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RELEASE OF TOLMETIN FROM CARBOMER GEL SYSTEMS

Terence Macedo[1,3], Lawrence H. Block[1] and Atul J. Shukla[2]

[1]School of Pharmacy
Duquesne University
Pittsburgh, Pennsylvania - 15282

[2]College of Pharmacy
University of Tennessee
Memphis, Tennessee - 38163

[3]Current Address - Anthony Products Company
5600 Peck Road
Arcadia, California - 91006

ABSTRACT

Gel-formulations containing a nonsteroidal anti-inflammatory drug, tolmetin, were prepared using three different carbomers namely, Carbopol™ 934, 940 and 941. Effects of cosolvent composition, carbomer type, carbomer concentration and drug concentration on drug release from the gels were analyzed by factorial design. Gels with high aqueous content yielded significantly higher tolmetin release rates than gels with lower aqueous content. Although no significant differences in drug release characteristics were observed between the three carbomer gels, there was a trend in the release profiles; fastest drug release was observed from Carbopol™ 941 gels and the slowest drug release was observed from Carbopol™ 940 gels. Increasing the carbomer

concentration from 1% w/w to 2% w/w had no significant effect on drug release from gel formulations prepared with all the three different types of carbomers. However, increasing the tolmetin concentration in the gels from 1% w/w to 4% w/w resulted in a dramatic increase in drug release. An investigation of the mechanism of drug release from the gels revealed that tolmetin release was diffusion controlled, except at the outset.

INTRODUCTION

Oral therapy using nonsteroidal anti-inflammatory drugs (NSAIDs) has been the treatment of choice for degenerative joint disease (1). However, several adverse effects such as gastrointestinal distress including bleeding related to ulceration of the gastric mucosa and nausea, have been reported (2). Topical therapy with NSAIDs may offer a possible solution to some of the adverse effects of oral therapy. In addition, site specific application of these drugs may lead to longer persistence at the disease site and substantial local tissue uptake. Carbomers have been used to prepare gel formulations for topical use by several workers (3-10) because they exhibit high viscosities at low concentrations. Moreover, they are quite stable to heat with negligible batch to batch variability. They are also unaffected by aging, do not support bacterial or fungal growth and are non-toxic and non-irritating. Hence in the present investigation, carbomers were used as gel-forming polymers for a model NSAID, tolmetin.

The objectives of this investigation were to study the effect of varying solvent compositions, carbomer type, carbomer

concentration and varying drug concentration on in vitro drug release from gels prepared using three different carbomers, and to evaluate the mechanism of drug release from the gels.

MATERIALS AND METHODS

Preparation of Tolmetin Free Acid

Tolmetin free acid was prepared from the sodium salt (McNeil Pharmaceutical, Spring House PA) by dissolving a weighed quantity of the salt in deionized water, and precipitating out the free acid with an excess of concentrated hydrochloric acid. The precipitate was then washed with copious amounts of deionized water to remove unreacted hydrochloric acid. The tolmetin free acid was dried under vacuum at 40°C, to a constant weight. The dried acid was tested for purity against the reference standard (Tolmetin free acid, McNeil Pharmaceutical, Spring House, PA) by a UV assay and an infrared spectrum.

Preparation of Gel Formulations

Required amounts of propylene glycol and water were mixed together. This cosolvent was then divided into two parts. To one part, an appropriate amount of carbomer resin (Carbopol™ 934 or Carbopol™ 940, or Carbopol™ 941, B.F. Goodrich Co., Cleveland, Ohio) was added in small increments with constant stirring, using a magnetic stirrer. After all the resin was added, the stirring was continued for about 30 minutes at a reduced speed in order to prevent the entrapment of air. An appropriate quantity of tolmetin was added to the other part of the cosolvent with

stirring. Approximately one-half of the required quantity of triethanolamine (TEA) was added to the drug-cosolvent mixture, while the other half was mixed with the carbomer-cosolvent mixture, thus resulting in a stiff gel. The drug-cosolvent solution was then slowly added to the gel mixture in small portions with constant stirring. The final gel formulation was transferred to a tightly closed container which was stored in a dark place. The exact quantities used for preparing the gel formulations are listed in Table I.

