Chemotherapy induced nausea and vomiting (CINV) is an issue, which usually occurs in cancer patients. Despite high bioavailability of oral and intravenous administration, these have some drawbacks. The oral route causes hepatic first pass metabolism and intravenous route is invasive in nature. Hence, antiemetic drug by means of transdermal route is necessary to administer in such cases. The aim of the present investigation is to develop suitable Transdermal Therapeutic System (TTS) with an objective to enhance solubility and skin permeability properties of metoclopramide base. Preformulation study begins with an approach to enhance solubility of metoclopramide base by solid dispersion technique. Transdermal films were prepared with the solid dispersion as well as with pure drug. Phase solubility study at various temperatures reveals binding constants (Ka, 95-350 M⁻¹ for PVP K30; 56-81 M⁻¹ for HPβCD). Spontaneity of solubilization was justified by AL type linear profiles. The films showed satisfactory diffusion (%), permeation rate and flux after 8 h study. The transdermal patches as prepared were analyzed under FTIR, DSC and SEM. Both solubility and permeability rate in this investigation have been enhanced. So, it can be affirmed that this route would effectively enhance bioavailability.


INTRODUCTION

Transdermal drug delivery is well established unique dosage system, prepared in the form of a drug loaded patch or gel which delivers drug toward the epidermis by active or passive permeation to reach systemic circulation. The diffusion and permeation of drugs from the transdermal patch is triggered at a controlled manner by designing a proper blend of hydrophilic-lipophilic polymer mixture (Mukherjee et al., 2005; Walters, 1999; Chien, 1987). The drug may be loaded in the matrix structure of a polymeric film or stored in a reservoir in which a separate porous release membrane is required (Ghanghoria et al., 2012). In spite of some limitations in this dosage form, its benefits over oral and intravenous drug delivery systems are well understood from decades back.

Being stratum corneum, a biological barrier to intruding molecules from the environment, intended drug molecules need to be scrutinized on the basis of properties of drug and skin membrane during preformulation study (Alany, 2017). To overcome the opposition of barrier mechanism to some extent, permeation enhancer (penetrant) needs to be incorporated. Addition of plasticizer is a common practice to prevent brittleness and improve the smoothness of patch (Lofthson, Masson, 2001).

The transdermal therapeutic system covers a lot of benefits over the conventional administration, extending greater safety, efficacy, convenience of application and improves patients’ compliance (Patel, Patel, Patel, 2009). Now-a-days several transdermal products are existing in the market and these are being used for the treatment of diseases e.g. Alzheimer’s disease, Parkinson's disease, pain management, hormone replacement therapy and...
motion sickness. Notably, transdermal patches of scopolamine had been spearheaded in this category with USFDA approval in 1970 (Alany, 2017).

There are several reasons which cause nausea and vomiting. Cancer patients with multi-day chemotherapy suffer from severe nausea and vomiting (Boccia et al., 2011). These problems are often associated with the gut problem as well as indigestion. Almost 70-80% of chemotherapy receivers are affected with chemotherapy-induced nausea and vomiting (CINV) (Sun et al., 2012). Anxiety, dehydration and electrolyte imbalances occur due to CINV that affect the physical and mental condition and hamper the quality of life (Rajabalaya, Chen, David, 2013). Antiemetic therapy for chemotherapy-induced nausea and vomiting (CINV) frequently is initiated before the onset of chemotherapy and continues as long as the risk of nausea persists. In chemoreceptor trigger zone (CTZ) 5-Hydroxytryptamine3 (5-HT3) receptor antagonists play a major role to govern CINV. The mechanism was commonly linked with the selective blockade of 5-HT3 receptors in visceral-vagal afferent fibers (Jordan, Schmoll, Aapro, 2007; Sun et al., 2012).

Metoclopramide (MET), a benzamide derivative is structurally allied to procainamide with formidable antiemetic and antispasmodic effects (Suleiman et al., 1989). It is chemically known as 4-amino-5-chloro-[2-(diethyl amino) ethyl]-2-methoxy benzamide. It is weakly basic in nature (pKa 9.47; log P = 2.66). The high log P value reveals the fact that metoclopramide base (Met base) is poorly water soluble (0.2 mg/mL at 25 ºC) (Pitre, Stradi, 1987). Hence, to raise the solubility, different approaches like solid dispersion (SD) technique (Das et al., 2012), insertion of cosolvents (Nayak, Panigrahi, 2012), prodrug (Beaumont et al., 2003), salt formation (Serajuddin, 2007), complexation (Kalimuthu, Khanam, 2014) and size reduction (Jinno et al., 2006) are generally adopted.

Out of innumerable approaches (Wu et al., 2012) SD technique has been utilized successfully to augment the solubility of the poorly aqueous soluble drug because it is easier to develop and is cost effective. So far, several methods have been practiced to prepare amorphous SDs such as solvent evaporation, kneading, hot-melt extrusion, spray drying and freeze drying (Kalimuthu, Khanam, 2014).

To overcome CINV and also to make effective antiemetic therapy it is proposed to develop transdermal dosage form of MET. To enhance permeation rate of this drug some modifications are required. The first approach is to modify solubility of drug by SD technique and the second approach is to fabricate transdermal patch with SDs.

In many researches, SD alone and transdermal films, microemulsions, nanoemulsions, and gels were reported earlier (Ghanghoria et al., 2013; Palem et al., 2013; Desai, 2004; Shakeel et al., 2009; Nayak et al., 2014). Malak and his co-workers developed SD of celecoxib by kneading method with various carrier substances, such as polyethylene glycol-4000 (PEG 4000), polyvinyl pyrrolidone K30 (PVP K30) and hydroxy propyl-β-cyclodextrin (HPβCD) to enhance the solubility and dissolution rate. They observed that the kneaded SDs, when blended with o/w cream, improved the permeation rate to the rabbit skin than that of pure celecoxib (Malak et al., 2011).

The proposed work emerges with an idea of development of SD using different carriers (HPβCD and PVP K30) for improving solubility of drug and its incorporation into transdermal patch to increase the permeability rate of Met base. The objectives of the current work are: (i) To assess the binding capacity of drug and carrier by phase solubility study and to assess solubility of the drug (ii) To characterize drug loaded SDs and patches. This approach in developing transdermal drug delivery system (TDDS) with Met base-SD has not been reported so far.

**MATERIAL AND METHODS**

**Materials**

Hydroxypropyl-β-cyclodextrin (HPβCD, MW: 1380) was obtained from Tokyo Chemical Industry Co. Ltd., Tokyo, Japan. Polyvinyl pyrrolidone K-30 (PVP K-30, MW: 45,000) was purchased from Loba Chemie, Mumbai. Ethyl cellulose was produced from Sigma Aldrich Chemicals and HPMC (Hydroxypropyl methyl cellulose) was obtained from Colorcon Asia Pvt. Ltd., Goa, India. Dibutyl phthalate (DBP) was purchased from Merck specialities Pvt. Ltd. Mumbai, India. Cellophane membrane having molecular weight cut-off (MWCO) 6000-8000 was procured from Sigma Aldrich Chemicals and Backing layer (SCOTCHPAK 9733), release liner (1022 Fluoropolymer release liner), adhesive tape (CoTran TM 9698, Nonwoven polyurethane) were purchased from 3M Drug Delivery, U.S.A.
Sodium hydroxide (NaOH) was procured from Yarrow Chem. Ltd., Mumbai, India. Chemicals and reagents used in this work were of analytical grade.

