Organogels, hydrogels and bigels as transdermal delivery systems for diltiazem hydrochloride

Mahmoud Mokhtar Ibrahim a,b,*, Salma A. Hafez a, Mahmoud M. Mahdy a

a Department of Pharmaceutics, Faculty of Pharmacy, Zagazig University, Zagazig, Egypt
b Department of Pharmaceutics, Faculty of Pharmacy, Najran University, Najran, Saudi Arabia

Abstract

In the present study, gel formulations of organogels, hydrogels, and oleo-hydrogel (bigels) were evaluated as transdermal drug delivery systems for diltiazem HCL (DH). Organogels were prepared using soya-bean oil (SO) as a solvent and span 60 (Sp 60), cetyl alcohol (CA) or lecithin-pluronic (PLO) as organogelators without and with different surfactants (2% w/w) namely span 80 (Sp80), tween 20 (T20) and tween 80 (T80). On the other hand, hydrogels were formulated using Hydroxypropyl-methylcellulose (HPMC) polymer and bigels were prepared by mixing organogels with HPMC hydrogels. The prepared gels were analyzed microscopically, thermally by DTA and for pH, and viscosity. The effect of gelator used, surfactant types and pH of the sink on DH release from cellophane membrane was investigated. In addition, the DH permeability across the rabbit skin was evaluated. Finally, the in vivo performance of various gel formulations was assessed based on the hypotensive effects of the drug using hypertensive albino male rat models. The microscopical analysis indicated that the solid fibers formed by gelator particles form the backbone of the organogels while bigels appeared as emulsion like. The addition of surfactants showed an increase in organogel viscosity. The thermal analysis of organogels indicated that the drug present in amorphous not in crystalline form. The release studies indicated that DH release from organogels, hydrogels and bigels could be controlled. The included surfactants decreased the DH release and permeation from organogels compared to those without surfactants using either Sp60 or CA. HPMC hydrogel and Bigels showed higher DH release and permeation rates when compared to organogels. The percent DH released in different pH values was in the following descending order: pH5.5 > pH1.2 > pH6.8 > pH7.4. The in vivo antihypertensive activity of DH using different transdermal gels is arranged as following: hydrogels > PLO organogel > bigel > Sp 60 organogel.

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1. Introduction

The development of new drug molecules is time consuming and expensive. On the other hand, the existing marketed and patented drug substances with known therapeutic effects can be used with the modification of their pharmacotherapeutic characteristics. This was achieved by incorporating the drug in a suitable drug delivery system [1]. Diltiazem HCl (DH) is a calcium channel blocker belonging to the benzothiazepine family. It is widely prescribed for the treatment of hypertension and angina [2]. Although DH is well absorbed from the gastrointestinal tract, it undergoes substantial hepatic first-pass effect. Therefore, DH elimination half-life is very short (3–4.5 h) and frequent administration of the drug required to maintain therapeutic effect. The drug dosage is reported to be 30 mg 4 times a day and may increase as necessary up to 360 mg/day in divided doses in order to maintain adequate plasma levels [3]. Transdermal application of the drug was our target of this investigation to minimize the frequency of DH administration and overcome its side effects after oral administration of conventional dosage forms.

The transdermal route of drug administration is definitely one of the potential routes for local and systemic delivery. This route provides a controlled diffusion of drugs into the systemic circulation, breaks many barriers in medical therapy like the need of assistance, intermediate dosing and uncomfortable administration and improves patient compliance [4,5]. In general, gel-based products may be categorized either as hydrogels or organogels depending on the polarity of the external liquid component. Water is the external liquid component of hydrogels while organogels were formulated using non-polar solvents such as hexane, isopropyl myristate, sunflower oil, corn oil or others.

