doi.org/10.36721/PJPS.2020.33.3.REG.923-928.1

Gelation and rheological characterization of Carbopol® in simulated gastrointestinal fluid of variable chemical properties

Rania Hamed[1]*, Areej Kamal[1] and Ahlam Zaid Alkilani[2]
[1]Department of Pharmacy, Faculty of Pharmacy, Al-Zaytoonah University of Jordan, Amman, Jordan
[2]Department of Pharmacy, Faculty of Pharmacy, Zarqa University, Zarqa, Jordan

Abstract: Carbopol® is a hydrophilic polymer commonly used in the preparation of oral controlled-release matrix tablets. These matrices are subjected to dissolution testing to investigate the rate and mechanism of drug release. The rate of drug release from these matrices is influenced by the viscoelastic properties of the gel layer formed upon hydration and surrounded tablet core. This study evaluates the gelation behavior and rheological characterization of Carbopol® in dispersion media, of varied chemical properties, commonly used in dissolution testing. The rheological properties of Carbopol® polymer underwent gelation were determined using a controlled-stress rheometer. Carbopol® gelation was not found in simulated gastric fluid of low pH (1.2-5.0) and simulated intestinal fluid of pH (5.0-6.5) during fasted (Fa) and fed (Fe) conditions. However, in water and at high pH (6.8-7.8), gelation occurred in phosphate buffers of high buffering capacity (β). Furthermore, no gelation was found in sodium chloride solutions of different ionic strengths (μ). These results highlight the importance of investigating the gelation behavior and rheological characterization of Carbopol® in dispersion media prior to dissolution testing. These preliminary studies can give an insight on the formation/absence of the gel layer around Carbopol® matrices which is responsible for controlling the release of drugs.

Keywords: Carbopol®, gelation, viscoelastic properties, simulated gastrointestinal fluid, dissolution.

INTRODUCTION

Hydrophilic polymers such as polyacrylic acid (Fayed *et al.*, 2013), methyl cellulose derivatives (Gavan *et al.*, 2017), xanthan (Ofori-Kwakye *et al.*, 2016), dextran (Abioye and Kola-Mustapha, 2016), and poly(ethylene oxide) (Zhang *et al.*, 2016) are ordinarily used in the development of oral controlled-release matrix tablets. The rate of drug release from these hydrophilic matrix tablets is usually influenced by the viscoelastic properties of the gel layer formed upon hydration surrounded the dry core of the tablets, where gel layer controls the release of drug by acting as a barrier for drug diffusion (Hamed *et al.*, 2016a). The viscoelastic properties of this gel layer depend on the type, molecular weight, hydrophilicity, degree of crosslinking, degree of substitution and concentration of polymer(s) used in matrix development, where all these parameters may influence the swelling and erosion of matrices (Colombo *et al.*, 2000; Ghori and Conway, 2015; Körner *et al.*, 2009).

Dissolution studies are generally carried out to investigate the rate of release of drug-loaded matrix tablets using dissolution media of different chemical composition such as 0.1 N HCl, acetate and phosphate buffers (pH 4.5-7.4), and distilled water (Hiremath and Saha, 2008; Kulinowski *et al.*, 2015; Savaşer *et al.*, 2013). Studies have shown that the chemical properties of the matrix-forming polymer affect the rate of drug release (Lubrizol, 2011; Majumder *et al.*, 2016). For instance, due to the anionic nature of polyacrylic acid, Carbopol®-based matrix tablets exhibit pH-dependent drug release profiles (Lubrizol, 2011; Obeidat *et al.*, 2015). Whereas, owing to the nonionic nature of methyl cellulose derivative, hydroxypropyl methylcellulose (HPMC)-based matrix tablets exhibit pH-independent drug release profiles (Majumder *et al.*, 2016). In addition to the chemical properties of the polymer, it has been shown that the pH and buffer capacity (β) with total ionic strength (μ) of the dissolution media can influence the rate of drug release (Asare-Addo *et al.*, 2013; Asare-Addo *et al.*, 2011; Hamed *et al.*, 2017).