**Methods**

**Conversion of metoclopramide hydrochloride to metoclopramide base form**

Required amount (4 g) of metoclopramide hydrochloride (Met HCl) was dissolved in requisite volume of double distilled water (DDW) followed by stirring until the total amount of drug got equally dispersed. The solution was neutralized by 1 M sodium hydroxide (NaOH) solution to form precipitate. The precipitate was collected by filtration and washed several times with DDW to remove excess NaOH. The precipitate was dried in a hot air oven at 50 ºC. Afterwards the solid material was cooled at room temperature (25 ºC). After that, the dried solid material was treated with acetone (~150-200 mL) to make a saturated solution and stirred continuously at 56 ºC (boiling point of acetone) followed by filtration (maintaining 56 ºC) of saturated drug solution (using Whatman filter paper, pore size 11 µm) to eliminate impurities. The solution was allowed to attain ambient temperature (25 ºC) and thereafter it was kept in a refrigerator. Crystals were collected and dried at 50 ºC in a hot air oven. The material was cooled and stored at 20-25 ºC for further use (Kahali, Khanam, 2018).

**Study of saturation solubility**

This method was performed to determine the maximum amount of drug dissolved in the media. The saturation solubility analysis helps to determine the volume of media as well as selection of media. Saturation solubility of Met base was measured by addition of excess amount of drug to 5 mL DDW (~pH 6) in graduated stoppered test tubes and placed in a water bath for 24 h at a constant temperature (37 ± 0.5 ºC). The test tubes were shaken at 30 min interval until the equilibrium was achieved. The material present in the containers were centrifuged and the supernatants were filtered through Whatman filter paper (pore size 11 µm). Suitable dilutions were prepared and absorbances were noted at λmax 272 nm by UV spectrophotometer (Kalimuthu, Khanam 2014). The similar technique was adopted in an aqueous media of pH 7.4 pH 6.8 and pH 5.5 respectively.

**Measurement of partition coefficient**

The most fundamental aspect in this study is to determine the partition coefficient. The partition coefficient is important parameter as it controls absorption of the drug which is a common mechanism of passive diffusion. This mechanism is, as a matter of fact, solely dependent on partition coefficient of the drug. The experiment was performed three times at 25±1 ºC. Similar volume of n-octanol and DDW/ pH 7.4 buffer (15 mL each, pH 7.4 buffer is considered as in-vitro study fluid in this work) were placed in a separating funnel and shaken vigorously for 6 h to obtain saturation. After that 10 mg Met-base was accurately weighed and added to the mixture of solvent. The whole mixture was shaken again for 24 h in a mechanical shaker. The solution mixture having been properly shaken in the separating funnel was taken for further experiment. Thus, two distinct phases (water/7.4 buffer and n-octanol) occurred due to density difference. After that the stop cock of separating funnel was opened and the heavier liquid (water/pH 7.4 buffer) was taken out and collected in a separate test tube. Suitable dilutions were made and the concentration of drug in aqueous phase was determined spectrophotometrically at 272 nm. Partition coefficient (K_{o/w}) of Met base was represented by the ratio of the concentration of the analyte distributed in two immiscible solvents (n-octanol and water/pH 7.4 buffer).

**Phase solubility studies**

Phase solubility analysis is an uncomplicated and effective physical method for the quantitative determination of the composition of material and is suited to all kinds of molecules. This method helps to ascertain the solubility of impurities in the substance as also to determine the solubility of substance itself (Mader, Higuchi, 1970). In accordance with the report focused in (Higuchi, Connor, 1965) method, the phase solubility diagram was established. In this study PVP K-30 and HPβCD were used as carriers. As Met base is a poorly aqueous soluble drug, the carriers stated above were used to improve the solubility of drug. Moreover PVP K-30 acts as bioavailability enhancer (Kathe, Kathpalia, 2017). Cyclodextrins are naturally occurring hydrophilic cyclic oligosaccharides which is composed of α-1,4-linked d-glucopyranose units. Amongst all HPβCD has a higher solubility in water than beta
cyclodextrin (βCD). Due to their higher molecular mass, relatively less water solubility, probable parenteral toxicity and possibility of reduction of their workable quantity in pharmaceutical products are the inclusion of satisfactory substitutes (hydroxyl acids, organic solvents, water soluble polymers) which would increase the solubilizing capability of cyclodextrin (Kalimuthu, Khanam 2014). Aqueous solutions of carriers, e.g.: Met-base-PVP K-30 (1:0, 1:1, 1:2, 1:3 and 1:5) and Met-base-HPβCD (1:0, 1:1, 1:2, 1:3 and 1:5) were produced at concentrations of 1, 2, 4, 6, 8, and 10% w/v. In different aqueous media like: DDW, pH 7.4, and pH 5.5 the experiment was conducted. Excess quantum of Met-base was added to each stopper test tube containing 5 mL of aqueous solution. The test tubes were shaken for 24 h in a mechanical shaker maintaining a constant temperature at 25, 37, 40 and 45 ± 0.5 ºC. The material present in each test tube was centrifuged and the supernatant solutions were filtered via Whatman filter paper (pore size 11 μm). Suitable dilutions were prepared and the concentration of drug was measured by UV spectrophotometer at λ_{max} 272 nm. The experiment was repeated three times in each case. Phase-solubility curve was designed by plotting solubility of Met-base (mole/L) against concentration of the carrier (mole/L). From each profile slope and intercept were obtained and the same were used to calculate apparent binding constant (K_a) of the complex system from Eq. (1). Intercept denotes intrinsic solubility of drug in the absence of carrier at different temperatures and the thermodynamic parameters were calculated upon the complex formation between drug and carrier applying Van’t Hoff Eq. (2).

\[
K_{1:1} = \frac{\text{Slope}}{\text{Intercept} \times (1 - \text{Slope})}
\]

\[
\ln \frac{K_{a2}}{K_{a1}} = \Delta H \frac{T_2 - T_1}{R T_1 T_2}
\]

where and are the stability constants at 25 and 37 ºC as well as, represents the corresponding temperature in Kelvin. Gibbs free energy change - and entropy were also calculated. is the universal gas constant.

**Preparation of solid dispersion by solvent evaporation method**

The method of SD is adopted in this study because it improves solubility and enhances the permeation rate of drug. So, the bioavailability of poorly soluble drugs was notably enhanced. SDs were prepared by using different carriers (HPβCD and PVP K-30) and Met-base at appropriate ratios of (1:1, 2:1, 3:1 and 5:1 w/w). This technique was adopted by creating a dispersion of a physical mixture of drug and polymer in an organic solvent mixture (dichloromethane-ethanol 1:1 v/v) and it was left at room temperature (25 ºC) for 24 h and evaporated under vacuum until a transparent and solvent-free thin layer was obtained. Then the resultant content was dried at the 37±0.5 ºC until constant weight was attained. The solid mass was pulverized and passed through sieve (mesh no. 120).

