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Research Article

DEVELOPMENT OF VALDECOXIB TOPICAL GELS: EFFECT OF FORMULATION VARIABLES ON THE RELEASE OF VALDECOXIB

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ABSTRACT

Topical gels of valdecoxib were prepared using two different gelling agents (viz, carbopol and hydroxypropylmethylcellulose). Formulations were evaluated for pH, rheological behavior, drug content and in vitro drug diffusion. Formulations of both the gelling agents appeared to be non-Newtonian and pseudo plastic. Drug content was found to be high (>98%) and uniform in gels. Effect of solvents, propylene glycol and ethanol on the release of drug from the gels was studied. Drug release from the gels increased with increase in the concentration of propylene glycol up to 10%. However, drug release decreased with further increase in the concentration of the propylene glycol to 20%. In case of carbopol gels, drug release increased with the addition of ethanol. However, in case of hydroxypropylmethylcellulose gels, addition of ethanol decreased the release of valdecoxib. The release of VLD from the gels followed the Higuchi model. It can be concluded that propylene glycol acts as a good solvent in carbopol and hydroxypropylmethylcellulose based valdecoxib gels.

Key words: Valdecoxib; topical gel; In vitro release.

INTRODUCTION

Valdecoxib is non steroidal anti-inflammatory drugs (NSAIDs)[1]. Valdecoxib is chemically, 4(5-methyl-3-phenyl-isoxazolyl) benzene sulfonamide and is a diaryl substituted isoxazole. It exhibits anti-inflammatory activity, analgesic and antipyretic properties[2] . For local inflammation or pain, topical application of valdecoxib may be a better alternative that also reduces the side-effects associated with oral therapy[3, 4]. Jagtap et al[5] studied the efficiency, safety and tolerability of valdecoxib gel (1%) in adult patients. The study confirmed that valdecoxib gel is an effective and safe option for the management of painful inflammatory joint condition. Of the many dosage forms available today, most of them are administered by oral route. Oral route of drug administration follows GI-side effects, first-pass metabolism and results in decreased bioavailability. Whereas, topical preparations avoid GI-irritation, prevent the metabolism of drug in the liver and increase the bioavailability of the drugs and provide its action directly at the site of action[6]. Although gel formulation of valdecoxib appears to be highly useful, there is lack of literature on the formulation development of valdecoxib topical gels. Therefore, main objective the present work was to develop topical gels of valdecoxib and study the formulation variables affecting the release of drug.

MATERIAL AND METHODS

Materials

Valdecoxib was a gift sample from Virdev Intermediates Pvt. Ltd. Surat. Carbopol 940, propylene glycol, triethanolamine and sodium lauryl sulphate were purchased from S.D.Fine.Chem.Pvt. Ltd., Mumbai. HydroxypropylMethylcellulose was received as a gift sample from Aurobindo Pharmaceuticals Ltd. Hyderabad.

Methods

Preparation of gel

Valdecoxib gel formulations were prepared using carbopol 940 and hydroxypropylmethyl cellulose as gelling agents. Gelling agent was dispersed in a small quantity of distilled water and then stored overnight to ensure complete hydration. Valdecoxib in a suitable solvent (propylene glycol or ethanol) was added to the dispersion. Other excipients (methyl paraben and propyl paraben) were also added slowly with continuous stirring. In carbopol gels, pH of the vehicle was brought to neutral by using TEA (Triethanolamine). The final weight of the gel was adjusted to 50 gm with distilled water. Entrapped air bubbles were removed by keeping the gels in vacuum desiccators. Table 1 shows the composition of the carbopol and hydroxypropylmethylcellulose gels.

Drug content analysis

In drug content analysis, about 1gm of gel was weighed accurately and dissolved in aqueous solution of sodium lauryl sulphate (1%w/v SLS). After appropriate dilutions, valdecoxib content was analyzed spectrophotometerically (Pharma Spec UV-1700, Shimadzu, Japan) at 239 nm.

Rheological studies

Rheological behavior of the gels were evaluated using a viscometer (Brookfield LVDV III+CP, USA) by applying increasing values of the shear rate in order to reveal the possible flow behavior of the gels. All rheological measurements were performed at 30±0.2°.

Table 1: Composition of Valdecoxib topical gel formulations

Ingredients (gm)	C1	C2	C3	C4	C5	C6	H1	H2	H3	H4	H5	H6
Valdecoxib	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Carbopol	0.5	0.5	0.5	0.5	0.5	0.5	-	-	-	-	-	-
Hydroxypropyl methylcellulose	-	-	-	-	-	-	1.50	1.50	1.50	1.50	1.50	1.50
Propylene glycol	-	2.5	5	10	5	5	-	2.5	5	10	5	5
Alcohol	-	-	-	-	5	10	-	-	-	-	5	10
Methyl paraben	0.32	0.32	0.32	0.32	0.32	0.32	0.32	0.32	0.32	0.32	0.32	0.32
Propyl paraben	0.62	0.62	0.62	0.62	0.62	0.62	0.62	0.62	0.62	0.62	0.62	0.62
Triethanolamine	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	-	-	-	-	-	-

