which explains the observed Higuchi behaviour.

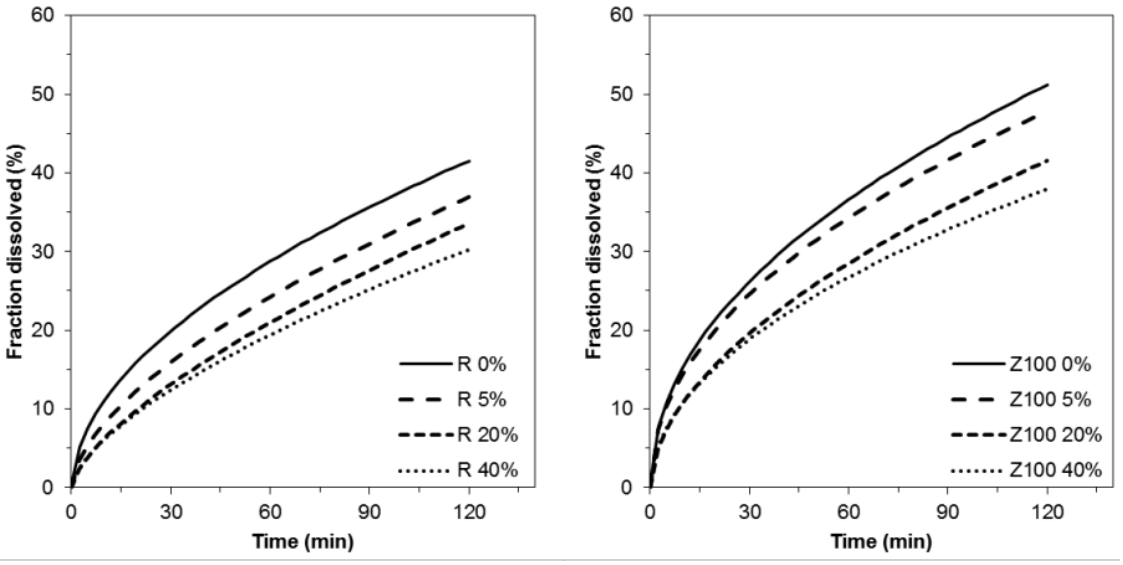

Figure 3.
Estimated *in vitro* dissolution profile for the reference listed drug (R) and Z100 generic product, using Korsmeyer-Peppas kinetic models for fitting of experimental data

Although non-similar in terms of qualitative composition, the formulation strategies used for manufacturing of the tested controlled-release oral dosage forms of tramadol hydrochloride seems to be adequate for providing robust performance in presence of alcohol. The lower release observed for gradually increases in ethanol content also suggested abuse-deterrent characteristics. It should be considering that other intended or unintended misuses such as alteration of matrix integrity by splitting or crushing can still generate safety concerns. *In vitro* approaches may be developed, as a scientifically based and ethical alternative to the *in vivo* studies. However, additional studies can be considered in order to adapt and validate the methodology to the particularities of the modified release dosage forms. i.e. selection of apparatus and hydrodynamic conditions, volume of media closer to the physiological range, use of enzymes and tensioactives in presence of alcohol.

Conclusions

Commercially available controlled-release oral solid dosage forms containing tramadol hydrochloride were evaluated *in vitro* for potential alcohol-induced dose dumping phenomena. The increase of alcohol content of the compendial acidic media revealed a gradual inhibition of the fraction of active pharmaceutical ingredient released. The kinetic model suggesting a combined, non-Fickian mechanism controlling the *in vitro* behaviour, was preserved, irrespective of strength and hydro-lipophilic nature of the matrix. The results confirmed the robustness of performance on a wide range of ethanol content in acidic media, with beneficial consequences in terms of safety profile.

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