**Aqueous solubility study**

Aqueous solubility study of SD was determined by adding excess amount of SD in 5 mL of aqueous phase (DDW, phosphate buffer pH 7.4, phosphate buffer pH 6.8 and pH 5.5 buffers) in a 10 mL graduated volumetric flask and shaken into mechanical stirrer at 37 ºC. After 24 h the content of the volumetric flask was filtered through Whatman filter paper and suitably diluted. Afterwards absorbances were measured spectrophotometrically and solubility of each binary system was determined (Kalimuthu, Khanam 2014).

**Measurement of drug content (%) of solid dispersion**

10 mg SDs (Met base SD) were taken from each sample and extracted with 2 mL methanol. After that each sample was diluted with different aqueous media to adjust the volume up to 100 mL in a volumetric flask. Suitable dilutions were made and drug content was measured in UV spectrophotometer (ANALAB, model of UV-180).

**Characterization of formulations and drug and ingredients**

Characterizations of pure drug, SDs, pure drug loaded patches, SD loaded patches and other excipients were performed by instrumental analysis such as Fourier Transform Infrared Spectroscopy (FTIR) analysis, Differential Scanning Calorimetry (DSC) study and Scanning Electron Microscopy (SEM).

**Fourier transform infrared spectroscopic (FTIR) analysis**

To observe the stability of the drug in presence of excipients/polymer and to confirm drug-polymer
interaction FTIR analysis was performed. FTIR of samples was executed using Shimadzu Co., Kyoto; Japan along with Quick Snap sampling modules by the KBr disc method over wavenumber range of 4000-400 cm$^{-1}$ (Das et al., 2018). Polymers, Met base, and patches were run individually as controlling factors.

**Differential scanning calorimetric analysis (DSC)**

DSC analysis was carried out for Met HCl, Met base, SDs and physical mixture (PM) to analyze the crystallinity and amorphous nature of compounds. DSC analysis was done in (Pyris diamond TG/DTA; Perkins Elmer Instruments, Mumbai, India) supported by a thermal analyzer. 10 mg of sample (Met HCl, Met base, polymer substances, and SDs) was placed in a closed aluminum pan under a nitrogen flow of 150 mL/min and heated at a scanning rate of 10 ºC/min over the temperature range of 20 to 300 ºC (Das et al., 2018).

**Scanning electron microscopic study (SEM)**

Scanning electron microscopy technique was performed (SEM, JSM-6700F, JEOL Ltd., Japan) to observe the surface morphology of powder samples as well as patches. The samples were placed into the aluminium stub with two side adhesive tape and to make it electrically conductive; the aluminium stub is coated with thin layer of platinum under reduced pressure 2.54 Pa. The analysis was operated under 25 mA current with the voltage of 10 kV.

**Fabrication of transdermal patch**

At first known amount of carriers such as EC, PVP K30 and HPMC (25:125:12.5-mg w/w) were blended in 3 mL chloroform to get a homogenized mixture. After that 25 mg Met base was added to the mixture and stirred until the whole amount of drug was dispersed uniformly. After blending dibutyl phthalate (30-50% v/w DBP) was added to it to form clear viscous liquid to provide the plasticity. Subsequently, the transparent viscous liquid was cast on the backing layer (117 cm$^2$, SCOTCHPAK 9733) by an applicator (thickness 350 micron, wet patch) and dried under ambient temperature for 24 h to form a transdermal patch. After the film gets dry, backing layer was transfixed with adhesive tape (CoTran$^{TM}$ 9698) with matrix part kept upward. Theoretical amount of drug loading per square cm of the polymeric patch was determined by mass balance. The practical amount of drug loading was determined by assay method. The composition of different films were illustrated in Table I.

**Drug Content determination of transdermal patch**

A sample patch of a certain area (1 square cm) was cut out from a master patch of each formulation (n=3) and extracted with 2 mL methanol in a volumetric flask and shaken for 2 h in a mechanical shaker. After that centrifuge each sample at 5000×g for 20 min. After that volume was adjusted to 100 mL with aqueous media (Banerjee et al., 2014). Afterwards, the solution was sonicated for 20 min and filtered via Whatman filter paper (11 µm pore). Absorbance was noted after proper dilution at $\lambda_{\text{max}}$ 272 nm.

**Percentage moisture content**

The prepared patches were weighed individually and placed in a desiccator containing fused calcium chloride for 72 h at 45 ºC. The patches were reweighed till constant weight was not achieved. The difference in weight was used to calculate moisture content with respect to the initial weight of sample patch.

**Percentage moisture absorption**

Weighed patches were kept in a desiccator with a relative humidity of 82% for 72 h. The sodium chloride solution was kept into a desiccator and simultaneously the patches were placed in the same condition. The patches were then periodically weighed to obtain a constant weight.

**Measurement of thickness of patches**

The thickness of the dried patches (F1-F6) were determined by using digital micrometer screw gauge (Mitutoyo, Japan) at three different places and the average value was calculated (Prajapati, Patel, Patel, 2011).

**Adhesion test (thumb tack test)**

In the sample the thumb was put with a little pressure for a short while and then withdrawn immediately. With variation of pressure and contact time as well as notifying the difficulty to pull out the thumb from adhesive, it is not hard to identify how strong bond was attained between
TABLE I – An overview of the composition of transdermal devices

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Ratio of PVP K-30:EC:HPMC and PVP K-30-Met base SD+EC</th>
<th>Total weight of carriers (mg)</th>
<th>Chloroform (mL)</th>
<th>% DBP Drug (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1*</td>
<td>5:1:0.5</td>
<td>187.5</td>
<td>3</td>
<td>30% v/w of polymers 25</td>
</tr>
<tr>
<td>F2*</td>
<td>5:1:0.5</td>
<td>187.5</td>
<td>3</td>
<td>40% v/w of polymers 25</td>
</tr>
<tr>
<td>F3*</td>
<td>5:1:0.5</td>
<td>187.5</td>
<td>3</td>
<td>50% v/w of polymers 25</td>
</tr>
<tr>
<td>F4**</td>
<td>10:2:1</td>
<td>325</td>
<td>3</td>
<td>30% v/w of polymers 25</td>
</tr>
<tr>
<td>F5**</td>
<td>10:2:1</td>
<td>325</td>
<td>3</td>
<td>40% v/w of polymers 25</td>
</tr>
<tr>
<td>F6**</td>
<td>10:2:1</td>
<td>325</td>
<td>3</td>
<td>50% v/w of polymers 25</td>
</tr>
</tbody>
</table>

* In cases of (F1-F3) formulations plain drug (25 mg) was added separately to the polymer blend, ** In cases of (F4-F6) formulations equivalent amount (25 mg) of drug-loaded SD was added.

In vitro diffusion study

In-vitro diffusion study was carried out in glass built diffusion cell which is modified form of Franz diffusion cell. It consists of two distinct parts, one is donor cell and another is receptor cell. The donor compartment is elongated cylindrical tube open at both ends of which lower part fits with the neck of receptor part, and receptor cell’s volume is 50 mL. The receptor cell was connected with water bath and externally jacketed through which water circulates continuously to maintain the temperature at 37±0.5 °C. The receptor compartment was mounted on the multicell magnetic stirrer and then it was filled with 50 mL phosphate buffer pH 7.4 medium. Release liner/patch of circular area was attached with cellophane membrane and (3.935 cm²) fixed at the bottommost part of the donor cell. During experiment samples (5 mL) were withdrawn from the port of receptor cell.

