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IMPACT OF ALCOHOLIC BEVERAGES ON IN VITRO DRUG RELEASE OF ORAL TABLETS WHEN CO-ADMINISTERED WITH BEER, TEQUILA AND WINE

MD. Betzabeth Jaime-Escalante, PhD Horacio Sandoval, MD. Zacnite Sánchez and PhD. Luz María Melgoza*

Departamento de Sistemas Biológicos. Universidad Autónoma Metropolitana, Calzada del Hueso 1100, Villa Quietud, Coyoacán, 04960 Ciudad de México, México.

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***Corresponding Author**
PhD. Luz María Melgoza
Departamento de Sistemas Biológicos. Universidad Autónoma Metropolitana, Calzada del Hueso 1100, Villa Quietud, Coyoacán, 04960 Ciudad de México, México.

ABSTRACT

Oral tablets are designed to be taken with water; however, often they are ingested with alcoholic beverages. In this study, it was analyzed on in vitro drug release of three over-the-counter oral dosage forms: immediate-release acetylsalicylic acid (ASA), immediate-release metformin hydrochloride (Met-HCl) and extended-release sodium diclofenac (DCL-Na) co-administered with beer, tequila and wine. It was compared the effect of these alcoholic beverages and ethanol on drug-releasing profiles too. Appropriate dissolution media (Pharmacopeia) for ASA and Met-HCl (500 mg) and sodium diclofenac (Na-DCL) (100 mg) were supplemented with beer, tequila, or white wine, at a proportion of 13 g of pure ethanol. Furthermore, the results were compared with the FDA proposed method (40% ethanol). It was shown release ASA tablets were significantly different ($P<0.05$) to FDA, beer and wine. While DCL-Na dosage forms dissolution profiles have a significant difference ($P<0.05$) respect to all alcoholic beverages and ethanol. Moreover Met-HCl dosage forms dissolution profiles showed significant difference ($P<0.05$) in FDA, ethanol and tequila dissolution profiles. Nonetheless, comparing only ethanol effect on dissolution profiles, ethanol showed a significant difference ($P<0.05$) to FDA, beer and wine dissolution profiles in all cases, whereas ethanol vs tequila showed no significant difference, except on DCL-Na dosage forms dissolution profiles.

KEYWORDS: Acetylsalicylic acid**,** alcohol consumption, alcoholic beverages, diclofenac sodium, drug dissolution, metformin hydrochloride.

INTRODUCTION

Oral dosage forms are designed to be taken with water; however, often they are ingested with other drinks, even with alcoholic beverages. In 2005, the U.S. Food and Drug Administration (FDA) alerted about the ethanol-related dose dumping because of co-consumption of hydromorphone controlled-release dosage form and alcoholic beverages.[1] Consequently, the FDA established a regulatory framework to assess the risk of ethanol-induced dose dumping by using hydroalcoholic media to simulate *in vitro* the gastrointestinal environment during co-consumption of oral dosage forms and alcoholic beverages.[2]

However, evaluating the potential effect of consumption of alcoholic beverages on oral dosage form release *in vitro* is a complex issue. For example, some ethanol proportions used in the hydroalcoholic media proposed by the FDA may be difficult to achieve in the human body.[3] This is because ethanol is not the major component in almost any alcoholic beverages, which only contains 13 g on average.[4] therefore, performing the release profiles using hydroalcoholic media may not represent the real effect of alcoholic beverages on oral dosage forms release. Additionally, the physicochemical characteristics of the dosage form can modify the release of the drug, particularly those affecting solubility.

Additionally, because of the effect on drug-releasing by physicochemical components in oral dosage forms and in different beverages, it is probable that the high chemical variations on alcoholic beverages, and not just ethanol, will influence drug-releasing patterns.

In this study, it was analyzed over-the-counter oral dosage forms such as anti-inflammatories and pain relievers. Immediate-release acetylsalicylic acid (ASA), extended-release sodium diclofenac (DCL-Na), and immediate-release metformin hydrochloride (Met-HCl), an antihyperglycemic drug frequently used in diabetes treatment.

