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RESEARCH PAPER

In Vitro Release Studies of Flurbiprofen from Different Topical Formulations

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ABSTRACT

The release profiles of flurbiprofen (F) from different gel and ointment formulations were studied in order to evaluate factors governing the release process. Carbopol 934P (CAB), poloxamer 407 (POL), and eudragit S100 (EUD) gel bases were used, while emulsion (EML) and polyethylene glycol (PEG) ointments were employed. The release studies were conducted using membraneless diffusion cells and lipophilic receptor medium, isopropyl myristate (IPM). The effects of gelling agent concentrations and the initial drug load on drug release were determined. Hydrogels were observed to give higher amounts of drug release than hydrophobic EUD gel and ointments, despite the lower bulk viscosity of these bases. Flurbiprofen release from CAB gels was 3.06–1.56-fold higher than from other formulations. Over a 4-hr period, the amount of F released was 492.8 and 316.0 $\mu g/cm^2$ from 2% CAB and 25% POL gels, while it was 213.05, 168.61, and 160.9 $\mu g/cm^2$ from EML, 40% EUD, and PEG bases, respectively. The diffusivity of F in the gel bases was an inverse function of the polymer concentrations over the range of 1–3% CAB, 20–30% POL, and 35–45% EUD gels. Drug release was increased from the bases as the initial F concentration increased over the range 0.25–1.0%, while the diffusion coefficient observed an inverse relationship. The CAB and POL gels could be the vehicles of choice for the rapid release and onset of F after topical application.

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INTRODUCTION

Topical and transdermal products are important classes of drug delivery systems, and their use in therapy is becoming more widespread. Although topical formulations to treat ailments have existed from ancient times, transdermal products, for which the skin is used as an alternative route for systemic and regional therapy, are relatively new entities.[1] The purpose of topical dosage forms is to conveniently deliver drugs to a localized area of the skin.[2] Topical creams and gels for the regional therapy of non-steroidal anti-inflammatory drugs (NSAIDs) have been used in many countries, and an effective therapy requires sufficient drug concentrations to evoke a desired pharmacological effect within target tissues. Recent studies[3,4] have shown that after topical application, significant levels of anti-inflammatory drugs were found in deep tissues such as facia, muscle, and synovium, which is a desirable feature for the relief of local symptoms, while reducing potential systemic side-effects. Rabinowitz et al.[5] found that topical application of salicylates resulted in higher drug concentrations in articular tissues and synovial fluids than did oral aspirin in dogs. To develop an effective topical dosage form for regional therapy, one must also take into account many formulation variables that affect drug efficacy, such as the flux of the drug across skin, the reservoir capacity of the dosage forms, efficient drug release, and permeability through the skin, as well as localization of the drug in the target site.[2] Flurbiprofen is a propionic acid-type NSAID, highly effective for the treatment of many types of inflammatory and arthritic diseases such as many forms of rheumatoid arthritis, arthralgia, ankylosing spondylitis, and other related conditions.[6] As is the case for the many NSAIDs, oral administration of flurbiprofen often produces gastric irritation, and sometimes patients can develop ulceration and severe gastrointestinal bleeding.[6,7] In order to minimize these adverse effects associated with oral administration, topical and transdermal delivery of flurbiprofen have been studied.[8,9] Among the many potential factors that can affect drug permeation across the skin from topical/transdermal formulations, diffusion of the drug from the vehicle toward the skin surface and subsequent partitioning into the stratum corneum are of particular importance. For these reasons, in this study, different vehicles were used to evaluate and compare the release rates of F. In addition, the major formulation variables that could affect the release and absorption of drugs in topical formulations, such as the vehicle type, concentration of gelling agent, and initial drug concentration in the formulations, were studied.

MATERIALS

Flurbiprofen, stearyl alcohol, and isopropyl myristate (Sigma Chemical Co., St. Louis, MO), Carbopol 934P (B.F. Goodrich Co., Cleveland, OH), Poloxamer 407 (BASF Corp., Parsippany, NJ), Eudragit S100 (Rohm, Darmstad, Germany), polyethylene glycol 400 and 4000 (Union Carbide Corp., Danbury, CT), sodium hydroxide (J.T. Baker Chemical Co., Phillipsburg, NJ), ethanol (Florida Distillator Co., FL), propylene glycol and glycerol (Fisher Scientific Co., Fair Lawn, NJ), and white petrolatum (Gallipot Inc., St. Paul, MN) were used as received. All other chemicals and solvents were of highest grade commercially available.