Hydrogels are prepared using natural or synthetic hydrophilic polymers which form a colloidal network of polymer chains in water. They possess a degree of flexibility which is very similar to natural tissue. Moreover, hydrogels are of many uses such as essential controlled drug delivery systems, in cell culture, dressing for healing of wounds. Their easy way of preparation and availability made them of high value in the pharmaceutical field [6]. On the other hand, the use of organogel based products is increasing due to their easy method of preparation and inherent long-term stability [7]. Depending on the mechanism of the formation of the three dimensional gel skeleton, the organogels are considered as fluid-filled structures and solid-fiber based gels [8]. They are thermoreversible and have the ability to accommodate both hydrophilic and hydrophobic compounds within the gel structure. This property has also widened the scope of the organogels uses as controlled drug delivery systems which can be taken via several routes of administration. The gelators which compose the major components of an organogel are generally amphiphilic substances, such as sorbitan monostearate (Sp60) and sorbitan monopalmitate (Sp40). Moreover, Lecithin organogels can be obtained by the addition of a critical amount of water to its component of hydrogels while organogels were formulated using non-polar solvents such as hexane, isopropyl myristate, sunflower oil, corn oil or others.

2. Materials and methods

2.1. Materials

Diltiazem HCl (DH) was a gift from Egyptian Pharmaceutical industrial company (E.P.I.Co), Egypt. Sp60, Sp80, T20, T80, CA, Pluronic F127, HPMC, and SO were purchased from Sigma chemical Co., St. Louis, MO, USA. The Epikuron 200 phospholipids (>92% SPC) were a gift from Lucas Meyer, Hamburg, Germany. All other chemicals were of analytical grades and obtained from the El-Nasr Company for pharmaceutical chemicals, Cairo, Egypt.

2.2. Gels preparation

Different organogels, hydrogels and bigels were prepared by different procedures which are briefly described below and the formulations are listed in Table 1. The final DH concentration was adjusted to be 150 mg/g in all the formulations.

2.2.1. Organogels

Organogels were prepared by dissolving 10% w/w of Sp60 or CA in SO vehicle into the SO in wide mouth vials, without or with additional 2% w/w of different surfactants such as Sp80, T20 or T80. The vials were kept in a water bath at 60 °C, until a homogenous clear solution was obtained. The hot solutions were allowed to cool down at room temperature so as to allow organogel formation.

150 mg of DH was loaded into each 1 g of the organogel formulations by the mixing 0.2 ml of heated DH (60 °C) solution (750 mg/ml) in distilled water with the surfactant hot oily solution while magnetic stirring at 500 rpm. The mixture was allowed to cool giving the medicated organogel formulas [12].

2.2.2. PLO gels

The aqueous phase (10% w/w Pluronic F127 solution in water) of PLO was prepared by the cold process reported by Murdan [10]. PLO gels were obtained by adding the oil phase (solution of PC in SO) to the aqueous phase with vigorous stirring. The hydrophilic DH solution was added to the aqueous phase with stirring before the addition of the oil phase [10].

2.2.3. Hydrogels

HPMC hydrogels were prepared by allowing the weighed quantities of HPMC (10% w/w) to be soaked in distilled water
for a period of 2 h until complete hydration and gel formation. DH solution (750 mg/ml) was added to the dispersions with continuous stirring until homogenous gel was formed and the drug concentration was adjusted to be 150 mg/1 g.

2.2.4. Bigels
The prepared gels were stored separately at 4 °C for at least 24 h, then bigels were prepared by mixing HPMC hydrogels with the Sp60 or CA organogels (1:1 w/w) prepared without or with different surfactants.

2.3. Microscopic study
A compound optical microscope (Olympus B 41) was used for analyzing the microstructure of the organogel, hydrogel and bigels. Attempts were used to understand the mechanism of the gel formation by varying the composition and proportion of the ingredients used and analyzing their microstructure.

2.4. Thermal analysis
Thermal properties of organogels were studied using differentials thermal analysis (TA-50 thermal analyzer, Shimadzu, Japan). Samples were heated from 0 °C up to 600 °C, at a rate of 6 °C/min.

