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Hydro-Alcoholic Media: An Emerging *in vitro* Tool for Predicting Dose Dumping from Controlled Release Matrices

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Abstract: In present study, the release profiles of hydrochlorothiazide from polyacrylic acid polymer (carbopol 71G) matrices in hydro-ethanolic media were done. Percent drug released increased with increasing levels of ethanol in the dissolution media, but there was no direct correlation with the drug's solubility in the media. Although, the result showed that an initial rapid release was observed in the media containing 30% ethanol, this could not be regarded as dose dumping of hydrochlorothiazide. Release in this medium was considered to be both erosion and diffusion-mediated, in contrast to the release in 0, 10, 20, 40 and 50% ethanol media, where erosion-controlled release dominated. Image analysis of matrix swelling and swelling kinetics suggests a complex interaction between ethanol, hydrochlorothiazide and Carbopol 71 G accounting for the suppressed drug release in the ethanolic-media.

Key words: Carbopol 71 G, hydro-ethanolic media, sustained release, hydrochlorothiazide, matrices

INTRODUCTION

The report of US FDA in July 2005 that a potentially serious dose dumping of an opiod analgesic, hydromorphone from a controlled release capsule was possible if consumed with significant quantity of alcoholic beverage is generating interest among scientists (Roberts *et al*., 2007). However, studies in human volunteers involving co-administration of a drug and alcohol poses very serious ethical challenges, it is therefore appropriate to consider in vitro studies to provide insight on the release mechanism in hydro-alcoholic media, thereby guiding formulators in assessing the potential for alcohol-related dose dumping (Roberts *et al*., 2007).

For many reasons, oral drug delivery continues to be the preferred route of drug administration and the use of hydrophilic matrices in achieving this is increasingly becoming important especially in controlling the release rate of drugs from solid dosage forms (Vazquez *et al*., 1992; Varshosaz *et al*., 2006; Sujja-areevath *et al*., 1996; Emeje *et al*., 2006a, b). These systems are attractive approaches from economic as well as process development view point (Juarez *et al*., 2001; Emeje and Kunle, 2004; Conti *et al*., 2007). A sustained release matrix tablet consists of a compressed compact containing a mixture of one or more bioactive agent (s) with one or more matrix former (s), which retards drug release (Conti *et al*., 2007). Hydrophilic swellable polymers have widely been used to control the release of drugs from matrix tablet formulations in the last three decades (Sujja-areevath *et al*., 1996; Emeje *et al*., 2005; Emeje *et al*., 2006) and the increasing need for suitable polymers to achieve the desired drug release profile makes pharmaceutical research to widely screen a large variety of both synthetic and natural polymers which show drug release retarding ability.

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Historically, carbopol polyacrylic acid polymers have demonstrated many useful performance properties in tablet applications (Aditya *et al*., 2004; Grabovac *et al*., 2005; Ganesh *et al*., 2006). They are useful at low levels (1-3%) as binders and at higher levels (5-30%), they achieve modified or even zero order controlled release of bioactives. Carbopol 71 G is one member of the carbopol family of polymers that is suitable for use in oral dosage forms since it was polymerized in ethyl acetate, a relatively non toxic solvent. It is a water-swellabe high molecular weight polyacrylic acid cross linked with allyl ethers of pentaerythriol (Anonymous, 2006). Due to their extremely efficient thickening and gelling characteristics, carbopol resins have been widely used in various pharmaceutical applications, including beads, gels and ointments (Ganesh *et al*., 2006). Information available to us from the manufacturer indicate that carbopol 71G is the latest polyacrylic acid derivative and literature survey reveal that very few reports exist on it (Varshosaz *et al*., 2006). In the present study, we assess the influence of alcohol on the rate and mechanisms of release of hydrochlorothiazide from carbopol 71G hydrophilic matrices.

MATERIALS AND METHODS

Materials

Carbopol 71G was a gift from Noveon, USA, Hydrochlorothiazide was a gift from Evans Nig. Plc. Absolute ethanol was standard reagent grade.