Drug Content Studies

Drug content of the gels was determined by dissolving an accurately weighed quantity of gel (about 100 mg) in about 50 mL of Sorensen's buffer. These solutions were quantitatively transferred to volumetric flasks and appropriate dilutions were made with Sorensen's buffer. The resulting solutions were then filtered sequentially through Whatman No. 42 filter paper and 0.45 μm membrane filters before subjecting the solutions to spectrophotometric analysis for tolmetin at 313 nm.

In vitro Drug Release Studies

Tolmetin release from gels was studied using Franz diffusion cells with cellulose acetate dialysis membrane having a molecular weight cutoff of 6,000 (Fischer Scientific Co., Pittsburgh, PA) placed between the donor and the receptor compartments. The membrane was soaked in Sorensen's buffer overnight and then washed before using it. A known weight (2-3 g) of gel was added to the donor side and a known volume of Sorensen's buffer to the receptor side. The receptor compartments were maintained at $37^{\circ} \pm 0.5^{\circ}C$ throughout

Table I. Weight in grams needed to make 20 grams of gel-formulations

Amount of Drug		Carbopol™ 934, 940 or 941		Propylene Glycol:Water (1:1) grams		(1:3)		Triethanolamine TEA	
grams	(%)	grams	(%)	PG	W	PG	W	grams	(%)
0.2	(1)	0.2	(1)	9.2	9.2			1.2	(6)
0.2	(1)	0.4	(2)	9.1	9.1			1.2	(6)
0.4	(2)	0.2	(1)	9.1	9.1			1.2	(6)
0.4	(2)	0.4	(2)	9.0	9.0			1.2	(6)
0.8	(4)	0.2	(1)	8.9	8.9			1.2	(6)
0.8	(4)	0.4	(2)	8.8	8.8			1.2	(6)
0.2	(1)	0.2	(1)			4.60	13.80	1.2	(6)
0.2	(1)	0.4	(2)			4.55	13.65	1.2	(6)
0.4	(2)	0.2	(1)			4.55	13.65	1.2	(6)
0.4	(2)	0.4	(2)			4.50	13.50	1.2	(6)
0.8	(4)	0.2	(1)			4.45	13.35	1.2	(6)
0.8	(4)	0.4	(1)			4.40	13.20	1.2	(6)

the experiment. At predetermined time intervals, over a 24 hour period, the buffer was removed in toto from the receptor compartments and analyzed spectrophotometrically at 313 nm. The withdrawn samples were replaced immediately with an equal volume of fresh buffer. A control experiment was carried out using a gel formulation with no drug, in order to ascertain any interference in the analysis by either the formulation or the membrane.

RESULTS AND DISCUSSION

Effect of Varying Cosolvent Compositions

A comparison of tolmetin release profiles from all the three types of carbomer gels prepared with two different cosolvent compositions revealed that increasing the aqueous content of the gels from 1:1 propylene glycol (PG) : water (W) to 1:3 (PG:W) significantly increased drug release from the gels. A typical release profile depicting the effect of increasing aqueous content of Carbopol™ 940 gel on drug release is shown in Figure 1. This suggests that tolmetin free acid forms a hydrophobic complex with TEA, whereas, the carbomers are hydrophilic. Hence, an increase in the aqueous content of the gels may have possibly increased the escape tendency of the relatively hydrophobic drug-TEA complex. Although all the three carbomers appear to be affected by the co-solvent system to a similar extent, drug release was the fastest from gels prepared with Carbopol™ 941 and slowest from Carbopol™ 940 (Figure 2). This may be due to the differences in the cross-link density of the carbomers: cross-link density being the highest for Carbopol™ 940 and the lowest for Carbopol™ 941 (11).