EQUIPMENT

Corning pH Meter (Model 7, Corning Medical, MA, USA), Brookfield Digital Viscometer (Erweka, Germany), Haak Model F-4391 Water Pump (Polyscience Corp., Evanston, IL), Three-Blade Stirrers (Arrow Engineering Co., Inc., NJ, USA), Poulsen Diffusion Cells and Cary 118 Spectrophotometer Conversion (Gateway On Line Instrument System Inc., CA).

METHODS

Preparation of Flurbiprofen Topical Formulations

Flurbiprofen concentration was 1% w/w in all formulations while it was set at 0.25–1.0% w/w to study the effect of initial drug load on release.

Poloxamer 407 gels (20–30% w/w) containing different concentrations of F were prepared by the cold method described by Schmolka.[10] The weighed amounts of POL were slowly added to water over a period of 3–4 min with gentle mixing. The mixture was left in a refrigerator (4°C) overnight to complete the dissolution of the polymer. After the formation of a clear viscous solution, an ethanolic solution of flurbiprofen (10% w/w ethanol) was added to the cold POL solution and thoroughly mixed with a glass rod. The solution was then left at room temperature until a clear gel was formed.

Carbopol 934P gels (1–3% w/w) containing different concentrations of F were prepared by the slight modifications method adopted by French et al.[11] Small portions of carbopol were added to a dispersion of the drug in water with vigorous mixing with a rotating propeller. After complete addition of the polymer and mixing, the gels were spontaneously formed with the addition of 2 M NaOH. Gels with partially wetted polymer lumps were discarded. Air bubbles were removed from the gel by centrifugation for 12 min at 3000 rpm. The pH of the polymer gel was adjusted to 7.3 with 2 M NaOH solution.

Eudragit S100 organogels (35–45% w/w) containing different concentrations of F were prepared by a slight modification of the method described by Kawata et al.[12] The prescribed amount of the polymer was added to a predissolved flurbiprofen in a small amount of propylene glycol (15% w/w) in glycerol, and completely mixed with a glass rod until the gel was formed. Propylene glycol was added to complete solubilization of the drug in glycerol.

Emulsion (o/w) ointments were prepared by melting stearyl alcohol and white petrolatum in a steam bath at 75°C. The solution of other ingredients and the weighed amount of F, previously dissolved in water and warmed at 75°C, were added with agitation and the emulsion was stirred until the ointment congealed.

Polyethylene glycol ointments containing different concentrations of F were prepared using the heat and mechanical incorporation method described in the USPXXII. Polyethylene glycol of MW 400 and 4000 was placed in a beaker and heated in a steam bath then removed while stirring until congealed. The specified amount of F was incorporated into the ointment by agitation.

Viscosity and pH Measurements

The removable sample holder of the Brookfield Digital Viscometer was filled with the sample, and then inserted into a flow jacket mounted on the viscometer. A small sample adapter (RV-7 spindle), rotated at a speed of 20 rpm, was used to measure the viscosity of the preparations. The temperature of the sample was kept at 37°C by circulating water through the thermostatted water jacket. The sample was allowed to settle for 5 min prior to taking the reading. A Corning pH Meter was used to measure the pH of the CAB gels. The electrode was inserted into the sample 10 min prior to taking the reading at room temperature.