2.5. pH measurement
The pH of the organogel, hydrogel and bigel samples was detected by using digital pH meter (Cole-parner instrument Co., U.S.A). The pH of the gels was measured by bringing the probe of the pH meter in contact with the sample [13].

2.6. Determination of viscosity
The viscosity of all the gel formulations was determined by using Visko Star-R FUNGILAB viscometer, sample spindle (R6) and speed of 10 rpm at 25 °C. The value of the viscosity is displayed in the form of cP.

2.7. In vitro release study
In vitro release of DH from different gel formulations was performed using shaker water bath (Serve well Instruments and Equipment, Pvt. Ltd. India) maintained at temperature of 32 °C ± 1 °C and allowed to agitate at 50 rpm. One gram of the gel was weighed in plastic holders then attached to a permeation cell previously specified by Mahmoud et al. and covered with the cellophane membrane (soaked in phosphate buffer pH 5.5 for 24 h before use) [14]. The cell was immersed to the depth of 1 cm below the surface of the phosphate buffer (pH 5.5) in the receptor compartment (50 ml). Samples of 3 ml each from the receptor compartment (50 ml). Samples of 3 ml each from the receptor compartment (50 ml). Samples of 3 ml each from the receptor compartment (50 ml). Samples of 3 ml each from the receptor compartment (50 ml). Samples of 3 ml each from the receptor compartment (50 ml). Samples of 3 ml each from the receptor compartment (50 ml). Samples of 3 ml each from the receptor compartment (50 ml). Samples of 3 ml each from the receptor compartment (50 ml). Samples of 3 ml each from the receptor compartment (50 ml). Samples of 3 ml each from the receptor compartment (50 ml). Samples of 3 ml each from the receptor compartment (50 ml). Samples of 3 ml each from the receptor compartment (50 ml). Samples of 3 ml each from the receptor compartment (50 ml).

2.8. In vitro skin permeation studies
Abdominal skin of male rabbits (2–2.5 kg) was used in this study. Before the permeation study, the skin was hydrated in phosphate buffer pH 5.5 at 4 °C overnight and the adipose tissue layer of the skin was removed by rubbing with a cotton swab [15]. The permeation experiments were run by using the same cells previously described in the in vitro release studies but the abdominal rabbit skin rather than semi-permeable cellophane membrane was used to cover the gel preparation with the stratum corneum side face [16]. The experiment was continued as described above. The cumulative amount of DH permeated per unit surface area was plotted vs. time.

2.9. In vivo study of DH as transdermally applied antihypertensive agent
This study was done using adult albino male rats weighing 250–300 g obtained from the animal breading center, Faculty
of Veterinary medicine, Zagazig University, Egypt. Animals were treated according to Ethical committee of animal handling in Zagazig University "ECAHZU". Firstly, hyperten-
sion was induced in rats by complete left renal artery ligation according to the method described by Cangiano et al. [17]. Postoperatively, the rats were given penicillin G (100,000 units I.M.) per rat for three successive days, and were allowed free access to food and water for 28 days till the complete induc-
tion of hypertension [18]. In vivo studies were done using DH formulations of Sp60/SO organogel, HPMC hydrogel, PLO and Sp60/HPMC bigel to evaluate their antihypertensive effects when administered transdermally. Results were compared with that of the non treated rats as negative controls and those administered oral DH solution as positive controls. Animals were divided into six groups as listed in Table 2. Each group consisting of six rats (n = 6) and allowed the application of 0.2 g of different gel formulations which containing 30 mg of DH on the hairless skin of the abdomen region (about 4 cm² in size). The negative control group was received placebo hydrogel free from drug. The positive control group (300 g weighed rats) received the dose of 0.027 ml of oral DH solution which containing 2.025 mg of DH.