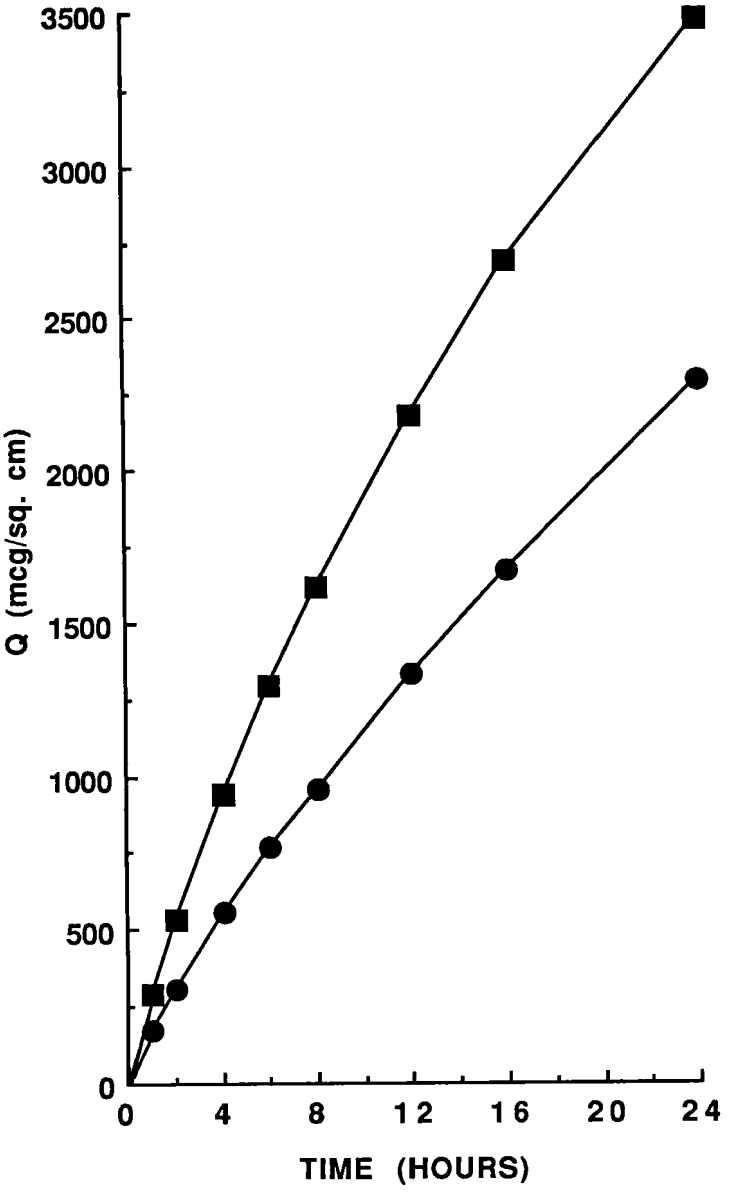

Figure 1: Effect of Cosolvent Composition of Carbopol™ 940 Gels on Drug Release Characteristics (2% Polymer and 1% Drug).

(●) PG:W - 1:1; (■) PG:W - 1:3

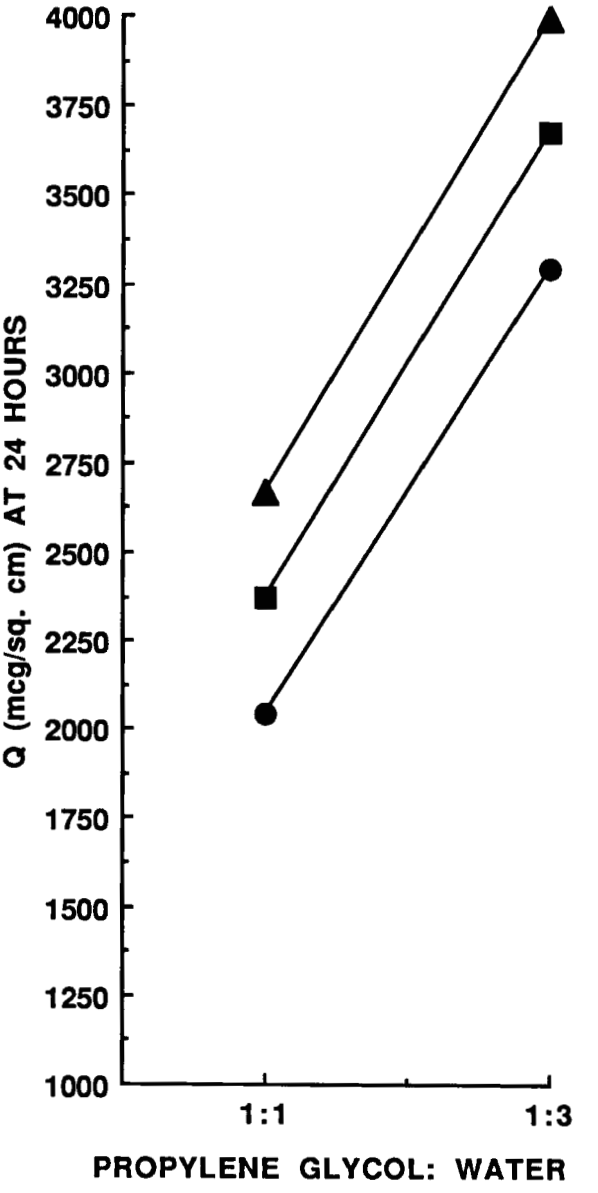

Figure 2: Effect of Cosolvent Composition of All Three Carbopol Gels on Drug Release Characteristics (2% Polymer, 1% Drug, PG:W - 1:1)

