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RESEARCH ARTICLE

In-vitro release and in-vivo performance of tolmetin from different topical gel formulations

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Abstract This study was designed to evaluate the suitability of Pluronic F-127, different grades of Carbopol and cellulosic polymers as gel bases containing tolmetin, a non-steroidal anti-inflammatory drug. In vitro release characteristics, effect of enhancers, viscosity and the mechanism of drug release for different gel bases was studied as well as the anti-inflammatory activity were evaluated. The results showed that the HPMC gel has the superior percent of drug release than the others. The percent released of drug from Carbopol and the Pluronic F-127 gels is concentration defendants. It was found that the drug release from the tested gel bases obeyed the diffusion mechanism. The use of propylene glycol and urea in different concentrations (3.0, 5.0 and 10 % w/v) had enhanced the percent of drug release significantly ($p < 0.05$). The anti-inflammatory activity of the drug in Carbopol gel formulation showed excellent anti-inflammatory activity. These finding highlight the potential local application of tolmetin gel as topical anti-inflammatory medication.

Keywords Tolmetin · Gel formulations · Anti-inflammatory activity

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Introduction

Tolmetin is a pyrrole, acetic acid derivative, non-steroidal anti-inflammatory drug commonly used for the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and periarticular disorders. It inhibits cyclooxygenase activity with a reduction in the tissue production of prostaglandins (Lindsley 1999; Katzung 2004). Topical products are important class of drug delivery systems and their uses in the therapy become more widespread. The purpose of topical dosage form is to conveniently deliver drugs to localized area of the skin (Cooper 1990). Considering the fact that most inflammatory diseases occur locally and near the surface of the body, topical application of NSAIDs on the inflamed site can offer the advantage of delivering a drug directly to the disease site and producing its local effects. This occurs while avoiding gastric irritation and reducing adverse systemic effect (Rafiee and Mehramizi 2000).

It is well known that transdermal gels are more popular among all topical preparations due to ease of application and better percutaneous absorption than other semisolid dosage forms. Although many researches concerning the topical application of non-steroidal anti-inflammatory drugs exist in the literature, little information is available about the release study of tolmetin from gel bases (Macedo et al. 1993). Flurbiprofen was incorporated in different carriers like sodium alginate gel, calcium alginate microspheres, gelatin nanoparticles and complex with β-CyD and incorporated in polyethylene glycol bases (Singh et al. 1994). Other authors were studied the behavior of different drugs in different gel formulations such as Meloxicam (El-Badry 2009) and Celecoxibe (El-Badry and Fetih 2011).

The enhancing effect of naturally occurring terpenes on the in vitro percutaneous absorption of diclofenac sodium

from Carbopol gels containing propylene glycol was investigated (Arellano et al. 1996). Suh and Jun (1995) investigated the physicochemical properties and the release of naproxen from poloxamer gels. The effect of penetration enhancers on the piroxicam release from poloxamer 407 gel was studied by Shin et al. (2000).

In this study, the effect of various polymer carriers and different concentrations of them on the in vitro drug release has been explored where the drug release rate of a topical agent may be influenced by drug-vehicle interaction. The aim of this article is to investigate the in vitro release of tolmetin from different gel bases as well as the in vivo effect of those formulae having the best in vitro release characteristics.

Materials and methods

Materials

Tolmetin, Standard cellophane membrane (molecular cut of range = 1,200), Hydroxy propyl methylcellulose (HPMC), Carrageenan and Urea were supplied from Sigma Aldrich (St Louis, MO, USA). Carboxymethyl cellulose sodium (CMC sod), Methyl cellulose (MC), Pluronic F-127, Carbopol 934 and 940 were purchased from C.P. Evans Co. (England). Propylene glycol (PG) was obtained from El-Nasr Pharm. Chem. Co. (Cairo, Egypt). Dimethyl formamide (DMF) was supplied from BDH Chemicals Ltd (poole, England). Male albino rats weighing 90-110 gm were obtained from Animal house (Assuit University, Egypt).

Preparation of gel bases

The constituents of the gel bases used are illustrated in Table 1.