Release Studies

The release of flurbiprofen from the formulations into isopropyl myristate (IPM) was determined using the membraneless diffusion cells described by Poulsen et al.[13] Because of certain shortcomings associated with the use of membranes as barrier in drug release studies, such as a slow release, diffusional resistance, and osmotic back flux, among others, a practical alternative model without the use of membrane as a barrier has been used. The advantage of this model is that the base is in direct contact with the receptor medium, and thus factors influencing drug partitioning from aqueous phase into lipid vehicle could be determined without a barrier membrane.[14] The cell consists of two parts; the removable sample holder (0.5 cm height × 2.7 cm i.d.) and the thermostatically jacketed glass cell (6.5 cm height × 2.8 cm i.d.). The clean pre-weighed sample holder was completely filled with the sample serving as the donor phase. The excess sample was removed from the surface using the edge of a spatula to obtain an even and smooth surface area (5.71 cm^2). This was weighed again to determine the exact amount of sample employed in the experiment. The sample holder was fitted into the bottom of the diffusion cell, which was maintained at 37°C by a circulating water pump. A three-blade stirrer (2.5 cm wide) was placed at 0.7 cm above the base surface in the diffusion cell and was rotated constantly at 70 rpm to provide adequate mixing. Twenty milliliters of IPM, which was preheated at the experimental temperature, was poured over the sample. For the next 4 hr and at a predetermined interval (0.5 hr), 0.2 mL was removed from the

receptor phase at the same location each time and diluted to the appropriate volume with IPM for the quantitation of flurbiprofen released spectrophotometrically at 254 nm against IPM as blank. The sample removed was replaced with an equal volume of IPM equilibrated at the same temperature. The studies were performed in duplicate, and the mean values were used for the release rates measured.

Treatment of Data

A Higuchi equation[15] was used to analyze the released data of flurbiprofen from different formulations, which is valid if the release process from a solution-type semi-solid slab meets the following assumption:[16]

$$Q = 2C_0\sqrt{\frac{Dt}{\Pi}}$$

where Q is the amount of drug released per unit area (mg/cm^2); C_0 the initial drug concentration in the vehicle (mg/cm^3); D is the diffusion coefficient (cm^2/sec); and t is time. This equation was derived based on the following assumptions: (1) a single drug species is present in the vehicle, (2) only the drug molecules diffuse into the receptor phase, (3) the diffusion coefficient is invariant with respect to time or position within the vehicle, (4) the total drug release is less than 30%, (5) the drug reaching the receptor site is diluted instantaneously. The experimental conditions employed in the present study were within the scope of the above model, namely: (1) only flurbiprofen was present and diffused out of the vehicle, (2) the total amount of flurbiprofen resulting from the bases was less than 30%, and (3) the receiving medium provided the sink condition, where solubility of flurbiprofen in IPM was reported as 16.84 g/L at 32°C.[17] The data of drug release from all the bases was plotted against the square root of time, and the diffusion coefficients, D, were calculated from the slope of this equation.

RESULTS AND DISCUSSION

Effect of Polymer Concentration on Drug Release

The release of F from the gels of three varying polymer concentrations, CAB (1%, 2%, and 3%), POL (20%, 25%, and 30%), and EUD (35%, 40%, and 45%), was evaluated in reference to that of the EML and PEG ointments. The initial concentration of F in all of the vehicles was set constant at 1%. Since the rheological properties are likely to play an important role in drug release from semi-solid vehicles, the viscosity of plain vehicles was determined and presented as shown in Table 1. The bulk viscosity of the bases decreased in the order of 25% POL > 2% CAB > PEG > EML > 40% EUD, and the effect of increasing the viscosity upon increasing concentration of the gelling agents was also seen. However, drug release after a 4-hr period decreased in the order of 2% CAB > 25% POL > EML > 40% EUD > PEG as shown in Fig. 1; the EUD profiles do not appear in the figures for clarity. This apparent lack of correlation indicates that the bulk viscosity is not the primary factor that affecting the release of F, and the release mostly depends on the drug–vehicle interaction rather than the viscosity. The results show that the release rate of F from gel preparations decreases as an inverse function of polymer concentration. As shown in Fig. 1, when the cumulative amounts of F released were plotted as a function of the square root of time, linear correlations ($r > 0.997$) were observed, indicating that the release of F from the vehicles was in compliance with the Higuchi diffusion model described for the release of drugs from the semi-solid slab. A one-way analysis of variance (ANOVA) test was used to evaluate any significant difference of drug release among formulations ($p < 0.05$). It is shown that the release of F was not significantly different upon increase of the polymer concentration. Among the selected polymer concentrations, 2% CAB and 25% POL, and the ointment formulations containing 1% of the drug, a highly significant difference of F released was observed, indicating that the drug release has been influenced by type of base. The diffusion coefficient values calculated from Higuchi plots for the different vehicles are shown in Table 1, and were found to decrease inversely as a function of polymer concentration, which is in agreement with the data of Chen-Chow and Frank[14] in their study on lidocaine release from poloxamer gels. In our study, the finding that higher polymer concentrations resulted in lower drug release from the vehicles is in agreement with Lauffer's molecular diffusion theory of polymer gels,[18] which stated that the diffusion coefficient of a solute is inversely