(●) Carbopol™ 940; (■) Carbopol™ 934; (▲) Carbopol™ 941

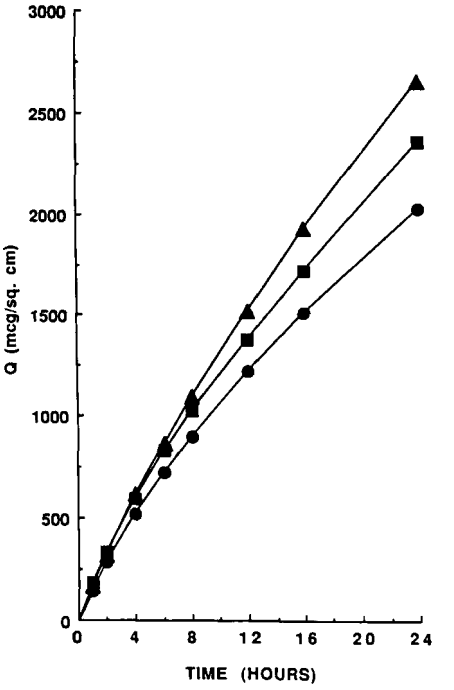

Figure 3: Effect of Carbomer Type on Drug Release Characteristics (2% Polymer, 1% Drug, PG:W - 1:1)

(●) Carbopol™ 940; (■) Carbopol™ 934; (▲) Carbopol™ 941

Effect of Carbomer Type

Figure 3 is a representative figure showing drug release from gels prepared with all three carbomers types. Although no significant difference in drug release characteristics were observed for all the three gels, there seems to be a trend in the release profiles showing fastest drug release from gels prepared with Carbopol™ 941 and slowest drug release from Carbopol™ 940 gels. Drug release from Carbopol™ 934 gels was intermediate. This could be attributed to the differences in cross-link density as noted

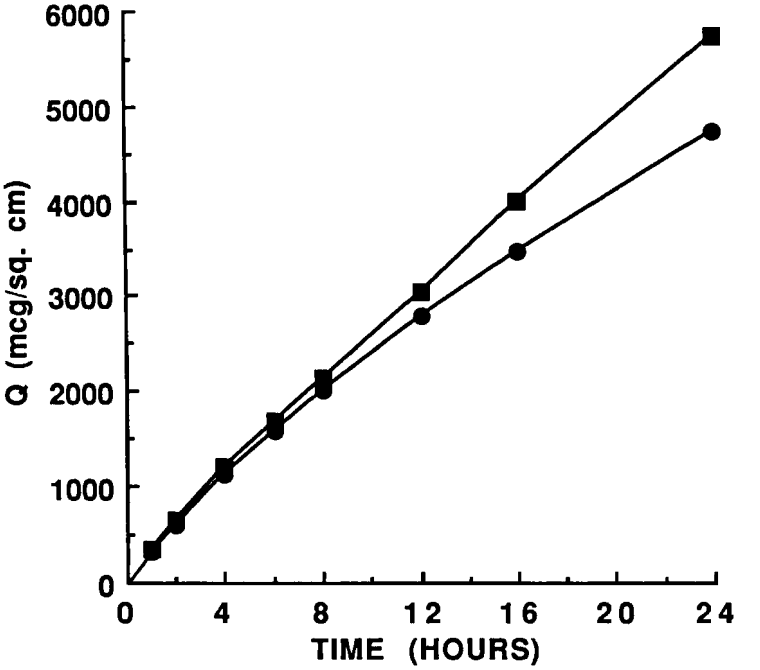

Figure 4: Effect of Carbomer Concentration on Drug Release Characteristics From Carbopol™ 934 Gel (1% Drug, PG:W - 1:1)

(●) 2% Polymer; (■) 1% Polymer

before. Increasing the cross-link density of a polymer increases the tortuosity of the matrix through which the drug has to diffuse, thus decreasing drug release.