Finally, it was determined and compared the effect of different alcoholic beverages and ethanol on drug-releasing profiles *in vitro* for three over-the-counter oral dosage forms: immediate-release acetylsalicylic acid (ASA), immediate-release metformin hydrochloride (Met-HCl) and extended-release sodium diclofenac (DCL-Na).

MATERIALS AND METHODS

Materials

It was tested the anti-inflamatories and pain relievers ASA (500 mg) immediate release tablets and DCL-Na (100 mg) extended-release tablets, and the antihyperglycemic Met-HCl (500 mg) immediate release tablets. The alcoholic beverages tested were light beer (4.5% alcohol), tequila (35% alcohol), and white wine (11.5% alcohol). We obtained the oral dosage forms and alcoholic beverages from the national market. Reference drugs of ASA (99.9%) and Met-HCl (99.7%) were purchased from Mexican pharmacopeia[5] and Na-DCL (100%) from USP. Ethanol, reagent grade, hydrochloric acid, sodium chloride, sodium hydroxide, dipotassium phosphate, and monopotassium phosphate were obtained from J.T. Baker.

Equipment

Release profiles were performed in a Hanson 72 dissolution tester, for solubility test a Digital Orbital Shaker-HS120460 was used, and a Cary 50 UV-VIS spectrophotometer for drugs quantification.

System validation

It was constructed calibration curves for drug quantification using the drug reference and the dissolution media described in Table 1. Five concentration levels were considered.

For all drugs, we prepared stock solutions and took aliquots to create five concentration levels. For ASA was prepared stock solutions of 1 mg/mL and took aliquots of 0.5 mL-2.5 mL. For DCL-Na the stock solutions were 250 µg/mL and aliquots of 200-1000 µL. Finally, for Met-HCl, we prepared stock solutions of 200 µg/mL and aliquots of 40-120 µL. All aliquots were placed in 10 mL volumetric flasks, and each concentration was repeated in triplicate.

Precision should be assessed using a minimum of 9 determinations over a minimum of 3 concentration levels covering the specified range (e.g., 3 concentrations /3 replicates each of the total analytical procedure).

To evaluate the linearity of each drug, we plot the values of absorbance against the five concentration levels for each drug. Accuracy was corroborated by calculating the variation coefficient of three levels of concentration: high, medium, and low for each drug. Finally, it

was used the same procedure to analyze precision by performing the tests for each drug by two independent observers. These analyses were conducted accordingly to the International Council for Harmonization (ICH).

Drug solubility

To evaluate the solubility on each dissolution media (table 1), we prepared saturated solutions of ASA, DCL-Na and Met-HCl drugs (active pharmaceutical ingredient). The solutions were left in an incubator shaker at 300 rpm for 24 h at 37 ± 0.5 °C. Samples of approximately 2 ml were taken, centrifugated at 1500 rpm for 10 minutes and diluted appropriately. Finally, for drug quantification UV/VIS spectrometry was used at wavelength of 270 nm (ASA), 275 nm (DCL-Na) and 233 nm (Met-HCl) respectively. The solubility studies were performed in triplicate.

Release profiles

To construct the *in vitro* release profiles, we designed different scenarios to simulate the *in vivo* conditions of alcohol ingestion by adding tablets of each drug to different dissolution media (n = 6). *In vitro* release profiles were made based on the Mexican Pharmacopoeia <MGA 0291>, using the rotatory basket. pH dissolution media of ASA and Met- HCl was controlled by adding the conjugate acid or base to each solution. Sink conditions were maintained in all test media used.

In the first scenario, the dissolution media were performed without ethanol, in pharmacopeia conditions (control). For the second scenario, the dissolution media consisted of 40% v/v ethanol, according to the FDA (simulating the worst scenario). In the third scenario, the dissolution media consisted of 13 g of ethanol, simulating a standard alcoholic beverage. In the following's scenarios, the effect of alcoholic beverages (beer, tequila, and white wine) was evaluated by adding each beverage until reaching a proportion to 13 g of ethanol. Volumes of alcoholic beverages and ethanol used in dissolution media are shown in Table 1.