Drug Content uniformity

Drug content uniformity was analyzed by storage of patches in a desiccator for 5 months to determine the effect of variation of drug content on stability of films. Met base and SD loaded patches (F1-F6, 1 cm² each) were placed in volumetric flask (100 mL) consisting of 2 mL methanol and stirred for 1 h for extraction of drug. After that rest volume was adjusted upto 100 mL with an aqueous phase of pH 7.4 media and sonicated for 2 h. All the samples were filtered and suitable dilutions were made and the same were measured by using UV-spectrophotometer.

skin and adhesive. Inspite of some demerits (data that were obtained, less quantified) it is most easy, simple and effortless method to analyze skin-adhesive bonding. All the samples were tested concurrently (Minghetti, Cilurzo, Montanari, 1999).
at predetermined time intervals (time difference of withdrawal between first two samples was 30 min and the time difference of withdrawal of rest samples was 1 h from each other) and replaced by the equal amount of fresh buffer (pH 7.4). The drug concentration of samples as collected was estimated by UV spectrophotometer at wavelength of 272 nm. Amount of drug diffused through cellophane membrane was calculated, and cumulative percent of release (CPR) was determined.

**Statistical analysis**

All assessed data were stated as mean±standard deviation (S.D.) and each measurement was done three times. The difference among the sets was tested by student’s t-test at the level of p < 0.05 where required.

**RESULTS AND DISCUSSION**

**Saturation solubility study of metoclopramide with respect to pH**

Saturation solubility was measured by addition of excess amount of Met base in several aqueous media (DDW, pH 7.4, pH 6.8 and pH 5.5). According to British Pharmacopoeia 1980, 10% aqueous solution of Met base yields pH range between 4.6 and 6.5 (the difference between 6.5 and 6.8 is negligible). It may be mentioned here that the stability of Met base was found maximum at pH 7.6 which is nearer to pH 7.4. Hence, in the present study the values of pH 6.8, pH 5.5 and pH 7.4 respectively were chosen (Pitre, Stradi, 1987). The concentration of Met base in DDW, pH 7.4, pH 6.8 and pH 5.5 was found 190.5±0.002; 1347±0.006; 3500±0.005 and 5539±0.01 µg/mL respectively. The solubility of Met base was increased markedly in acidic media due to its ionization and alkalinity. This nature manifests that Met base is slightly soluble in higher pH media and remains unionized which facilitates permeation of drug through biological membrane.

**Measurement of the partition coefficient**

The partition coefficient (log P) of Met base in octanol-water (K_{o/w}) and octanol-buffer (pH 7.4) was found to be 2.65 and 2.52 respectively. These values of partition coefficient ensure that the range remains within (1.0-3.0) and this is obviously a potential parameter in the field of transdermal drug delivery system (Arora, Mukherjee, 2002). In determining drug partition coefficient in between skin and *in vitro* study fluid, a standard of octanol and pH 7.4 buffer are considered necessary. Result obtained therefrom reveals the factor of lipophilicity of drug which consummates the necessary criteria in formulating it into transdermal patch. The biphasic nature of drug absolutely imitates skin’s biphasic nature and, therefore, it helps easy penetration through the skin.
Phase solubility studies

The phase solubility assessment was performed in order to determine the binding constant ($K_a$) of drug-carrier complexes. These complexes duly alter the biopharmaceutical parameters of the drug. Phase solubility study was carried out in binary systems such as (Met base-HPβCD and Met base-PVP K30) to observe the effect of the binding capacity of the individual carrier system. The phase solubility diagrams (Figure 1) represent AL type linear isotherms at different temperatures at different aqueous media. Solubility enhancement of a guest molecule has been described by AL type linear profile as a function of carrier concentration. The values of intercept and slope were different as the temperature and pH of media were changed (Table II). Slope and intercept as obtained from each profile were used to calculate stability constant ($K_a$).

The thermodynamic parameters such as change of free energy ($\Delta G$), change of enthalpy ($\Delta H$), change of entropy ($\Delta S$) and apparent stability constant ($K_a$) of phase solubility studies having different aqueous media (DDW, pH 7.4, pH 5.5) at several temperatures are tabulated in Table III.

Change in free energy for each binary combination was found negative which indicates spontaneous solubilization. Free energy change varies from -9.8 to -15.24 kJ/Mole. It suggests that drug may bind with the carrier molecules and hold by weak physical forces like Van der Waals force, hydrogen bonding, and some hydrophobic forces.

Influence of temperature (25, 37 °C and 40 °C) on $K_a$ was much proterubent in DDW as compared to pH 5.5 and 7.4. As the temperature increases, the motility of ionic species of Met base increases in acidic media of pH 5.5 which causes possible inhibition of complex formation with carriers. The stability constants were found low at higher temperature whereas the intrinsic solubility was found increased. The reduction of binding of the drug with carrier might be due to the improved bonding of the molecules of the carrier with the molecules of water at elevated (45 °C) temperature. At low pH stability constant was lowered (pH 5.5 < pH 7.4) in presence of HPβCD. With the decrease of pH, the degree of dissociation was increased; this fact may not facilitate hydrophobic binding. Thus, $K_a$ value reduces in acidic pH (Domanska, Pelczarska, Pobudkowska, 2011). This is because of small interaction between ligand and guest molecules.

Exothermic type of complexation (-$\Delta H$), negative entropy changes (AL) and negative $\Delta S$ were found in pH 5.5 on the other side positive $\Delta S$ and $\Delta H$ was found in higher pH and higher temperature. $\Delta G$ is supported by negative $\Delta H$ and positive $\Delta S$ as well as spontaneous complex formation are ensured by negative $\Delta G$. Negative entropy change and lower $K_a$ values in acidic pH may be elucidated as the ligand molecules are much ionized at pH 5.5 and molecules of water are relatively more ordered.

In comparison with Met base-HPβCD system, higher $K_a$ value was observed in Met base-PVP K30 system. Positive entropy change and negative $\Delta G$ values suggest that complexation is in favor of higher pH than the lower pH. High stability constant signify more stable complex formation. As a consequence, burst drug release was minimized from the complex state.

Aqueous solubility studies and drug content of solid dispersion

Determination of aqueous solubility of different SDs was done at 37 °C and the values of solubility in different media were illustrated in Table IV. Met base is sparingly soluble in DDW (pH ~6). So, the solubility of Met base was found low (~190 μg/mL). When the fraction of HPβCD and PVP K30 is increased, the solubility of Met base is also enhanced linearly. Higher solubility is observed in case of Met base-PVP K30 binary system as compared to Met base-HPβCD binary system. The exceptional case is observed in Met base-PVP K30 (1:5 w/w) binary system in DDW. As the pH of DDW found ~6, it is quite evident that DDW is slightly acidic in nature. Thus in DDW protonated molecules might not get complexed with PVP K30, hence the possibility of complexation is less, though the acidic environment supports solubilization (pH<pK_a). High solubility was achieved at pH 6.8 and 5.5 with respect to the pure drug due to ionization of drug in the corresponding media (Singh et al., 2009). In pH 7.4 the solubility was found low as compared to pH 5.5 and pH 6.8 but higher than DDW. This is because of basic nature of the drug being stable and unionized in basic media. Enhancement of solubility of drug in presence of PVP K30, a synthetic hydrophilic carrier was ranged ~2-4 folds in DDW, ~1-3 folds in pH 7.4, ~1-2.5 fold in pH 6.8 and ~2-4.3 folds in pH 5.5. Though PVP K30 is watersoluble polymer, it also has an amphiphilic characteristic. Due to its amphiphilic nature, the molecules of the pure drug may strongly bind with apolar parts (-CH) methane.
An attempt to enhance solubility of metoclopramide base by Solid dispersion strategy and its application on development of Transdermal device

**FIGURE 1** – Phase solubility diagram of Met base at different temperatures: (a) in presence of DDW and PVP K30; (b) in presence of DDW and HPβCD; (c) in presence of pH 7.4 and HPβCD; (d) in presence of pH 5.5 and HPβCD.