Recently, dissolution studies of hydrophilic matrix tablets were carried out using media that better simulate the gastrointestinal fluid (GIF). This necessitates using media of various buffer composition and chemical properties to simulate the typical properties of the gastrointestinal tract (GIT) during fasted (Fa) and fed (Fe) conditions (Hamed *et al.*, 2017; Hiremath and Saha, 2008; Klancar *et al.*, 2015). However, the effect of the chemical properties of these media on the gelation behavior of matrix–forming polymer and hence the viscoelastic properties of gels formed upon dispersing these polymers in simulated GIF is still not very clear.

Therefore, the objective of this study was to evaluate the gelation behavior and rheological properties of gels formed using the hydrophilic polymer, Carbopol®, commonly used in the preparation of orally controlled-release matrix tablets. Owing to the ability of the hydrophilic polymers, particularly anionic polymers, to

**Corresponding author:* e-mail: rania.hamed@zuj.edu.jo

change the rate of drug release as a response to the changes in the chemical properties of the dissolution media, Carbopol® has been proposed to test whether it can form gels in dissolution media of simulated GIF with various chemical properties. Thus, a question certainly arises regarding whether Carbopol® forms gels in these dissolution media or not.

In this study, Carbopol® 971 P was dispersed in simulated GIF composed of different buffer types and concentrations and various salt concentrations to attain the typical chemical ranges (pH, buffer capacity (β), and ionic strength (μ)) of gastrointestinal tract (GIT) during Fa and Fe conditions. The dispersion of Carbopol® in these dissolution media may lead to gel formation (gelation). Carbopol® that underwent gelation was characterized in terms of their viscoelastic properties (elastic G' and viscous G" shear moduli). The shear moduli G' and G" were then correlated to the chemical properties of dispersion media. Although Carbopol® has been the subject of many studies; however, issues concerning gelation and rheological behavior of this polymer in dissolution media of varied chemical properties still remain unclear. Studying these mechanical properties is important to predict the mechanism of the drug release from Carbopol®-based drug delivery systems. To our knowledge, no study has extensively investigated the gelation and rheological characterization of Carbopol® in media commonly used in dissolution testing.

MATERIALS AND METHODS

Carbopol® 971P was a kind gift from Lubrizol® (OH, USA). Chemical reagents used in the preparation of the dispersion media were of analytical grade. Double-distilled water was obtained using a water-distilling apparatus.

Methods

Dispersion media

Dispersion media of simulated GIF described previously (Hamed *et al.*, 2017) were used to prepare Carbopol® gels. Media were prepared without adding pepsin, pancreatin, lecithin, and bile salts (i.e. blank dispersion media). Dispersion media used to simulate gastric fluid were simulated gastric fluid sine pepsin (SGFsp, pH 1.2), and during Fa and Fe conditions (FaSSGF (pH 1.6) and FaSSGF (pH 5.0), respectively). Dispersion media used to simulate intestinal fluid during Fa and Fe conditions were FaSSIF (pH 6.5) and FeSSIF (pH 5.0), respectively. To further evaluate the effect of pH on Carbopol® gelation, phosphate buffers of high concentration (100mM) and pH 7.2 and 7.8 were used which simulate the pH of the ileum and colon, respectively, in Fa condition. In addition, the effect of β on Carbopol® gelation was evaluated using phosphate buffers of constant pH (6.8) at low (6.25 and 25mM), medium (50mM), and high (100 mM) phosphate concentrations. These phosphate buffers obtain media with variable β range of 0.003-0.047 M/ΔpH. Furthermore, the influence of μ on Carbopol® gelation was evaluated using salt solutions of sodium chloride (NaCl) concentration range of 0.1 to 0.4 N of μ range of 0.1-0.4 M. Salt solutions of NaCl were used to attain the typical μ range of the GIF during Fa and Fe conditions (Hamed *et al.*, 2017). Double-distilled water, lacking β and μ, was used as a reference for phosphate buffers and NaCl solutions. The chemical properties of the dispersion media are summarized in table 1.