For ASA tablets, dissolution media (control) consisted of 500 mL of sodium acetate and acetic acid solution, pH 4.5, 0.1M, at rotatory speed 50 rpm, sampled at 5, 10, 15, 20, and 30 minutes. Dissolution media for DCL- Na tablets (control) consisted of 500 mL simulated gastric fluid, (SGF), pH 1.2, at 37°C, at rotatory speed 30 rpm, and sampling at 20 minutes intervals. After 1 h, the SGF was replaced by 900 mL simulated intestinal fluid (SIF) to switch the pH from 1.2 to 7.5. Samples were withdrawn from each vessel at 1, 2, 3, 4, 5, 7, 9,

and 11 hours. For Met-HCl tablets, the dissolution media (control) was 500 mL of dibasic potassium phosphate and monobasic potassium phosphate solution, pH 6.8, 0.1 M at 37°C, at rotatory speed 100 rpm. Samples were collected from each vessel at 5, 10, 20, 40 y 45 minutes.

The concentration of dissolved drugs in the media was measured at a UV wavelength of 275 nm for ASA, 270 nm for DCL-Na, and 233 nm for Met-HCl, and then quantified by using the regression equations obtained from calibration curves.

Table 1: Volume of ethanol and alcoholic beverages added to the dissolution media.

Scenario	Ethanol (mL)	Alcoholic beverages (mL)	Solution volume (mL)[a]	SIF (mL)[b]
Control	-----	-----	500	900
FDA	200, 360[b]	-----	300	540
Ethanol	16.4	-----	483.6	883.6
Beer	-----	366	134	534
Tequila	-----	46	454	854
Wine	-----	150	350	750

a: solution volume used for simulated gastric fluid (DCL-Na), ASA and Met-HCl

b: solution volume used for simulated intestinal fluid (DCL-Na)

**Ethanol density 0.789 g/mL was considered.*

Data analysis

The release profiles for all drugs were analyzed by Sigma plot through two-way ANOVA using a post-hoc Tukey test.

RESULTS AND DISCUSSION

Although concomitant alcoholic beverages consumption with oral dosage forms is contraindicated, this is a common practice observed in daily life, so it must be a consideration in drug analysis to determine if alcoholic beverages are capable to interfere in drug release.

Several studies have been conducted to elucidate the effects of alcoholic beverages on medications.[3,6] Most of these studies used ethanol as the only component of alcoholic beverages, concluding that ethanol increases drug release.[7,8]

Instead, in this study, we found that ethanol increase ASA and DCL-Na solubility (Figure 1). More interesting, different effects were observed on alcoholic beverages and ethanol (13 g y 40%) ASA and DCL-Na solubility even when the same content of ethanol was used,

suggesting that the chemically active substances found in these beverages,[9] other than ethanol, can interact with both the excipients and the drugs and modify the drug release and the dissolution process.

ASA solubility in control dissolution media was 90.13 mg/mL, while in FDA, ethanol, beer, tequila and wine dissolution media were 228.85 mg/mL, 105.71 mg/mL, 94.48 mg/mL, 107.48 mg/mL and 83.67 mg/mL respectively.

Whereas the solubility of DCL-Na is dependent of the dissolution media, in control media saturated solubility was 120.64 mg/mL, in ethanol, tequila and wine media was 114.82 mg/mL, 114.70 mg/mL and 83 mg/mL respectively, while solubility increase to 808.39 mg/mL in FDA media and 569.88 mg/mL in beer media. Also Met-HCl solubility were dependent on the dissolution media used, in control media solubility was 2.24 g/mL, for FDA media was 2.1 g/mL, for ethanol and tequila 2.8 g/mL, for wine 2.6 g/mL and 2 g/mL for beer.

