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Characterization of Thermosensitive Gels for the Sustained Delivery of Dexketoprofen Trometamol for Dermal Applications

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Abstract

In this report, the release properties of dexketoprofen (DEX) from propylene glycol (PG) and poloxamer gel systems were investigated. After formulation of gel systems composed of poloxamer 338 and PG, rheological experiment was conducted to investigate effects of PG on temperature-dependent viscoelasticity of poloxamer 338-based gels. It appeared that PG and poloxamer 338 could form gel systems with good thermosensitive properties, the gel system containing 2.5% and 5% PG showed similar thermosensitive properties. In vitro release studies were performed at two different temperatures, room temperature (25 ˚C ± 0.1 ˚C) and skin temperature (32 ˚C ± 0.1 ˚C), using Franz diffusion cells and showed decreased the release rate of DEX at skin temperature (32 ˚C) according the thermosensitive properties of poloxamer 338. Also released amount of DEX were decreased due to the use of high poloxamer concentration. At both temperatures, the highest release (39.35% at 32 °C and 31.78% at 25 ˚C in 8 hours) was obtained with 20%poloxamer + 5%PG, the lowest release (29.46% at 32 °C and 26.23% at 25 ˚C in 8 hours) was obtained with 25% poloxamer + 5% PG. After the drug release amount was examined, kinetic models (zero order, first order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas) were investigated. In both temperatures (25 ˚C and 32 ˚C), the in vitro drug release profiles of poloxamer based formulations were fit to the Korsmeyer-Peppas kinetic model.

1. Introduction

Topical application of NSAIDs for the treatment of pain is quite common for providing locally sufficient drug concentration and reducing systemic side effects (Barkin, 2015). Different topical dosage forms could be used such as ointments, emulsions or gel systems for this purpose. Thermosensitive gels are widely studied formulations in topical application of NSAIDs.

Thermosensitive gels exhibit sol-gel transition depending on the ambient temperature and accordingly change their properties such as viscosity and drug release (Gandra, 2013; Leung et al., 2020). They can remain in the application area for a longer period of time with in situ gelling at body temperature and perform more effective drug release (Inal & Yapar, 2013). The most common polymers used to prepare thermosensitive gel formulations are poloxamers. Poloxamers are widely used in pharmaceutical and biomedical fields since they are synthetic polymers that show thermoresponsive behavior with a sensitive $T_{sol\text{-}gel}$ (Soliman, Ullah, Shah, Jones & Singh, 2019). Poloxamers are nonionic polyoxyethylene –polyoxypropylene – polyoxyethylene (PEO n –PPO n – PEO n) tri-block copolymers (Ricci, Lunardi, Nanclares & Marchetti, 2005). The chemical structure of these copolymers comprising two hydrophilic chains (polyoxyethylene chains at both terminals) and a hydrophobic chain (polyoxypropylene chain in the core) provides amphiphilicity (Fakhari, Corcoran & Schwarz, 2017). Thus, it can be used in various formulations as gelling agents, surfactants, dispersing agents, emulsifying agents, solubility enhancers and bioavailability enhancers (Lin & Kawashima, 1985). These copolymers are available as registered trademarks (eg, Pluronic®, Synperonic® or Koliphor®) and can be present in liquid, paste and solid forms.

The aqueous solutions of poloxamers have thermosensitive properties and interactions between different segments of the copolymer result in thermogelation (Dumortier, Grossiord, Agnely & Chaumeil, 2006). As the system fluidity decreases suddenly, it leads to formation of gel by aggregating at a certain temperature upon heating and micelles are formed by poloxamers. On the other hand when the gel is cooled, it returns to its original sol state, which means that this process is reversible (Soliman et al., 2019). The gel formation dependent on increased temperature is also associated with poloxamer concentration. Fakhari et al. found that the minimum concentration required for gel formation of the commonly used poloxamer 407 was 12.6% w/v (Fakhari et al., 2017).