The oral dose calculated according to Paget’s equation [19]:

\[
\text{Therapeutic dose for rat weighing } 200 \text{ g} = \frac{18 \times \text{Adult human therapeutic dose (75 mg)}}{1000} = 1.35 \text{ mg}
\]

On the other hand, according to Fick’s first low, the drug efflux increased across the skin as the concentration gradient increased [20]. To reach the maximum thermodynamic activity, the drug concentration in the donor compartment applied transdermally must be maximum or in the saturation state. Accordingly, DH concentration in the transdermal gels to be tested was kept as high as possible (30 mg/0.2 g gel).

The blood pressure measurements were done using Oscillograph (Washington, 400 MD 4C, Bio Science, Sheerness, Kent, U.K) at time intervals from 0 to 6 h. The rats were anaesthetized with urethane (ethyl carbamate) in a dose of 1.75–2.0 g/kg body weight then injected I.P as 25% freshly prepared aqueous solution. Intra arterial cannulation was done and the systemic arterial blood pressure was recorded and the blood pressure of rats was determined employing the method of Burden et al. [21].

The antihypertensive effects of the selected formulations were studied after induction of hypertension into rats and the results were compared to that of the control (group I). For in vivo performance, gels which showed the highest release rates both through the cellophane membrane and the permeability across rabbit skin were selected. The antihypertensive activity was studied at different time intervals after application (1, 2, 3, 4, 5 and 6 h) to differentiate between the onset of action of the oral DH solution and transdermal gel formulations. The mean arterial blood pressure was calculated according to the following equation [22]:

\[
\text{Mean arterial B.P} = \frac{\text{Systolic B.P} – \text{Diastolic B.P}}{3} + \text{Diastolic B.P}
\]

2.10. Statistical analysis

All values were expressed as mean ± SD. Data were analyzed statistically using one way analysis of variance (ANOVA) test. The level of significance was considered at P < 0.05.

3. Results and discussion

Different organogelators were dissolved in the hot oil phase until a clear homogenous solution was obtained. As the temperature cooled down, the gelators precipitated in the oil due to changes in the solubility parameters. The precipitated gelators grown in size as fibers or reverse cylindrical micelles. The fibers or the micelles physically entangled with each other to form a three dimensional networked structure [23]. The gel containers were then inverted and observed for any flow (Fig. 1). Samples were considered as organogels if they did not flow [12]. All the prepared gels except those of the PLO were white to pale yellow in color, oily in touch, opaque in nature and no odor.

Concerning PLO, it was jelly like in appearance with yellow color, and aqueous touch. On the other hand, the prepared DH hydrogel was transparent, homogenous, clear and smooth with aqueous touch because the liquid compartment is water. In addition, bigels (combined forms of hydrogels with organogels) were white in color, creamy in appearance with homogenous smooth non oily touch. It is well known that a large number of emulsifiers could affect the properties of lamellar lipids of the intracellular matrix of the SC, resulting in the increased transepidermal water loss and several irritant re-
actions [24]. However, the simple composition of organogels, bigels and hydrogels is therefore beneficial considering the safety of these formulations.

3.1. Gel morphology

The variations in the microstructure of organogels were studied as the gelator and/or surfactant types changed (Fig. 2). The results showed the presence of needle shaped clusters of Sp60 when 10% (w/w) gelator concentration was used (Fig. 2). As another surfactant added such as T80, T20, or Sp80, these clusters aggregated to form fiber-like structures. These fiber-like structures were in the form of networked skeleton which could help in the immobilization of the oil. Hydrogel

<table>
<thead>
<tr>
<th>Groups</th>
<th>Formulation</th>
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<tbody>
<tr>
<td>Group (I)</td>
<td>Control and received placebo gels free from drug (–ve control).</td>
</tr>
<tr>
<td>Group (II)</td>
<td>Received 0.2 g of Sp60/SO organogel which containing 30 mg of DH.</td>
</tr>
<tr>
<td>Group (III)</td>
<td>Received 0.2 g PLO about which containing 30 mg of DH.</td>
</tr>
<tr>
<td>Group (IV)</td>
<td>Received 0.2 g of Sp60/HPMC bigel which containing 30 mg of DH.</td>
</tr>
<tr>
<td>Group (V)</td>
<td>Received 0.2 g of HPMC hydrogel which containing 30 mg of DH.</td>
</tr>
<tr>
<td>Group (VI)</td>
<td>Received 0.027 g of oral solution which containing 2.025 mg of DH (+ve control)</td>
</tr>
</tbody>
</table>
showed Blank pictures where bigels appeared emulsion like with the oil phase dispersed in a continuous aqueous one.

