Nanoemulsions (NEs) are isotropic mixtures of oils, surfactants, and co-surfactants that can be used as drug carriers. The typical droplet size falls from 20–200 nm (1). This nano-size provides a large surface area which increases the dissolution rate, thus the absorption and the bioavailability (2, 3). NEs are nontoxic and nonirritant, therefore, they are excellent candidates for drug delivery (4). They protect the drug from hydrolysis and oxidation due to encapsulation in oil-droplet (5). They enhance the permeation of a drug through the skin (4) as well as the blood-brain barrier (6).

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NEs are being investigated for the potential applications through the different routes of administration; transdermal (7), parenteral (8), ocular (9), oral (10), pulmonary (11), buccal (12) and nasal delivery (13). NEs are being engineered to overcome the different drug delivery barriers for each route of administration.

The buccal route is becoming the most commonly used drug delivery as an alternative to the oral route. It offers unique advantages of ease accessibility, unidirectional drug flux, and hepatic first-pass metabolism bypass, that leads to bioavailability enhancement as well as patient compliance (14). Different dosage forms were used for buccal delivery such as gels (15), tablets (16), patches (17) and sprays (18). All formulations were employed to optimize drug release profile in-vivo.

Abstract: The aim of the study was to develop and characterize mucoadhesive buccal patches of valsartan (VAL) in nanoemulsion (NE) form and to evaluate the impact of nano-formulation in improving its solubility, mucoadhesive strength and in-vitro permeation in comparison to the traditional mucoadhesive VAL patches. A thermodynamic stable VAL-loaded NE was developed with a mean droplet size of 22.5 nm. It was composed of 40% w/w water, 10% w/w oleic acid : Labrasol® at a ratio of 2 : 1 v/v, and 30% w/w polysorbate 20 : Transcutol®-P at a ratio of 1 : 3 v/v. Bi-layered patches were prepared using 3% w/v ethylene vinyl acetate in dichloromethane as the backing layer and 1.5% w/v Carbopol® 971P aqueous solution mixed with VAL-loaded NE as the mucoadhesive layer. Patches showed acceptable weight variation, thickness, folding endurance, mucoadhesive strength, and in-vitro permeation. NE-based patches were more effective in enhancing the penetration of VAL than traditional patches, without significant difference in the mucoadhesive strength. They showed a higher steady-state flux and permeability coefficient than the traditional patches with a flux enhancement ratio of 2.36. The study concluded that NE-based patch is a promising approach that can be tailored to optimize drug release profile in-vivo.

Keywords: nanoemulsion, mucoadhesive, buccal patch, Carbopol®, Valsartan
Valsartan (VAL) is an orally active non-peptide triazole-derived antagonist of angiotensin II with antihypertensive properties. It is a poorly water-soluble (3.08 µg/mL) and highly permeable drug, belonging to class II of the biopharmaceutical classification system (BCS) (20). It exhibits a high log p-value of 5.8 and low oral bioavailability (< 25%). Furthermore, it undergoes extensive hepatic first-pass metabolism, high P-gp efflux and shows variable oral bioavailability in the presence of food, which decreases the AUC by 40%. Thus one of the progressive ways to increase the solubility, dissolution, and bioavailability of VAL is the preparation of NE. Accordingly, the central purpose of this study was to develop optimized nanoemulsion-based mucoadhesive patches of valsartan (VAL-loaded NE patch) using a blend of lipidic excipients, surfactants, and co-surfactants, and to evaluate the impact of NE formulation on VAL solubility, mucoadhesion strength and in vitro penetration in comparison to the traditional mucoadhesive valsartan patches.