Preparation of Compacts

Tablets comprising 99.0 mg C71, 99.0 mg HCTZ and 2 mg magnesium stearate (carbopol-HCTZ matrices) or 198 mg C71 and 2 mg magnesium stearate (carbopol tablet) were prepared by direct compression on a manesty single punch tablet press (THP, Shangai, China) fitted with 8.5 mm diameter, flat punches. Tablets were produced to crushing strengths in the range of 20.0-22.5 kN.

Dissolution Studies

Drug release was monitored using the British Pharmacopoeia (2004) Apparatus 1 (Erweka, GmbH, Germany) with rotation speed of 50 rpm, in 500 mL of medium at 37±0.5°C. Media comprised acetate buffer (BP) with 0, 10, 20, 30, 40 or 50% (v/v) absolute ethanol. For each medium, 6 tablets were tested and drug release was monitored spectrophotometrically at 299 nm (Shimadzu, Japan).

Data Analysis

Drug release data were analyzed using a modified power law equation (Eq. 1) proposed by Ford *et al*. (1991).

$$Q = k (t - l)^n$$

Where,

Q = Percentage of drug release at time t,
k = Constant incorporating structural and geometric property of the devices,
l = Lag time and n is the release exponent, indicative of the drug release mechanism.

Drug Solubility

The solubility of the drug in the different hydro-alcoholic dissolution media was determined spectrophotometrically (299 nm) at ambient temperature, using a solution of known concentration of HCTZ in the different media as a standard. To determine the solubility, the method of

Roberts *et al.* (2007) was slightly modified; a saturated solution was prepared by adding excess of drug to 10 mL of media. This solution was then shaken for 4 h and 5 mL was centrifuged (Beckman, London) at 3500 rpm for 5 min. The concentration of HCTZ in the clear supernatant was spectrophotometrically determined.

Swelling Studies

The dynamics of the swelling process were investigated by placing each compact (either carbopol-HCTZ matrix or carbopol tablet alone) in a small plastic Petri dish and adding 10 mL of medium at ambient temperature. The study was performed using the 0 and 50% ethanol media. Images of the compacts were captured (using a digital camera Fuji film, 7.5 mp) at varying time intervals; 0, 5, 10, 15, 20, 25, 35, 45, 60, 75, 90, 105 and 120 min.

Compact Swelling

Image analysis during C71G-HCTZ matrix and C71G tablet swelling showed increases in both axial and radial dimensions (Table 1, Fig. 1). Percent normalized size increase was calculated as the radial length increase with respect to the initial value to avoid error due to lens effect. Swelling rate was also calculated from the percent normalized size increase.

The differences in swelling rates significantly noticed within the first 30 min indicate a variation in the interaction between media and tablets in the initial period of contact, which maybe due to a different speed of medium penetration (Fig. 2). Such behavior may depend on a slower initial interaction between the ethanol and C71G and could equally account for the initial rapid release observed during dissolution. After the initial period, the formation of a less porous and stronger gel layer, which limits fluid uptake, could increase the diffusion pathway and also decrease gel erosion. The images in Fig. 1 are evidence of this theory, as it is possible to observe the polymer-drug and polymer-ethanol interactions as evidenced by the differences in tablet hydration. In the absence of drug (B2 and EB2), the presence of ethanol (EB2) resulted in faster hydration and spread of the polymer (increase in size). The presence of drug in the polymer (B1 and EB1) shows evidence of interactions between drug, polymer and ethanol, as the images show that the presence of ethanol prevented the rapid spread of the polymer earlier noticed with carbopol tablets alone. The boarder between medium and tablet was clearly visible in the 0% ethanolic medium (B1 and B2) and ethanolic medium with drug (EB1) until about 75 min when these boundary disappeared. However, the same boundary became less visible in the carbopol tablets without drug (EB2) from about 15 min in the medium. After 25 min in this medium, the tablets were characterized by slower swelling rate.