**TABLE II** – Equations of phase solubility profiles at different temperatures and different media

<table>
<thead>
<tr>
<th>Temperature</th>
<th>PVP K30, DDW</th>
<th>HPβCD, DDW</th>
<th>HPβCD, pH 7.4</th>
<th>HPβCD, pH 5.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 °C</td>
<td>y = 0.949x+0.0005</td>
<td>y = 0.426x+0.0005</td>
<td>y = 0.285x+0.003</td>
<td>y = 0.287x+0.004</td>
</tr>
<tr>
<td>37 °C</td>
<td>y = 0.903x+0.0006</td>
<td>y = 0.435x+0.0006</td>
<td>y = 0.425x+0.004</td>
<td>y = 0.326x+0.005</td>
</tr>
<tr>
<td>40 °C</td>
<td>y = 0.566x+0.0007</td>
<td>y = 0.435x+0.0007</td>
<td>y = 0.430x+0.004</td>
<td>y = 0.380x+0.005</td>
</tr>
<tr>
<td>45 °C</td>
<td>-</td>
<td>y = 0.0772x+0.0011</td>
<td>y = 0.444x+0.004</td>
<td>y = 0.409x+0.005</td>
</tr>
</tbody>
</table>
### TABLE III – Thermodynamic parameters and binding constants of Met base at different media and at different temperatures

<table>
<thead>
<tr>
<th>Carrier</th>
<th>t, °C</th>
<th>Medium DDW</th>
<th>Medium pH 7.4</th>
<th>Medium pH 5.5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>$K_a$, M$^{-1}$</td>
<td>($\Delta G$, $\Delta H$, $\Delta S$ kJ/mole)</td>
<td>$K_a$, M$^{-1}$</td>
</tr>
<tr>
<td>PVP K30</td>
<td>25</td>
<td>95.71</td>
<td>$\Delta G = -11.30$</td>
<td>$\Delta H = 26.60$</td>
</tr>
<tr>
<td></td>
<td>37</td>
<td>145.04</td>
<td>$\Delta G = -12.82$</td>
<td>$\Delta H = 237.47$</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>350.78</td>
<td>$\Delta G = -15.24$</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HPβCD</td>
<td>25</td>
<td>81.57</td>
<td>$\Delta G = -10.90$</td>
<td>$\Delta H = -10.39$</td>
</tr>
<tr>
<td></td>
<td>37</td>
<td>69.34</td>
<td>$\Delta G = -10.92$</td>
<td>$\Delta H = -7.88$</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>67.34</td>
<td>$\Delta G = -10.95$</td>
<td>$\Delta H = -6.46$</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>64.76</td>
<td>$\Delta G = -11.02$</td>
<td>56.12</td>
</tr>
</tbody>
</table>

$K_a$ = stability constant, $\Delta G$ = change in Gibbs-free energy, $\Delta H$ = change in enthalpy, $\Delta S$ = change in entropy

and (-CH$_2$) methylene groups of PVP K30 and hence less solubility was achieved when complexation occurred. Solubility enhancement of Met base of two carriers may be compared as follows: Met base-PVP K30 (1:0-1:3 w/w) > Met base-HPβCD (1:0-1:3 w/w), Met base-HPβCD (1:5 w/w) > Met base-PVP K30 (1:5 w/w) in DDW; Met base-PVP K30 > Met base-HPβCD in pH 6.8, 7.4 and 5.5 media. The solubility enhancement plots are depicted in (Figure 2).

In DDW, the enhancement of solubility of Met base-HPβCD (1:5 w/w) SD is ~4.6 times higher than a pure drug that is nearly similar to Met base-PVP K30 (1:5 w/w; ~4 fold). Because of the enhanced hydrophilicity of the polymer, HPβCD showed better solubility improvement in presence of DDW. The drug content of each complex system ranged from ~73-97.10%.

As sufficient amount of drug (more than 10 times of drug is incorporated in the patch) is dissolved in pH 7.4 and as it remains unionized, it has been chosen as in vitro study fluid to maintain sink condition (Arora, Mukherjee, 2002). This is, undoubtedly, a necessary factor for transdermal drug delivery system.
TABLE IV – Solubility analysis of Met base and SDs at 37 °C in different media (n=3)

<table>
<thead>
<tr>
<th>Binary System</th>
<th>DDW (μg/mL)</th>
<th>pH 7.4 (μg/mL)</th>
<th>pH 6.8 (μg/mL)</th>
<th>pH 5.5 (μg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Met base: HPβCD (1:0 w/w)</td>
<td>190.47±0.002</td>
<td>1346.97±0.006</td>
<td>3500±0.005</td>
<td>5539±0.010</td>
</tr>
<tr>
<td>Met base: HPβCD (1:1 w/w)</td>
<td>231.29±0.004</td>
<td>1537.41±0.004</td>
<td>3727.27±0.006</td>
<td>12695.03±0.003</td>
</tr>
<tr>
<td>Met base: HPβCD (1:2 w/w)</td>
<td>361.22±0.004</td>
<td>1891.15±0.003</td>
<td>4439.39±0.010</td>
<td>16241.13±0.005</td>
</tr>
<tr>
<td>Met base: HPβCD (1:3 w/w)</td>
<td>494.55±0.006</td>
<td>2578.23±0.005</td>
<td>5878.78±0.006</td>
<td>17801.41±0.005</td>
</tr>
<tr>
<td>Met base: HPβCD (1:5 w/w)</td>
<td>877.55±0.010</td>
<td>-</td>
<td>-</td>
<td>20212.76±0.007</td>
</tr>
<tr>
<td>Met base: PVP K30 (1:1 w/w)</td>
<td>383.67±0.010</td>
<td>1734.69±0.013</td>
<td>3772.72±0.001</td>
<td>10638.29±0.017</td>
</tr>
<tr>
<td>Met base: PVP K30 (1:2 w/w)</td>
<td>489.79±0.014</td>
<td>2224.48±0.004</td>
<td>4454.54±0.002</td>
<td>15744.68±0.004</td>
</tr>
<tr>
<td>Met base: PVP K30 (1:3 w/w)</td>
<td>603.40±0.006</td>
<td>2918.36±0.007</td>
<td>6181.81±0.006</td>
<td>21914.89±0.006</td>
</tr>
<tr>
<td>Met base: PVP K30 (1:5 w/w)</td>
<td>761.90±0.014</td>
<td>3952.38±0.010</td>
<td>8742.42±0.005</td>
<td>24184.39±0.006</td>
</tr>
</tbody>
</table>

Selection of solvent, plasticizer, solid dispersion formulation and carriers for transdermal delivery

As MET is basic in nature (pKa 9.47), it is stable in alkaline medium. As a consequence, ionization occurred due to saturation of drug in acidic media. Therefore, the In-vitro diffusion, as well as the permeation studies, were expedited in pH 7.4 media. Of all the SDs Met-PVP K30 (1:5 w/w) was found optimized as the solubility of this SD was more satisfactory and remains higher than other SDs.