Materials
Valsartan was kindly supplied by Macleods Pharmaceutical Limited, USA. Carbopol®-P 971 (CP) and sodium hydrogen phosphate were purchased from BBC chemicals. Ethylene vinyl acetate copolymer was supplied by Across (J. NJ, USA). Polysorbate 20 (Tego® SML 20), caprylic/capric triglycerides (TegoSoft® CT) and isopropyl myristate (TegoSoft® M) were kindly given as gifts by Evonik (Essen, Germany). Diethylene glycol monoethyl ether (Tanscutol® P), oleoyl polyoxy-6 glycerides NF (Labrafil® M1944CS) and Caprylocaproyl polyoxy-8 glycerides NF (Labrasol®) were kindly donated from Gattefosse (Saint Priest Cedex, France). Oleic acid was purchased from Fisher (Shanghai, China) and propylene glycol (PG) by Dow Chemicals (Midland, MI, USA). All other reagents used were of analytical grade.

Methods
Preparation of valsartan-loaded nanoemulsion

Saturation solubility of valsartan
Saturation solubility (Cs) of VAL was determined in various oils (oleic acid, TegoSoft® M, TegoSoft® CT, Labrafil® M1944CS), and combinations of oleic acid with either TegoSoft® M at a ratio of 3:1 v/v, or Labrasol® at a ratio of 2:1 and 3:1 v/v. Solubility was also investigated in the surfactant polysorbate 20, and the co-surfactants PG and Transcutol®-P. Moreover, solubility was determined in a phosphate buffer (PB) of pH 7.2. Briefly, the excess amount of VAL was dissolved in 2 mL of each of the selected oils, surfactants and co-surfactants in 8-mL stoppered vials. Samples were mixed at 1200 rpm using a vortex mixer and kept at 37 ± 1°C in an isothermal shaker for 24 h to equilibrate. The equilibrated samples were removed from the shaker and centrifuged at 3000 rpm for 30 min. The supernatant was taken, diluted appropriately with methanol, and filtered through a 0.45-µm membrane filter. The concentration of VAL in each sample was determined using UV spectrophotometry (Varian, Cary 50 UV/VIS spectrophotometer, Palo Alto, CA) at a maximum wavelength of 250 nm using a standard calibration curve of VAL. The calibration curve of the drug was found to be linear in the range of 2 – 20 µg/mL with a regression coefficient (R²) of 0.9987.

Pseudoternary system preparation
Based on the solubility studies, an oil phase of oleic acid and Labrasol® at a ratio of 2:1 v/v, surfactant (polysorbate 20) and co-surfactant (Transcutol®-P) were selected for NE formation. Double distilled water was used as an aqueous phase. Five combinations of the surfactant polysorbate 20 and the co-surfactant Transcutol®-P (Smix) were prepared by mixing different ratios (1:1, 1:2, 2:1, 1:3 and 3:1), as illustrated in Table 1. The five Smix mixtures were

Table 1. Composition of 5 pseudoternary systems of oil, Smix, and water selected based on their miscibility, clarity and flowability.

<table>
<thead>
<tr>
<th>No.</th>
<th>Smix Ratio (Polysorbate 20 : Transcutol®-P) (v/v)</th>
<th>Composition (% w/w)</th>
<th>Smix</th>
<th>Water</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 : 1</td>
<td>10</td>
<td>50</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>1 : 2</td>
<td>10</td>
<td>50</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>2 : 1</td>
<td>10</td>
<td>50</td>
<td>40</td>
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<tr>
<td>4</td>
<td>1 : 3</td>
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<td>50</td>
<td>40</td>
</tr>
<tr>
<td>5</td>
<td>3 : 1</td>
<td>10</td>
<td>50</td>
<td>40</td>
</tr>
</tbody>
</table>
tested visually for miscibility, transparency (clarity) and ease of flow (21). Smix mixtures that were immiscible, turbid or showed poor flowability were excluded from further studies. A series of pseudoternary mixtures consisting of oil, Smix, and water were developed using the aqueous titration method (22). Oil in water (o/w) NEs were prepared by mixing 10% w/w of oleic acid: Labrasol® (2:1 v/v), 40% w/w water and a fixed concentration of Smix (50% w/w). Initially, oleic acid: Labrasol® (2:1 v/v) and Smix were mixed together to get a clear mixture and then water was slowly added by titration to the oil/Smix mixture. Samples were vortexed at 2500 rpm for at least 15 min and left for equilibration between each addition of water. The systems were visually tested for transparency, miscibility, and ease of flow.