Table 1

Release Data of Flurbiprofen into Isopropyl Myristate from Several Topical Formulations After 4 hr Together with Viscosity Data

Formulation	Viscosity of Plain Base η (cps $\times 10^{-3}$)	Cumulative Flurbiprofen Released Q (μg/cm^2)	Diffusion Coefficient D (cm^2/sec)
Polymer concentration			
1% CAB gel+1% F	66.0	532.21	5.88×10^{-5}
2% CAB gel+1% F	102.0	493.00	5.66×10^{-5}
3% CAB gel+1% F	123.0	417.02	5.16×10^{-5}
20% POL gel+1% F	67.5	333.70	4.50×10^{-5}
25% POL gel+1% F	131.5	316.04	4.37×10^{-5}
30% POL gel+1% F	189.0	306.10	4.31×10^{-5}
35% EUD gel+1% F	6.60	177.50	3.27×10^{-5}
40% EUD gel+1% F	13.20	168.61	3.17×10^{-5}
45% EUD gel+1% F	25.00	140.30	2.89×10^{-5}
EML ointment+1% F	58.7	213.05	4.22×10^{-5}
PEG ointment+1% F	97.0	160.90	—
Flurbiprofen concentration			
2% CAB gel+0.25% F	—	320.54	1.71×10^{-4}
2% CAB gel+0.50% F	—	394.42	9.98×10^{-5}
2% CAB gel+0.75% F	—	429.83	6.83×10^{-5}
25% POL gel+0.25% F	—	124.30	1.07×10^{-4}
25% POL gel+0.50% F	—	170.23	6.30×10^{-5}
25% POL gel+0.75% F	—	241.04	5.07×10^{-5}
40% EUD gel+0.25% F	—	75.86	8.45×10^{-5}
40% EUD gel+0.50% F	—	116.76	5.24×10^{-5}
40% EUD gel+0.75% F	—	133.85	3.73×10^{-5}
EML ointment+0.25% F	—	68.90	7.74×10^{-5}
EML ointment+0.50% F	—	109.24	5.27×10^{-5}
EML ointment+0.75% F	—	164.70	4.23×10^{-5}
PEG ointment+0.25% F	—	36.92	—
PEG ointment+0.50% F	—	72.89	—
PEG ointment+0.75% F	—	118.95	—

proportional to the volume fraction occupied by the gel-forming agent.

Effect of Vehicle on Drug Release

It is well known that the nature of the vehicle has a great influence on drug release. In the present study, different hydrophilic and lipophilic gel and ointment bases were used to compare the release of F from these vehicles into IPM. The results indicate that the release rate of F differed significantly among the vehicles, suggesting that the choice of vehicle is of obvious importance for achieving a desired drug release profile. The diffusivity of the drug through any base depends on the nature and composition of the individual base.[16] The CAB gels exhibited a superior drug release followed by the POL gels, while EML, EUD, and PEG bases have shown the lowest amount of drug release, respectively, which might in part be related to the vehicle's nature, structure, and drug–vehicle interaction. Flurbiprofen release from CAB gels was 3.06–1.56-fold higher than from other formulations, as shown in Table 1. The structure of CAB and POL hydrogels has played an important role in drug release compared with the other vehicles. It is reported that the main barrier to the release of drugs from aqueous CAB polymer gels is a mechanical layer formed by the random network of the polymer molecules, which binds and entraps

