Lubrizol

TECHNICAL DATA SHEET

TDS-793
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Effect of Alcohol on the Drug Dissolution Properties of Tablets Formulated with Carbopol®* Polymers

INTRODUCTION

The interaction of alcohol with modified release systems may compromise the release-rate controlling mechanism and result in rapid drug release. Referred to as dose dumping, this effect can result in serious or even fatal adverse events in patients or facilitate the intentional misuse and abuse of drugs. Formulations containing active pharmaceutical ingredients (APIs) or controlled release excipients that exhibit improved solubility in alcohol can be more susceptible to dose dumping.

The crosslinked nature and high molecular weight of Carbopol® polymers (up to 3-4 billion) promote swelling, not solubility, in water and polar solvents such as alcohol. This inherent characteristic suggests that Carbopol® polymers would not promote the risk of dose dumping when incorporated into controlled release formulations.

The U.S. Food and Drug Administration (U.S. FDA) supports a regulatory approach that minimizes the risk of alcohol-induced dose dumping. In the case of Palladone™, the potential risk of dose dumping was determined to outweigh the benefits of the drug and the product was withdrawn from the market[1].

The U.S. FDA remains interested in the evaluation of formulations to determine the risk of alcohol-induced dose dumping. Dose dumping studies are included in various FDA issued drug guidance documents and are recommended as part of the drug submission process.

A pharmacokinetic approach to evaluating dose dumping is not always recommended. As a result, alternative test methods have been developed. One method suggested by the Office of Generic Drugs (U.S. FDA) [2] categorizes formulations based on the release profile as a function of ethanol concentration in dissolution medium (5, 20, and 40 % v/v). Following this method, a study was completed using several controlled release tablet formulations containing Carbopol® polymers to evaluate alcohol-induced dose dumping effects.

EXPERIMENTAL

Objective

Evaluate the effect of alcohol content in dissolution media on drug release from extended release tablets formulated with Carbopol® polymers and investigate the risk of alcohol induced dose dumping.

Materials

Guaifenesin (Delta Synthetic, Taiwan), Caffeine anhydrous granular 0.07/0.5 (BASF Corp., Florham Park, NJ), Metformin hydrochloride (Astroquim SA de CV, Ecatapec, Mexico), Carbopol® 971P NF polymer (Lubrizol Advanced Materials, Inc., Cleveland OH), Carbopol® 71G NF polymer (Lubrizol Advanced Materials, Inc., Cleveland OH), Emcocel® 50M microcrystalline cellulose (JRS Pharma LP, Patterson, NY), Microcrystalline cellulose PH-102 (Astroquim SA de CV, Ecatepec, Mexico), Lactose monohydrate (Kerry Bio-Science, Norwich, NY), Colloidal silicon dioxide (Astroquim SA de CV, Ecatepec, Mexico), Magnesium stearate (Ferro Corporation, Walton Hills, OH) (Compañias el Fuerte SA de CV, Miguel Hidalgo, Mexico)

Methods

Extended release tablets of various model drugs, guaifenesin (600 mg), caffeine (200 mg) and metformin hydrochloride (750 mg), were formulated

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using Carbopol® 971P NF and/or 71G NF polymers as matrix forming excipients (10-20% w/w)-Table 1. The drugs and excipients were granulated with deionized water. The dried granules were blended with the extragranular excipients and then compressed, using various standard-concave or capsule-shape punches to accommodate different tablet weights.

Table 1. Composition (%w/w) of Caffeine 200 mg, Metformin 750 mg and Guaifenesin 600 mg Extended Release Tablets

Ingredient (%w/w)	Caffeine	Metformin	Guaifenesin A	Guaifenesin B
Guaifenesin	-	-	75.0	75.0
Caffeine	75.0	-	-	-
Metformin hydrochloride	-	75.0	-	-
Carbopol® 971P NF polymer	10.0	9.0	10.0	20.0
Carbopol® 71G NF polymer**	-	7.0	-	-
Emcocel® 50M microcrystalline cellulose	4.5	-	5.0	4.5
Microcrystalline cellulose PH-102**	-	8.0	-	-
Lactose monohydrate	10.0	-	9.5	-
Colloidal silicon dioxide**	-	0.5	-	-
Magnesium stearate**	0.5	0.5	0.5	0.5
Total	**100**	**100**	**100**	**100**
Tablet weight (mg)	*266.7*	*1000*	*800*	*800*
Dose (mg)	***200***	***750***	***600***	***600***