Valsartan-loaded nanoemulsion preparation

Pseudoternary systems which passed visual tests of transparency, miscibility and ease of flow, were selected for drug loading. VAL was loaded in oleic acid: Labrasol® (2:1 v/v) at a constant concentration of 2% w/v. Smix of each selected system was added to the oil/valsartan mixture with continuous vortexing. Water was added using the aqueous titration method as described before to prepare VAL-Loaded NE.

Characterization of valsartan-loaded nanoemulsions

Thermodynamic stability studies

The thermodynamic stability of VAL-loaded NE was evaluated by centrifugation, heating/cooling cycles, and freeze/thaw cycles (23). Initially, NEs were centrifuged at 3500 rpm for 15 min. If no phase separation was observed, NEs were subjected to six heating (45°C) and cooling (4°C) cycles for 48 h. If NEs remained clear, they were subjected to three freeze (-21°C) and thaw (25°C) cycles for 48 h. This test was used to indicate the accelerated stability of the formulations; to eliminate the possibility of phase separation, and changes in droplet size, viscosity, color, and appearance. VAL-Loaded NEs passing the heat-cool cycles, centrifugation, and freeze-thaw cycles were further used in patch formulations.

Size distribution of nanoemulsions

The mean droplet size (MDS) of the stable NEs was measured by dynamic light scattering (DLS) using a Nicomp Nano Z3000 particle size/eta potential analyzer (Particle Sizing Systems, Santa Barbara, CA, USA). All measurements were performed in triplicate at room temperature.

Preparation of mucoadhesive patches

Bi-layered mucoadhesive patches of VAL were prepared using the solvent casting technique. The backing layer was prepared by casting 10 mL of a solution comprising 3 g of ethylene vinyl acetate (EVA) in 100 mL dichloromethane and leaving it for six hours to dry at room temperature until complete dryness. The mucoadhesive polymeric solution was prepared by dissolving 1.5 g CP® 971P in 100 mL aqueous solution containing 30% w/w glycerol as a plasticizer.

VAL was loaded in the mucoadhesive polymeric solution in two different forms. Traditional patches (A & B) were prepared by mixing 5 mg of the prepared mucoadhesive polymeric solution with different amounts of VAL dissolved in 2 mL PB of pH 7.2. Patch A was prepared by dissolving 5 mg of VAL, while 10 mg of VAL was used to prepare patch B.

VAL-Loaded NE patches (C & D) were prepared by mixing 5 mg of the prepared mucoadhesive polymeric solution with accurate amount of the resultant optimized stable VAL-Loaded NE formulation of a clear isotropic mixture with no observed precipitate. Patch C was prepared by mixing 2.5 mg of the VAL-Loaded NE, while patch D used 5 mg of the VAL-Loaded NE.

Each mix of every type of the patches was cast on the dried backing layer of EVA and left in the oven at 37°C for 3 days for complete dryness. An inverted funnel was placed over the cast to prevent fast evaporation of the solvent and assure patch uniformity.

Evaluation of the physicochemical properties of the patches

Thickness and weight variation

The thicknesses of the traditional and NE based patches were measured at three different places using a digital caliper (Mitutoyo Co., Japan) and the mean (± SD) values were calculated. Patches were subjected to a weight variation test by individually weighing 10 randomly selected patches and the average weights (± SD) were calculated.

Folding endurance

Folding endurance was evaluated by repeatedly folding the patches at the same place until it broke. The number of times where the patch could be folded at the same place without breaking gave the value of folding endurance. At least three measurements were taken and the mean (± SD) values were reported.
Drug content uniformity

VAL content in the patches was determined by dissolving the mucoadhesive medicated patches in 10 mL methanol and stirred for 24 h at room temperature. After proper dilution, the amount of VAL in each patch was measured using a UV/visible spectrophotometer at a maximum wavelength of 250 nm.