Drug Release

Generally, the presence of ethanol in the dissolution medium suppressed drug release. With the exception of 30% ethanol, retardation of drug release was proportional to the ethanol levels in the medium (Fig. 3). There was a clear evidence of no dose dumping. Release profiles in all the media were

Table 1: Effect of ethanol on the axial expansion of the C71G tablets/matrices

Time (min)	B1 (cm)	B2 (cm)	EB1 (cm)	EB2 (cm)
5	1.3±0.00	1.2±0.00	1.1±0.00	1.2±0.00
10	1.3±0.05	1.2±0.05	1.1±0.00	1.2±0.00
15	1.4±0.00	1.1±0.02	1.3±0.00	1.2±0.10
20	1.5±0.10	1.0±0.00	1.3±0.00	1.2±0.00
25	1.5±0.10	1.0±0.00	1.2±0.05	1.3±0.00
35	1.6±0.05	1.1±0.05	1.2±0.00	1.3±0.00
45	1.6±0.05	1.0±0.00	1.2±0.00	1.3±0.10
60	1.6±0.00	0.9±0.00	1.2±0.00	1.3±0.00
75	1.8±0.05	1.8±0.00	1.5±0.00	1.4±0.00
90	1.8±0.00	1.8±0.20	1.6±0.05	1.6±0.05
105	1.9±0.01	1.8±0.10	1.6±0.00	1.9±0.00
120	1.9±0.05	1.8±0.05	1.7±0.02	1.9±0.05

(n = 3±standard deviation)

