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Transcutaneous permeation of antiviral agents

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ABSTRACT

The two-pronged approach to antiviral drug development involves the design of new chemical entities capable of targeting the viral enzymes or the development of new drug delivery strategies. Transdermal drug delivery has attracted considerable interest over the last few decades as it combines the advantages of oral and parenteral modes of drug administration. New enhancement methods aimed at facilitating transcutaneous permeation such as Pheroids™ are being developed and existing techniques such as ethosomes, microemulsions or iontophoresis are being applied to a wide variety of compounds. This review discusses transdermal drug delivery technologies and their application to antiviral agents. Although, progress has been made, safety concerns remain and with more research, antiviral agents will ultimately be delivered through the transdermal route.

Contents

1. Introduction

Viruses are small intracellular holoparasites, with either a RNA or DNA genome surrounded by a protective protein coat called capsid [1,2]. Retroviruses are enveloped (about 100 nm in diameter), icosahedral viruses with an RNA of about 7–10 kb [3]. There are currently two known species of HIV, namely, HIV-1 and HIV-2, with their respective subspecies [4]. Human immunodeficiency virus-1 (HIV-1) is a retrovirus that primarily infects components of

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the human immune system, such as $CD4^+$ T cells, macrophages and dendritic cells [5]. HIV-2 is more prevalent in West Africa, and takes a longer time to develop into immunodeficiency from infection than HIV-1 [4].

The HIV virus infects the host cell by binding the viral gp120 protein to two transmembrane receptors, namely, $CD4^+$ and either of the two chemokine receptors, CCR5 and CXCR4 [4]. HIV infects macrophages and T-helper lymphocytes ($CD4^+$); but the significant feature of AIDS is the depletion of $CD4^+$ cells [4]. The viral genome contains three structural genes – *gag, pol and env* – and six regulatory genes – *tat, rev, nef, vif, vpr and vpu* [4]. HIV infection in the human body results essentially from the integration of the viral genome into the host cell for the purpose of cell replication leading sometimes to AIDS which is the advanced stage of the disease [4]. It has been estimated that 40 million people are currently infected with HIV (with and without AIDS) globally, 1.2 million of whom are in the United States [6]. Acquired immunodeficiency syndrome is the most advanced stage of HIV infection, characterized by clinical signs and symptoms that take an average of 2–15 years to manifest [7]. Numerous medications have been developed to inhibit viral replication including protease, nucleoside reverse transcriptase, non-nucleoside reverse transcriptase, integrase, and fusion inhibitors [7].

Herpes simplex viruses (HSV can be classified into herpes simplex virus-1 (HSV-1), herpes simplex virus-2 (HSV-2), varicella zoster virus, cytomegalovirus, Epstein-Barr virus, human herpesviruses 6 and 7 as well as Kaposi's sarcoma associated herpesvirus (type 8) [8]. HSV-associated diseases are among the most common infections, affecting nearly 60%–95% of adults [8]. Infections caused by the herpes simplex virus (HSV) are widespread: from 50 to 95% of the world adult population possess antibodies to HSV-1, and 20–30% are carriers of HSV-2 by the age of 15–29 years [9]. Herpes Simplex Virus Type 1 (HSV-1) is a double-stranded DNA virus with a very high infection rate in humans [10].

The hepatitis B virus (HBV) is a small DNA virus which belongs to the Hepadnaviridae family and has features similar to retroviruses [11]. HBV is classified into eight genotypes, A to H. The infectious HBV virion possesses a spherical, double-shelled structure 42 nm in diameter, comprising a lipid envelope containing hepatitis B surface antigen (HBsAg) that surrounds an inner nucleocapsid composed of hepatitis B core antigen (HBcAg) complexed with virally encoded polymerase and the viral DNA genome [11].

Although there are several pathogenic viruses, reports on the transdermal drug delivery of antiviral agents are sparse. Understandably, not all antiviral molecules are amenable to this mode of administration due to several reasons-both physicochemical and biological.