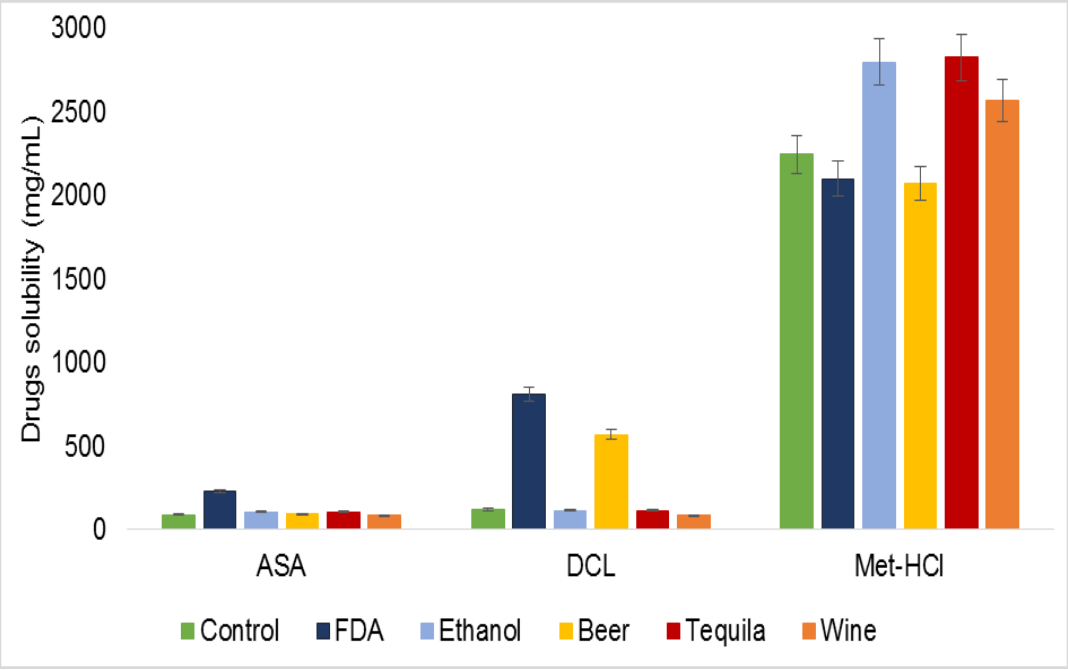

Figure 1: Solubility test of ASA, DCL-Na and Met-HCl drugs. (Mean ± SD, n = 3).

On the other hand, release profiles of ASA and Met-HCl immediate-release formulations showed an initial rapid release with progressively reducing the releasing rate over time. Whereas DCL-Na extended-release formulation was characterized by lag-times from one hour in the control media to up to 3 hours in some scenarios, followed by an accelerated release that progressively reduced over time.

ASA control profile reached 85% dissolved drug after 30 minutes, meanwhile high concentrations of ethanol (FDA) accelerated drug release, reaching 100% ASA dissolved after 10 minutes. Release profiles containing ethanol and tequila both showed a similar behavior although there is a slight change in release rate: 81% and 78% after 30 minutes, respectively. On the other hand, beer not only delayed ASA released in the first minutes but also decreased to 67% ASA release after 30 minutes. Finally, wine accelerated initially ASA release, reaching 57% in just five minutes, and 81% after 30 minutes. The release profiles of ASA are shown in Figure 2.

This behavior can be explained since, even when salicylates as ASA are highly soluble in ethanol (BCS class III, pKa 3.5),[10] the small amounts of ethanol added to dissolution media are not enough to act as cosolvent. The same was observed for tequila, whose composition based primarily on ethanol, water, and other components in small quantities,[11] do not interact significantly in the release of drugs. The contrary effect was observed in FDA media, which contains high amounts of ethanol (40%) and increased the solubility of ASA.