Preparation of Carbopol® gels

Carbopol® gels (1% *w/w*) were prepared by dispersing 1 g of Carbopol® 971P in an appropriate quantity of dispersion medium with continuous gentle stirring to form gels. Gels were then kept overnight for complete gel hydration.

Rheological characterization of Carbopol® gels

The gelation of Carbopol® was evaluated using a controlled-stress rheometer (CSR, Anton Paar MCR 302; Graz, Austria) with 50mm cone-plate geometry, 1° cone angle and 0.1mm gap maintained at 37±1°C. Rheological characterization of Carbopol® gels was performed as previously described (Hamed *et al.*, 2016b). Briefly, about 1g of gel was placed onto the lower plate. Gels were left for ~2min to relax and equilibrate with temperature. G′ and G″ were determined using RheoPlus 3.62 software. The linear region (LR) of the viscoelastic moduli G' and G" and critical strain (γ_c) were evaluated over a strain range of 0.001 to 100% at a frequency of 6.28 rad/s. A strain of 0.1, within the LR, was selected for the frequency-dependent G′ and G″ experiments over a frequency range of 0.1-100 rad/s. G′ reflected the solid or elastic behavior and G″ reflected the liquid or viscous behavior of the gels. Rheological characterization of Carbopol® gels was performed for at least three independent samples. Data are presented as mean ± SD, calculated using Excel.

RESULTS

Dispersion of Carbopol® in simulated gastric fluid (SGFsp, FaSSGF, and FeSSGF) and simulated intestinal fluid (FaSSIF and FeSSIF) led to no gelation. In addition, no gelation was observed for Carbopol® in phosphate buffers at low concentrations (6.25 and 12.5mM) and low buffer capacity (0.003-0.006 M/ΔpH). Furthermore, the dispersion of Carbopol® in NaCl solutions of ionic strength range 0.1-0.4 M resulted in no gelation. Whereas, dispersion of Carbopol® in phosphate buffers at high concentrations (25, 50 and 100mM) and high buffering capacity (0.012-0.047 M/ΔpH) and 100mM phosphate buffer of high pH (7.2 and 7.8) and high buffering capacity (0.058 and 0.032 M/ΔpH, respectively) led to

gelation. table 1 illustrates the gelation behavior of Carbopol® gels in these dispersion media.

Frequency–dependence rheological characterization of Carbopol® gels was conducted in the LR. Here, the frequency–sweep studies of gels were conducted at a constant low oscillatory strain of 0.1, within the LR, to assure that the structure of the gels is not damaged during oscillation (Jain *et al.*, 2016). At the end of this region (LR) and at a point known as critical strain (γ_c), both G' and G" drop by 10% of their constant values (Durmuş *et al.*, 2007; Jain *et al.*, 2016). The LR and γ_c of Carbopol® gels in the dispersion media are illustrated in table 1.

Fig. 1A illustrates the rheological properties of Carbopol® gels in 25, 50 and 100 mM phosphate buffers (pH 6.8) over 0.1-100 rad/s. The elastic modulus G' dominated the viscous modulus G", which indicates the formation of gel network with more elastic behavior. In addition, the shear modulus G' of Carbopol® gels increased in the order 25 mM >50mM >100mM. Thus, G' increases with increasing the buffering capacity of phosphate buffers. This suggests that high buffering capacity increases the rigidity of Carbopol® gels. Whereas G" of the three Carbopol® gels were nearly similar, particularly at low frequencies (<10 rad/s). A linear positive correlation was found between G' and the concentration of phosphate buffers. Alternatively, a negligible correlation was found between G" and the concentration of phosphate buffers (fig. 1B). G' and G" at 6.31 rad/s (~1 Hz) were used in this correlation. In addition, the dispersion of Carbopol® in water resulted in highest gelation, where viscoelastic properties (G' and G") were the highest among those of Carbopol® in phosphate buffers (25-100mM) (fig. 1A).