Depending upon dielectric constant (DEC), chloroform (DEC= 4.81) was chosen as casting solvent for the preparation of the transdermal device. As chloroform is a non-polar solvent, so when introduced with the drug for blending, it abolishes the crystallinity of drug in the matrix of the patch (Pattnaik et al., 2011).

Plasticizer plays a key role on development of transdermal device because it imparts mechanical strength to the polymeric matrix. In the present study DBP was chosen as an essential element due to its low molecular weight (278.35 g/mol). Because of its low molecular weight, DBP reduces the secondary bonds (hydrogen bonding) of polymer chains. Low molecular weight helps improving miscibility with polymer. It reveals that increasing of compatibility is the cognizance of robust mutual bonding. It is seen that as interaction of polymer chains is weakened, tensile strength and glass transition temperature is decreased. Therefore, flexibility of polymer films is enhanced (Gungor, Erdal, Ozsoy, 2012).

HPMC E-15 (Hydroxypropyl methyl cellulose E-15), EC (Ethyl cellulose) and PVP K30 are the choice of carriers for the preparation of the transdermal device. As SDs are means for solubility improvement, PVP K30– Met-base complex (1:5 w/w) when applied to form the transdermal device, enhances the solubility of the drug. Therefore, the device should be coated with the hydrophobic film former like ethyl cellulose to control the excessive release of drug and to improve release rate constants. This result can be assigned to the leaching of a hydrophilic compound which yields formation of pores. As a result, this phenomenon reduces the mean diffusion path length of drug molecules into the dissolution media. Apart from that PVP K30 functions as an antinucleating agent which hampers the crystallinity of drug. Hence,
PVP K30 and EC play a major role to increase solubility of drug (Kandavilli, Nair, Panchagnula, 2002).

HPMC is used generally in controlled drug delivery. It also has matrix formation property for transdermal formulation. As HPMC is a highly aqueous soluble carrier, it produces clear film because of the sufficient solubility of the drug in the carrier (Kandavilli et al., 2002; Guyot, Fawaz, 2000; Rogers, 2009).
Percentage moisture content, percentage moisture absorption studies and drug content analysis

Table V showed the mean drug content, percentage moisture content, and uptake of each patch. The mean drug content (~90-93%) confirms almost equal distribution of drug into the film. Low moisture uptake provides protection from microbial growth and loftiness of patches. Lower moisture content ensures the stability and the patches remain dried as well.

**TABLE V** – Data of percentage moisture content, percentage moisture uptake and percentage drug content. \( (n=3) \)

<table>
<thead>
<tr>
<th>Patch code</th>
<th>% Moisture content</th>
<th>% Moisture uptake</th>
<th>% Drug content</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>1.82±0.8</td>
<td>1.13±0.28</td>
<td>92.42±0.001</td>
</tr>
<tr>
<td>F2</td>
<td>1.45±0.49</td>
<td>1.37±0.97</td>
<td>91.58±0.001</td>
</tr>
<tr>
<td>F3</td>
<td>1.28±0.86</td>
<td>1.89±0.84</td>
<td>90.99±0.002</td>
</tr>
<tr>
<td>F4</td>
<td>1.83±0.7</td>
<td>1.53±0.32</td>
<td>92.17±0.002</td>
</tr>
<tr>
<td>F5</td>
<td>1.33±0.21</td>
<td>1.44±0.65</td>
<td>90.48±0.0015</td>
</tr>
<tr>
<td>F6</td>
<td>1.89±0.49</td>
<td>1.61±0.58</td>
<td>93.48±0.0011</td>
</tr>
</tbody>
</table>

**Thickness, adhesion property and content uniformity**

The resultant thickness of all transdermal patches yields satisfactory results. The thickness of each pure drug loaded patch (F1-F3) ranged 0.08±0.01-0.09±0.008 and thickness of SD loaded patches (F4-F6) ranged 0.086±0.01-0.091±0.005 mm. Enhancement of thickness of patch can cause enhancement of tightness of molecules and hence the mobility of molecules is decreased triggering drug release from patch in a very controlled manner.

The results of adhesion property yields excellent adhesive nature in all cases except F1 and F4 formulation. The adhesion property was found better because of presence of higher amount of PVP which itself has an adhesive property (Kathe, Kathpalia, 2017) and when admixture with DBP, hardness of patches is reduced. It was observed that higher quantity of DBP increases the pliability and thereby enhances adhesive property.

The content uniformity of drug after storage for 0-5 months showed optimized results for pure drug loaded patches as well as (1:5 w/w) Met-PVP SD patches. No significant differences were found between pure and SD patches. Drug contents were found uniform with slight standard deviation (87.07±0.6-92.31±1.0) values in each formulation (F1-F6). This result confirms that the drug was distributed well throughout all the patches. No interference was observed in drug content uniformity due to temperature as well as relative humidity. The results of above mentioned properties are illustrated in Table VI.

**TABLE VI** – Thickness, adhesion property and content uniformity of different patches \( (n=3) \)

<table>
<thead>
<tr>
<th>Patch code</th>
<th>Thickness (mm)</th>
<th>Adhesion property</th>
<th>Drug content uniformity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.083±0.009</td>
<td>**</td>
<td>90.30±0.9</td>
</tr>
<tr>
<td>F2</td>
<td>0.080±0.01</td>
<td>***</td>
<td>87.07±0.6</td>
</tr>
<tr>
<td>F3</td>
<td>0.09±0.008</td>
<td>***</td>
<td>89±1.0</td>
</tr>
<tr>
<td>F4</td>
<td>0.086±0.01</td>
<td>**</td>
<td>89.28±1.5</td>
</tr>
<tr>
<td>F5</td>
<td>0.087±0.005</td>
<td>***</td>
<td>87.76±0.3</td>
</tr>
<tr>
<td>F6</td>
<td>0.091±0.005</td>
<td>***</td>
<td>92.31±1.0</td>
</tr>
</tbody>
</table>

** denotes good adhesion, *** symbolizes excellent adhesion property

**In vitro diffusion study**

**In vitro** diffusion study was carried out in an **in-vitro** version of Franz diffusion cells. As a standard, an equivalent amount of Met base and Met-PVP K30 complexed (the same amount which is present in patch, loaded in donor cell, ~840 μg) solution were tested in phosphate buffer pH 7.4 (data not shown) and total quantum of Met base was diffused about 94% after 8 h as more free molecules of drug was present in the solution and can enter through the barrier much efficiently than
that of matrix form. The *in-vitro* diffusion different patches were performed at 37±0.5 °C.

From (Figure 3a-b) it is clear that as the percentage of DBP is increased the drug release from the patches (pure drug) is enhanced. Whereas the patches with SD (PVP K30-Met base-EC 1:5:0.25 w/w) showed higher drug release than that of pure drug loaded patches.