There are many studies on gel formulations of poloxamers in the literature. The physical properties of the gels were investigated by using different poloxamer types and additives. Studies have shown that propylene glycol (PG) increases the adhesive properties of the poloxamer gel formulations (Gandra, 2013). In addition, mucoadhesive polymers such as hydroxypropyl methylcellulose (HPMC) increases the viscosity of the gel formulation. This has been reported to be an advantage for a more successful treatment (Inal & Yapar, 2013). PG is a non-toxic, biocompatible additive widely used for topical dosage forms and can be used for many purposes in the pharmaceutical field such as

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solubilizer, stabilizer, moisturizer etc. (Abrantes, Duarte & Reis, 2016; Dragicevic & Maibach, 2015). Trottet et al. showed that the increase in the percentage of PG increases drug permeation (Trottet, Merly, Mirza, Hadgraft & Davis, 2004).

Dexketoprofen trometamol (DEX) is a non-steroidal anti-inflammatory drug (NSAID) that has been in clinical use since 1996. DEX, which is enantiomer and salt of ketoprofen, has better absorption properties than ketoprofen (Öztürk, Yenilmez & Yazan, 2019). DEX has analgesic effects and is used as a treatment for painful musculoskeletal disease (Ilbasmis-Tamer, 2017). Gel formulations of DEX's are commercially available under the various tradenames.

In this study, we developed and characterized thermosensitive gel formulations of DEX containing different proportions of poloxamer 338 and PG. We also evaluated the effects of factors such as temperature, viscosity, different percentage of poloxamer and PG on drug release. The mucoadhesive properties of poloxamer gels prepared with a different preparation technique were also examined.

2. Material and Method

2.1. Materials

Dexketoprofen trometamol was obtained from Hunngshi Shixing Pharmaceutical Co. Ltd. (China). Poloxamer 338 (Kolliphor® 338) was provided by BASF (Germany). Propylene glycol was purchased from Aklar Kimya (Turkey). The commercial product containing an equal amount of the DEX belongs to the Nobel Pharmaceuticals (Turkey). All the other chemicals and reagents used were of pharmaceutical and analytical grade.

2.2. Methods

2.2.1. Preparation of gel formulations

DEX was dissolved in distilled water at room temperature, and then PG was added. While this mixture was being mixed with a top stirrer at 500 rpm, the poloxamer was slowly added. The mixture was stirred for 45 min until it was formed. All the formulations were prepared in the same manner.

2.2.2. Measurement of viscosity

By employing a stress-controlled cone and a plate rheometer, the viscosity measurements of gel formulations were achieved (Brookfield, DV-III Rheometer with spindle type CPE-52) at two different temperatures, 25 °C and 32 °C. Ostwald-de-Waele equation (Power-Law) was applied to viscosity values to compare flow consistency (Eq. (1))

$\sigma = k.\gamma^n$ (Eq.1)

where σ (N/m^2) is the shear stress, γ(1/sec) is the shear rate, k$(Pa.s)^n$ is the consistency index, n is the flow behavior index (de Francisco et al., 2019).

2.2.3. In vitro release study

The release study was performed using Franz diffusion cells. The diffusional sectional area was 1 $cm^{2,}$ and the receptor phase volume was 2.5 mL. Cellulose nitrate membrane was used to determine the release properties. Samples of the formulation (0.2 mL) were placed in the donor compartment. By employing a magnetic bar at 100 rpm, phosphate buffer (pH 5.2) was used as the receptor compartment. At certain time intervals, samples were withdrawn from receptor compartment, and then

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replaced with an equal volume fresh buffer. The released amount of DEX from gel formulation was determined using UV-Vis spectrophotometry at λ = 260 nm.

2.2.4. Drug release kinetic and mechanism

In order to understand drug release pattern, the in vitro drug release data were fitted to different kinetic models such as zero order, first order, Higuchi model, Hixson-Crowell and Korsmeyer-Peppas with DDsolver (Jain & Jain, 2016; Zhang et al., 2010). R^2_{adj} (close to 1), AIC (lower), and MSC (higher) factors were used to determine the mathematical model with higher goodness of fit to drug release data (Sorasitthiyanukarn, Rojsitthisak & Rojsitthisak, 2017).