Fig. 2A illustrates the rheological properties of Carbopol® gels in 100mM phosphate buffers pH 7.2 and 7.8. Carbopol® gels exhibited viscoelastic properties with more elastic behavior (G' dominated G"), similar to that found in 25-100mM phosphate buffers (pH 6.8). When

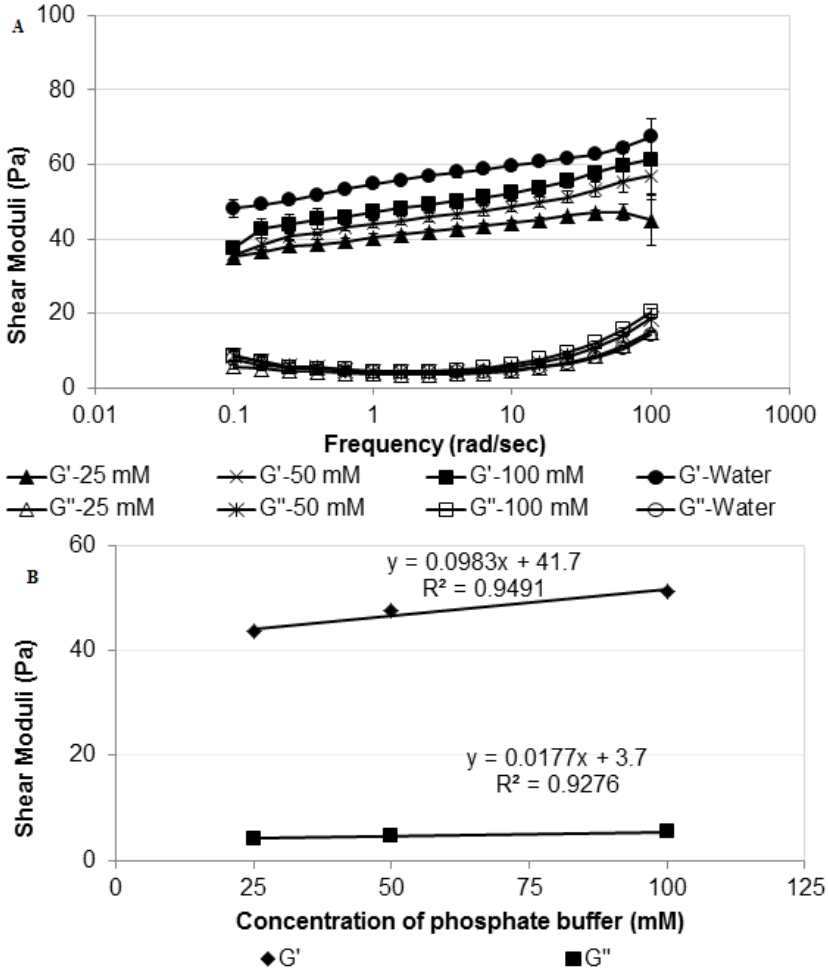

Fig. 1: (A) Viscoelastic properties of Carbopol® gels in phosphate buffers 25, 50 and 100 mM (pH 6.8) and water over a frequency range 0.1-100 rad/s. Data are plotted in semi-log scale and presented as mean ± SD (n = 5); (B) Dependence of G' and G" at 6.31 rad/s on the concentration of phosphate buffers (25-100 mM).

comparing G' and G" of Carbopol® gels in 100mM (pH 7.2 and 7.8) to those in 100mM (pH 6.8), G' increased in the order of pH 6.8 >7.2 >7.8. A linear positive correlation between G' at 6.31 rad/s and the pH of phosphate buffers was found (fig. 2B). Whereas the frequency–dependent G" of Carbopol® gels in phosphate buffers (pH 6.8-7.8) were superimposable, particularly at low frequencies (<6.31 rad/s), and then increases for pH 7.2 and 7.8. Therefore a relatively weak linear correlation was found between G" and the pH of phosphate buffers at 6.31 rad/s (fig. 2B).

