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EVALUATION OF IN VITRO RELEASE OF DICLOFENAC SODIUM FORMULATED GELS THROUGH DIFFUSION CELL

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ABSTRACT

The purpose of this study was to formulate diclofenac sodium into various types of gel formulations, namely isopropyl alcohol gel, micro-emulsion gel, hydrogel and hydroalcoholic gel using different ingredients. The ensuing goal was to evaluate these gels in terms of in vitro drug release. A modified form of Franz cell was used for diffusion studies. Six different formulations of diclofenac sodium were prepared. Duplicate runs were performed to know the difference in their release extent extending upto 6 hours and the reasons of these differences. The order of release of the drug from various gel formulations was as follows: Hydroalcoholic gel> hydrogel> microemulsion gel> isopropyl alcohol gel.

Keywords: *Diclofenac sodium; membrane diffusion; modified Franz cell; formulation dependent release.*

INTRODUCTION

Diclofenac sodium (DS), an NSAID is a preferential inhibitor of cyclooxygenase-2 and has demonstrated potent analgesic and anti-inflammatory activity. After oral administration, systemic side effects and GI irritation at the usual dose are common. Considering the fact that most inflammatory diseases occur locally and near the surface of the body, topical application of DS on the inflamed site can preclude the systemic side effects and GI irritation.

However the barrier properties of intact skin limit the permeability of a wide variety of substances including active pharmaceutical ingredients. The delivery of drugs into and through the skin is recognized as effective means of therapy for local dermatological and systemic diseases. In recent years transdermal delivery of drugs for systemic and local effect has gained considerable attention because they eliminate the first pass effect, provide sustained plasma levels and improve patient compliance[1, 2].

To overcome these problems, the development of a topical vehicle system for rapid skin permeation of DS was, undertaken. Different techniques are reported in the literature[3] for quantifying the release of drugs from semi-solid dosage forms. A modified form of Franz diffusion cell[4] employing synthetic membrane has been used for this purpose in this study.

The purpose of this study was to formulate DS into various types of gels using different functional ingredients such as oils, bases, surfactants, release enhancers and mobile (solvent) liquids.[3]

EXPERIMENTAL

Materials

Diclofenac Sodium reference standard and manufacturing grade material was donated by Gulf Pharmaceutical Industries, Ras-al-Khaima. All other chemicals used were of analytical grade except those used in formulation were of manufacturing grade. The semi-permeable cellophane membrane (25,000 MWCO) was from Fischer Co., London.

DIFFUSION CELL

A simple diffusion cell was assembled simulating various parts of the Franz cell. A glass tube 2.9 cm in diameter, 10 cm high was used as a donor cell. A semi-permeable cellophane membrane, cut to the suitable diameter of the cell was boiled in distilled water for 1 hour and soaked in phosphate buffer pH 7.4 overnight. The dried membrane was tightly tied to the smooth end of the cell for placing the gel sample. The donor cell was hung in a beaker of 250 ml capacity containing 100 ml of phosphate buffer pH 7.4 (receptor cell). The donor cell is hung in the beaker in a way that the membrane stays immersed to a depth of 1cm below the surface of the buffer maintained at 37 ^{o}C and agitated by a magnetic stirrer at 50 rpm throughout the release study (Figure 1).

SAMPLING

Three ml samples withdrawn from the receptor cell (beaker) at 0.25, 0.5, 1, 2, 3, 4, 5 and 6 hours were replaced immediately with fresh phosphate buffer. The last sample withdrawn was at 24 hours. The samples were measured for DS released against buffer blanks obtained after permeation of gel samples without DS by a spectrophotometer at $ë_{max}$ 285 nm[5]. The

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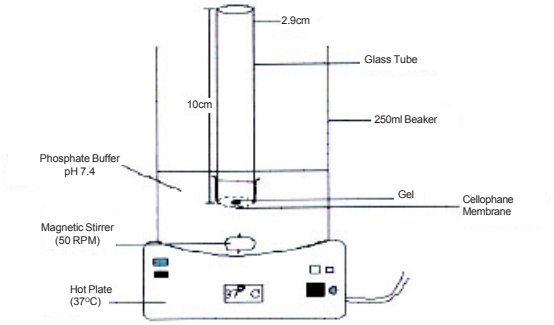

Fig. 1: *Modified diffusion cell assembly*

concentration in timed samples was determined with reference to the absorbance of Reference Standard in the form of a standard curve.

PREPARATION OF GEL FORMULATIONS

Composition of gels prepared and their batch size are tabulated in Table 1, along with their pH values. All the gel formulations stored in proper containers were watched for their physical appearance for a period of 3 months.

Isopropyl Alcohol Gel (IPA)

Hypermellose (HPMC 4000) was dissolved in hydro alcoholic solution until a clear gel results. A mixture of propylene glycol and Tween 80 was added to HPMC gel and mixed thoroughly. One percent by weight of DS powder (mesh # 60) based on the weight of the gel mix was incorporated in small portions until uniformly mixed.