3. Results and discussion

3.1. Viscosity measurement

The thermosensitive gel formulation should be in sol state at room temperature and form gel at the skin temperature after application for topical application. Therefore, viscosities of the formulations were measured at two different temperatures, 25 °C and 32 °C. The measurement results are given in Figure 1. As is clearly seen from the graphs, the viscosity increased with the increase in temperature as expected.

In the present study, since all formulations show non-newtonian flow, their viscosities were compared using the power consistency index (K) obtained from the Power-Law equation (Table 1). The prepared gel formulations had higher K values compared to that of commercial product. However, the K value in 25 °C increased with the increase of the poloxamer concentration. An increase in the K value indicates the increase of the viscosity. The increase in the PG ratio in the formulations resulted in a decrease in the K value. This means that viscosity was reduced. Here, n<1 indicates that the formulation has shear thinning properties.

While the formulations prepared were determined to show shear thinning flow properties, it observed that the commercial product had shear thickening properties due to the n value of greater than 1 (de Francisco et al., 2019).

Poloxamer gel formulations have the advantage of being used as a controlled drug delivery system, which is liquid at room temperature or below but transforms into a gel structure at body temperature (Tirnaksiz & Robinson, 2005). The formulation, which has the highest viscosity and stronger gel properties at body temperature, is more successful holding of the drug in the formulation (Dewan et al., 2015). Fakhari et al. stated that with the increase in the concentration of poloxamer, a decrease in $T_{sol\text{-}gel}$, and an increase was observed in the drug stored. Higher poloxamer concentration resulted in gel formation at lower temperatures. Stronger gel formation was observed using higher concentrations of poloxamer (Fakhari et al., 2017). With stronger gel formation, drug release rate was more controlled and the side effect was reduced and treatment was performed in the desired area. Similar to previous studies, in the current study, as the poloxamer concentration increased, the viscosity increased and the total release amount of DEX was decreased.

Ricci et al. examined the effect of poloxamer concentration on viscosity in gel formulations containing lidocaine hydrochloride. They concluded that the increase in polymer concentration increased the viscosity of the gels, thereby changing the release properties of lidocaine from the formulation.

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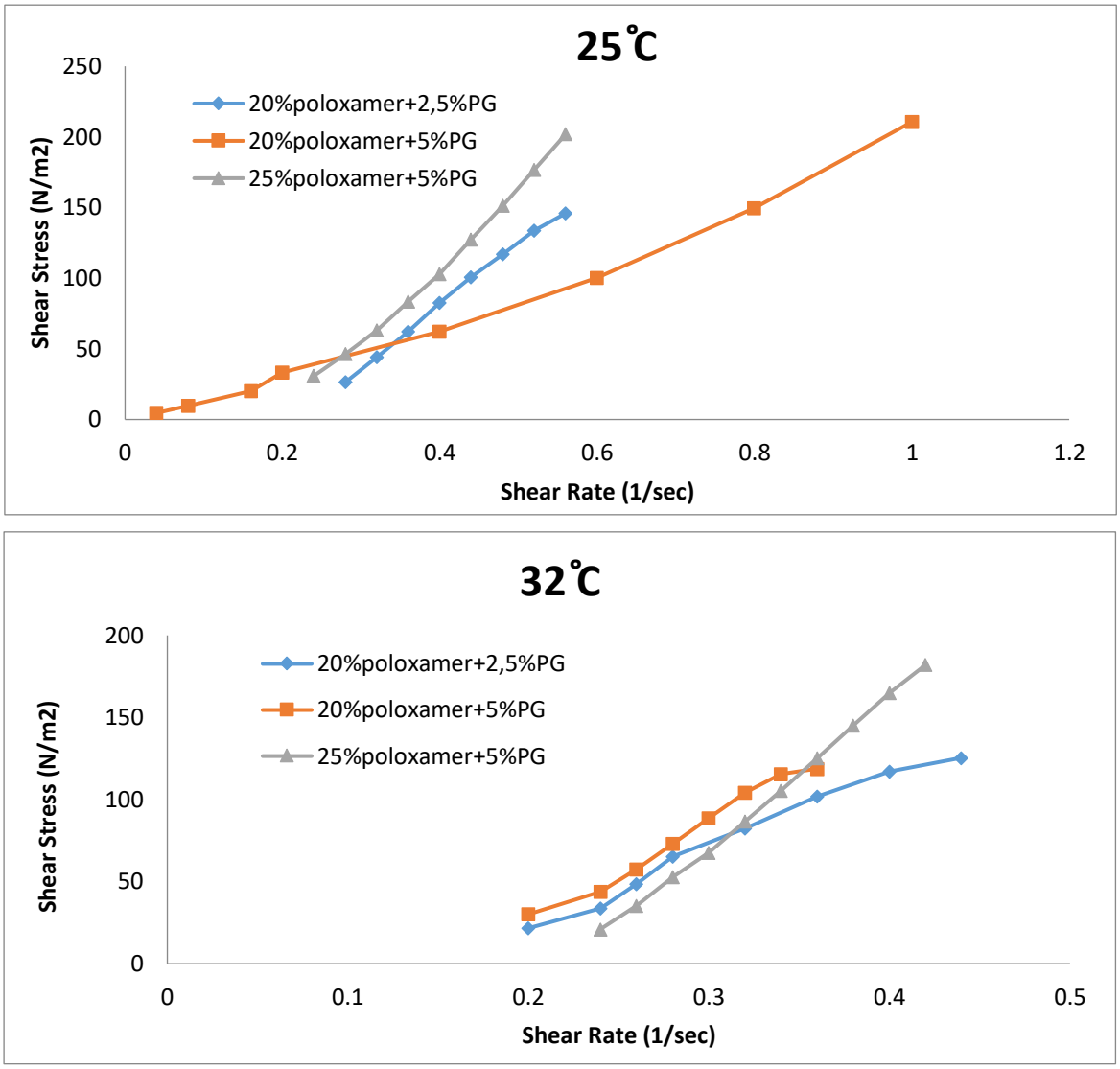