Mucoadhesion strength

Mucoadhesive strength was determined for the traditional and the NE based patches (n = 6) using an adopted apparatus previously designed and validated; the modified balance method (24). Chicken pouches were used to study the mucoadhesion strength (25). The freshly cut chicken pouch was excised, washed, and equilibrated at 37°C for 30 min in PB of pH 7.2 before being attached to the pan of the balance with a cyanoacrylate adhesive solution. The patch was attached to a plate and lowered to contact the chicken pouch. The patch was pasted to the chicken pouch with a constant weight of 50 g placed over the film for 2 min. The plate started to rise with adding weights and the force (g) was taken until the membrane attached to the plate was completely detached from the patch. Data of the mucoadhesive strength of the patches was analyzed using independent measures T-test. Results were considered significant when $p < 0.05$ (95% confidence interval).

In vitro permeation study

The in vitro permeation of VAL from the patches was determined using Franz diffusion cells with an effective diffusion area of 2.84 cm$^2$ and a receptor compartment volume of 15 mL. A dialysis membrane was mounted on the receptor compartment. Patches were placed on top of the membrane in such a way that the backing layer was facing the donor cell and the adhesive layer facing the dialysis membrane. The donor cell was loaded with 1 mL of PB of pH 7.2 and occluded by crock. The temperature of the receiver vehicle of PB of pH 7.2 was maintained at $37 \pm 0.5^\circ C$ by a thermostatic pump and was constantly stirred by a magnetic stirrer during the experiment. At specific intervals of 0.25, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 7.0 and 8.0 h, one milliliter of the receiving medium was withdrawn via the sampling port and was analyzed for drug content by UV/visible spectrophotometer at 250 nm. All experiments were repeated three times and averaged. The cumulative amount of the drug permeating (Q) through a unit surface area of the dialysis membrane (µg/cm$^2$) was plotted versus time, and the flux (Jss, µg/cm$^2$/h) was calculated from the slope of the linear (steady state) part of the line obtained using linear regression analysis of the data (17). Enhancement ratio (ER) was calculated by dividing the Jss of NE- based patch over the Jss of the traditional patch. Apparent permeability (P) was calculated according to the following equation (26).

$$P = \frac{J_{ss}}{C_s}$$

where $C_s$ is the drug concentration in the donor solution, assuming that the drug concentration in the receiver compartment is negligible under sink condition. The data are presented as mean ± SD.

RESULTS AND DISCUSSION

Preparation of valsartan-loaded nanoemulsion

Owing to the lipophilic nature of VAL, it was likely to become an ideal candidate for loading into lipid-based nanocarriers, namely NEs. Thus the saturated solubility and pseudoternary system were constructed.

Saturation solubility of valsartan

Figure 1 illustrates the solubility of VAL in oils, surfactants, and co-surfactants. Based on these solubility data, NE’s components were selected. The selection of oil is very important in determining the capability of NE to upload the drug in the dissolved state. Selecting an oil of low drug solubility would require higher amounts of oil to incorporate the desired dose of a drug, which necessitates a higher amount of Smix to maintain the miscibility of oils that might increase the side effects and toxicity of the system. The solubility of VAL in Labrafilm® M1944CS was the highest among other oils (100.1 ± 5.3 mg/mL). However, it was not selected as an oil phase, as immiscible and turbid pseudoternary systems were formed. Therefore, oleic acid: Labrasol® (2:1 v/v) of solubility of 50.5 ± 2.5 mg/mL was selected as the oil phase. The non-ionic surfactant polysorbate 20 of solubility of 116.7 ± 5.8 mg/mL was used in formulating NE. Nonionic surfactants were selected since they are known as safe, biocompatible, and less affected by the changes in pH and ionic strength (22). Co-surfactants were selected to obtain NE with lower surfactant concentration. They further reduced the interfacial tension and increased the fluidity of the interfaces. Although VAL exhibited a higher solubility of 116.7 ± 4.7 mg/mL in PG, Transcutol®-P with a solubility of 108.3 ± 7.6
mg/mL was selected. This selection was based on the fact that the co-surfactant Transcutol®-P exhibited lower viscosity compared to that of PG – 3.85 versus 48.6 mPa.s (27) – which was reflected in higher flowability. The solubility of VAL in all the constituents of the NE was much higher than its solubility value in PB of pH 7.2 (17.2 ± 0.3 mg/mL).