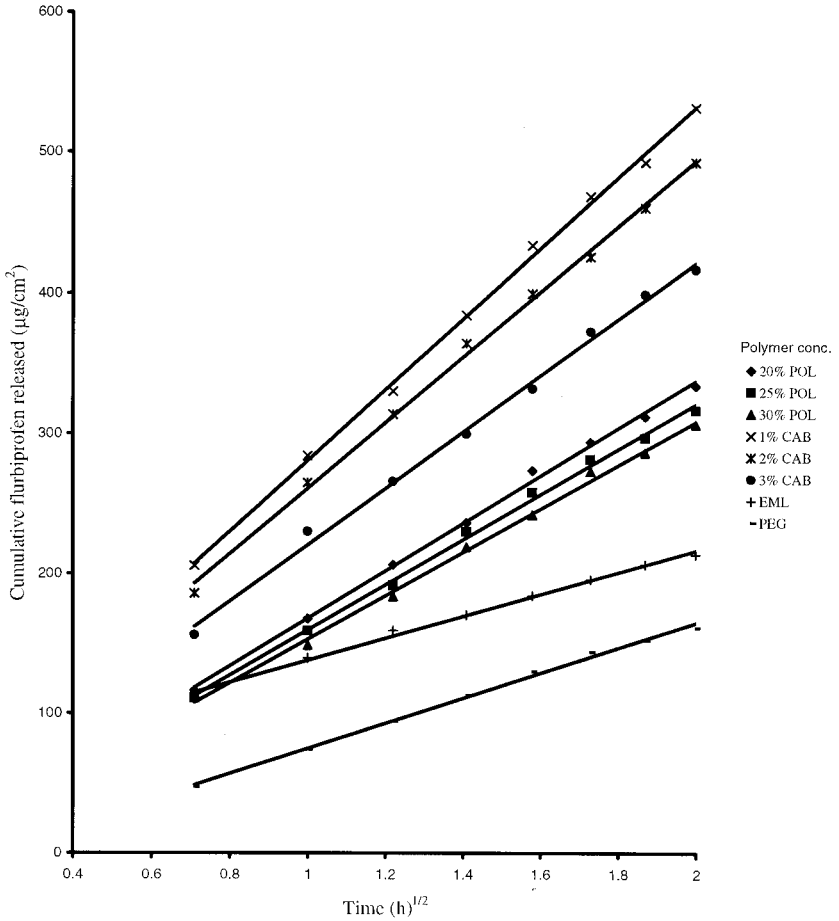

Figure 1. Release profiles of flurbiprofen from emulsion and polyethylene glycol ointments, poloxamer and carbopol gels as a function of polymer concentrations.

surrounding water.[19] This aqueous phase in the polymer network may be the region responsible for diffusion of the drug in the gels. Parased et al.[20] mentioned that an aqueous solution of POL gels is largely composed of micelles formed by the polymer and aqueous phase, the latter being the region, as channels, from which the drug is immediately available for release. So, the drug release from POL gels depends on the number and size of the micelles, which adversely affects the number and size of water channels. A change of polymer concentration in these two gels could affect the diffusional pathways and thus drug release. Therefore, the fact that hydrogels have shown a greater release of the drug over other gel and ointment bases might be related to the ease of drug diffusion through the aqueous channels or diffusional pathways formed within the gel network, which are not found in ointments. The higher F released from hydrogels can also be explained on the basis that hydrophilic gels give a higher payload of lipophilic flurbiprofen into the lipophilic receptor medium, IPM. It is obvious that the type of base affects the released amount of the drug. Although EUD gels showed the lowest viscosity among the vehicles used, they exhibited the slowest release profile among gels, which was probably attributable to the strong affinity of flurbiprofen to the hydrophobic EUD gels. The solution-type ointment, EML, showed a higher release rate of F than the suspension type, PEG. This is in agreement with the results of other workers.[16] It is well known that the solubility of a drug in the vehicle affects drug release and diffusion. If a drug is poorly soluble in the base, only the drug

molecules at the surface of the base would quickly be released due to the slow molecular diffusion in the internal phase. An analogous situation has been reported by Hekimoglu et al.[21] They found that the release of caffeine from a PEG ointment, in which the drug is soluble, to water was faster than that from petrolatum base, in which the drug is only slightly soluble. El-Magid and El-Mohsen[22] and Idson[23] also reported that the release rate of drugs from several semi-solid bases was closely related to the solubility of that agent in both the donor and receiving phases. Since F is soluble in EML ointment and incorporated as suspended particles in PEG ointment, this could explain the higher release profiles observed from the former ointment. Also, the slower release profiles of F exhibited from the PEG ointment may be attributed to the higher affinity of F to the base, resulting in complexation and subsequently retarding drug release.