The cumulative percentage release for 30%, 40% and 50% v/w DBP loaded patches obtained

65.80±1.26, 70.67±0.74 and 82.87±2.66% drug release respectively after 8 h. Enhancement of drug release for pure Met base was expressed as F1>F2>F3. A higher percentage of plasticizer augments flexibilities of polymer macromolecular segments. Thus, it leads to the occurrence of loosening of the tightness of intermolecular forces (Bergo, Sobral, 2006). Dibutyl phthalate (DBP) is a low molecular weight plasticizer. This nature of plasticizer yields to the easy entrance of

---

**FIGURE 3** – *In vitro* diffusion study of pure Met base (a) and PVP K30-Met base 5:1 SD loaded patches (b).
molecules through the polymer chain of the film and can interplay with individual functional groups of the carrier (Gal, Nussinovitch, 2009). The flow property of drug molecules enhances relatively with the increase of the volume of plasticizer. Thus higher release is achieved.

In case of SD loaded patches (F4-F6), the percentage release was found higher than in case of pure form because of two reasons. The first one is the presence of DBP which flexibilizes the patches and thereby improves plasticity of drug-polymer matrix which may cause easy penetration of drug molecules from the matrix to the aqueous media. Secondly, the enhancement of drug release occurred due to incorporation of SD that contains higher extent of PVP K-30 which facilitates the solubility of drug and improves release of drug from matrix patch. The cumulative percent release for the above-mentioned patches was found 72.56±0.058, 80.62±0.016 and 90.79±0.048% respectively after 8 h.

**Evaluation of skin component interference and ex vivo skin permeation study**

After constant evaluation upto 8 h, it was observed that there is no interference of skin components upto 5 h. Very negligible amount was obtained after 5 h which may be due to presence of least quantity of aqueous soluble UV absorbing compounds present or released through the skin.

Before the evaluation of drug-carrier loaded patches, it is necessary to observe whether the plain drug can permeate through the skin or not. Therefore, the study was conducted at 37±0.5 °C by attaching the skin on the donor cell and a solution (0.84 mg in 3 mL chloroform) of pure drug was mounted above the skin portion and the upper opening of donor is sealed with parafilm. Approximately 49% (Data not included) drug was permeated through the skin having the flux 10.48±0.17 µg/cm²/h.

Ex-vivo permeation was performed for selected formulations (F1-F6) followed by application of excised porcine ear portion (3.935 cm²). The cumulative amount permeations showed more prominent drug permeation for Met base-PVP K30 SD patches as compared to patches with the pure drug. The amount of permeation of pure drug loaded patches and SD loaded patches were found ~481.34±21.4, 557±32.8, 617.6±17.2 and ~560.20±16, 667.14±16.8, 744.55±10.13 µg respectively through 3.935 cm² area of skin after 8 h. This may be due to the presence of PVP K 30, which improves solubility as well as thermodynamic actions in the medium that leads to enhancement of the permeability of the drug.

The permeation factors are calculated and illustrated in Table VII and the permeation plots are depicted in Figure (4a-b). The enhancement of flux (Jₑ) in PVP K30 SD loaded patches (F4-F6) and pure drug-carrier loaded patches (F1-F3) were found higher 1.9-2.20 and 1.38-1.70 times more than that of plain drug because PVP K30 influences the penetration enhancing effect. This effect may also be ascribed on the decrease of the drug’s particle size, increase of wettability and restraint of its aggregation with PVP K30 that gave rise to increased dissolution rate. Saleem et al. (2011) had, in the same way, found the improved permeation flux of ketoprofen when compared to pure drug. They also observed that the in vitro permeation results were also correlated to the solubility studies. Thus, from the results obtained earlier, it can be perceived that the overall in vitro permeation was profoundly correlated with solubility studies. Hence, PVP K30-Met base (5:1 w/w) SD was selected as an optimized vehicle to apply in the transdermal formulation.

The influence of permeation enhancer in this study is not effective because after 8 h adequate amount of drug is released through the skin. A peculiar release of drug (~98-99%) was observed after 8 h in the cases of SD loaded patches before incorporation of EC (data not shown). This does not favor transdermal formulation because as soon as the drug is penetrated across the skin, it would have the tendency to be excreted out from the body and thus the process of formulation is continued time and again. In this context, incorporation of EC (1/5th of PVP K30) into the SD loaded patches retards the burst release of drug and hence the drug was maintained in the systemic circulation for long time.

A best fit kinetic profile of drug release from matrix system generally follows zero order release kinetics. A constant quantity of active ingredient within time unit with a specific dose imparts the presence of drug at the therapeutic level in human body (Balcerzak, Mucha, 2010). More or less rectilinear graphic data were obtained when cumulative percentage of drug permeated per centimeter square of patches via porcine skin, anatomically similar to human body (Schmook, Meingassner, Billich, 2001), was plotted against time (h) in case of F1-F6. The similar kinetic data was observed by (Prajapati, Patel, Patel, 2011). Drug release upto 8 h during in vitro study followed zero order release kinetics (R²= 0.973-0.996) in as much as the dispersed
FIGURE 4 – Permeation profiles of pure Met base (a) and SD containing patches with different volume of DBP (b).

TABLE VII – Permeation data of pure drug loaded and patches containing SD with DBP variation

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>R² value</th>
<th>Flux (μg/cm²/h)</th>
<th>Kp (cm/h)</th>
<th>Enhancement factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure Met base</td>
<td>0.970</td>
<td>10.48±0.17</td>
<td>0.24±0.2</td>
<td>-</td>
</tr>
<tr>
<td>F1</td>
<td>0.988</td>
<td>14.5±0.5</td>
<td>0.26±0.06</td>
<td>1.38</td>
</tr>
<tr>
<td>F2</td>
<td>0.992</td>
<td>17.2±1.0</td>
<td>0.29±0.03</td>
<td>1.65</td>
</tr>
<tr>
<td>F3</td>
<td>0.996</td>
<td>17.7±1.2</td>
<td>0.22±0.01</td>
<td>1.70</td>
</tr>
<tr>
<td>F4</td>
<td>0.973</td>
<td>22.51±1.4</td>
<td>0.52±0.15</td>
<td>2.1</td>
</tr>
<tr>
<td>F5</td>
<td>0.973</td>
<td>20.7±2.5</td>
<td>0.34±0.07</td>
<td>1.9</td>
</tr>
<tr>
<td>F6</td>
<td>0.996</td>
<td>22.89±5.7</td>
<td>0.25±0.01</td>
<td>2.20</td>
</tr>
</tbody>
</table>

R²= Coefficient of determination according to zero order kinetics, Kp= permeation coefficient.
drug matrix confirmed constant concentration. The values found better than first order ($R^2= 0.875-0.961$) and Higuchi model ($R^2= 0.887-0.967$). Diffusion in most controlled devices including transdermal patches governs the process of drug release (Andersson et al., 2000). The polymer matrix has an abiding influence on diffusivity because the motion of a small molecule is confined to three dimensional networks of polymer chains. Reports are already available on variation of the cross-linking and modification of structural arrangements of polymers with the help of different mixtures (Fan, Singh, 1989). Different in vitro drug release profiles from different blends of PVP and EC formulations could be accredited to different cross-linking networks of the polymeric chains of blends made of polymeric transdermal experimental formulations because diffusion pathway and tortuosity varied. It is also reported that they cause variation of drug as also duration of diffusion (Arora, Mukherjee, 2002). It implies that skin permeation of drug on release rate profiles in respect of experimental formulations cannot be defied because the skin plays a potential role in variation of “release kinetics” (Johnson, Blankschtein, Linger, 1997). In steady state of skin permeation diffusion of drug through skin appendage (sebaceous gland, hair follicles and sweat ducts) is considered much significant. The variation of shunt pathways from one part of the skin to other may be one of the causes of variation in release profiles of experimental formulations.