Figure 1. Shear rate (1/sec) against shear stress (N/m^2) profiles of the prepared formulations obtained from viscosity measurements at two different temperatures, 25 °C and 32 °C.

Also, according to the study, gel viscosity decreased with increasing shear rate and the solutions became more fluid. Poloxamer gels are pseudoplastic; therefore, their viscosity decreases when the shear is deformed (Ricci, Bentley, Farah, Bretas & Marchetti, 2002).

With the increase in temperature, the K value of commercial product decreased and the K value of poloxamer based formulations increased as expected. While at higher temperatures -around gelling temperature (T_g) and higher- poloxamer solutions behave as thermoplastic gels (Jalaal, Cottrell, Balmforth & Stoeber, 2017). This provides a significant advantage in controlling drug release at body temperature after easy application of the formulation at room temperature (Tirnaksiz & Robinson, 2005).

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Table 1: Parameters for Power-Law equations at two different temperatures, 25 °C and 32 °C.

Power-law		Commercial product	20%poloxamer +5%PG	20%poloxamer +2,5%PG	25%poloxamer +5%PG
25 °C	K±SE	19.147 ± 0.015	194.044 ± 0.021	676.993 ± 0.069	759.018 ± 0.019
	n±SE	2.378 ± 0.053	0.851 ± 0.020	0.401 ± 0.029	0.453 ± 0.009
	R^2±SE	0.997 ± 0.014	0.860 ± 0.037	0.918 ± 0.048	0.990 ± 0.016
32 °C	K±SE	10.285 ± 0.049	1734.156 ± 0.072	975.752 ± 0.109	5271.550 ± 0.111
	n±SE	2.086 ± 0.137	0.390 ± 0.020	0.418 ± 0.038	0.251 ± 0.015
	R^2±SE	0.972 ± 0.048	0.957 ± 0.029	0.865 ± 0.064	0.947 ± 0.055

'K'is the consistency index of power law equation,' n' is the flow behavior index, 'R^2'is coefficient of determination,'SE' is standard error