Micro-emulsion Gel (ME)

Amounts mentioned in the formula were weighed and transferred to a screw-capped vial of 150ml capacity. The mixture was stirred using a magnetic stirrer. Then the micro-emulsion was prepared by adding 25g of water in installments with continuous stirring by a Vortex mixer. The gel was stored for 24 hours for equilibration before use.

Hydrogel (HD)

Powdered Carbopol 940 was added at intervals in small amounts into the mixture of water and propylene glycol while mix was stirred briskly. DS powder was then mixed in small amounts till uniformly mixed. The gel was properly stored at room temperature.

Hydro Alcoholic Gel (HDA)

Powdered Carbopol 940 was added at intervals in small amounts to the mixture of water, absolute ethanol and propylene glycol while briskly stirring the mixture. Powdered DS was incorporated into the mixture being stirred by a magnetic stirrer. The gel was stored in tightly closed container before use.

Table 1: *Composition of Prepared Gels.*

INGREDIENTS	Isopropyl Alcoholic Gel	Microemulsion Gel	Hydrogel	Hydroalcoholic Gel
Diclofenac Sodium	1.060 g (1% w/w)	1.025 g (1% w/w)	1.010 g (1% w/w)	1.010 g (1% w/w)
HPMC 4000	1.75 g (1.63%)			
Isopropyl Alcohol 70% (70 : 30 water)	68.55 g (64.03%)			
Popylene Glycol	4.0 g (3.73%)	10 g (7.92%)	20 g (19.60%)	20 g (19.60%)
Tween 80	1.70 g (1.58%)	50 g (39.6%)		
Carbopol 940			1 g (0.98%)	1 g (0.98%)
Distilled water	30 g (28.02%)	25 g (19.80 %)	80 g (78.42%)	40 g (39.20%)
Oleic Acid		40 g (31.68%)		
Ethanol, Absolute		40 g (31.68%)		40 g (39.20%)
Batch Size	107.06 g	126.25 g	102.01 g	102.01 g
pH	7.2	7.0	6.9	6.8

pH DETERMINATION

The pH of various gel formulations was determined with the help of Inolab Digital pH meter and these values are reported in Table 1.

PHYSICAL APPEARANCE

The gels after having set in containers were watched for homogeneity, color, separation and granulation by visual inspection for 3 months. No discernible changes were noted in these apparent physical properties of gels.

RESULTS AND DISCUSSION

The formula details of gels are given in Table 1. The average cumulative percent release data of duplicate runs is plotted in Figure 2.

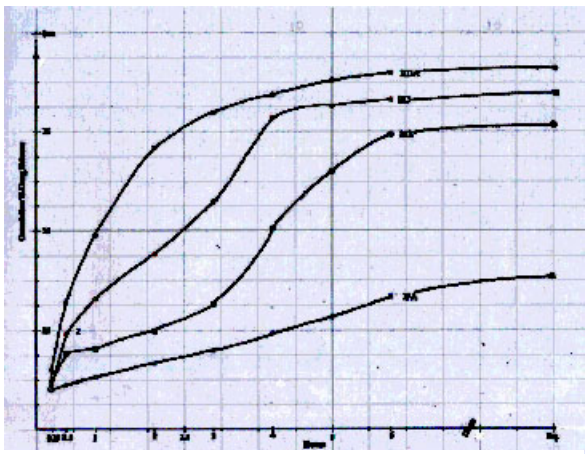

Fig. 2: *Drug Release Profile of Diclofenac Sodium from Formulated Gels IPA=isppropyl Alcohal Gel, ME=Microemulsion Gel, HD=Hydrogel, HDA=Hydroalcoholic Gel*

Batch 1 and 2 containing glycerin, NaCMC, Acacia, PEG 600, PEG 3350, Methyl paraben and DS were prepared which resulted in gel formulations with ointment-like consistency. Both the formulations when studied for drug release in the diffusion cell recorded poor release (approximately 10%) over 24 hours

(results not reported). It is reported in literature[6] that maximum permeation and 1-5 fold increase in drug release was achieved from a micro-emulsion gel of a drug compared to the release from lipogel (ointment like) formulation of the same drug. Similarly in our studies, low drug release was obtained during 24 hours from the two formulations prepared at the start of the investigation. These formulations appeared to have higher consistency and cohesive texture and did not soften in the cell during release studies. Therefore, changes in the composition were made to include ingredients that would confer hydrophilic and softening properties at body temperature. In recent years gel based formula have been shown to make drug molecules move easily from the system than creams and ointments[7, 8]. Over the last few decades, the use of cellulosic polymers and carbopols has gained popularity as vehicles for topical drug delivery systems. The formulations containing such polymers entail acceptable viscosity and good bioadhesion properties[9] with the desired drug release pattern. These polymers were used in forthcoming gel formulations to enhance the drug release.