Characterization of solid dispersion and transdermal devices

Fourier transform infrared spectroscopy (FTIR)

The spectrum of Met HCl Figure 5A showed several absorption bands at 3568.6 cm$^{-1}$ (O-H stretching manner of hydrate); 3397.1 cm$^{-1}$ (symmetric NH$_2$ stretching); 3300.2 and 3195.1 cm$^{-1}$ (N-H stretching manner of amide). NH$_2$ scissoring and/or C=O stretching bands were observed at 1631.9 and 1595.9 cm$^{-1}$. At 1540.6 cm$^{-1}$ (N-H band of amide) was also present. Whereas, the IR

![Figure 5](image_url)

**FIGURE 5** – i) FTIR spectra of HPβCD; ii) PVP K30; a) Met-HPβCD 1:1 SD; b) Met-HPβCD 1:2 SD; c) Met-HPβCD 1:3 SD; d) Met-HPβCD 1:5 SD; e) Met-PVP K30 1:1 SD; f) Met-PVP K30 1:2 SD; g) Met-PVP K30 1:3 SD; h) Met-PVP K30 1:5 SD; A) Met HCl; B) Met base; C) Met-PVP K30 SD loaded patch; D) Pure drug (Met base) loaded patch.
spectra of Met base Figure 5B showed absorption bands at 3399.8 cm\(^{-1}\) (symmetric NH\(_2\) stretching) and N-H stretching manner for amide was observed at 3325.1 and 3214.5 cm\(^{-1}\). The O-H bending for water was not prominently observed in the spectra of Met HCl, but the same is observed prominently in the spectra of Met base at 1654 cm\(^{-1}\) which may be due to the purification of drug. NH\(_2\) stretching and N-H band for amide were observed at same position as Met HCl and the C=O stretching band was observed at 1590.4 cm\(^{-1}\). The IR spectra of 6i) HPβCD and ii) PVP K30 showed broad absorption bands at 3401 and 3403 cm\(^{-1}\) (O-H stretching vibration); C-H stretching were also present at 2932 and 2926.77 cm\(^{-1}\). On the other hand, an aromatic ring C-C stretching vibration was observed at 1593 cm\(^{-1}\). With very slight shifting all the characteristic peaks of Met base were observed in SDs Figure 5a-h. In view of the above findings we can come to the conclusion that in all the SDs there may be partial interaction between drug and excipients. The absorption peak at 2926.77 cm\(^{-1}\) was shifted ~9 cm\(^{-1}\) in case of pure drug loaded patch Figure 5D at 2917 cm\(^{-1}\). On the other hand, 3399 (NH\(_2\) stretching) and N-H stretching at 3325 and 3214.5 cm\(^{-1}\) of Met base were absent in SD loaded patch and the O-H bending of Met base was found ~3 cm\(^{-1}\) forward shifting in patch with SD Figure 5C. From above detections it can be concluded that solid binary systems confirm inclusion complex formation between carrier and drug. No chemical incompatibility was observed in patches prepared with Met-PVP K30-Met base (5:1 w/w SD)-EC as well.

**Differential Scanning Calorimetry (DSC) study**

To evaluate the interactions between guest and host in solid-state DSC study is performed. In this study thermograms of Met HCl, Met base, PVP K30-Met base physical mixture (1:1 w/w PM) and PVP K30-Met base (5:1 w/w) solid complex were illustrated in Figure 6, that confirm the interactions between excipients as well as solid-state change. The DSC thermogram of Met HCl showed a sharp endothermic peak at 99.01 ºC (Figure 6a). (Mitchell, 1985) was of opinion that the DSC profile of Met base has its existence as two enantiotropic polymorphs, and the transformation of the Form I (stable at room temperature, 22 ºC) to stable Form II occurs promptly at 125 ºC. It is seen that Form II melts at 147 ºC. But in case of Met base, Figure 6b, two prominent endotherms were observed at 122.10 ºC and 149.11 ºC. This confirms that some extent of impurities was present in hydrochloride form of drug. These impurities are removed by purification of drug followed by crystallization. (Wang et al., 2011) had spearheaded his studies on the thermal effect on solid state characteristics of metoclopramide hydrochloride monohydrate (Met HCl, H\(_2\)O) by DSC, TG and thermally responsive FTIR microspectroscopy and they had properly clarified the changes occurred due to process of dehydration (loss of H\(_2\)O) amorphization and recrystallization as proven by endothermic peak at 85 ºC, 184 ºC and 105 ºC which are probably related to recrystallization of amorphous sample. The characteristic peaks of PVP K30-Met base (1:1 w/w and 5:1 w/w) PM, Figure 6c-d was observed at 128.49, 144.98 ºC and 141.9 ºC respectively which give rise almost similar report as Met base but the intensity and the peak height of the endotherms were decreased. This is due to the partial complex formation in PM between drug and carrier. The thermogram of PVP K30-Met base SD (5:1 w/w) depicted in Figure 6e showed, the endothermic peaks of drug were nearly vanished. This phenomenon indicated that the drug was molecularly dispersed in the cavity of PVP K30 (Jain et al., 2011).

**Scanning Electron Microscopy (SEM)**

Figure 7 elucidates the surface morphology of PVP K30-Met base PM, PVP K30-Met base 5:1 SD, pure drug loaded patch and SD loaded patch. Slightly rough surface was observed in PVP K30-Met base 1:1 PM with crystals of pure drug and carrier (Figure 7a). Figure 7b, PVP K30-Met base 5:1 SD showed ruptured surface morphology with tiny lucid formation. This kind of morphology confirms the complex formation between drug and carrier (Koh et al., 2013; Choonara et al., 2014). The pure drug loaded patch (Figure 7c) showed fractional amorphous nature of matrix of the film. On the other hand, Figure 7d represents an amorphous matrix of film with SD, which may be due to the presence of chloroform and PVP K30. Presence of chloroform reduces crystalline nature of drug and PVP K30 acts as anti-nucleating constituent which also minimizes crystallinity of the drug (Kim, Choi 2002; Raghavan et al., 2001).

**CONCLUSION**

From the above survey it is concluded that the 1:5 SD loaded patch in presence of EC suits better than pure
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**FIGURE 6** – DSC curves of Met HCl (a), Met base (b), PVP K30-Met base PM (1:1 w/w) (c), PVP K30-Met base PM (5:1 w/w) (d) and PVP K30-Met base SD (e).

**FIGURE 7** – Scanning electron micrographs of PVP K30-Met base PM (a), PVP K30-Met base 5:1 SD (a), Pure drug (Met base) loaded patch (c) and SD loaded patch (d).
drug loaded patch. The adhesive property, drug content uniformity and stability were found satisfactory in each case. The SEM images of SD loaded patch in this present work revealed an approximately amorphous nature of film matrix. The results indicate that the developed transdermal device with SD successfully enhances the permeation rate of drug. Thus it may be easily predicted that the bioavailability of drug can also be improved.

CONFLICT OF INTEREST

The authors report no conflicts of interest.

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