Effect of Carbomer Concentration

Carbopol™ 934

No significant difference in drug release from gels prepared with 1% and 2% carbomer concentration was observed. However, there appears to be a definite trend in the release profile as shown in Figure 4, where drug release is faster from gels prepared with 1% carbomer compared to those prepared with 2% carbomer. An

increase in tortuosity of the gels with increased carbomer concentration may be a possible reason for decreased drug release since the drug molecules have to traverse a longer path.

Carbopol™ 940

No significant difference in drug release from gels prepared with 1% and 2% carbomer concentration was observed (Figure 5).

Carbopol™ 941

No significant difference in drug release was observed for gels prepared with Carbopol™ 941 when the concentration of the carbomer was doubled from 1% to 2% (Figure 6).

Effect of Drug Concentration

An approximately two-fold increase in drug release was observed between the gels prepared with 1%, 2% and 4% drug for all the three cabomer types. Typical results are depicted in Figure 7. This could be attributed to an increased concentration gradient of the drug between the donor and the receptor phases with increased drug concentration of the gels in the donor phase.

Mechanism of Drug Release

An investigation of the mechanism of drug release from the gels revealed that the drug release data could be fitted to Higuchi's model (12) as described below:

$$Q = 2\ C_o\ (Dt/\pi)^{1/2}$$

where Q = amount of drug released per unit area of application

C_o = initial concentration of drug in the gel

D = diffusion coefficient of drug in the gel

t = time after application

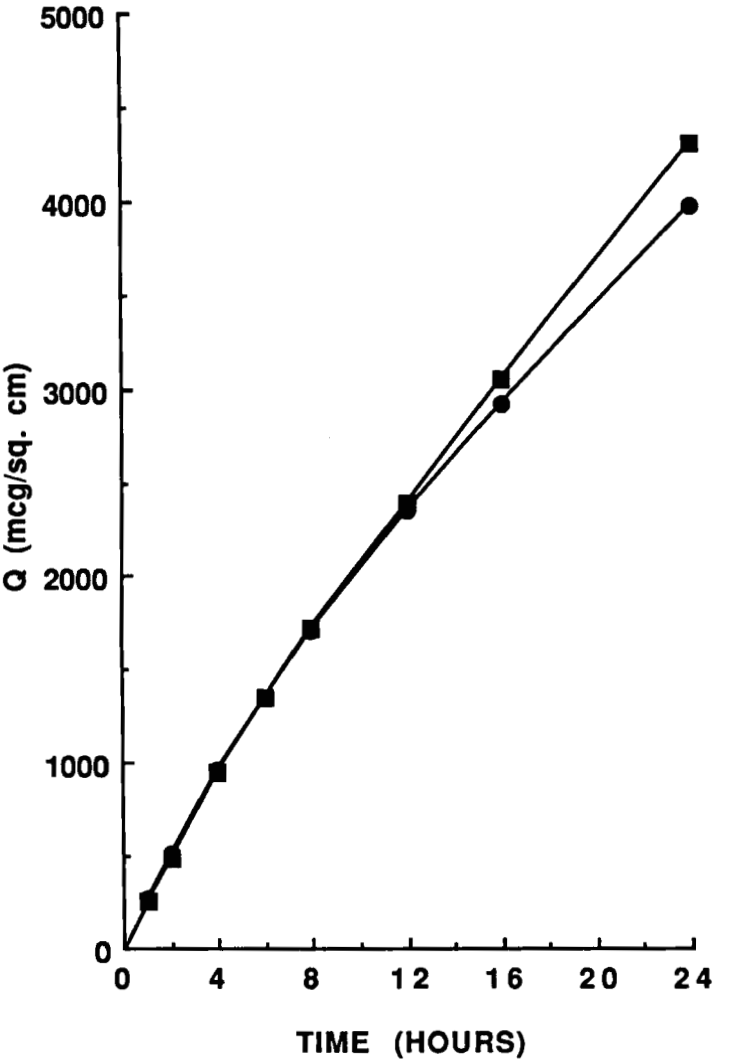

Figure 5: Effect of Polymer Concentration on Drug Release Characteristics From Carbopol™ 940 Gel (1% Drug, PG:W - 1:1)

(●) 2% Polymer; (■) 1% Polymer.