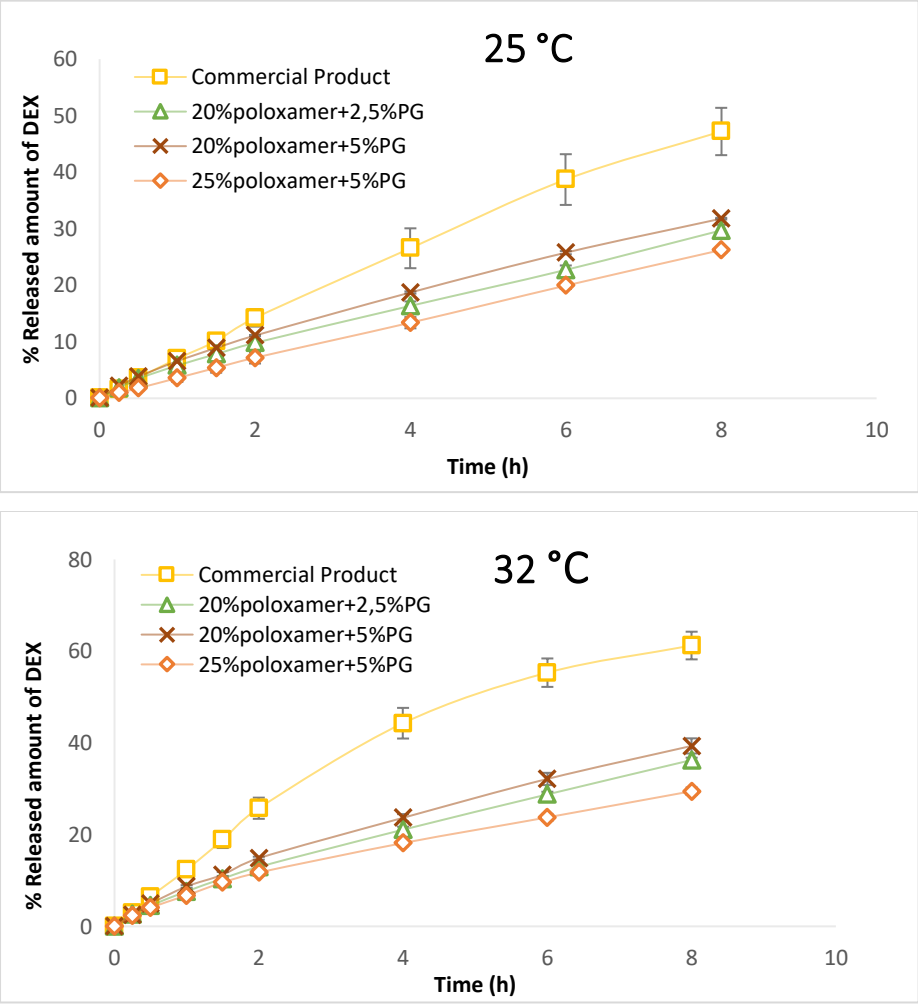

Figure 2. In vitro drug release profiles of DEX from poloxamer gel system through cellulose nitrate membrane at two different temperatures, 25 °C and 32 °C.

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3.2. In vitro release study

Measurements of in vitro drug release from all the prepared formulations were done in phosphate buffer of pH 5.2 and at two different temperature (25 °C and 32 °C), the data are represented in Figure 2. At both temperatures, the release rate of DEX from the gel structure was increased with the increase of the concentration of PG and decrease of the concentration of poloxamer. The commercial product showed the highest release rate compared to the prepared formulations.

Gels prepared using poloxamer consist of micelles and water channels, and drug release occurs through these channels. Drug release from poloxamer gels is affected by many factors such as the viscosity of the gels, the size of the aqueous channels and the distribution of the drug in the micelle and aqueous regions. Since poloxamers form viscous isotropic liquid crystal gels are composed of micelles, the drug is likely to be released from the extra micelle channels of the gel by a diffusion mechanism (Djekic, Čalija & Medarević, 2020; Mendonsa et al., 2018). According to this study, drug release from poloxamer gels is controlled by drug diffusion from the gel matrix. Also, poloxamers are used for gelling as the temperature increases and showing the liquid state at room temperature.This make easy application at room temperature, and after application at body temperature, the system can increase consistency that promotes long-term retention and modified drug release (de Francisco et al., 2019).