DISCUSSION

Carbopol® is a crosslinked polyacrylic acid polymer. Carbopol® absorbs water and gets hydrated. It swells up to 1000 times its former volume. Carbopol® solution is a rheology modifier which thickens in the presence of an excess of electrolytes and high pH due to the ionization of the carboxylic acid groups (Di Giuseppe *et al.*, 2015; Samani *et al.*, 2003). In this study, the rheological properties of Carbopol® gel was described as a function of pH, buffer concentration, and ionic strength of the dissolution media, maintaining constant Carbopol® concentration of 1% w/w.

The lack of Carbopol® gelation in the dispersion media of a pH range 1.2-6.8 is consistent with previously reported results, where it has been shown that Carbopol® dispersion requires a neutralization up to pH 7.0 to form a gel (Speedy, 2014). In addition, the absence of Carbopol® gelation in NaCl solutions is due to the fact that salts decrease the efficiency of gelation of Carbopol® polymers (Rathapon *et al.*, 2005; Sharmin *et al.*, 2010; Taylor and Bagley, 1974).

The gelation of Carbopol® in 25, 50, and 100mM phosphate buffers (pH 6.8) can be related to the high

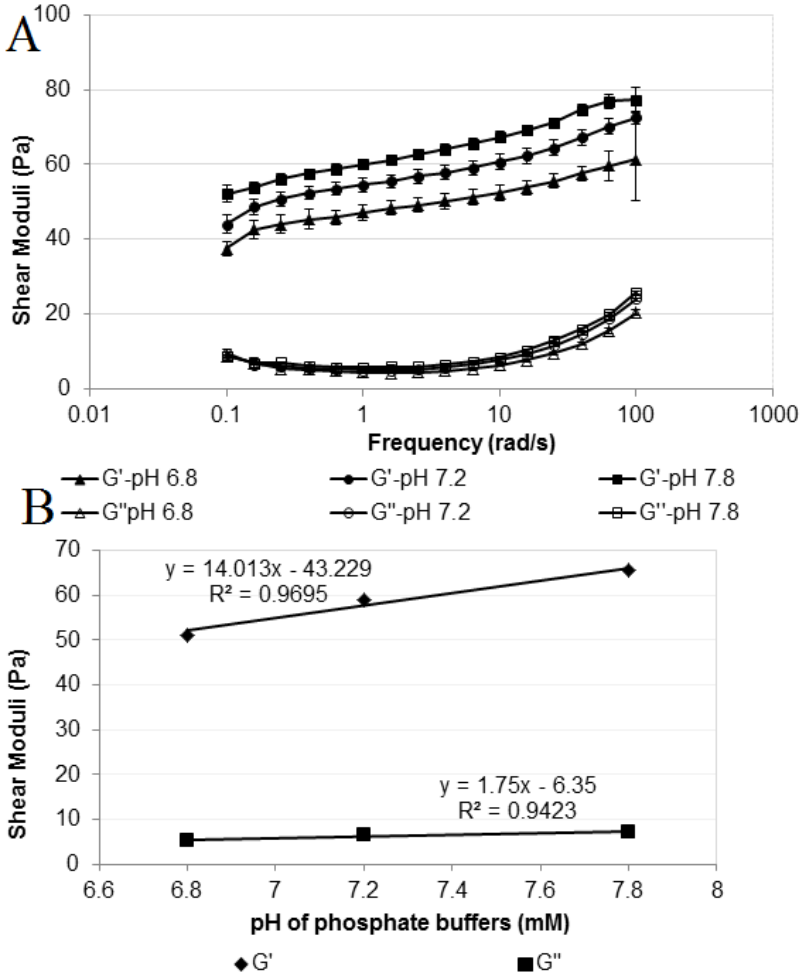

Fig. 2: (A) Viscoelastic properties of Carbopol® gels in phosphate buffers 100mM (pH 7.2 and 7.8) over a frequency range 0.1-100 rad/s. and the viscoelastic properties of phosphate buffer 100mM of pH 6.8 was added to the figure for comparison. Data are plotted in semi-log scale and presented as mean ± SD (n=4); (B) Dependence of G' and G" at 6.31 rad/s on the pH of phosphate buffers (6.8-7.8 mM).

Table 1: Chemical properties (pH, β, and μ), gelation, linear viscoelastic region (LR), and critical strain (γ_c) of Carbopol® gels in each dispersion medium.

Dispersion medium	pH	β (M/ΔpH)	μ (M)	Gelation	LR (%)	γ_c (%)
SGFsp	1.2 ± 0.1	-	0.118	No	-	-
FaSSGF	1.6 ± 0.1	-	0.070	No	-	-
FeSSGF	5.0 ± 0.1	0.025	0.273	No	-	-
FaSSIF	6.5 ± 0.1	0.120	0.200	No	-	-
FeSSIF	5.0 ± 0.1	0.130	0.304	No	-	-
Phosphate buffer 6.25mM	6.8 ± 0.1	0.003	0.013	No	-	-
Phosphate buffer 12.5mM	6.8 ± 0.1	0.006	0.025	No	-	-