In vitro permeation study

Procedure

Valdecoxib release from the gels was examined through a cellophane membrane using a modified Keishery-Chein cell. Prior to study, cellophane membrane was soaked in diffusion medium for 4 h and then placed on the support screen of the diffusion cell assembly. All the joints were properly sealed with adhesive tape to avoid the penetration of diffusion medium. Aqueous solution of SLS (1% w/v) was used as the receptor medium and 1gm of the test gel was placed on the donor side. The receptor medium was kept at 37 ± 0.5°C. At predetermined time intervals, 5 ml sample was taken from the receptor compartment and replaced with the same volume of fresh 1% SLS. Absorbance of the solutions was measured spectrophotometerically at 239nm.

Statistical analysis of data

Each gel formulation was prepared in duplicate, and each analysis was duplicated. Effect of formulation variables on release parameters were tested for significance by using one-way ANOVA with Turkey post *t*-test using Graph Pad Prism software-5 version (Graph Pad Software Inc., San Diego, CA, USA) with the aid of Microsoft® Excel 2002.

RESULT AND DISCUSSION

When all the formulations were subjected to physical examination, the gels appeared to be translucent suggesting that the drug was not completely solubilized rather dispersed/suspended in the gel matrix. In order to neutralize the carbopol gels and adjust the pH of the gel compatible with the normal pH of the skin (pH 6-7), triethanolamine was used. All the systems showed non- Newtonian flow and exhibited pseudoplastic behavior, suggesting that gels do not flow at low shear stress and room temperature. The drug content analysis of the formulations showed that the drug content was high (>96%) with a low standard deviation (<1.76) and uniformly distributed in the matrix. Although no correlation is found between drug transfer through the synthetic membranes and natural ones, synthetic membranes can be used for assessing the product performance in quality assurance[7]. Since, before the drug reaches the skin surface and percutaneous transfer occurs, drug dissolves in the vehicle and solubilised drug diffuses through the vehicle to the barrier membrane. Therefore, the solubility of the drug in the vehicle[8] and selection of appropriate vehicle[9,10] are the crucial factors influencing the release of drug. In the present study, effect of propylene glycol alone and in combination with ethanol was evaluated in two different vehicles. The transport behavior of valdecoxib was investigated systemically by varying the concentration of propylene glycol (5 to 20% w/w) and alcohol (20 to 50 % w/w) in the vehicles. The influence of propylene glycol on the penetration of valdecoxib from the carbopol and hydroxypropylmethylcellulose gelling agents through the cellophane membrane was examined and the release profiles are presented in Fig.1 and 2. From the release profiles it is observed that, initially (~0.5hr), drug releases rapidly (burst effect) followed by a steady-state for the rest of the time. Initial burst effect could be due to the release of the drug immediate to the surface of the barrier membrane. Thus, the drug easily accessible to the solvent at the interface immediately dissolves and diffuses resulting in a burst effect. As the time advances, there exists a greater resistance to the penetration of the solvent to the inside of the gel matrix resulting in a steady-state effect. When the amount of drug released were plotted against square root of time[11], a linear relationship was obtained for each vehicle (R^2>0.970, Table 2), indicating that the release of valdecoxib from the gels was described by the Higuchi model where the rate controlling step is the process of diffusion through the gel matrix. This relationship is observed in systems in which the drug is fully dissolved or suspended in the gel, and thus the membrane has no significant effect and the properties of the formulation control the release of the drug[12]. It indicates that valdecoxib release from prepared carbopol and hydroxypropylmethylcellulose vehicles was more diffusion controlled through the gel matrix than by the cellophane membrane.