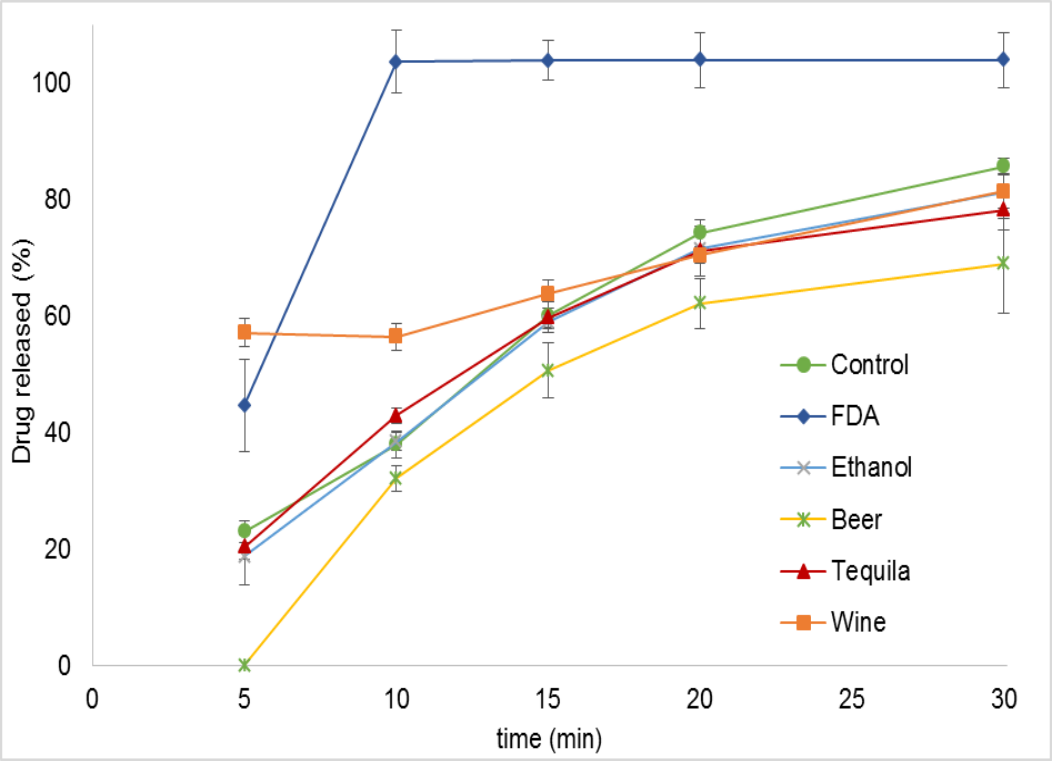

Figure 2: ASA immediate-release tablets on media containing ethanol (FDA) and alcoholic beverages. (Mean ± SD, n = 6).

In the case of DCL-Na release profiles, lag-time was not affected in the control scenario, however, all scenarios with ethanol increased lag-time up to 3 hours. DCL-Na released in

control media reached 99% after 12 hours, meanwhile FDA, tequila, and wine scenarios, DCL-Na released reached 89%, 95%, and 84% after the same period. On the contrary, scenarios with beer and ethanol reached only 11% and 5%, respectively of DCL-Na released after 12 hours. The release profiles of DCL-Na are shown in Figure 3.

In the case of DCL-Na dosage forms, there are two factors that could influence the decrease in DCL-Na release profiles with ethanol. First, DCL-Na is a weak acid of low solubility (BCS class II, pKa 4),[12] and these physicochemical characteristics hinder the dissolution process *per se* in gastrointestinal fluids under normal conditions. And second, as it has been reported that some water-soluble polymers used as excipients for the preparation of hydrophilic matrix systems with controlled-release profiles, in ethanol presence, undergo a rapid process of water uptake that close tablet pores and prevent drug release.[13] Also, as solubility test showed, the tablets excipients interact with the components of alcoholic beverages and decrease drug release.

Additionally, it has been suggested that the high content of organic compounds in alcoholic beverages[9] can reduce the dielectric constant of the dissolution media and therefore the polarity.[14] Low polarity media can reduce the solubility of ASA molecules, and especially molecules with low solubility such as DCL-Na, whose solubility decreased in alcoholic beverages scenarios.