Table 1 Composition of the investigated gel bases and its viscosity

Base type	Composition (gm % w/v)	Viscosity mPa.s
Cellulose derivatives		
Methyl cellulose	5.0	1,195
Hydroxy propyl methyl cellulose	2.5	990.5
Carboxy methyl cellulose sodium	2.0	1,095
Carbopol bases		
Carbopol 934	2.0	1,123
Carbopol 940	2.0	1,220
Pluronic bases		
Pluronic F-127	20.0	990
Pluronic F-127	30.0	1,020

Preparation of CMC Na and HPMC gel bases

Tolmetin was dissolved in the calculated amount of hot distilled water containing 50 % (v/v) DMF. The calculated amounts of each CMC Na (2 % w/v) and HPMC (2.5 % w/v) were separately weighed and added gradually to the drug solution with gentle stirring (120 rpm) using a magnetic stirrer. Stirring was continued until no lumps were observed and the content left overnight in refrigerator (4 °C) to complete solubility and gel formation.

Preparation of methyl cellulose (MC) gel bases

The amount of methyl cellulose (5 % w/v) was sprinkled onto the surface of drug solution in water containing 50 % DMF. The mixture was heated at 70 °C and stirred using a hotplate with magnetic stirrer. The mixture was allowed to cool just before use in the release study.

Preparation of Carbopol gel bases (Carbopol 934 & 940)

The amount of Carbopol was dispersed in the distilled water. The drug was dissolved in the remainder distilled water containing the amount of triethanolamine (TEA) as neutralizing agents. The added amount of TEA was 1.65 ml per 100 gram gel. In order to have a homogeneous sample without entrapped air, the sample is kept under vacuum while stirring for 12 h.

Preparation of Pluronic F127 Gels

Pluronic F-127 was used in concentrations of 20, and 30 % (w/v). An appropriate amount of PF-127 was slowly added to cold distilled water (5–10 °C) while constant agitation with a magnetic stirrer, the dispersion was left overnight in a refrigerator, a clear viscous solution was formed. The drug was dissolved in DMF at 5–10 °C and mixed with the gel.

Determination of gel viscosity

Rheological experiments were performed to examine the viscosity of the different gel formulations. Viscosity measurements of gels were performed on a Brookfield Model DV-II+ digital viscometer (Brookfield Engineering Laboratories, INC, Stoughton, United States) in a thermostatted bath at 32 °C.

In-vitro release of tolmetin from gel formulations

In-vitro release of the drug from different gel formulation evaluated using semi permeable membrane as reported by

EL Maghraby (2008). This employed the FDC-6 Transdermal Diffusion Cell Drive Console (Logan Instrument Corp., NJ. USA). The system is fitted with VTC-200 heater circulator with jacketed vertical glass Franz diffusion cells. The semipermeable cellulose membrane with cutoff 1,200 Dalton, (Cellulose tubing, Sigma diagnostics, St. Louis, MO, USA) was mounted between the donor and acceptor compartments of the diffusion cell. The receptor compartment was 12 ml and the cells have a diffusional area of 1.7 cm^2. The receptor cell was filled with phosphate buffer (pH 6.8). The system was adjusted at 32 °C ± 0.5. A 1.0 g of the tested formulations was loaded into the donor compartment and occluded using a parafilm. Aliquots (1.0 ml) were withdrawn at specific time intervals 30, 60, 90, 120, 150, 180 min and replace with fresh media. The samples were measured spectrophotometrically (UV-spectrophotometer, Schmidzu-50-02, Kyoto, Japan) at maximum wave length of 324 nm against blank similarly treated. The percent cumulative amount of drug released was calculated. All experiments were carried out in triplicate and the average values were calculated ± the standard deviation.

Kinetic treatment of the release data

The in vitro release data of the drug from the investigated gel formulations was studied by curve fitting method to different kinetic models of zero-order, first-order and Higuchi models.

– Zero-order release:

$$M_t/M_\omega = kt \quad (1)$$

– First-order release:

$$\text{Ln}\,(1 - M_t/M_\omega) = -kt \quad (2)$$

– Higuchi model:

$$(M_t/M_\omega)^2 = kt \quad (3)$$

– The Korsmeyer-Peppas equation:

$$M_t/M_\omega = kt^n \quad (4)$$

It was used to study drug release mechanism by analyzing n as the diffusion exponent. According to this equation if $n \leq 0.45$ the Fickian mechanism, $0.5 \leq n \leq 0.8$ the Non-Fickian and if $0.8 \leq n \leq 1$ a zero-order mechanism is governing the drug release mechanism from the gel Varshosaz et al. 2008).