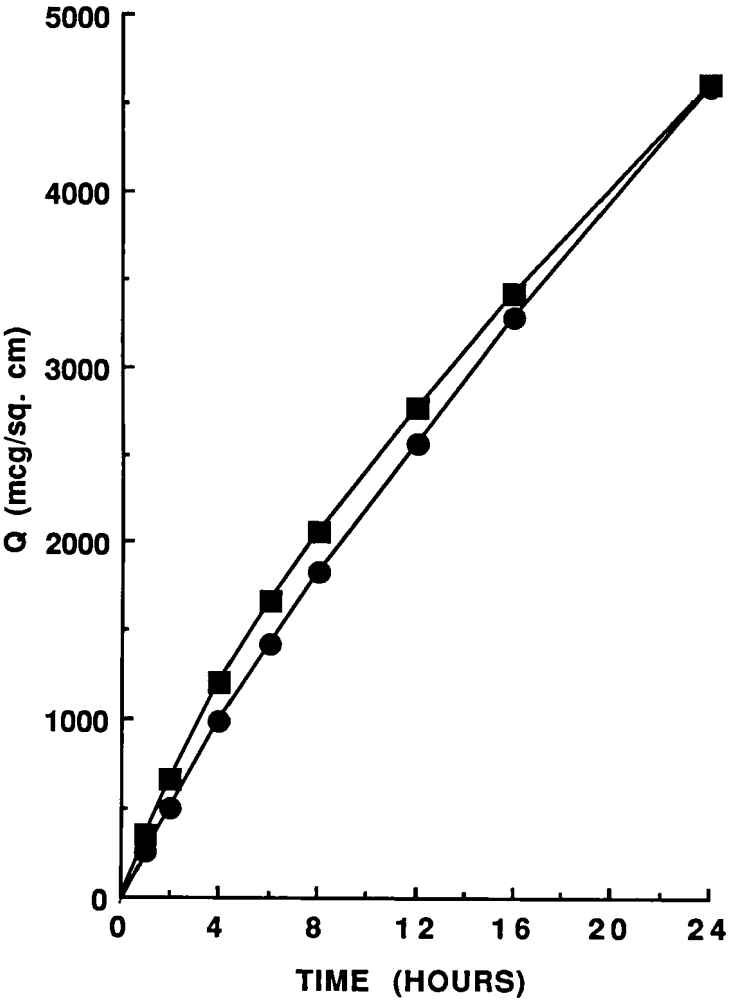

Figure 6: Effect of Polymer Concentration on Drug Release Characteristics From Carbopol™ 941 Gel (1% Drug, PG:W - 1:1)

(●) 2% Polymer; (■) 1% Polymer.

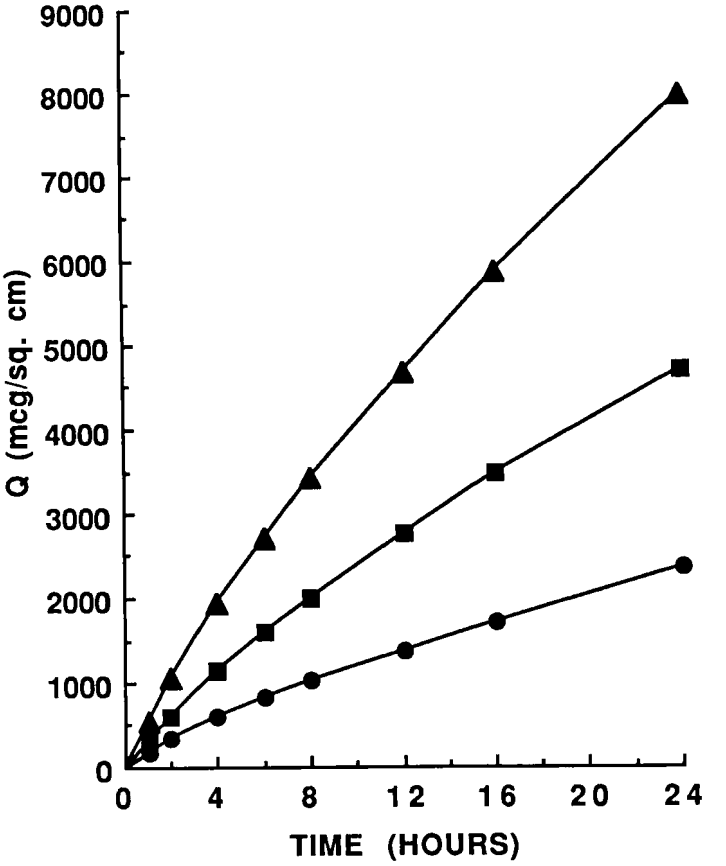

Figure 7: Effect of Drug Concentration on Drug Release Characteristics From Carbopol™ 934 Gel (2% Polymer, PG:W - 1:1)