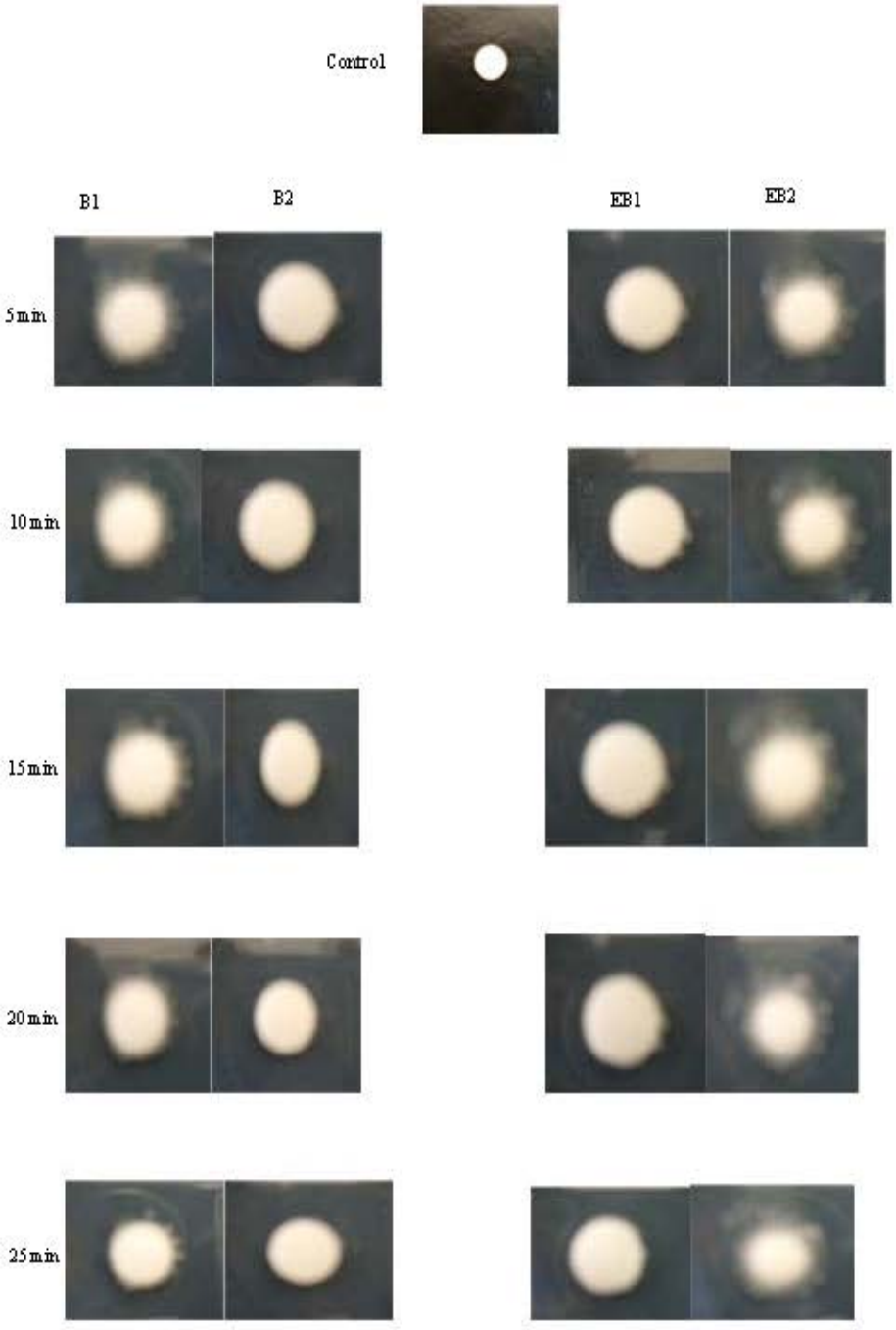

Fig. 1: Contined

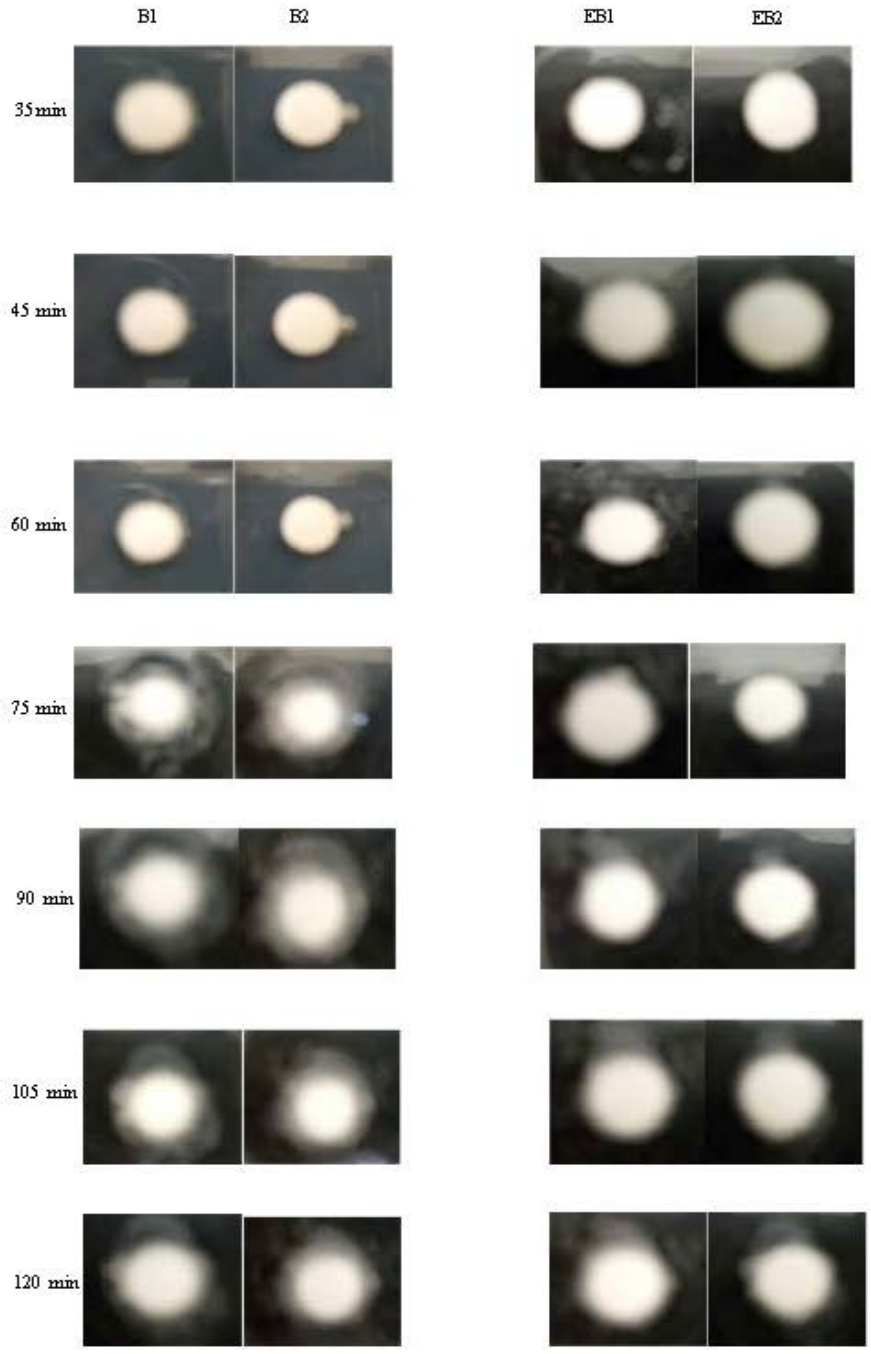

Fig. 1: Swelling behaviour difference with matrix swelling in 0% ehtanol

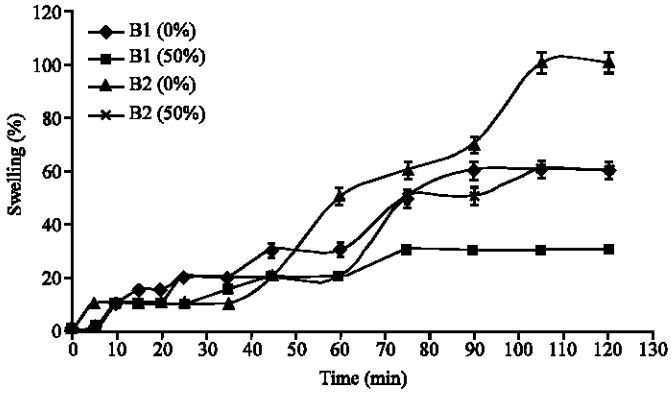

Fig. 2: Effect of Alcohol on the swelling property of C71G tablets and matrices

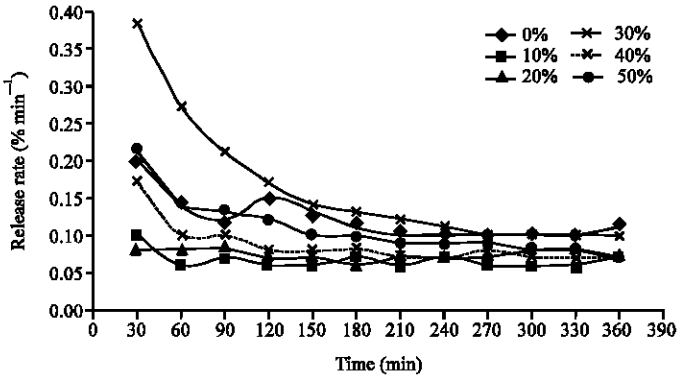

Fig. 3: The effect of time on the release rate of HCTZ from C71G matrices in various hydro-alcoholic dissolution media

characterized by an initial rapid release with rate progressively reducing over time, suggesting that diffusion controlled release mechanism predominated. The 50% ethanol data had the lowest correlation, this maybe indicative of non-uniform gel generation causing inconsistency in drug release.

Analysis of release data using equation 1 shows that with the exception of 30% ethanol medium which has the lowest n value indicative of diffusion and erosion mechanism, release mechanism in the other media appears to be predominated by diffusion and erosion (Ford *et al*., 1991). The release rates in the various media indicate a similar trend for all media after 30 min, although rates were different particularly for the 30% ethanol medium. Significant differences occurred during the first 30 min when the release in 30% ethanol medium was much higher, although this could not be equated to dose dumping especially as the batch with 0% ethanol medium had the highest drug release (Cmax) at end of dissolution. After 1 h in the 0% ethanol medium, it became difficult to accurately measure the tablet size due to the visual absence of a well defined tablet-medium boundary. For 0% ethanol medium, after 1 h in static conditions, the superficial gel layer has a low polymer concentration and low viscosity, probably with a higher erosion rate, which agrees with the power law analysis of drug release. This observation is consistent with that of Roberts *et al*. (2007).