***Added extragranularly*

The tablets were evaluated for weight variation, mechanical strength, and friability (USP). Drug release was tested in USP apparatus I (100 rpm) or II (50 rpm) in 900 ml of 0.1N HCl solution containing various concentrations of ethanol (0, 20, or 40% v/v).

RESULTS

All formulations were characterized by acceptable tablet properties – Table 2.

Table 2. Physical Properties of the Caffeine, Metformin, and Guaifenesin Tablets

Formulation	Weight (mg) (average ±SD)	Thickness (mm) (average ±SD)	Hardness (kP) (average ±SD)	Friability (%)
Caffeine	266.0±1.5	5.20±0.03	11.45±1.08	0.206
Metformin	1004.0±20.5	5.87±0.01	18.20±4.05	0.130
Guaifenesin A	800.6±5.5	7.38±0.03	16.45±0.80	0.093
Guaifenesin B	798.5±10.4	7.44±0.02	12.25±1.09	0.245

No risk of alcohol induced dose dumping was observed for the drugs/formulations tested, thus indicating the robustness of these extended release systems formulated with Carbopol® polymers.

Slower drug release was observed for caffeine and metformin hydrochloride tablets exposed to 20 or 40% v/v ethanol solution compared with exposure to 0.1N HCl – Figures 1 and 2. This can be explained by a change in drug solubility in the various media. The solubility of caffeine (1:60 water and 1:130 ethanol)[3] or metformin hydrochloride (1:2 water and 1:100 ethanol)[3] is lower in ethanol than in water.

In the case of guaifenesin (solubility 1:33 water, and 1:11 ethanol) [3], slightly slower drug release in the presence of alcohol was observed for tablets containing 10% w/w Carbopol® polymer – Figure 3. No alcohol effect was observed for the guaifenesin tablets formulated with 20% Carbopol® polymer – Figure 4.

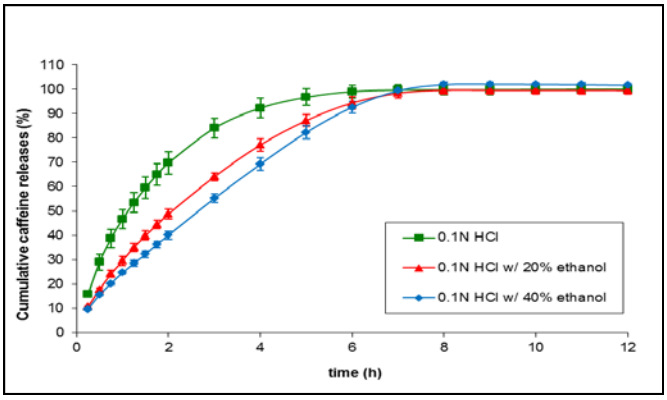

Figure 1. Influence of ethanol on the dissolution of caffeine (200 mg) tablets with 10% w/w Carbopol® 971P NF polymer in 0.1N HCl [Apparatus II, 50 rpm]

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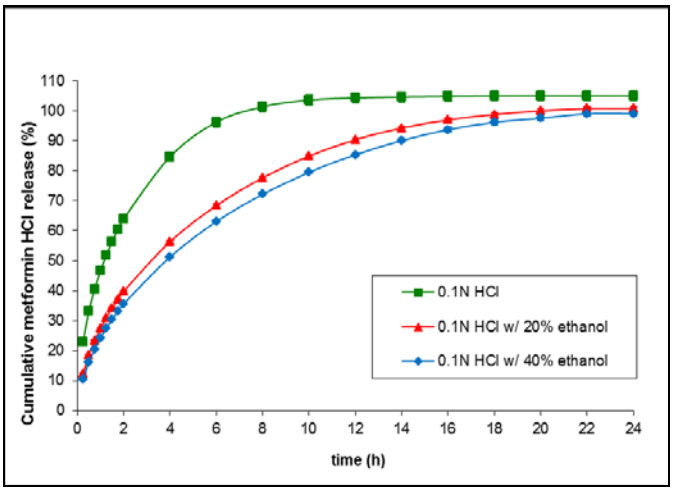