Effect of certain release enhancers on the release of tolmetin from gel bases

Carbopol gel containing tolmetin was chosen for further studies to see whether the release of tolmetin, anionic drug, affected by cationic characters of Carbopol gel and to clarify the effect of enhancers on the release rate and the biological effect of the drug from this cationic gel. At the same time the difference between the in vitro drug release from HPMC and Carbopol is not so more.

The effect of different penetration enhancers namely propylene glycol and urea in different concentrations (3.0, 5.0 and 10 % w/w) on the release of drug from Carbopol 940 was studied. The amount of these penetration enhancers was added during the preparation of gel formulations. The same procedure was carried out as for the in vitro release. Use of urea and propylene glycol up to 10 % as release and penetration enhancers for drugs from gel bases is reported by Goffin et al. (2000).

In-vivo study of the anti-inflammatory activity

Acute inflammatory activity model, carrageenan induced rat paw edema method was applied in this study. Measurements of the in vivo anti-inflammatory activity of the formulae conformed to guide lines of the Institutional Animal Ethical Committee of Assiut University. The experiment was conducted on male albino rats weighing 90–110 g divided into five groups. Each group consisting of six rats. Paw edema was induced using the method described by Winter et al. (1962) and Padi et al. (2004). Briefly, subcutaneous injections of 0.1 ml of 1 % carrageenan in physiological solution in the plantar surface of rat hind paw. The rats were fasted for 16 h before the experiment with free access to water. The rats were anaesthetized by urethane (0.5 ml 25 % w/v ip) and 100 mg of each topical preparation were applied to the right hind of the rat. The treated area was immediately covered by a thin polyvinyl sheet and gauze 2 h before injection of edema. The first group is the control (injected with carrageenan). The second group of rats was given indomethacin orally by stomach tube in a dose of 2.5 mg per kg as a standard drug (Pinto et al. 1998). The third group treated with 100 mg of Carbopol 940 gel base. The fourth group treated with 100 mg of Carbopol gel base containing 5 % propylene glycol as an enhancer. The last group treated with 100 mg of Carbopol gel base containing 5 % urea as an enhancer. The thickness of the paw edema was measured by micrometer. The thickness of edema determined before and immediately after injection of carrageenan. Subsequent measurements were carried out at 1, 2, 3, 4 and 5 h after induction of edema. The anti-

inflammatory effect was expressed as percentage swelling of edema thickness compared with control according to the following equation:

$$\% \text{ inhibition of edema } = (T_0 - T_t)/T_0 \times 100.$$

Where T_0 is the edema thickness in control group, T_t is the edema thickness in treated group (Prakash et al. 2010).

Statistical analysis for the obtained results

All studies performed in triplicate and values were expressed as mean ± SD. The data were analyzed by two-way analysis of variance (ANOVA) and value of $p < 0.05$ was considered as significant.

Results and discussion

In vitro release of tolmetin from gel bases

The polymers used in this study are non-toxic, safe and has been widely used for pharmaceutical and medical application. In this work, cellulosic derivatives, Carbopol and Pluronic F-127 were used as gel forming agents to study the performance of tolmetin release behaviour. Visual inspection of the freshly prepared formulae revealed smooth homogenous topical preparations with acceptable spreadability. The release profiles of tolmetin from the tested gel bases are graphically represented in Figs. 1 and 2. It is noticed that, the percentage of drug release was the highest from hydroxypropyl methyl cellulose gel (52.5 %), sodium carboxymethyl cellulose gel had (44.8 %), while methylcellulose gel had the lowest percent of drug release (32.3 %). The observed differences in drug release may be attributed to the differences in the structures and viscosity of the gel.