1.1. Transcutaneous permeation

The transdermal pathway is one of the most promising drug delivery routes due to the merits associated with this pathway in comparison with other drug delivery routes such as oral or injections [12].

The advantages of this route include improved patient compliance, sustained release, avoidance of gastric irritation, convenience as well as elimination of pre-systemic first-pass metabolism [13]. However, not all medications can be delivered through the skin [13]. For a drug to be delivered though this route into systemic circulation, it must meet certain criteria: low dose, optimal aqueous and oleaginous solubility, optimal partition coefficient (log P of between 1 and 3) and low molecular weight [14]. Even then, the stratum corneum, which is the outermost layer of the skin, hinders the penetration of most compounds [15].

The skin is the largest organ of the human body and even though the average thickness of skin is only 1 mm, the stratum corneum and epidermis constitute significant barriers for the transcutaneous permeation of medications into the bloodstream [16]. Conventionally, only lipophilic drugs with low molecular weight can permeate the skin barrier [16]. The challenge of crossing the skin barrier is attributed the unique anatomic features of the skin. The thin (20–40 mm) outermost layer of human skin, called the stratum corneum (SC) is the main barrier to the transfer of water, chemicals, and microorganisms [17].

The SC comprises the corneocytes and an intercellular matrix [18]. The SC is a multiphasic, anisotropic membrane comprising about 8–20 layers of flattened, hexagonal shaped, keratin-enriched corneocytes with highly organized lipid lamellae filling the extracellular space between the corneocytes [17]. The extracellular lipid matrix in the stratum corneum consists of ceramides (CERs), cholesterol (CHOL) and free fatty acids (FFAs) and involves two lamellar phases: the short periodicity phase (SPP) and the long periodicity phase [19]. It is obvious that certain antiviral agents cannot be delivered through the transcutaneous route due to the fact that these molecules do not meet the physicochemical criteria (partition coefficient, solubility, molecular weight, low dose, etc). An important consideration is that high dose antiviral medications may not be amenable to this route of delivery since the existing transdermal enhancement technologies may not provide therapeutic concentrations.

Numerous techniques have been developed for the enhancement of transdermal drug delivery. These include ethosomes [20,21], microemulsions [22], iontophoresis [23–25], Pheroid™ [26] and chemical penetration enhancers [27]. This review will focus on the percutaneous transport of antiviral agents. Techniques for the transdermal delivery of selected antiviral agents are summarized in Table 1.

1.2. Ethosomes

Ethosomes (Fig. 1) are vesicular formulations which contain phospholipids, alcohol (ethanol/isopropyl alcohol) in relatively high concentration and water [20,28,29]. It was previously thought that vesicular systems cannot coexist with high concentrations of ethanol due to the interdigitation effect of the later [20]. However, Touitou showed that lipid vesicles with ethanol in relatively high concentrations (ethosomes) are not only feasible but also capable of increasing the transcutaneous flux values of medications [20]. Ethosomes are different from classic liposomes and transfersomes, by their structure, mode of application and mechanism of action [30]. As earlier emphasized, ethosomes contain soft phospholipid vesicles in a hydroethanolic milieu and it has been demonstrated that with ethanol concentrations of up to 45%, phosphatidylcholine is organized in bilayers exhibiting a lineshape, which is characteristic for spherically organized phosphatidylcholine (PC) bilayers [30]. Paramagnetic-ion NMR experiments, fluorescent anisotropy and differential scanning calorimetry (DSC) measurements have also shown that the phospholipid bilayers in ethosomes are packed less tightly, possess a high degree of fluidity and have a lower transition temperature in comparison with liposomes [20,30]. It has been postulated that the incorporation of ethanol in ethosomes facilitates increased drug deposition and permeation due to the interaction between ethanol and the lipid molecules, which improves lipid fluidity and cell membrane permeability [21].

1.3. Microemulsions

Microemulsions (MEs) are transparent, optically isotropic, monophasic and thermodynamically stable systems made from water, oil, surfactant and a co-surfactant [22,31–33]. A hypothetical