Effect of Drug Loading on Release

The effect of the initial drug concentration on the drug release was evaluated for 2% CAB, 25% POL, 40% EUD, EML, and POL bases each containing 0.25%, 0.50%, 0.75%, and 1.00% F. The data showed that the release of F from all the vehicles increases with an increase of the initial load in the vehicles. This effect is probably due to the increase in thermodynamic activity of the drug, which is related to its concentration in the base. In different bases the thermodynamic activity of the drug increases linearly with concentration until it reaches the same limiting value, which is the value of a saturated solution.[24] In the present work, the

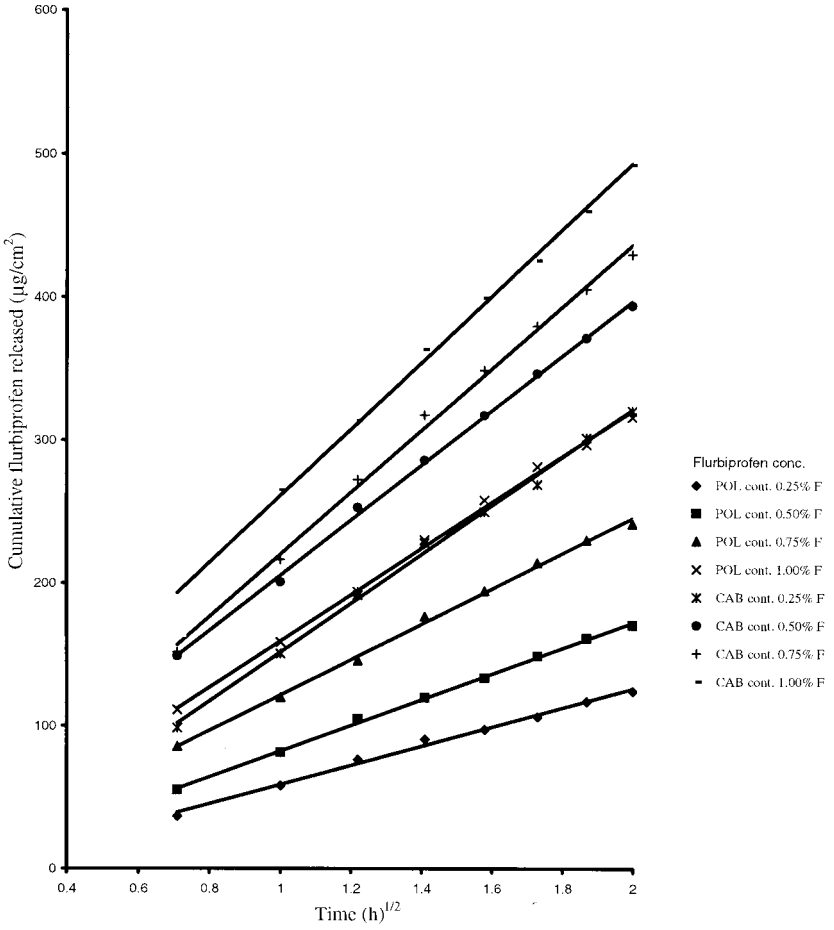

Figure 2. Release profiles of flurbiprofen from poloxamer and carbopol gels as a function of initial drug concentration.

