FORMULATION AND IN VITRO EVALUATION OF SORBITAN MONOSTEARATE / MONOPALMITATE ORGANOGELS CONTAINING IMIQUIMOD FOR TOPICAL APPLICATION

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INTRODUCTION

Imiquimod, which is an immunomodulating drug, is used topically to treat certain diseases of the skin, including skin cancers (basal cell carcinoma, Bowen's disease, superficial squamous cell carcinoma, some superficial malignant melanomas and actinic keratosis) as well as genital warts (1). It has been approved for use by the US FDA for topical treatment of external genital and perianal warts and actinic keratosis and has been recently approved by the US FDA as a topical cream formulation for the treatment of superficial basal cell cancer of the skin (2).

A successful therapy can be achieved by applying and keeping imiquimod at the treatment area of the skin for 6-8 hours. However, imiquimod can cause side effects such as redness, swelling, pain, burning following topical application (1), and therefore, imiquimod cream should be removed by washing the treated area after 6-8 hours. On the other hand, skin cancer treatments may require longer term application, therefore, formulations of controlled release drug delivery systems containing low imiquimod concentrations might be needed.

In this respect, organogels containing imiquimod were chosen to be suitable for this purpose. These systems are opaque, thermoreversible semisolids whose microstructures consist of interconnected tubular aggregates leading to a three-dimensional network. Nonionic surfactant-based organogels, containing pharmaceutically acceptable excipients may have a potential as delivery systems for hydrophobic and hydrophilic drugs. Organogels can be used as transdermal delivery systems; moreover, controlled release could be achieved for local applications (3).

The aim of this study was to formulate organogels containing imiquimod in order to achieve controlled drug release and to decrease the side effects of imiquimod.

MATERIALS AND METHODS

Materials

Imiquimod was kindly supplied by Topharman®, Shanghai, P.R. China. Sorbitan monostearate (Fluka, Germany), sorbitan monopalmitate, ethyl oleate, stearyl alcohol, cetyl alcohol, polysorbate 60 (Merck, Germany), glycerine (Emir Kimya, Turkey), white vaseline, tragacanth gum (Birka, Turkey) were used.

Preparation of the Organogel Formulations

Sorbitan monostearate or sorbitan monopalmitate organogels containing 1% (w/w) imiquimod were prepared by dissolving the sorbitan monostearate or sorbitan monopalmitate (20% w/w) in ethyl oleate in a water bath at 60°C while stirring the mixture. Then, 1% (w/w) of imiquimod was added and stirring was continued for 30 minutes. The resulting solution was allowed to cool at room temperature (3).

The w/o sorbitan monostearate or w/o sorbitan monopalmitate organogels (20% w/w) were prepared by adding water (10% w/w) dropwise to the mixture containing sorbitan monostearate or sorbitan monopalmitate and imiquimod in ethyl oleate while vortexing at medium speed at 60°C (4).

Preparation of the o/w Cream

An o/w cream, similar to the commercial imiquimod cream, containing glycerine, polysorbate 60, tragacanth gum, distilled water, isostearyl isostearate, stearyl alcohol, cetyl alcohol, white vaseline, and sorbitan monostearate was developed.

Light Microscopy

Organogels were examined under the light microscope. An inverted light microscope (Leica, Germany), equipped with a DFC 320 microcamera (Leica, Germany) was used.

In Vitro Release Studies

In vitro release studies of imiquimod from organogels and cream formulations were performed at 37±0.5°C using modified Franz diffusion cell and cellophane membrane (MWCO 12000-14000). 0.1 N HCl solution (10mL) was used as the receptor medium. Samples were withdrawn at predetermined times, replaced with fresh medium and analyzed at 318 nm using a UV 160A Shimadzu spectrophotometer.

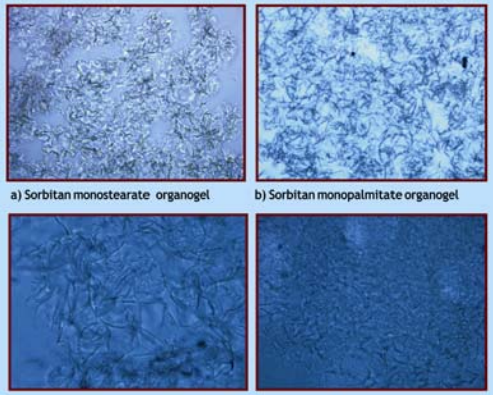
RESULTS AND DISCUSSION

Organogel Structure

Sorbitan monopalmitate organogels were observed to be physically less stable than sorbitan monostearate organogels. Organogels without water were more stable than organogels containing water.