Phosphate buffer 25mM	6.8 ± 0.1	0.012	0.050	Yes	0.0025–1.0	1.0
Phosphate buffer 50mM	6.8 ± 0.1	0.024	0.100	Yes	0.0016–1.0	1.0
Phosphate buffer 100mM	6.8 ± 0.1	0.047	0.200	Yes	0.0010–1.0	1.0
Phosphate buffer 100mM	7.2 ± 0.1	0.058	0.244	Yes	0.0010–1.0	1.0
Phosphate buffer 100mM	7.8 ± 0.1	0.037	0.283	Yes	0.0039–1.0	1.0
0.1 N NaCl	-	-	0.1	No	-	-
0.2 N NaCl	-	-	0.2	No	-	-
0.4 N NaCl	-	-	0.4	No	-	-
Water	-	-	-	Yes	0.0039–1.0	1.0

buffering capacity, where Merclin *et al.* have reported that the anionic nature of Carbopol® can maintain stable gels at high buffering capacity which may contribute in maintaining the pH value desired for gelation (Merclin *et al.*, 2004).

In phosphate buffers (pH 7.2 and 7.8), the combined effect of the high pH and buffering capacity led to Carbopol® gelation, where it has been shown that gelation increases with increasing pH (Islam *et al.*, 2004). The rigidity of Carbopol® gels increased with increasing the pH of phosphate buffers, where repulsion between the negatively charged carboxylic acid of Carbopol® at high pH resulted in maximum uncoiling system which becomes closely packed and entangled (Islam *et al.*, 2004; Merclin *et al.*, 2004).

CONCLUSION

The evaluation of Carbopol® gelation in dispersion media, used frequently in dissolution studies of oral controlled–release tablets, are essential for predicting the rate and mechanism of drug release from these matrices. Results showed that Carbopol® gelation only occurs in dispersion media with high pH and high buffering capacity. Carbopol® gels in these media exhibited viscoelastic properties with more elastic behavior. However, no gelation was found in dispersion media of pH 1.2 to 6.8 and in media of high ionic strength. Nevertheless, gelation was found in dispersion media of pH 6.8 of high buffering capacity. Our findings provide valuable guidance for understanding the rheological properties of the gel layer that surrounds the tablet core and controls drug release for better selection of appropriate dissolution media during the development process of controlled–release matrix tablets made of Carbopol®.

