

Iontophoretic Delivery of Cream and Gel Formulations of Acyclovir

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ABSTRACT:

The aim of this work was to study cream and gel formulations of acyclovir contained in a delivery cartridge for maximized transdermal iontophoretic delivery of acyclovir. Delivery from a formulated 5% acyclovir cream was comparable to the Zovirax™. However, gel formulations were more effective than creams.

INTRODUCTION:

Acyclovir (ACV) is a synthetic analogue of 2' - deoxyguanosine with a molecular weight of 225. It is an ampholyte with pKa 2.4 and 9.2. ACV is used to treat cutaneous viral infection caused by herpes simplex virus type1 (HSV-1). It is also effective against HSV-2 and to a lesser extent against Epstein – Barr virus and cytomegalovirus. ACV is commercially available as intravenous, oral and topical dosage forms. The oral bioavailability is very low (20%) and IV administration has side effects such as nephrotoxicity; therefore, topical administration is preferred. However, acyclovir being a hydrophilic molecule its permeation through intact skin following topical administration is quite low. To increase ACV concentration at the target site(basal epidermis), Iontophoresis (ITP), which utilizes small electric currents to drive ionized and unionized drug molecules into the skin, has been suggested as a potential enhancing technique. This method can also improve patient compliance since it is intended as a single treatment per herpes outbreak.

In our previous work with solution formulations (data not shown), cathodal ITP showed the potential for enhanced delivery of ACV. In this study the effect of different cream (anodal) and gel (cathodal) formulations on ITP delivery was studied using a single use drug cartridge and low current density iontophoresis.

EXPERIMENTAL METHODS:

The delivery of ACV was studied using iontophoresis (0.2 mA/ cm² applied for 1 hr) applied to gel or cream formulations directly or in a drug cartridge. *In vitro* studies (n ≥ 3) were performed using freshly excised hairless rat skin mounted on vertical Franz diffusion cells.

The cream formulations were placed in a clean beaker and heated to 60°C for about 10 mins. A small amount was syringed out while mixing continuously, weighed and injected into the drug cartridge (Fig. 1). The gel formulations were simply

taken in syringe, weighed and injected into the drug cartridge. For ITP, the stainless steel electrode in the cartridge acted as the delivery electrode while platinum or Ag/AgCl was used as the return electrode. The receptor compartment contained phosphate buffer (50 mM) of pH 7.4. The electrodes were connected to the current source (Fig. 2) and samples were taken periodically. For *in vivo* microdialysis, a linear probe was inserted into the skin and PBS was used as perfusate (2). A cartridge filled with an ACV formulation was placed on the skin in the region where the probe was inserted, and samples were collected every 0.5h for 4hrs.

Samples were analyzed by HPLC, using Varian Microsorb C18 column. Mobile phase was composed of 0.1% acetic acid (98%) and ACN (2%). Flow rate was 1.2 mL/min and detection wavelength was 254nm (1).

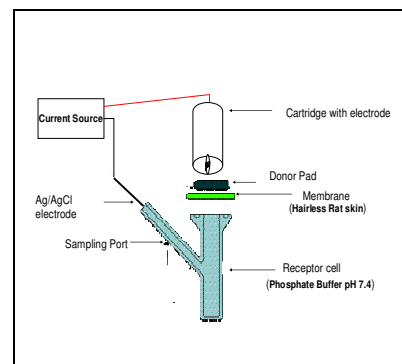


Figure 1

Figure 2

RESULTS AND DISCUSSION:

The results for different formulations are summarized in Table I. For, both 5% ACV cream formulation and Zovirax™ delivery by ITP across hairless rat skin was significantly greater than passive (Fig. 3).

Much higher delivery was observed for the gel formulations as compared to cream formulations (Table 1).



Figure 3

Table (I)

Formulation	Cum. Amt. permeated \pm SE (mcg/sqcm)
Zovirax®	2.02 \pm 0.04
5%ACV cream	2.64 \pm 0.10
Aqueous ACV	3.79 \pm 0.60
5%ACV cream	4.41 \pm 0.28
4% ACV Gel	22.95 \pm 6.43
3% ACV Gel	12.34 \pm 1.43
2% ACV Gel	5.53 \pm 2.08
4%ACV Gel with glycerin	21.51 \pm 5.64
4% ACV Gel with PG	30.39 \pm 12.48

The cream formulations have a pH of 6.8, at which point ACV had very poor aqueous solubility and is virtually un-ionized (pKa 2.27 and 9.25). In contrast, the gel formulations have a pH of about 11, which solubilized all ACV in the formulation and 98% is in deprotonated (anion) form and thus more suitable for cathodal Iontophoresis.

Since the octanol/water partition coefficient (log P value) of ACV is -1.56, it is expected to be less soluble in the oil phase of the cream. Therefore, the aqueous phase is expected to contribute to the delivery of ACV from the cream. This was confirmed by the results from a study which showed comparable delivery from the aqueous phase of the cream, which has ACV content of about 0.3%, and the 5% ACV cream (Fig.4).

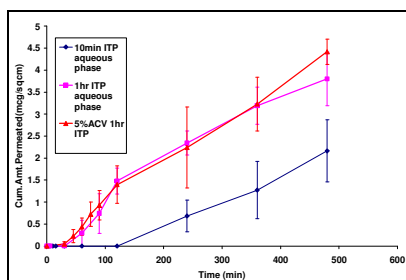


Figure 4

The delivery of ACV increased with increase in ACV Concentration in gels (Fig.6). The delivery of ACV from 4% ACV Gel-G (containing glycerin as co solvent) and 4% ACV Gel-PG (containing propylene glycol as co solvent) showed no difference when tested in the in vitro model (Table 1). An *In Vivo* microdialysis study was done to confirm the results. The concentration of ACV where the probe was

placed was 105.25 ± 19.8 (mcg/ml) for 4% ACV with Glycerin and 10.80 ± 1.43 (mcg/ml) for PG formulation at 2hrs. One possible explanation for this is the fact that the flux of PG across the skin is far more than the ACV due to the differences in the MW, and this may leave less solvent for ACV in the donor.

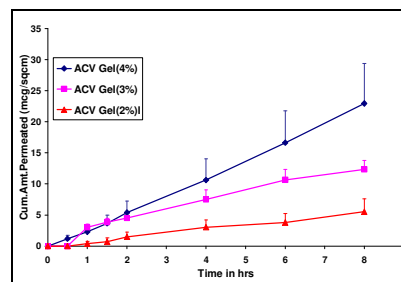


Figure 6

CONCLUSIONS:

ITP delivery of ACV creams showed a better delivery than passive. The aqueous phase in ACV cream formulation plays a major role for the amount delivered by ITP. ACV gels at pH 11 are better formulations for ITP delivery of ACV than creams at pH 6.8. The composition of the gel formulations also plays a very important role in the ITP delivery of ACV.

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