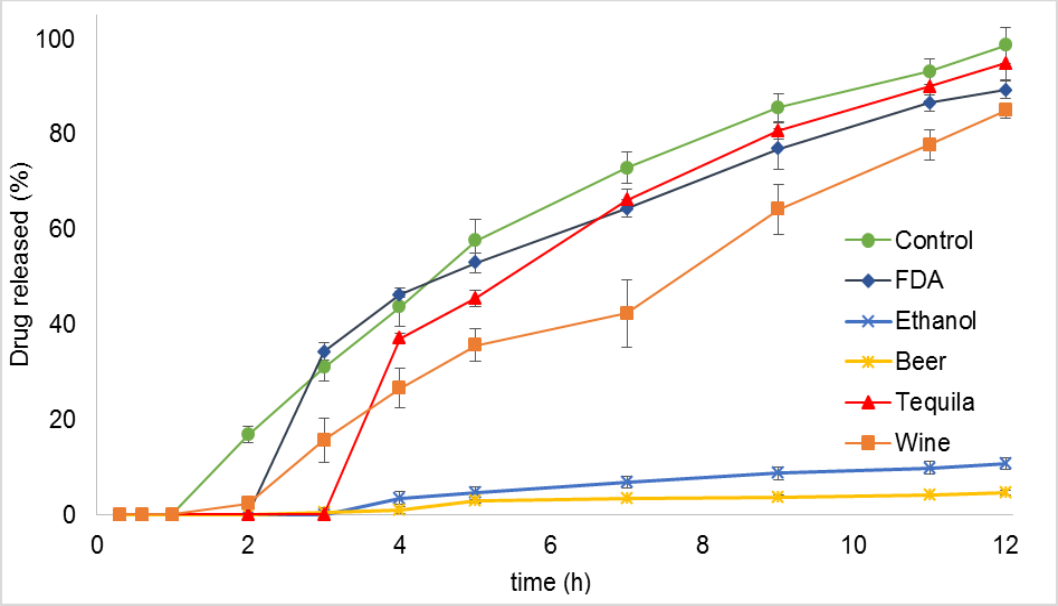

Figure 3: DCL-Na extended-release tablets, the first hour simulated gastric fluid (SGF) was used, then, for the next 11 hours the media was changed for simulated intestinal fluid (SIF), both with and without ethanol or alcoholic beverages. (Mean ± SD, n = 6).

On the other hand, we found in release profiles that ethanol increased the release of Met-HCI in FDA and ethanol scenarios, but no differences were observed in alcoholic beverages, except for tequila scenario that also increased drug dissolution. It is worth to mention that Met-HCl saturation solubility was 2,500-fold higher than dissolution media (1 mg/mL).

Met-HCI profiles shown that the control scenario reached 88% drug dissolved after 45 minutes, while the FDA release profile reached 100% in only 20 minutes. After 45 minutes ethanol and wine release profiles reached 95% of drug dissolved. Finally, beer and tequila scenarios reached 91% and 97% respectively. The release profiles of DCL-Na are shown in Figure 4.

Met-HCI is a highly soluble drug (BCS class III; pKa 2.8 and 12.4),[10] a factor that increases its dissolution in polar solvents such as ethanol. Even when all scenarios in this study contained ethanol, the organic components found in beer and wine reduced the solvent effect of ethanol by decreasing the polarity of the media and therefore reducing Met-HCI low solubility. As we mentioned before, tequila is composed mainly of ethanol, so it affected the Met-HCl dissolution in a similar way than ethanol media.

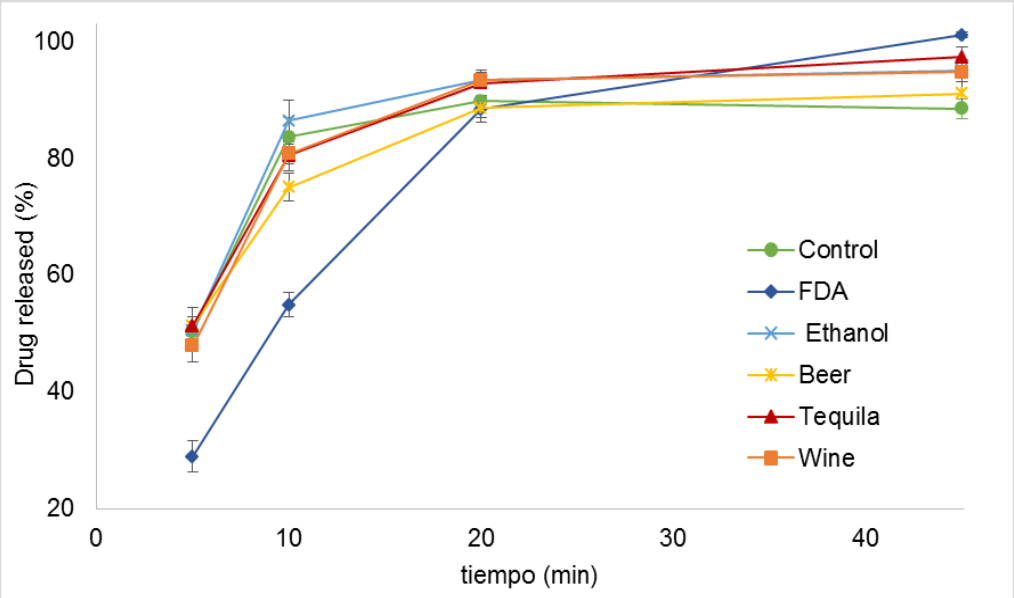

Figure 4: Met-HCl immediate-release tablets on media containing ethanol (FDA) and alcoholic beverages. (Mean ± SD, n = 6).