Figure 2. Influence of ethanol on the dissolution of metformin hydrochloride (750 mg) tablets with 9% w/w Carbopol® 971P NF polymer and 7% w/w Carbopol® 71G NF polymer in 0.1N HCl [Apparatus I, 100 rpm]

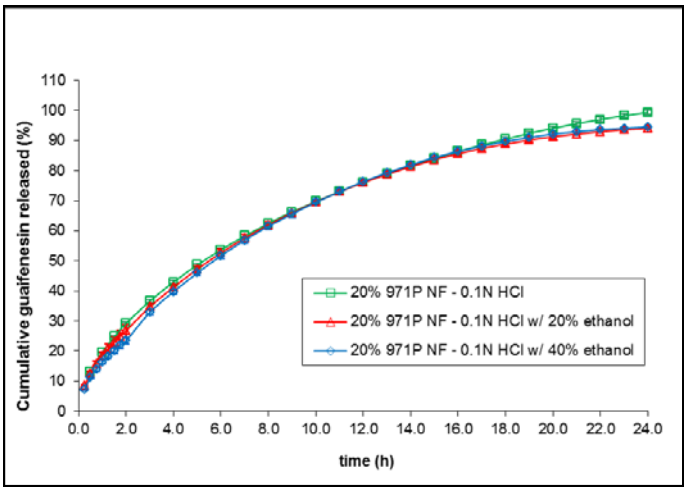

Figure 4. Influence of ethanol on the dissolution of guaifenesin (600 mg) tablets with 20% w/w Carbopol® 971P NF polymer in 0.1N HCl [Apparatus II, 50 rpm]

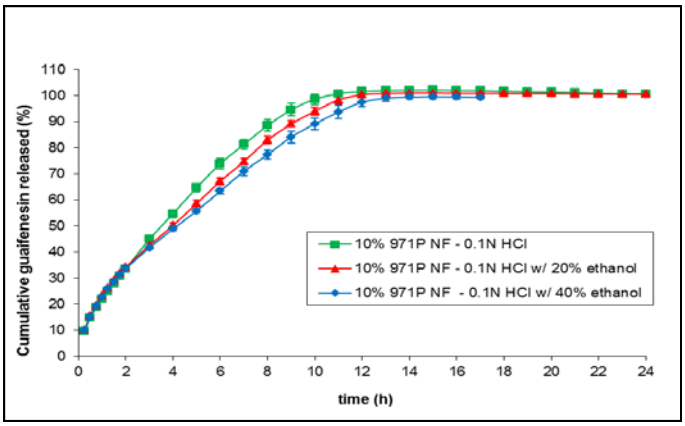

Figure 3. Influence of ethanol on the dissolution of guaifenesin (600 mg) tablets with 10% w/w Carbopol® 971P NF polymer in 0.1N HCl [Apparatus II, 50 rpm]

CONCLUSIONS

In vitro dissolution testing of extended release tablets of guaifenesin, caffeine and metformin hydrochloride formulated with Carbopol® polymers (10 - 20% w/w) did not indicate any alcohol-induced dose-dumping effect. Similar or slower drug release was observed when tablets were exposed to 0.1N HCl or 0.1N HCl with up to 40% v/v alcohol content.

REFERENCES

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2. Pharmaceutical Science Advisory Committee Meeting, October 25-26, 2005, http://www.fda.gov/ohrms/dockets/ac/cder05.html#PharmScience
3. Moffat, A.,Osselton, N., and Widdop, B.(2004). Clarke's Analysis of Drugs and Poisons 3rd Ed., The Pharmaceutical Press, London.

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