Figure 2 showed the percent of drug release from Carbopol 934 was superior to the Carbopol 940 gel formulation, This may be due to the difference in cross-linking density. Increasing the cross-linking density of polymer increases the tortuosity of matrix through which the drug has to diffuse and thus decreasing the drug release (Guzman et al. 1994). These results may be also attributed to the fact that Carbopol 934 gel exhibits a lower viscosity value than that of Carbopol 940 gel base and so it released the drug rapidly. Moreover, Macedo et al. (1993) studied the release of tolmetin from gels prepared with different grade of Carbomers. They found that there is a trend in the release profiles showing fastest drug release from Carbopol 941 and slowest drug release from Carbopol 940 gels and drug release from Carbopol 934 gels was intermediate.

The percent of drug release from Pluronic F-127 (30 % w/v) was lower than the percent release of drug from Pluronic F-127 (20 % w/v) ($p < 0.05$). The low release rate obtained with the higher pluronic concentration is in agreement with Laufter's diffusion theory in gels which states that, the diffusion coefficient of a solute is inversely proportional to the volume fraction occupied by the gel forming material (Lauffer 1961).

In addition, since the Pluronic F-127 gel is believed to consist of large population of micelles resulting in a reduced concentration of diffusible solute is also probable as the drug is included within the micelle (Miyazaki et al. 1986).

The general rank order of the release of the drug was observed to be HPMC gel > sodium carboxymethyl cellulose > Methyl cellulose gel that is for cellulosic

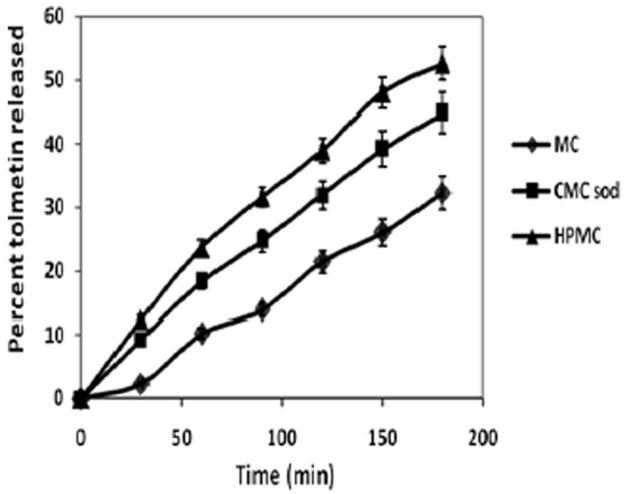

Fig. 1 Release profile of tolmetin from different cellulosic gel bases (±SD). *MC* methyl cellulose, *HPMC* hydroxy propyl methyl cellulose, *CMC sod.* carboxy methyl cellulose sodium

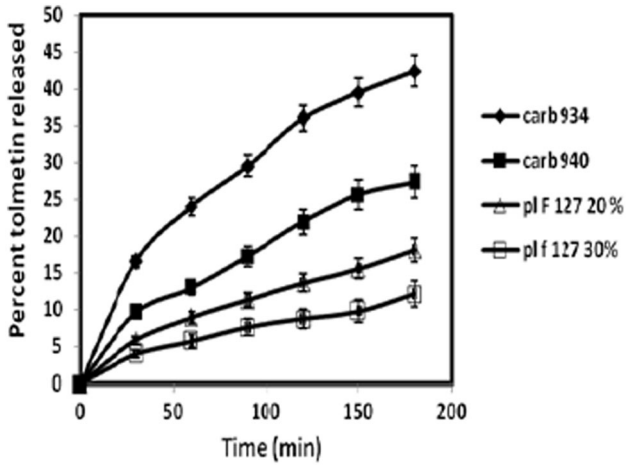

Fig. 2 Release profile of tolmetin from Carbopol 934 and Carbopol 940 as well as different concentrations of Pluronic F-127 gel bases (±SD)

derivative gels. From another side, the rank order of the percent of drug release was Carbopol 934 > Carbopol 940 > Pluronic F-127 (20 % w/v) and finally Pluronic F-127 (30 % w/v). It is well known that, the nature of the vehicle has a great influence on drug release. In the present study, different hydrogel bases with different polymer structure were used to compare the release profile of the drug from these vehicles. The release rate of the drug through any base depends on the nature and composition of the individual base (Babar et al. 1990).