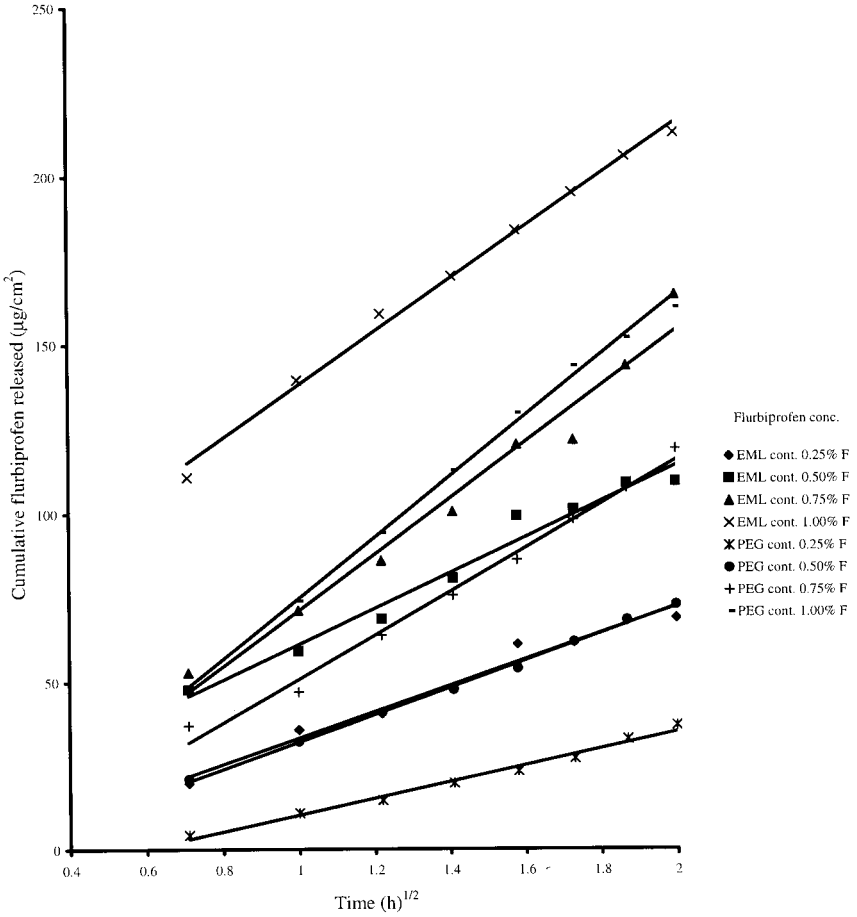

Figure 3. Release profiles of flurbiprofen from emulsion and polyethylene and glycol ointments as a function of initial drug concentration.

release was increased at all levels of drug concentrations used. Also, the increase in release profiles with increment in the loading dose may be due to the higher availability of the drug on the base surface. Almost all formulations have shown a linear relationship ($r > 0.994$) when the amount of drug released is plotted against the square root of time, as shown in Figs. 2 and 3. However, it was found that when F in the gel formulations was increased from 0.25% to 1.0%, the diffusion coefficients were decreased and independent of the initial concentration as shown in Table 1, although each of the individual release profiles exhibited a good fit to the Higuchi equation. Suh and Jun[25] reported similar results in their study on naproxen release from poloxamer gels. The same relationship was also reported by Fredrik et al.[26] for lignocaine release studies from o/w cream.

CONCLUSION

This in vitro study is considered a useful methodology for screening flurbiprofen topical formulations which could provide a base for developing a topical dosage form of the drug having a desirable release profile. Different hydrophilic and lipophilic topical formulations of flurbiprofen were made and examined under different formulation variables. The physicochemical nature of the vehicles, and the drug interaction with these vehicles, have influenced drug release profiles. The general rank order of flurbiprofen release from the formulations was carbopol gel > poloxamer gel > emulsion ointment > eudragit gel > polyethylene glycol ointment. Gel formulations of carbopol and poloxamer have been observed to give higher values of drug release, which is due to the higher solubility of the drug

in these vehicles and the ease of drug diffusion through the gels. The solution-type ointment, emulsion base, gave a release profile higher than the suspension-type one, polyethylene glycol ointment, due to increased thermodynamic activity of the drug in the former base, which is related to drug solubility. Other formulation variables have affected the drug release from the bases. Higher release rates were observed at lower polymer concentrations, while no substantial effect of the viscosity among the vehicles was seen. An inverse relationship was observed between the initial drug concentration and the diffusion coefficient. Data showed that aqueous polymeric vehicles could be of value for topical application of flurbiprofen.

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