Drug release characteristics

Isopropyl alcohol gel (IPA)

High molecular weight cellulose polymers are used to produce viscid, jelly-like aqueous dispersions. A gel was formulated to contain HPMC 4000. HPMC, a water-soluble cellulose derivative and isopropyl alcohol, a mobile liquid may act as a skin penetrant. IPA gel is formulated with HPMC 4000, IPA, Propylene Glycol and Tween 80.

As noted from Figure 2, only one-third (34%) release of DS was obtained at the end of 6 hours and about 38% at the end of 24 hours. IPA gel formulation contains isopropanol, which may have evaporated during release study; the DS might have precipitated out due to drying resulting in slower drug release.

Micro-emulsion (ME) Gel

Further, to enhance the drug release, a micro-emulsion comprising of propylene glycol, Tween 80 and oleic acid was prepared. The formulation recorded a higher cumulative release of about 75% at 6-hr interval and about 77% at 24 hours with a gradual increment at increasing intervals (Figure 2). This may be due to the effect of the emulsified system of the micro-emulsion that has combined effect of lipophilic and hydrophilic domains[10]. In case of *in vitro* studies, the hydrophilic domain can hydrate the membrane that may enhance the diffusion, and lipophilic domain *in vivo* may favor skin permeation. The gel has low viscosity and the hydrophilic property causes the softening of the gel at 37 ^{o}C.

Hydrogel (HD)

In order for DS to exhibit higher release, hydrogel formulation comprising of propylene glycol and Carbopol 940 was prepared as mentioned under Preparation of Gels in Table 1.

A report in literature[11] indicates that the use of Sodium Lauryl Sulfate (SLS) as a pretreatment of the membrane has shown higher diffusion of drug through membrane. Therefore, the membrane was soaked overnight in 2% SLS solution. It is evident from Figure 2 that the percent release further increased, reaching about 83% at the end of 6 hours (84.61 % at 24 hours) in comparison to about 74% from micro emulsion gel. Enhanced release with SLS-soaked membrane from Hydrogel is in agreement with the higher diffusion of drug particles occurring as a result of pretreatment with anionic emulsifiers[12,13].

Carbopol incorporated into hydrogel formulation may also have aided in the diffusion of DS through membrane as carbopol has been shown to be good release additive for drug permeation through cellophane membrane[14].

Hydro alcoholic gel (HDA)

The fourth preparation is hydro alcoholic gel whose composition is presented in Table 1 and release in Figure 2. Hydroalcoholic gel is formulated with ethanol (absolute) in addition to Carbopol 940 as also used in Hydrogel. The HDA gel resulted in maximum cumulative release of about 90% at 6 hour interval and about 92 % at 24 hours demonstrating about 7 % higher release than Hydrogel formulation at 6 hour interval. The enhanced drug release from hydro alcoholic gel could be attributed to the fact that ethanol decreases the high viscosity due to Carbopol which leads to improved drug release and penetration from the gel[15] by augmenting the solubility and partitioning of the drug into the membrane.

In earlier studies[16,17], the effect of ethanol has been ascribed to increased partitioning co-efficient of drug and vehicle solubility resulting in enhanced permeation as evidenced in our studies as well.

Referring to an earlier study[18] that ascertained the effect of solvent release enhancers as propyl alcohol, ethanol and isopropyl alcohol on release of DS and diclofenac diethylamine, it was observed that the values of flux of DS through cellulose membrane were 0.059, 0.040, and 0.038 mg/hr/cm^2 for formulations containing propyl alcohol, ethanol, and isopropyl alcohol respectively. These results are in agreement with the higher DS release obtained from HDA gel (ethanol containing) formulation and lower release from isopropyl alcohol gel. Because of strong correlation between water phase concentration and the flux values, the authors explained the higher flux and release from gels containing co-solvent system on the basis of water phase concentration. The HDA gel has higher water phase content (39.21% w/w) and higher release in comparison

to lower water phase content (27.88% w/w) and consequently lower release from isopropyl alcohol gel (Figure 2); thus our findings support the results of the earlier research reports[18,19].

Cellulose media (cellophane) membrane with MWCO of 25000 Daltons used theoretically does not offer any hindrance to the passage of drug molecules of usual molecular weight drug as that of DS (MW 318.13) used in this study. It is the permeation and the freedom of the drug particles from the bases which seem to be dominantly controlling the diffusion of the drug. Preservatives and plasticizers used in the manufacture of synthetic membrane may leach into receptor chamber solution and interfere with the subsequent analysis procedures. The removal of such substances, therefore, is carried out by soaking and boiling the membrane in distilled water for complete removal of the additives[1].

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