### 3.2. Thermal analysis

The thermogram of DH showed a single sharp endothermic peak at 207.55 °C and another broad one at 245.50 °C (Fig. 3(a)). The sharp endothermic peak is corresponding to the melting point of the drug where the broad one is corresponding to its decomposition [25]. Also, Fig. 3 (b and c) showed strong endothermic peaks at 48.78 °C and 50.93 °C which indicated the melting points of CA and Sp60, respectively. DTA-thermogram of DH-CA organogel showed a small and broad peak of DH appeared at 208 °C (Fig. 3(d)). However, Sp60-DH organogel showed shifting of DH peak from 207 °C to 188 °C and become smaller than that of pure DH. This indicated the interaction of the gel clusters of Sp60 and DH which pointed to the presence of the drug in the amorphous nature (Fig. 3(e)). These results agree with that of Sultana et al., who found that the endothermic peak of DH in alginate microspheres was not distinctive indicating that, the drug was no longer present in the crystalline form [26].

### 3.3. Measurements of the gel pH and viscosity

The pH values of the organogels, hydrogels and bigels were found to be in the range of 4.66–5.91 (Table 3), which were close to skin pH 4.5–7 [27]. This enhances a safe application to the skin without irritation problems. All gel formulations were found to have viscosities in the range of 870 cP to 34900 cP, and as a general observation, the incorporation of surfactants

![Fig. 1 – Gelation process of the organogel (a) Clear solution after heating; (b) Uniform, cloudy suspension upon cooling and standing; (c) Opaque, semi-solid gel upon further standing.](image)

![Fig. 2 – Microscopic study of different gel formulations, a) Sp60/50 organogel. b) Sp60/Sp80 organogel. c) HPMC hydrogel. d) microstructure of bigel.](image)
such as T80, T20, or Sp80 resulted in increasing the viscosity of the gel as listed in Table 3.

### 3.4. In vitro release of DH across semi-permeable cellophane membrane (pH 5.5)

For transdermal drug delivery, in vitro drug release tests are often performed before transdermal permeation studies. From the in vitro release studies it is possible to determine how the viscosity and the ingredients of the vehicle affected the drug release profiles of each formulation [28]. The release of DH from organogels of SO formulated using different gelling agents is demonstrated in Fig. 4. From Fig. 4, it is clearly illustrated that DH was slowly released from organogels where different gelators used. About 43.7%, 49.4, and 50.4% of the drug was released after 360 min from organogels of the PLO, Sp60, and CA gelators, respectively. The drug release was dependent on the solid skeleton network formed by the gelator molecules [29,30]. CA and Sp60 organogels exhibited a similar drug release pattern (no significant difference, P > 0.05) due to the similarity in their transition temperatures (about 50.93 °C and 48.78 °C for Sp60 and CA, respectively). Concerning PLO, the significant lower DH release rate may be attributed to the high affinity between the freely water soluble DH and PLO surfactants concentrated on the emulsion interface. A similar study showed the release of 81.56% piroxicam at 48 h from PLO organogels, however the solubility of piroxicam in water was low [30]. The authors attributed the result to the amphiphilic nature of pluronic and the weak affinity between pluronic and piroxicam which may facilitate the release of poor water soluble drugs from organogels.