**Pseudoternary systems**

The five prepared pseudoternary systems which were composed of oleic acid: Labrasol® (2:1 v/v), Smix combination of polysorbate 20 with Transcutol®-P and water were investigated for their miscibility, clarity, and flowability. All systems were clear and miscible. NE system containing Smix ratios of polysorbate 20 with Transcutol®-P at a ratio of 2:1 and 3:1 v/v exhibited lower flowability compared to the other systems containing Smix ratios of 1:1, 1:2 and 1:3 v/v. Therefore, systems containing Smix ratios of 2:1 and 3:1 v/v were excluded from any further study. However, systems containing Smix ratios of 1:1 v/v (Formulation 1), 1:2 v/v (Formulation 2) and 1:3 v/v (Formulation 3) were loaded with VAL of 2% w/w to produce VAL-loaded NEs.

**Characterization of valsartan-loaded nanoemulsions**

**Thermodynamic stability studies**

The three formulations of VAL-loaded NEs were physically stable with no creaming, cracking or phase separation after passing centrifugation, heating–cooling cycles, and freeze–thaw cycles.

**Size distribution of valsartan-loaded nanoemulsions**

Formulation 3 which is composed of 10% w/w oleic acid: Labrasol® (2:1 v/v), 50% w/w polysorbate 20 : Transcutol®-P at a ratio of 1:3 v/v and 40% w/w water was selected as the optimized VAL-Loaded NE. Formulation 3 exhibited MDS of 22.5 nm while formulations 1 and 2 were not in the ideal nanoemulsion MDS range, which ranged from 20 – 200 nm. Therefore, formulation 3 was selected to be formulated as a patch and to be used in subsequent in vitro permeation studies, while formulation 1 and 2 were not used for any further studies.

**Evaluation of the physicochemical properties of the patches**

All formulated patches (traditional & NE based) were visually inspected for their color and clarity. All patches were transparent in nature, smooth in appearance, and flexible in nature. No appreciable difference was found in the physical properties between traditional patch and NE based patch. The prepared patches demonstrated an excellent uniformity in thickness, weight and drug content. The thickness of the NE based patches ranged between 0.22 ± 0.05 and 0.25 ± 0.09 mm in comparison to the range between 0.15 ± 0.06 and 0.19 ±

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**Figure 1. Saturation solubility of VAL in various oils, surfactants and cosurfactants.** Data are represented as mean ± SD (n = 3)
0.02 mm for the traditional patches. Moreover, the thickness increased with the increase in the drug loading which was all acceptable for buccal administration.

The weight uniformity was satisfactory for all the patches. Average weights of all the prepared traditional and NE based patches ranged from 92.34 ± 5.09 to 105.7 ± 7.88 mg and from 294.44 ± 5.13 to 299.4 ± 2.43 mg, respectively.

The drug content in all of the patches was found to be in the range of 90.42 to 93.22%. The observed results of drug content uniformity indicated that the drug was uniformly dispersed, with minimum intra-batch variability.

The folding endurance test indicated good strength and elasticity for the patches. They all showed folding endurance of above 200. It was found in between 295 to 305 times for the prepared patches.