In general, the result suggests that for C71G-HCTZ matrices with C71G concentrations > 50%, swelling properties are controlled by the polymer and the dissolution medium. These results are consistent with those by Vargas and Ghaly (1999), where the authors reported the release profile of theophylline to be independent of the diluent type for HPMC K4M concentrations above 30-40%.

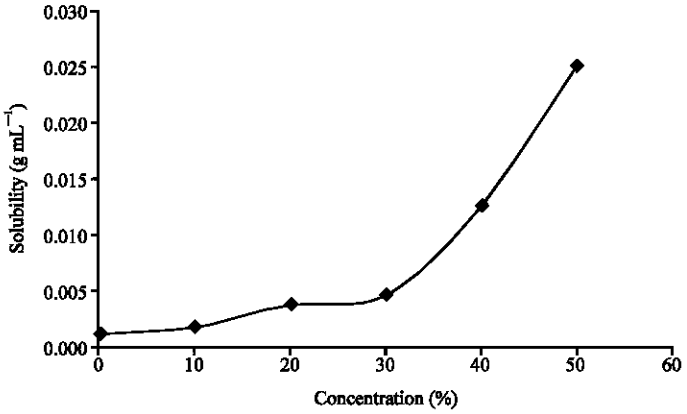

Fig. 4: Effect of alcohol concentration on the solubility of HCTZ in sifferent hydro-alcohlic media

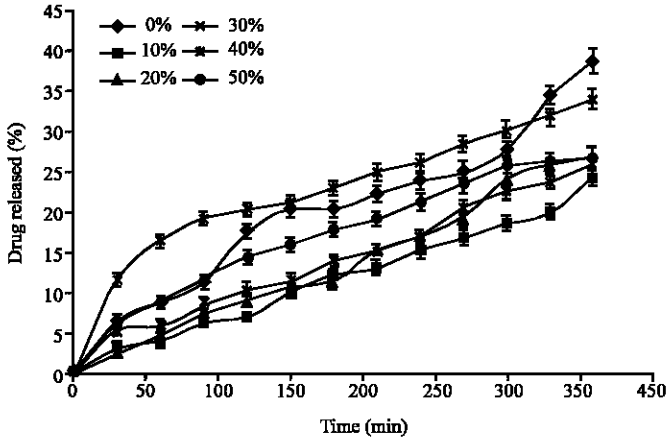

Fig. 5: Effect of concentrations of alcohol on the release profile of HCTZ from C71G tablet

Drug Solubility

The solubility of HCTZ measured in each of the six dissolution media are presented in Fig. 4. The result shows that there was no direct correlation between the solubility and the percent drug released, as shown in Fig. 5. The solubility of the drug in the media appears not be able to account for the different release behaviors observed during the dissolution studies. This observation is contrary to that of Roberts *et al*. (2007), where the authors reported a direct correlation between the solubility and dissolution of aspirin in different hydro-ethanolic media, thereby adducing aspirin's release to its increased solubility in the ethanolic media. Therefore, different release behaviors observed in the different dissolution media and the rapid release observed in the 30% ethanol medium suggests that some other factors, such as polymer-drug and/or polymer-alcohol interactions rather than solubility, influence the release of HCTZ from carbopol 71G matrices.

CONCLUSIONS

Present study have shown that hydro-alcoholic media can affect the kinetics and mechanism of drug release from matrix-based controlled release formulations in a manner related to the ethanol

content. Release retardation could have been caused by polymer-drug, or polymer-alcohol interactions rather than the drug solubility in the dissolution medium. Polymer-alcohol interaction maybe responsible for the initial rapid release observed in the first 30 min. In these studies, 30% ethanol appeared to be the threshold for polymer-alcohol interaction. Image analysis of the matrix swelling behavior supports the theory that the ethanol interaction with carbopol, particularly in the initial period of contact, was crucial in drug release, but did not result in a dose dumping effect.