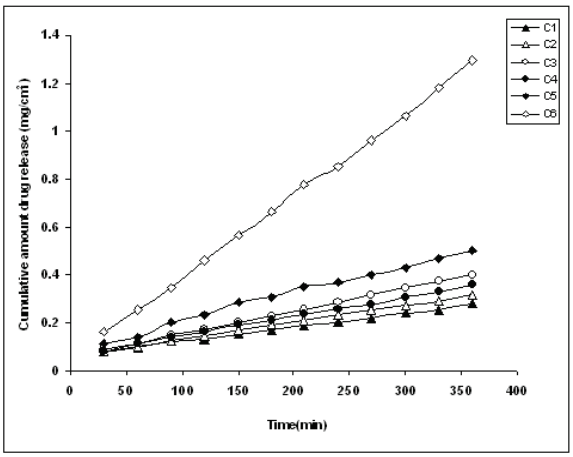

Fig. 1: Diffusion profiles of Valdecoxib from Carbopol gels

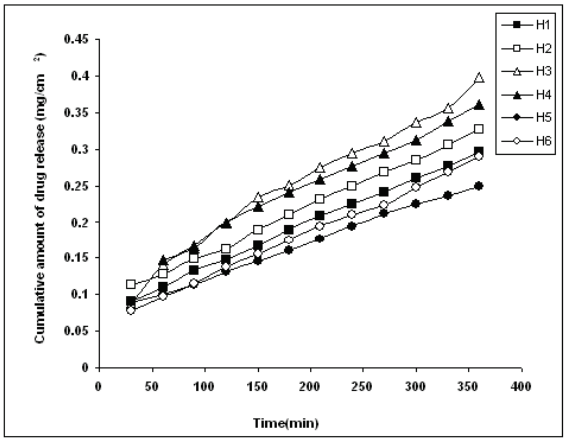

Fig. 2: Diffusion profiles of Valdecoxib from Hydroxypropylmethylcellulose gels

The amount of valdecoxib released from these gels is listed in Table 2. The release rates of valdecoxib increased with the addition of propylene glycol in the gels. At higher concentrations of propylene glycol (10 %), the enhanced steady-state flux of ACL in presence of propylene glycol therefore could be due to the greater solubility of the drug in the presence of propylene glycol suggesting that propylene glycol provided the drug in the more solubilised from in the vehicle. It is supposed that increasing the concentration of an active compound with in the solvent (propylene glycol) can give rise to persistent solvated complexes and evidence for that higher permeation of drug. However, further increase in the concentration of propylene glycol (to 20%), decreased flux significantly ($p<0.05$) were found. Analogous results that are lower release rates with higher concentrations of propylene glycol have been reported[13, 14]. The decrease in release may be attributed to the higher solubility and affinity of valdecoxib in the vehicle. These results show the action of propylene glycol as a cosolvent, because flux declines as the affinity of the drug to the vehicle rises[13,14]. Therefore, it is recommended to use of suspensions in order to optimize the thermodynamic activity of the drug in its vehicle to achieve maximum flux[15]. Thus in the present study, higher fluxes were noticed with formulations containing modest amount (i.e. 10%) of propylene glycol indicating that the drug was in more suspended state.

It is reported that propylene glycol has a greater effect on the penetration of drugs when it is used in combination with ethanol[16, 17]. In the present study, to evaluate the combined effect of propylene glycol and ethanol on the release of valdecoxib, gels containing 5% propylene glycol with two different concentrations of ethanol (C5, C6, H4 and H5) were prepared. In carbopol gels, valdecoxib release rate increased ($p<0.05$) in presence of ethanol and increased dramatically with further increase in the concentration of ethanol. The observed increase in the valdecoxib penetration with ethanol could be due to the enhanced solubility of drug[18] as well as thermodynamic activity of the drug by the ethanol in the vehicles. However, in case of hydroxypropylmethylcellulose gels, release rates decreased (H4 and H5) with the addition of ethanol. The microprecipitation induced by the addition of the alcohol, a non-solvent, within hydroxypropylmethyl cellulose may be attributed to decreased drug release.

Table 2: Evaluation parameters of Valdecoxib topical gel

Formulation Code	pH	Drug content (%) (±SD, n=4)	Jss mcg/cm^2/h (±SD, n=4)	Drug released at 360 min (Q/A) (±SD, n=4)	(Higuchi model) R^2
C1	6.5	96.15±0.34	0.06±0.0001	0.27 ± 0.10	0.9805
C2	6.7	101.85±0.21	0.08±0.0001	0.32 ± 002	0.9839
C3	6.6	96.35±1.35	0.09±0.0001	0.39 ± 0.09	0.9816
C4	6.6	97.95±1.76	0.07±0.0001	0.35 ± 009	0.9707
C5	6.3	99.45±0.21	0.12±0.0001	0.50 ± 0.15	0.9824
C6	6.7	99.95±1.17	0.35±0.0001	1.29 ± 0.39	0.9712
H1	6.5	96.66±0.89	0.060±0.0007	0.29± 0.27	0.9859
H2	6.5	98.21±3.42	0.07±0.0007	0.32 ± 0.09	0.9957
H3	6.6	97.48±1.52	0.09±0.0007	0.35± 0.15	0.9864
H4	6.4	99.27±0.10	0.065±0.0007	0.36 ± 0.02	0.9818
H5	6.4	100.23±0.49	0.05±0.0001	0.25 ± 0.31	0.9840
H6	6.5	98.33±1.37	0.06±0.0001	0.29 ± 0.12	0.9827

CONCLUSION

Valdecoxib topical gels were developed using carbopol and hydroxypropyl Methylcellulose as gelling agents. The effect of cosolvents, propylene glycol and ethanol on the in vitro release of valdecoxib was studied. The concentration of propylene glycol in formulations was found to be critical in deciding the release of the drug. Ethanol acted as cosolvent in carbopol gels and enhanced the drug release. Whereas, addition of ethanol to the hydroxypropyl methylcellulose gels, decreases the drug release. Apart from the choice of the cosolvents with poorly soluble drug, valdecoxib, the choice of combination of gelling agent and cosolvents is crucial in regulating the release of the drug from topical gels.

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