**Mucoadhesion strength**

Mucoadhesion strength was measured to assure the binding capability of the patches to the mucosa. Chicken pouches were used previously as a model for biological tissue. They had a uniform surface that provided reproducible results with low standard deviations. The mucoadhesion strength was measured for the traditional patch B and the NE based patch D which had the same drug loading. No significant difference (p = 0.054) was found among mucoadhesive strength (10.9 ± 9.6 N) of the patches. The mucoadhesive property depended on the nature and concentration of the polymer used. CPα was the key component for mucosal adhesion which was kept constant in all patches. Obviously, CPα formed secondary mucoadhesive bonds with mucin as a result of swelling and interpenetration of the polymer chains in the interfacial region. NEs served as inert vehicles for VAL delivery, where the non-ionic interactions between NE components and mucosa were not obvious.

**In vitro permeation study**

Bi-layer design of the patch was selected to obtain unidirectional release of the drug and a greater surface area of contact. The backing layer of EVA restricted the contact of the patch with the receptor fluid. Drug release from the backing layer confirmed the unidirectional release, as the drug concentration obtained after 24 h of release was found to be less than 1%.

Permeation profiles of the traditional patches A & B and the optimized VAL-loaded NE based patches C & D, which were carried out at a temperature of 37°C using PB of pH 7.2 were shown in Figure 2. The drug permeation studies portrayed that optimized VAL-loaded NE based patches exhibited significantly (p < 0.05) higher drug permeation than the traditional ones which were loaded with equal amounts of VAL. It was very obvious that the NE based patch D exhibited significantly (p < 0.05) higher drug diffusion than the traditional patch B, even though both patches had the same loaded amount of VAL (1.44 mg). Similarly, the VAL-loaded NE based patch C exhibited a significantly (p < 0.05) higher drug permeation than the traditional patch A, although they both had the same drug loading (0.77 mg).

Moreover, loading the patches with a higher amount of VAL exhibited significantly higher permeation rate, regardless of the type of patch used. The traditional patch B, as well as the NE-based patch D, exhibited significantly higher permeation rates than the patches A and C, respectively. It was observed that during the diffusion study, the patches swelled forming a gel layer on the exposed film surface thus allowing the easy release of VAL. All previous results were assured by calculating the permeation parameters for the traditional and VAL-loaded NE based patches which were presented in Table 2. The traditional patch A exhibited the lowest cumulative amount of valsartan diffused across the membrane after 8 h (Q₈); a value of 192.59 ± 3.21 µg/cm².

### Table 2. *In vitro* permeability parameters at 37°C and phosphate buffer pH of 7.2 for the NE based patches and the traditional patches.

<table>
<thead>
<tr>
<th>Type of patch</th>
<th>Q₈ (µg/cm²)</th>
<th>Flux (Jss) (µg/cm²/min)</th>
<th>P (cm/hr)</th>
<th>ER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traditional Patch A</td>
<td>192.59 ± 3.21</td>
<td>0.69</td>
<td>0.63</td>
<td>Reference</td>
</tr>
<tr>
<td>Traditional Patch B</td>
<td>224.54 ± 2.21</td>
<td>0.90</td>
<td>0.79</td>
<td>1.34</td>
</tr>
<tr>
<td>NE based patch C</td>
<td>338.02 ± 4.26</td>
<td>0.79</td>
<td>0.99</td>
<td>1.18</td>
</tr>
<tr>
<td>NE based patch D</td>
<td>633.80 ± 2.55</td>
<td>1.58</td>
<td>1.03</td>
<td>2.36</td>
</tr>
</tbody>
</table>
Whilst VAL-loaded NE based patch D exhibited the highest cumulative amount of valsartan diffused across the membrane at 8 h (Q8), a value of 633.80 ± 2.55 µg/cm². The flux (Jss) and permeability coefficient (P) of VAL-loaded NE based patch were significantly higher (p < 0.05) than those of the traditional patch with an ER value of 2.36. Jss for the patches B & C were 0.90 & 0.79 µg/cm²/min, respectively and P values of 0.79 & 0.99 (cm/hr), respectively.