REFERENCES

Abioye AO and Kola-Mustapha A (2016). Formulation studies on ibuprofen sodium-cationic dextran conjugate: Effect on tableting and dissolution characteristics of ibuprofen. *Drug Dev. Ind. Pharm.*, **42**(1): 39-59.

Asare-Addo K, Conway BR, Larhrib H, Levina M, Rajabi-Siahboomi AR, Tetteh J, Boateng J and Nokhodchi A (2013). The effect of pH and ionic strength of dissolution media on *in-vitro* release of two model drugs of different solubilities from HPMC matrices. *Colloids Surf. B. Biointerfaces*, **111**: 384-91.

Asare-Addo K, Levina M, Rajabi-Siahboomi AR and Nokhodchi A (2011). Effect of ionic strength and pH of dissolution media on theophylline release from hypromellose matrix tablets Apparatus USP III, simulated fasted and fed conditions. *Carbohydr. Polym.*, **86**(1): 85-93.

Colombo P, Bettini R, Santi P and Peppas NA (2000). Swellable matrices for controlled drug delivery: Gel-layer behaviour, mechanisms and optimal performance. *Pharm. Sci. Technolo. Today.*, **3**(6): 198-204.

Di Giuseppe E, Corbi F, Funiciello F, Massmeyer A, Santimano T, Rosenau M and Davaille A (2015). Characterization of Carbopol® hydrogel rheology for experimental tectonics and geodynamics. *Tectonophysics*, **642**: 29-45.

Durmuş A, Woo M, Kasgoz A, Macosko CW and Tsapatsis M (2007). Intercalated linear low density polyethylene (LLDPE)/clay nanocomposites prepared with oxidized polyethylene as a new type compatibilizer: Structural, mechanical and barrier properties. *Eur. Polym. J.*, **43**(9): 3737-49.

Fayed MH, Mahrous GM, Ibrahim MA and Sakr A (2013). Influence of Carbopol 71G-NF on the release

of dextromethorphan hydrobromide from extended-release matrix tablets. *Pharm. Dev. Technol.*, **18**(5): 971-81.

Gavan A, Porfire A, Marina C and Tomuta I (2017). Formulation and pharmaceutical development of quetiapine fumarate sustained release matrix tablets using a QbD approach. *Acta. Pharm.*, **67**(1): 53-70.

Ghori MU and Conway BR (2015). Hydrophilic matrices for oral control drug delivery. *Am. J. Pharmacol. Sci.*, **3**(5): 103-9.

Hamed R, Al Baraghthi T, Alkilani AZ and Abu-Huwaij R (2016). Correlation between rheological properties and in vitro drug release from penetration enhancer-loaded Carbopol® gels. *J. Pharm. Innov.*, **11**(4): 339-51.

Hamed R, Al Baraghthi T and Sunoqrot S (2018). Correlation between the viscoelastic properties of the gel layer of swollen HPMC matrix tablets and their in vitro drug release. *Pharm. Dev. Technol.*, **23**(9): 838-48.

Hamed R, AlJanabi R, Sunoqrot S and Abbas A (2017). The effect of pH, buffer capacity and ionic strength on quetiapine fumarate release from matrix tablets prepared using two different polymeric blends. *Drug Dev. Ind. Pharm.*, **43**(8): 1330-42.

Hiremath PS and Saha RN (2008). Controlled release hydrophilic matrix tablet formulations of isoniazid: Design and *in vitro* studies. *AAPS Pharm. Sci. Tech.*, **9**(4): 1171-8.

Islam MT, Rodriguez-Hornedo N, Ciotti S and Ackermann C (2004). Rheological characterization of topical carbomer gels neutralized to different pH. *Pharm. Res.*, **21**(7): 1192-1199.