At both temperatures, the highest release (39.35% at 32 °C and 31.78% at 25 °C) was obtained with 20%poloxamer+5%PG, the lowest release (29.46% at 32 °C and 26.23% at 25 °C) was obtained with 25%poloxamer+5% PG. It is observed that with the increase in poloxamer concentration, the release decreased. In the study of Parhi et al., it is reported that with a higher poloxamer concentration, a longer diffusion path was formed and gel porosity decreased (Parhi & Suresh, 2015). Accordingly, the decrease in drug release rate can be explained by lower porosity and long diffusion path.

In this study, two formulations (20% poloxamer + 2.5% PG and 20% poloxamer + 5% PG) containing the same amount of poloxamer and different amounts of PG were used to investigate the effect of PG on release. PG is widely used as a penetration enhancer in preparations used for dermatological purposes. It can be used with other penetration enhancers or alone (Dragicevic & Maibach, 2015). The mechanism of action is to penetrate the stratum corneum by dividing the stratum corneum or increasing the solubility in the stratum corneum (Trottet et al., 2004). The formulation containing high amount of PG showed the high drug release. This was attributed to the increase of PG due to decrease of formulation viscosity.

3.3. Evaluation of drug release with kinetic models

Different kinetic models (Zero order, First order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas) were applied to in vitro release data to evaluate the release of DEX from the poloxamer gel system with DDsolver. As for the kinetic evaluation, it was found that the Korsmeyer-Peppas kinetic was predominantly valid for poloxamer based gel formulations at 25 °C (Table 2).

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Table 2: Results of fitting factors obtained by applying kinetic models to in vitro drug release data at 25 °C.

25 °C		Commercial Product	20%poloxamer +2.5%PG	20%poloxamer +5%PG	25%poloxamer +5%PG
Zero order	R^2_{adj}	0.9910	0.9773	0.9682	0.9921
	AIC	27.1368	27.4411	32.7943	16.7559
	MSC	4.5970	3.4974	3.0736	4.5412
First order	R^2_{adj}	0.9961	0.9889	0.9864	0.9930
	AIC	19.6051	20.8722	25.0591	10.5411
	MSC	5.4339	4.2273	3.9330	5.2318
Higuchi	R^2_{adj}	0.8780	0.9194	0.9330	0.8611
	AIC	52.6836	39.5284	39.5713	42.4732
	MSC	1.7585	2.1544	2.3206	1.6838
Hixson-Crowell	R^2_{adj}	0.9971	0.9858	0.9815	0.9932
	AIC	13.3468	23.0573	27.8996	13.1450
	MSC	6.1292	3.9845	3.6174	4.9425
Korsmeyer-Peppas	R^2_{adj}	0.9897	0.9968	0.9996	0.9988
	AIC	30.6039	8.9564	-5.9313	0.3315
	MSC	4.2118	5.5513	7.3764	6.3662
	n	0,9213	0,7806	0,7706	0,9655

*"R^2adj" means adjusted coefficient of determination, "AIC" means Akaike information criterion and "MSC" means model selection criteria, 'n' is the diffusion exponents, indicative of the drug release mechanism.

The selection criterias of the first order and the Hixson-Crowell were nearly equal for the commercial products. It is clear from Table 3 that selection criterias of Korsmeyer-Peppas kinetic was more compatible than criterias of the other release kinetic models for all formulations at 32 °C.

One of the aims of this study was to characterize DEX release mechanism from the prepared gel systems. Mathematical models and different equations have been used to describe the relationship between drug release behavior.

All data are subjected to the Korsmeyer-Peppas equation to interpret the drug release mechanism.

$M_t / M_\infty = k.t^n$ (Eq.2)

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Table 3: Results of fitting factors obtained by applying kinetic models to in vitro drug release data at 32 °C.