It is evident from Figure 2 and Table 2 that the drug permeation increased with the increase of drug loading in the patches. The increment in the drug loading from 0.77 to 1.44 mg in the patches A & B, respectively was accompanied by the increment in the flux values from 0.69 to 0.90 µg/cm²/min. In addition, the increment in the drug loading from 0.77 to 1.44 mg in the patches C & D, respectively was accompanied by an increment in the flux values from 0.79 to 1.58 µg/cm²/min. The thermodynamic activity of the drug in the formulation is a significant driving force for the release and the penetration of the drug. These results are in agreement with Nair et al who formulated a mucoadhesive film embedded with different loading amounts of acyclovir in biopolymeric nanoparticles. The study showed a significant increase in the permeation rate of acyclovir with the increase of drug loading (28).

Overall, the studies implicated that the NE based carrier contributed significantly to the enhancement of the membrane permeation. The NE technology with reduced particle size provided more surface area that improved the solubility of VAL as well as its permeation. This enhancement was similarly reported with propranolol loaded nanoparticle films that showed higher permeability across porcine buccal mucosa (29). In addition, pure valsartan exists in crystalline form and it is most probably converted into an amorphous state when formulated in NE which could be responsible for higher drug solubility.

Furthermore, the oil phase of VAL-loaded NE based might act as a carrier that allows more drugs to be diffused without being diffused as itself (30). On top of that, CP* not only helped in adhesion to the buccal mucosa, but its role would also be expected to be equally as important in controlling the diffusion of the drug from the gel layer formed to the mucosal surface for absorption where hydration is a prerequisite for adhesion and drug release. CP* absorbed water and hydrated itself well to formulate a gel layer which allowed the drug to be easily dispersed and diffused across it. The carboxyl groups provided by the acrylic acid backbone of the CP polymer are responsible for its properties. These groups are assumed to be protonated at a lower pH value which decreased the repulsion between coiled chains, enabling the hydrogen bond forming capability with other proton acceptor compounds. These groups are assumed to form a hydrogen bond with the acceptor group of VAL which has two proton dissociating groups; a carboxyl group and a tetrazole. Any interaction with these groups may change its solubility, dissolution rate and consequently the drug release and permeability. Combining VAL-NE

![Figure 2. Comparative in vitro drug permeation profiles at 37°C of the traditional patches (A & B), optimized VAL-NE based patches (C & D) in pH 7.2 phosphate buffer. Data presented are cumulative drug permeated versus time (minutes) in terms of mean ± SD (n = 3)](image-url)
with CP decreased the rigidity of the CP structure with a noticeable increase in the amount of the drug permeated. It decreased the carboxyl group’s protonation in CP, increased the repulsion between the chains which uncoiled the chains and consequently facilitated the drug release and permeation.

The data observed here validates our objective of potential dosage form development and enhancement of VAL solubility and permeation by incorporating the drug in NE and further embedding it into a mucoadhesive patch.

CONCLUSION

The present study successfully developed a mucoadhesive patch of VAL employing nanocarrier for augmenting its buccal penetration. Owing the lipophilic nature of VAL, it was likely to become an ideal candidate for loading into lipid-based NE. Combined with CP as a mucoadhesive polymer, the optimized NE of VAL would allow for higher penetration of this antihypertensive drug candidate across the dialysis membrane, due to improved solubilization.

In vitro permeation studies showed that VAL-loaded NE based patches had a significantly higher drug permeation rate than traditional patches. They also showed a significantly ($p < 0.05$) higher steady-state flux and permeability coefficient than the traditional patches with an enhancement ratio of 2.36. No appreciable difference was found between the traditional patch and NE based patch, in physicochemical properties and mucoadhesion test results.

Acknowledgment

Authors acknowledge and thank Al-Ahliyya Amman University, Salt-Jordan for the financial support and Areej Kamal for the technical work.

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Received: 16.04.2018