Inclusion of surface active agents into gels is well known to affect drug release and permeability across biological membranes [31]. Different surfactants of different acyl chain lengths and unsaturation such as Sp80, T20 or T80 were used in concentrations of 2% w/w to modify the release profile of DH from the organogels of Sp60/SO or CA/SO. From Fig. 5(a and b), it was observed that the percentage DH released after 360 min from different organogels containing 2% of Sp80, T20, or T80 were 38.48%, 33.80%, and 27.56%, respectively with Sp60/SO organogels and was 44.21%, 40.04% and 39.52%, respectively with CA/SO organogels. Generally, all surfactants had significantly decreased the drug release (P < 0.05) from organogels compared to those without surfactants in both Sp60 and CA. This result might be due to the participated inverse tubular aggregation of Sp60 or CA that increased the viscosity and gel strength [32]. On the other hand, incorporation of Sp80 into organogels resulted in a significant higher DH release rate when compared to Tween incorporated gels for both Sp60 and CA organogels. The result might be due to the high degree of lipophilicity of spans compared to Teewens and this could lead to lower affinities to hydrophilic drugs [33]. The viscosity of the prepared gel might be another reason for the deviations recorded in drug release rates from different gels. The viscosity of organogels containing Sp80 was found too low when compared to those containing T80 or T20. Moreover, the lower DH release from organogels containing Tween surfactants may be ascribed to the longer fiber length of Tween surfactant which can cause an increased area of overlap and cross-linking, producing high gel strengths [30]. T20 has a comparatively lower gel-strengthening effect and showed higher fluxes than T80 [32]. The active participation of Teewens

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Viscosity (cP)</th>
<th>pH</th>
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<tbody>
<tr>
<td>Sp60/SO organogel</td>
<td>1000</td>
<td>5.61 ± 0.32</td>
</tr>
<tr>
<td>Sp60/Sp80 organogel</td>
<td>1800</td>
<td>5.29 ± 0.21</td>
</tr>
<tr>
<td>Sp60/T20 organogel</td>
<td>8000</td>
<td>4.98 ± 0.15</td>
</tr>
<tr>
<td>Sp60/T80 organogel</td>
<td>32,100</td>
<td>5.11 ± 0.40</td>
</tr>
<tr>
<td>CA/SO organogel</td>
<td>3400</td>
<td>5.04 ± 0.30</td>
</tr>
<tr>
<td>CA/Sp80 organogel</td>
<td>7000</td>
<td>4.98 ± 0.15</td>
</tr>
<tr>
<td>CA/T20 organogel</td>
<td>7200</td>
<td>4.85 ± 0.13</td>
</tr>
<tr>
<td>CA/T80 organogel</td>
<td>7400</td>
<td>4.90 ± 0.18</td>
</tr>
<tr>
<td>PLO</td>
<td>1900</td>
<td>4.66 ± 0.19</td>
</tr>
<tr>
<td>HPMC hydrogel</td>
<td>870</td>
<td>5.66 ± 0.33</td>
</tr>
<tr>
<td>Sp60/HPMC bigel</td>
<td>14,400</td>
<td>5.87 ± 0.40</td>
</tr>
<tr>
<td>Sp60/Sp80/HPMC bigel</td>
<td>9900</td>
<td>5.66 ± 0.17</td>
</tr>
<tr>
<td>Sp60/T20/HPMC bigel</td>
<td>27,000</td>
<td>5.14 ± 0.30</td>
</tr>
<tr>
<td>Sp60/T80/HPMC bigel</td>
<td>34,900</td>
<td>5.23 ± 0.15</td>
</tr>
<tr>
<td>CA/HPMC bigel</td>
<td>14,900</td>
<td>5.91 ± 0.23</td>
</tr>
<tr>
<td>CA/Sp80/HPMC bigel</td>
<td>8900</td>
<td>5.82 ± 0.18</td>
</tr>
<tr>
<td>CA/T80/HPMC bigel</td>
<td>15,900</td>
<td>5.15 ± 0.12</td>
</tr>
</tbody>
</table>
in micelle formation produced an increased area of micellar overlap might be the reason for linear increase in the viscosity of the organogel [34].