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REFERENCES

Aditya, S.T., K.A. Mehta, L.L. Augsburger and S.W. Hoag, 2004. Influence of methacrylic and acrylic acid polymers on the release performance of weakly basic drugs from sustained release hydrophilic matrices. J. Pharm. Sci., 939: 2319-2331.

Anonymous, 2006. Application of carbopol 71G NF polymer in controlled release tablets. No. 20. Noveon™ Technical Bulletin.

Conti, S., L. Maggi, L. Segale, E. OchoaMachiste, U. Conte, P. Grenier and G. Vergnault, 2007. Matrices containing NaCMC and HPMC 1. Dissolution performance characterization. Int. J. Pharm., 333: 136-142.

Emeje, M.O. and O.O. Kunle, 2004. Effects of two surfactants and mode of incorporation on the compaction characteristics of the hot water leaf extract of *ficus sur*. J. Nutraceuticals, Medical and Functional Foods, 3/4: 147-154.

Emeje, M.O., O.O. Kunle and S.I. Ofoefule, 2005. The effect of molecular size of cmc on the rates of hydration, matrix erosion and drug release from its matrix. Drug Delivery Technol., 3: 56-61.

Emeje, M.O., O.O. Kunle and S.I. Ofoefule, 2006a. Effect of the molecular size of carboxymethylcellulose and some polymers on the sustained release of theophylline from a hydrophilic matrix. Acta Pharm., 56: 325-335.

Emeje, M.O., O.O. Kunle and S.I. Ofoefule, 2006b. Compaction characteristics of ethylcellulose in the presence of some channeling agents. AAPS Pharm. Sci. Technol., 7 Article 58.

Ford, J.L., K. Mitchell, P. Rowe, D.J. Armstrong, P.N.C. Elliott, C. Rostron and J.E. Hogan, 1991. Mathematical modeling of drug release from hydroxypropylmethyl cellulose matrices: Effect of temperature. Int. J. Pharm., 71: 95-104.

Ganesh, S., B. Bommareddya, A.S. Paker-Leggs, K.K. Saripella and S.H. Neaua, 2006. Extruded and spheronized beads containing Carbopol® 974P to deliver no electrolytes and salts of weakly basic drugs. Int. J. Pharm., 321: 62-71.

Grabovac, V., D. Guggi and A. Bernkop-Schnu¨ rch, 2005.Comparison of the mucoadhesive properties of various polymers. Adv. Drug Delivery Rev., 57: 1713-1723.

Juarez, H., G. Rico and L. Villafuerte, 2001. Influence of admixed carboxymethylcellulose on release of 4-aminopyridine from HPMC matrix tablets. Int. J. Pharm., 216: 115-125.

Mitchell, K., J.L. Ford, D.J. Armstrong, P.N.C. Elliott, C. Rostron and J.E. Hogan, 1990. The influence of additives on the cloud point, disintegration and dissolution of hydroxypropylmethylcellulose gels and matrix tablets. Int. J. Pharm., 66: 233-242.

Roberts, M., M. Cespi, J.L. Ford, A.M. Dyas, J. Downing, L.G. Martini and P.J. Crowley, 2007. Influence of ethanol on aspirin release from hypromellose matrices. Int. J. Pharm., 332: 31-37.

Sujja-areevath, J., D.L. Munday, P.J. Cox and K.A. Khan, 1996. Release characteristics of diclofenac sodium from encapsulated natural gum mini-matrix formulations. Int. J. Pharm., 139: 53-62.

Vargas, C.I. and E.S. Ghaly, 1999. Kinetic release of theophylline from hydrophilic swellable matrices. Drug Dev. Ind. Pharm., 25: 1045-1050.

Varshosaz, J., N. Tavakoli and F. Kheirolahi, 2006. Use of hydrophilic natural gums in formulation of sustained-release matrix tablets of tramadol hydrochloride. AAPS Pharm. Sci. Technol., 7 Article 24.

Vazquez, M.J., B. Perez-Marcos, J.L. Gomez-Amoza, R. Martinez-Pacheco, C. Souto and A. Concheiro, 1992. Influence of technological variables on release of drug from hydrophilic matrices. Drug Dev. Ind. Pharm., 20: 2519-2526.