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Effect of casting solvent on crystallinity of ondansetron in transdermal films

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ABSTRACT

The purpose of the present investigation is to assess the influence of casting solvent on crystallinity of ondansetron hydrochloride in transdermal polymeric matrix films fabricated using povidone and ethyl cellulose as matrix forming polymers. Various casting solvents like chloroform (CHL), dichloromethane (DCM), methanol (MET); and mixture of chloroform and ethanol (C-ETH) were used for fabrication of the transdermal films. Analytical tools like scanning electron microscopy (SEM), X-ray diffraction (XRD) studies, differential scanning calorimetry (DSC), etc. were utilized to characterize the crystalline state of ondansetron in the film. Recrystallisation was observed in all the transdermal films fabricated using the casting solvents other than chloroform. Long thin slab-looking, long wire-like or spherulite-looking crystals with beautiful impinged boundaries were observed in SEM. Moreover, XRD revealed no crystalline peaks of ondansetron hydrochloride in the transdermal films prepared using chloroform as casting solvent. The significantly decreased intensity and sharpness of the DSC endothermic peaks corresponding to the melting point of ondansetron in the formulation (specifically in CHL) indicated partial dissolution of ondansetron crystals in the polymeric films. The employed analytical tools suggested chloroform as a preferred casting solvent with minimum or practically absence of recrystallization indicating a relatively amorphous state of ondansetron in transdermal films.

1. Introduction

Only a limited number of drugs so far were employed for drug delivery using transdermal drug delivery systems (TDDS). These drugs are mostly dissolved in the adhesive matrix of the TDDS forming a solid solution but can also exist as a solid dispersion. Since it is difficult to achieve a sufficiently high flux rate across the skin, various methods of penetration enhancement are used. Besides chemical enhancement or physical enhancement, the supersaturation of drugs in the patches is commonly employed to increase drug delivery (Cilurzo et al., 2005).

A softer alternative method consists in the use of a system which, having chemical potentials greater than those of the corresponding saturated systems, promote the partition of the drug from the vehicle to the skin. The efficacy of such approach was widely proven by using either solutions (Pellet et al., 1994, 1997), or monolayer transdermal patches (Kim and Choi, 2002). Monolayer transdermal patches containing drugs in supersaturated conditions can be easily obtained by fast solvent evaporation or, in the case of hot melt based system, by fast cooling of the matrix.

Even if in both processes the drug supersaturation can be easily reached, the system often results unstable. As a matter of fact, the systems are thermodynamically unstable and the drugs frequently re-crystallize during the storage. The growth of drug crystals in the formulation lead to a reduction of drug thermodynamic activity and this consequently may reduce the drug flux through the stratum corneum (Kim and Choi, 2002). Amorphization of drugs is thus desirable as the main expertise of formulation development for significant improvement of bioavailability (Mallick et al., 2008). From our laboratory, we have previously reported solid state amorphization of ibuprofen with enhanced bioavailability (Mallick et al., 2008). Therefore, inhibition of drug crystallization is imperative to maintain the efficiency and quality of transdermal systems and prolongs the shelf life of the product. Thus, the basic approach for reducing the induction time for drug crystallization in patches is the addition of a crystallization inhibitor into the matrix that could retard the nucleation process. The proposed antinucleant agents are low molecular weight excipients, such as silicon dioxide (Lipp et al., 1997), cholesterol, other steroidal molecules (Biali et al., 2002) and surfactants (Kim and Choi, 2002) or macromolecules. Among the last, the most widely used in the development of transdermal patches are water

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soluble polyvinyl pyrrolidones (Kim and Choi, 2002; Pattnaik et al., 2009a,b). The efficacy of copolymers of methacrylic acid with different functionalities on the inhibition of estradiol and norethisterone crystallization in polyacrylic pressure sensitive adhesive matrices was also proven (Kotiyan and Vavia, 2001). The efficacy of three low molecular weight excipients (propylene glycol, Cremophor® EL and Cremophor® RH) and of two copolymers of methacrylic acid (Eudragit® E 100 and Eudragit® RL 100) as ibuprofen crystallization inhibitors was tested in monolayer patch based on polydimethylsiloxane pressure sensitive adhesive (Cilurzo et al., 2005). However, all these antinucleating agents are useful only when, there is otherwise, chance of recrystallization. Prevention of recrystallization, of course, is technologically preferred than inhibition of crystallization.