(●) 1% Drug; (■) 2% Drug; (▲) 4% Drug

However, the model was only applicable for the drug release data after the first four hours. This was because the gels in the donor compartments of the Franz diffusion cells decreased in consistency over a period of time. This is most likely the result of electrolyte diffusion across the membrane from the buffer solution in the receptor phase and subsequent interaction with the

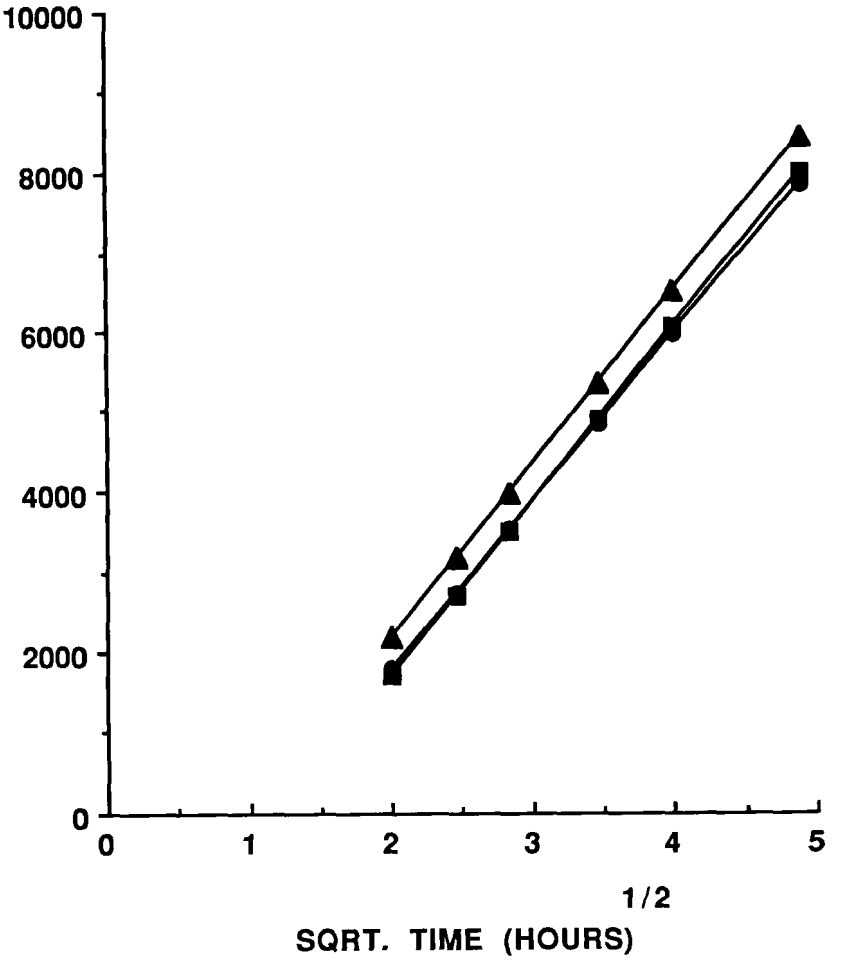

Figure 8: Higuchi Plots for Drug Release Data for All Three Carbopol™ Gels. (2% Polymer, 4% Drug, PG:W - 1:1)

(●) Carbopol™ 940; (■) Carbopol™ 934;
(▲) Carbopol™ 941.

carbomers. The resultant gel collapse could have contributed to the deviations observed in drug release characteristics during the first four hours, after which drug release from the gels obeyed Higuchi's model and hence became diffusion controlled. Figure 8 shows the typical Higuchi-model plot for drug release from the three carbomers after the first four hours.

CONCLUSION

It can thus be concluded from this investigation that factors such as varying solvent composition, carbomer type and drug concentration can affect drug release from the gel formulations. Hence, carbomer gels, when appropriately formulated in suitable cosolvent systems, may be used effectively as topical drug delivery systems.

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