The release of DH from HPMC hydrogel was also included in this study and compared with organogels. The percentage DH released from HPMC hydrogel was 55.64% after 360 min as shown in Fig. 5 (a and b). The hydrogels are three dimensional polymeric networks with chemical or physical cross links which can control the drug delivery via controlling the base viscosity [35]. The amount of DH released from hydrogels of HPMC was higher than that from all organogels. This may be due to the aqueous liquid component of hydrogels which can impede large amount of water or biological fluid [35]. On the other hand, organogels has a liquid organic (lipophilic) medium which make the release of freely water soluble drug more difficult.

Several formulations of bigels prepared by using different organogels of Sp60 or CA with SO with or without different surfactants (Sp80, T20 or T80) and mixed with HPMC hydrogel. From Fig. 5(c), it was illustrated that the percentage DH released after 360 min from different bigels of Sp60/HPMC, Sp60/Sp80/HPMC, Sp60/T20/HPMC and Sp60/T80/HPMC were 59.80%, 55.12%, 48.36% and 46.28%, respectively. While, 72.28%, 54.60% and 41.08% of DH were released from bigels of CA/HPMC, CA/Sp80/HPMC and CA/T80/HPMC, respectively as shown in Fig. 5(d). It is clear that all bigels gave significantly higher release rates than organogels (P < 0.05). This may be attributed to the fact that organogels are W/O type emulsions having an external lipid phase [11], while a bigel is a w/o/w type emulsion due to the incorporation of the organogel inside the hydrogel which have an external aqueous phase and capable of incorporating large amounts of water [35]. The hydrophilic nature of the external aqueous environment of a bigel facilitates the release of the hydrophilic drug from the external aqueous phase. The release would be faster for a hydrophilic drug in case of o/w emulsion, since it is in the continuum region. The diffusion is difficult when DH incorporated in w/o type emulsion base, since it gets trapped in water droplets. The reverse is true for hydrophobic drugs [36].

To show the effect of the pH of the external sink on DH release, CA/Sp80 organogel and CA/HPMC bigel were formulated and tested for DH release in different pH values. Fig. 5(a) showed that the percentage DH released from CA/Sp80 organogel and CA/HPMC bigel after 360 min was 50.4 and 72.28% when pH was 5.5, 33.80% and 51.48% at pH 1.2, 24.96% and 32.68% at pH 6.8, and 14.66% and 18.09% at pH 7.4, respectively. The amount of DH released in different pH values was in the following descending order: pH 5.5 > pH 1.2 > pH 6.8 > pH 7.4. Diltiazem is a basic drug and should be more soluble in the acidic media than neutral and alkaline media.
However, the decline in the DH solubility in HCl buffer pH 1.2 was attributed to the common ion effect, which provided unexpected trend in solubility of this medicament in the presence of chloride ion in the medium [37]. On the other hand, high amounts of DH were released in pH 5.5 which in turn were gradually decreased at pH 6.8 and 7.4. The result might be due to the acidic nature of DH salt of a basic drug having pKa of 7.7 and the molecule is freely soluble in water. The high the release profile of DH can be attributed to rapid ionization and higher solubility of the drug in pH 5.5, however the reduced release rate of DH in pH 7.4 could be due to the reduced extent of ionization and solubility of DH in basic media [37].