Kinetic of the in vitro release studies

In-order to develop an ideal kinetic model to interpret the release rate various kinetic models were applied to obtain the best fit of the data, namely, zero-order, first-order fashions, Higuchi diffusion mechanism and Korsmeyer–Peppas equation. The confirmation between the different mechanisms depends on the correlation coefficient (r) and diffusion exponent of Peppas equation (n), Table 2. The results indicate that, the correlation coefficient of release data fitted to Higuchi model. In most cases it is higher than other models. Also, in all cases the release exponent of Peppas equation was found to be 0.5. This indicates that, a Fickian mechanism is dominant and controls the drug release from the gels.

Effect of certain release enhancers on the release of tolmetin from gel bases

Although, HPMC gel gave the best drug release, the effect of enhancers was studied on Carbopol 940 gel base to study the performance of enhancer effect on the drug release. The effect of different penetration enhancers namely, propylene glycol and urea at different concentrations 3, 5 and 10 % (w/w) on the release of tolmetin from Carbopol 940 (2 % w/v) gel base were graphically shown in Figs. 3 and 4.

The most enhancing effect in all additives was found to be dependent on the additive concentrations. Habib and El-Shanawany (1989) studied the effect of various additives on the release of dexamethasone from different ointment bases. The results showed that the addition of Propylene glycol was found to possess a more pronounced

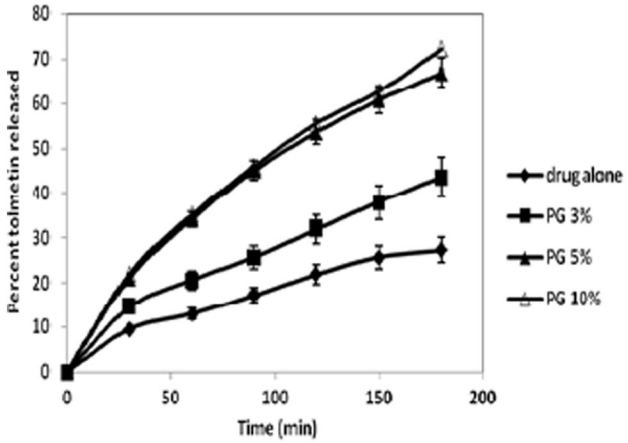

Fig. 3 Effect of different concentrations of Propylene glycol (PG) on the release profile of tolmetin from Carbopol 940 gel base (±SD)

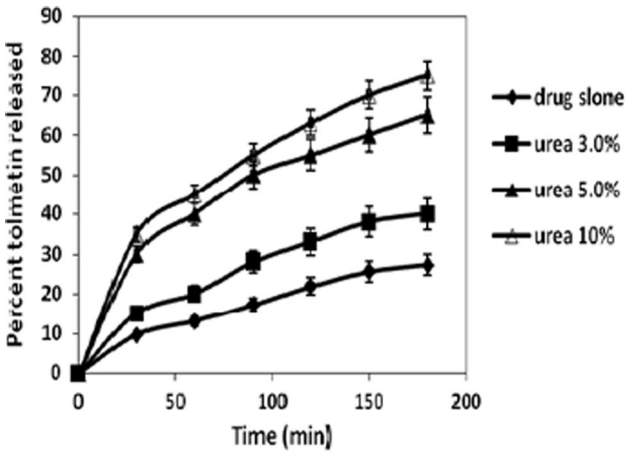

Fig. 4 Effect of different concentrations of urea on the release profile of tolmetin from Carbopol 940 gel base (±SD)

Table 2 Kinetic models of tolmetin release from different gels (±SD)

Gel form	Zero-order (r)	First-order (r)	Higuchi model (r)	n
HPMC	0.941 ± 0.025	0.840 ± 0.015	0.996 ± 0.011	0.45 ± 0.02
CMC-sodium	0.980 ± 0.003	0.945 ± 0.010	0.997 ± 0.002	0.45 ± 0.03
MC	0.989 ± 0.010	0.896 ± 0.023	0.997 ± 0.001	0.48 ± 0.01
Carbopol 934	0.969 ± 0.015	0.895 ± 0.025	0.991 ± 0.002	0.46 ± 0.02
Carbopol 940	0.978 ± 0.010	0.939 ± 0.021	0.992 ± 0.004	0.44 ± 0.03
Pluronic F-127 (20 % w/v)	0.955 ± 0.012	0.885 ± 0.031	0.994 ± 0.003	0.44 ± 0.03
Pluronic F-127 (30 % w/v)	0.930 ± 0.011	0.939 ± 0.022	0.975 ± 0.005	0.43 ± 0.02

r correlation coefficient, *n* release exponent of Korsmeyer–Peppas equation, *MC* methyl cellulose, *HPMC* hydroxy propyl methyl cellulose, *CMC sod* carboxy methyl cellulose sodium