Jain S, Patel N, Madan P and Lin S (2016). Formulation and rheological evaluation of ethosome-loaded carbopol hydrogel for transdermal application. *Drug Dev. Ind. Pharm.*, **42**(8): 1315-24.

Klančar U, Baumgartner S, Legen I, Smrdel P, Kampuš NJ, Krajcar D, Markun B and Kocevar K (2015). Determining the polymer threshold amount for achieving robust drug release from HPMC and HPC matrix tablets containing a high-dose BCS class I model drug: *in vitro* and *in vivo* studies. *AAPS Pharm. Sci. Tech.*, **16**(2): 398-406.

Körner A, Piculell L, Iselau F, Wittgren B and Larsson A (2009). Influence of different polymer types on the overall release mechanism in hydrophilic matrix tablets. *Molecules*, **14**(8): 2699-716.

Kulinowski P, Woyna-Orlewicz K, Rappen G-M, Haznar-Garbacz D, Węglarz WP and Dorożyński PP (2015). An understanding of modified release matrix tablets behavior during drug dissolution as the key for prediction of pharmaceutical product performance–case study of multimodal characterization of quetiapine fumarate tablets. *Int. J. Pharm. Tech.*, **484**(1-2): 235-45.

Lubrizol. Tablets, Formulating Controlled Release Capsules with Carbopol® Polymers. Lubrizol Pharmaceutical Bulletin, 2011.

Majumder T, Biswas GR and Majee SB (2016). Hydroxy propyl methyl cellulose: Different aspects in drug delivery. *J. Pharm. Pharmacol.*, **4**(8): 381-5.

Merclin N, Bramer T and Edsman K (2004). Iontophoretic delivery of 5-aminolevulinic acid and its methyl ester using a carbopol gel as vehicle. *J. Control Release*, **98**(1): 57-65.

Obeidat WM, Nokhodchi A and Alkhatib H (2015). Evaluation of matrix tablets based on Eudragit® E100/Carbopol® 971P combinations for controlled release and improved compaction properties of water soluble model drug paracetamol. *AAPS Pharm Sci Tech.*, **16**(5): 1169-1179.

Ofori-Kwakye K, Mfoafo KA, Kipo SL, Kuntworbe N and El Boakye-Gyasi M (2016). Development and evaluation of natural gum-based extended release matrix tablets of two model drugs of different water solubilities by direct compression. *Saudi Pharm. J.*, **24**(1): 82-91.

Rathapon A, Sirivat A and Vayumhasuwan P (2005). Viscoelastic properties of Carbopol 940 gels and their relationships to piroxicam diffusion coefficients in gel bases. *Pharm. Res.*, **22**(12): 2134-40.

Samani SM, Montaseri H and Kazemi A (2003). The effect of polymer blends on release profiles of diclofenac sodium from matrices. *Eur. J. Pharm. Biopharm.*, **55**(3): 351-5.

Savaser A, Tas C, Bayrak Z, Ozkan CK and Ozkan Y (2013). Effect of different polymers and their combinations on the release of metoclopramide HCl from sustained-release hydrophilic matrix tablets. *Pharm. Dev. Technol.*, **18**(5): 1122-30.

Sharmin N, Elias-Al-Mamun M and Jalil RU (2010). A novel method to study the effect of pH and excipients on water uptake and swelling behaviour of Carbopol polymers. *Bangl. Pharm. J.*, **3**(2): 1-7.

Speedy L (2014). The effects of shear on neutralized carbomers in aqueous conditions. Monash University, Australia, semanticscholar.org

Taylor N and Bagley E (1974). Dispersions or solutions? A mechanism for certain thickening agents. *J. Appl. Polym. Sci.*, **18**(9): 2747-2761.

Zhang F, Meng F, Lubach J, Koleng J and Watson N (2016). Properties and mechanisms of drug release from matrix tablets containing poly (ethylene oxide) and poly (acrylic acid) as release retardants. *Eur. J. Pharm. Biopharm.*, **105**: 97-105.