3.5. In vitro rabbit skin permeation study

The aim of this study was to examine the possibility of using organogels, hydrogels and bigels as transdermal delivery forms. Fig. 6(b) shows the cumulative amount of DH expressed in µg/cm² transferred from different gel formulations to the receptor compartment (phosphate buffer pH 5.5). Throughout the experiment period, the hydrogel of HPMC showed higher amount of DH skin permeability than other organogel formulations. After 360 min, about 1569.50, 1286.28, 1121.07, 1062.0, 979.46 and 483.83 µg/cm² of DH were permeated across rabbit skin from HPMC hydrogel, PLO, Sp60/HPMC bigel, CA/HPMC bigel, Sp60/SO and CA/SO organogel formulations, respectively. Firstly, it must be taken into consideration that the partitioning of a drug between the skin and the reservoir favors more lipophilic drugs because skin act as an organic phase [38]. Skin is a horny layer so penetration of drugs is very less. To improve the penetration of a drug into the skin, chemical enhancers are added. Incorporation of HPMC enhances the flux of drugs [39]. Hydrogel consists of an aqueous phase which facilitates the penetration of hydrophilic drug. Also, lower gel viscosity might be another reason for higher amount of DH permeated in rabbit skin using hydrogels of DH. Concerning PLO organogel, the amount of DH permeated was higher than Sp60/So and CA/So organogels due to the aqueous external compartment and the amphiphilic nature of phospholipids which can enhance skin penetration and absorption of both lipophilic and hydrophilic drugs [40]. The phospholipid tail of micelles could interact with the lipids in SC causing their rearrangement and thus facilitated drug penetration between epidermal cells into systemic circulation [41]. Also, bigels of Sp60/HPMC and CA/HPMC gave higher penetration rates than their organogels and this could be as discussed before due to the external aqueous phase of bigel as well as the surfactant activity of CA and Sp60. CA/So organogel gave the lowest fluxes which may be ascribed to its lower surface activity and higher viscosity (3400 cP) when compared to Sp60/So organogel (1000 cP).

3.6. In vivo study of DH

Fig. 7 shows the significant decrease in the mean arterial blood pressure in all hypertensive rats receiving transdermal DH gels compared to the group I (−ve control) at all time intervals. The one way ANOVA test revealed that the difference between the antihypertensive effects of DH in all transdermal groups was statistically significant (P < 0.05) when compared to control group at all time intervals of the experiment. Group VI which received oral doses of DH solution showed a sharp decrease in blood pressure after 1 h (92 mmHg) then gradually increased after the fourth hour. A statistical significant difference (P < 0.05) was found between oral solution group and all transdermal groups during the first 2 h. Meanwhile, no statistical significance (P > 0.05) was observed after 3 h till the end of the experiment between transdermally applied organogels, bigels and oral DH solution. On the other hand, group V which received HPMC hydrogel showed a statistical significant difference (P < 0.05) compared with oral solution group after 4 h till the end of the experiment. This result may be attributed to the
fact that the hydrogel gives faster antihypertensive effect when compared with other transdermal groups as it decreased the blood pressure gradually and maintained it. From these results all transdermal gels can give comparable results to oral solution and reveal a sustained antihypertensive effect. A statistical significant difference (P < 0.05) between group V (hydrogel) and group II (Sp60 organogel) was observed at all times of the experiment. However, groups III (PLO) and IV (bigel) showed no statistical difference (P > 0.05) at all times of experiment. The results which obtained with all transdermal groups revealed that, the antihypertensive effects of DH could be arranged in the following order: hydrogel > PLO > bigel > Sp60 organogel. As explained previously, this may be attributed to the external aqueous phase of hydrogels which facilitate DH release from the formula in contrast to organogels which has an external lipopholic phase that hinder the DH release. In addition the aqueous external phase provides epidermal cell hydration and swelling which enhances hydrophilic drug diffusion across SC. PLO and bigels both contain external aqueous phase facilitating the release of DH in addition to surface active components which can enhance skin penetration ability.

4. Conclusion

The above mentioned results revealed that, the natures of the active drug and other ingredients of the gels, as well as the viscosity of the matrix, will affect the drug release profiles from different gels. In vitro release and permeation studies indicated prolonged release of DH from the tested organogels, hydrogels and bigels. Hydrogel formulation gave better results among other tested formulations. In vivo studies indicated that all transdermal formulations can give sustained antihypertensive effects. Organogels can effectively enhance the hydrophilic drug delivery across the skin however this investigation revealed that they could not be suggested as the vehicle of choice for transdermal application of hydrophilic drugs. Conversely, watery gel systems like hydrogels, PLO and bigels may be tried as matrices which hold good promise for transdermal drug delivery of DH.

REFERENCES