Transdermal delivery systems are gaining a lot of momentum now a days and one of the major problem has been reported to be crystallization in the system leading to reduced percutaneous absorption. The casting solvent used during preparation of transdermal drug loaded films can alter the crystalline state of the drug in the transdermal product (Cho et al., 2008). Hence, in the present investigation, attempts has been made to study the effect of casting solvent on crystallinity of ondansetron hydrochloride in polymeric films meant for transdermal delivery as a screening method to further develop a suitable crystal-free transdermal system.

2. Materials

Ondansetron hydrochloride was obtained as a gift sample from Cipla Ltd. (Mumbai, India). Ethyl Cellulose (EC; ethoxy content 47.5–49%, viscosity 14 cps in 5% (w/w) solution in 80:20 toluene/ethanol at 25 °C) was purchased from BDH Chemicals Ltd., Poole, England. Polyvinylpyrrolidone (PVP; *K* value: 26–35) and polyvinylalcohol (PVA) were purchased from HiMedia Laboratories Pvt. Ltd, Mumbai, India and S.D. Fine-Chem. Ltd. Boisar, India, respectively. Di-n-Butylphthalate was purchased from Central Drug House (P) Ltd., Mumbai, India. All solvents were of analytical grade.

3. Fabrication of transdermal films

Transdermal films composed of EC and PVP (10:90) as matrix forming polymers containing ondansetron hydrochloride (50% of dry weight of polymers) were prepared (Table 1) by solvent evaporation technique (Pattnaik et al., 2009a,b) using various casting solvents like chloroform (CHL), dichloromethane (DCM), methanol (MET); and mixture of chloroform and ethanol (C-ETH). Another formulation using ondansetron free base was prepared using chloroform (B-CHL) as casting solvent. Di-n-butylphthalate was incorporated as a plasticizer at a concentration of 30% (w/w) of dry weight of polymers. Ondansetron hydrochloride (or free base) was dissolved in casting solvent followed by addition of polymers and plasticizer with constant stirring. The matrix was prepared by pouring the homogeneous dispersed solution on 4% PVA backing membrane in a flat bottomed petridish and dried at 40 °C for 12 h. The dried patches were removed and stored in desiccators until use.

4. Evaluation of transdermal films for crystallinity

4.1. Scanning electron microscopic (SEM) studies

The surface morphology of the film was recorded with a Jeol Scanning Electron Microscope (Model: JSM 5200, Japan). The samples were mounted on an aluminium stub by using a double-sided adhesive tape. Then it was placed in an ion coater unit (Model: IB-2, Hitachi, Tokyo, Japan) for gold coating (200 Å). During gold coating process the samples were exposed to vacuum of 10^{-50} mm. Afterwards, an accelerating voltage of 5 kV was applied and the image was photographed by Asia Pentex Camera of 35 mm film.