The similarity of the effect of tequila and ethanol in both ASA and Met-HCl suggests the feasibility to use ethanol (13g) to assess the effect of alcoholic beverages as spirits on

immediate-release dosage forms, excluding modified-release dosage forms or low-solubility drugs, as indicated by the results from the DCL-Na tablets.

CONCLUSIONS

This study shows that the FDA dissolution media added with 40% ethanol is not representative to analyze the effect observed by alcoholic beverages or the ethanol contained in a standard alcoholic drink. Moreover, ethanol by itself is not representative of the effect produced by an alcoholic beverage on the release profiles (except for tequila), highlighting the importance of using alcoholic beverages and not just ethanol when evaluating their influence on oral dosage forms.

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REFERENCES

1. US, FDA. Alert for healthcare professionals. Alcohol–PalladoneTM interaction, 2005.
2. Anand O, Lawrence XY, Conner DP, Davit BM. Dissolution testing for generic drugs: an FDA perspective. AAPS J, 2011; 13(3): 328.
3. Rubbens J, Brouwers J, Wolfs K, Adams E, Tack J, Augustijns P. Ethanol concentrations in the human gastrointestinal tract after intake of alcoholic beverages. Eur J Pharm, 2016; 86: 91-95.
4. Dawson DA. Methodological issues in measuring alcohol use. Alcohol Research & Health, 2003; 27(1): 18-29.
5. FEUM. Farmacopea de los Estados Unidos Mexicanos. Secretaría de Salud, Mexico, 2014; 11: 1502-1503, 1762-1763, 2061-2063.
6. Fadda HM, Mohamed MA, Basit AW. Impairment of the *in vitro* drug release behaviour of oral modified release preparations in the presence of alcohol. Int J Pharm, 2008; 360(1-2): 171-176.
7. Lennernäs H. Ethanol−drug absorption interaction: potential for a significant effect on the plasma pharmacokinetics of ethanol vulnerable formulations. Mol. Phar, 2009; 6(5): 1429-1440.
8. Walden M., Nicholls FA, Smith KJ, Tucker GT. The effect of ethanol on the release of opioids from oral prolonged-release preparations. Drug De. Ind Pharm, 2007; 33(10): 1101-1111.

9. Oliveira AS, Dalla FM, Mello RO, Mello PA, Tischer B, Costa AB, Barin JS. One-Shot, reagent-free determination of the alcoholic content of distilled beverages by thermal infrared enthalpimetry. Talanta, 2017; 171: 335-340.
10. Kasim NA, Whitehouse M, Ramachandran C, Bermejo M, Lennernäs H, Hussain A. Molecular properties of WHO essential drugs and provisional biopharmaceutical classification. Mol. Pharm, 2004; 1(1): 85-96.
11. Ryan R. Safety of Food and Beverages: Alcoholic Beverages. Encyclopedia of Food Safety. 1 st ed., San Diego California; Academic Press, 2014; 364-370.
12. Bertocchi P, Antoniella E, Valvo L, Alimonti S, Memoli A. Diclofenac sodium multisource prolonged release tablets-a comparative study on the dissolution profiles. J Pharm Biomed Anal, 2005; 37(4): 679-685.
13. Jedinger N, Khinast J, Roblegg E. The design of controlled-release formulations resistant to alcohol-induced dose dumpinga review. Eur J Pharm Biopharm, 2014; 87(2): 217-226.
14. Fagerberg JH, Al-Tikriti Y, Ragnarsson G, Bergström AS. Ethanol effects on apparent solubility of poorly soluble drugs in simulated intestinal fluid. Mol Pharm, 2012; 9(7): 1942-1952.