Organogel Microstructure

Microscopic examination of sorbitan monostearate and sorbitan monopalmitate organogels reveals a network of tubular aggregates in the liquid dispersed phase (Fig.1, a and b). Addition of water to the system changes the microstructures of the organogels and finally results in gel breakdown as aggregate integrity is lost (Fig.1, c and d).



a) Sorbitan monostearate organogel b) Sorbitan monopalmitate organogel

c) w/o sorbitan monostearate organogel d) w/o sorbitan monopalmitate organogel

Figure 1. Light microscopy (40X) photographs of organogels

In Vitro Release Studies

In vitro release of imiquimod from both sorbitan monopalmitate and sorbitan monostearate organogels was found to be slower than that form the o/w cream ($p<0.05$) (Fig.2). The rank order of imiquimod release rate was found to be, o/w cream> sorbitan monopalmitate organogel > sorbitan monostearate organogel, and release rates of imiquimod were found to be 3.60 $\mu g.cm^{-2}.min^{-1}$, 0.87 $\mu g.cm^{-2}.min^{-1}$, 0.22 $\mu g.cm^{-2}.min^{-1}$ respectively. In vitro release of imiquimod from sorbitan monopalmitate organogels was found to be faster than sorbitan monostearate organogels ($p<0.05$) (Fig. 2).

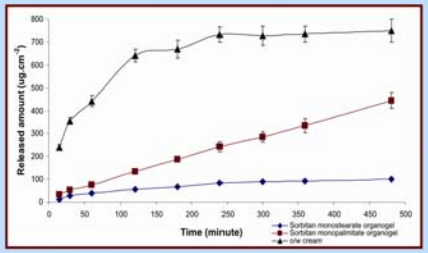


Figure 2. Release profile of imiquimod from different organogels and o/w cream.

The results of w/o emulsification of organogels can be seen in Figs. 3 and 4. In vitro release rate of imiquimod from w/o sorbitan monopalmitate organogels was found to be higher than w/o sorbitan monostearate organogels ($p<0.05$). The release rate of imiquimod from w/o sorbitan monopalmitate organogels and w/o sorbitan monostearate organogels was found to be 0.51 $\mu g.cm^{-2}.min^{-1}$ and 0.20 $\mu g.cm^{-2}.min^{-1}$, respectively. While the release rate of imiquimod from w/o sorbitan monopalmitate organogels decreased upon addition of water, no significant effect was observed on the release rate of imiquimod from w/o sorbitan monostearate organogels ($p>0.05$). Both w/o sorbitan monostearate and w/o sorbitan monopalmitate organogels have modified the release profile of imiquimod as compaired to the o/w cream.

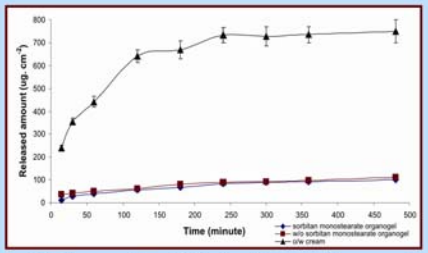


Figure 3. Release profile of imiquimod from sorbitan monostearate organogels and o/w cream.

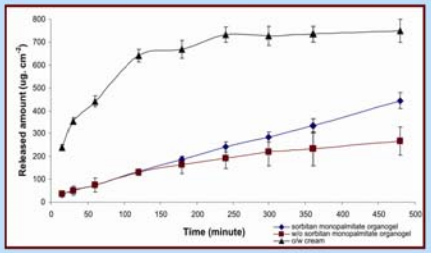


Figure 4. Release profile of imiquimod from sorbitan monopalmitate organogels and o/w cream.

CONCLUSION

The release of imiquimod from the two types of organogels were slower than that of the o/w cream whereas sorbitan monopalmitate and w/o sorbitan monopalmitate organogels have exhibited faster release compared to those of sorbitan monostearate and w/o sorbitan monostearate organogels. In conclusion, sorbitan monostearate/monopalmitate organogels (with/without water) exhibiting controlled release properties might be promising for the treatment of warts and skin cancer.

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