Table 3 Anti-inflammatory activity of tolmetin in different gel formulations

Rat group no.	Formulation	% Swelling of induced edema				
		1 h	2 h	3 h	4 h	5 h
1	Control	95 ± 0.5 (5.00)*	94.0 ± 0.5 (6.0)	93.0 ± 1.0 (7.2)	91.0 ± 0.6 (9.2)	90 ± 0.5 (10.0)
2	Oral administered	51.0 ± 0.5 (48.8)	40.1 ± 0.6 (59.4)	33.5 ± 0.5 (65.6)	30.3 ± 0.4 (69.5)	21.5 ± 0.3 (79.5)
3	Carbopol 940 gel	65.1 ± 0.4 (35.9)	60.2 ± 2.0 (39.9)	50.2 ± 1.5 (50.2)	45.3 ± 0.9 (55.5)	40.5 ± 2.5 (59.5)
4	Carbopol 940 gel containing 5 % PG	61.2 ± 0.8 (39.0)	54.3 ± 0.5 (45.1)	51.2 ± 0.7 (49.5)	45.1 ± 0.5 (54.4)	40.4 ± 1.5 (60.0)
5	Carbopol 940 gel containing 5 % urea	62.1 ± 0.4 (38.9)	54.5 ± 2.0 (44.9)	50.5 ± 1.2 (50.5)	45.3 ± 1.2 (54.9)	41.5 ± 1.1 (60.1)

PG polyethylene glycol

The value between parentheses indicates the % inhibition of edema

* Mean ± SD

effect on the drug release than the other additives. Regarding the release from Carbopol 940 (2 % w/v) gel base, low concentrations of enhancers (3 % w/w) produced no remarkable effect on the drug release from base. However, (5 % and 10 % w/w) of, urea and PG produced an observed effect on the release rate of the drug. Also, there was no significant difference between 5.0 % and 10 % concentration ($p = 0.1$).

Anti-inflammatory activity studies using paw edema method

Topical anti-inflammatory activity of semisolid preparations has been reported when applied 1 and 2 h before carrageenan treatment as mentioned by Hiramatsu et al. (1990). Clinically, it seems more reasonable to apply the anti-inflammatory topical preparations after the inflammation stimulus (Escribano et al. 2003). Table 3 illustrates the anti-inflammatory activity of different gel formulations on the hind paw of the rats. It is shown that all the gel formulations have a significant effect ($p < 0.05$) as anti-inflammatory vehicle, but to a variable extent (inhibition percentage about 35.9–58.5) over time course studied (1–5 h) as compared with control. After the first 2 h of the observation, Carbopol gel shows 39.9 % inhibition, Carbopol gel containing 5.0 % PG shows 45.1, while gel containing 5 % urea had 44.9 %. After 5 h, the inhibitory effect was 59.5 and 60.0 and 61.0 for the same gel forms respectively. The results showed that, the use of penetration enhancer increase the effect significantly ($p < 0.05$). Also there are no significant differences between the two used enhancers. This evident a strong correlation between the percent of drug release from the various gel formulations and the anti-inflammatory activity. These results are in agreement with that reported, when other non steroidal anti-inflammatory drugs were used (Huang et al. 2007; Gupta et al. 2008, 2001).

Conclusion

The results of this study showed that tolmetin exhibit a higher release rate from hydroxy propyl methylcellulose (HPMC) gel base. The effect of different penetration enhancer propylene glycol and urea at different concentration 3, 5 and 10 % on the release of tolmetin from Carbopol 940 (2 %) gel bases showed increase the percent of drug release significantly in the low concentration of enhancers, but at the higher concentration (10 %) showed no significant release. In vivo investigation of selected bases proved that these bases represent potential local application for tolmetin as anti-inflammatory drug.

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