32 °C		Commercial Product	20%poloxamer +2,5%PG	20%poloxamer +5%PG	25%poloxamer +5%PG
Zero order	R^2_{adj}	0,9320	0,9633	0,9556	0,9360
	AIC	52,6181	35,8424	39,4567	37,2953
	MSC	2,3424	2,9663	2,7543	2,3718
First order	R^2_{adj}	0,9906	0,9845	0,9822	0,9622
	AIC	34,7653	27,7408	30,5366	32,4563
	MSC	4,3261	3,8665	3,7454	2,9095
Higuchi	R^2_{adj}	0,9326	0,9371	0,9411	0,9567
	AIC	52,7974	41,0152	42,1294	33,9029
	MSC	2,3225	2,3916	2,4573	2,7487
Hixson-Crowell	R^2_{adj}	0,9787	0,9788	0,9752	0,9545
	AIC	42,1426	30,6720	33,8646	34,1601
	MSC	3,5064	3,5408	3,3757	2,7202
Korsmeyer-Peppas	R^2_{adj}	0,9517	0,9987	0,9913	0,9960
	AIC	49,8640	5,1548	22,7575	8,2918
	MSC	2,6485	6,3760	4,6098	5,5944
	n	0,7211	0,7492	0,7479	0,7260

*"R^2adj" means adjusted coefficient of determination, "AIC" means Akaike information criterion and "MSC" means model selection criteria, "n" is the diffusion exponents, indicative of the drug release mechanism.

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Where M_t/M_∞, is the fractional amount of the drug released at time t (release time), k is a constant in corporation structural and geometric characteristics of the system, n is the release exponent indicating the drug release mechanism (Korsmeyer, Gurny, Doelker, Buri & Peppas, 1983; Özyazici, Gökçe & Ertan, 2006; Peppas, 1985; Siepmann & Peppas, 2001). For spherical systems : $n \leq 0.43$ for purely Fickian diffusion, $0.43 < n < 0.85$ for anomalous (non-Fickian transport), n=0.85 for zero-order release systems, and values >0.85 indicate super case-II transport (Siepmann & Siepmann, 2008).

When looking at the release mechanisms of the prepared formulations at 25 °C, 20% poloxamer+2.5%PG (n=0.7806) and 20%poloxamer+5%PG (n=0.7706) formulations showed an anomalous (non-Fickian transport) release mechanism. The 25%poloxamer+5%PG (n=0.9655) formulation containing greater amounts of poloxamer showed an increased n value which may be due to swelling of the gel matrix (Table 2). In addition, according to the Korsmeyer-Peppas model, it can be said that all prepared formulations show anomalous (non-Fickian transport) release mechanism at 32 °C (n=0.7492 for 20%poloxamer+2.5%PG, n=0.7479 for 20%poloxamer+5%PG and n=0.7260 for 25%poloxamer+5%PG) (Table 3).

The non-fickian diffusion results obtained from the Korsmeyer-Peppas model for all prepared formulations was consistent with drug release profiles according to the First order kinetic. In the previous studies investigated the in vitro drug release from poloxamer gels, it reported that various mathematical models may be suitable (Katakam, Ravis & Banga, 1997; Parhi & Suresh, 2015; Wang, Jiang, Wang & Bie, 2017). Govind Soni et al. prepared poloxamer-based hydrogels containing etoposide and concluded that when they investigate to release kinetic models, they provided first order kinetics release (Soni & Yadav, 2014). Butt et al. stated that they were compatible with Korsmeyer-Peppas kinetics when they applied the release kinetics to their poloxamer-based formulation containing doxorobucin (Butt, Iqbal, Amin & Katas, 2015).

4. Conclusion

In the present study, gel formulations of DEX were prepared using different concentrations of poloxamer and PG. The prepared gel formulations provided a more controlled release than commercial products for both 25 °C and 32 °C. The increase in the amount of poloxamer reduced the drug release rate due to the increase in viscosity. The formulation containing a higher amount of poloxamer (25%poloxamer+5%PG) showed more controlled release properties at each temperature. It was also concluded that the amount of PG was effective on drug release. The increase in the diffusion rate together with the temperature caused the drug release rate to increase. However, as the poloxamers became more viscous with the increase in temperature, the increase in release rate was not as remarkable as the commercial product. These gel systems may find use in the development of bioadhesive, thermosensitive and controlled release formulations. In conclusion, such a thermosensitive gel of DEX could be effectively used as controlled drug delivery system.

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