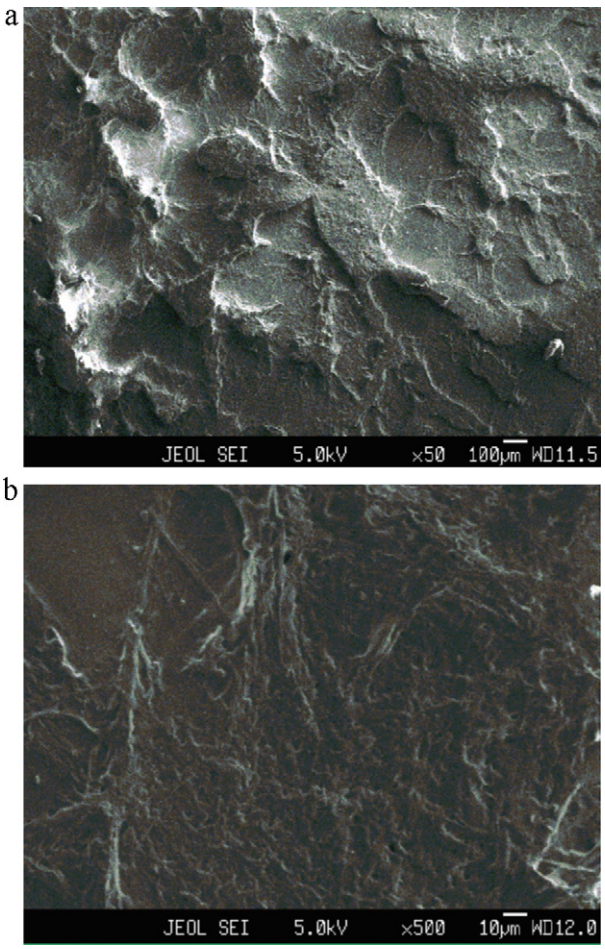

Fig. 1. (a) Scanning electron micrograph of transdermal film prepared using chloroform as casting solvent (CHL) at 50× magnification. (b) Scanning electron micrograph of transdermal film prepared using chloroform as casting solvent (CHL) at 500× magnification.

4.2. X-ray diffraction (XRD) studies

Samples of pure ondansetron, physical mixture of ondansetron with polymers and ondansetron loaded transdermal patches were assessed for crystallinity using X-ray diffractometer (Model: SEIFERT, C-3000, Germany) using Nickel-filtered CuK α radiation (λ = 1.54 Å). The voltage and current were 30 kV and 15 mA, respectively. Measurements were carried out in the angular scan range from 5° to 40° (2θ) at a scan speed of 1°/min.

4.3. Differential scanning calorimetry (DSC) studies

Thermal analysis was performed using a Jade DSC (Perkin Elmer, Switzerland) with Pyris software (Software Version: 9.0.1.0174). All samples (5 mg) were weighed and heated at scanning rate of 10 °C/min between 30 and 330 °C. Aluminium pans and lids were used and temperature calibrations were performed periodically using indium as standard. To evaluate the internal structure modifications after drug incorporation, analysis was performed on pure ondansetron, physical mixture of drug with polymers and drug

Table 1
Formulation of transdermal patches.

Formulation codes	EC:PVP	Drug loading[a] (%)	DBP[b] (%)	Ondansetron form	Casting solvent
CHL	10:90	50	30	HCl salt	Chloroform
DCM	10:90	50	30	HCl salt	Dichloromethane
MET	10:90	50	30	HCl salt	Methanol
C-ETH	10:90	50	30	HCl salt	Chloroform and ethanol (4:1)
B-CHL	10:90	50	30	Free base	Chloroform

[a] Ondansetron HCl or free base as percentage of total polymer (EC/PVP) weight.
[b] Dibutyl-pthalate as percentage of total polymer (EC/PVP) weight.

loaded transdermal patches.

5. Results and discussions

5.1. Scanning electron microscopic (SEM) studies

The surface morphology of the formulations was studied with SEM (Figs. 1–5). Literature reports suggest that PVP is amorphous, EC is partially crystalline and ondansetron is crystalline in nature (Guo and Gray, 1989; Kibbe, 2005). SEM studies indicated that EC, in the film, exists mainly in amorphous state since no crystals in terms of long thin slabs (in DCM, C-ETH, and MET) and spherulites (in B-CHL) were seen in CHL. Thus, the crystals seen in DCM, C-ETH, MET and B-CHL were mainly stemming from drug (Figs. 2–4).

The SEM images of DCM, C-ETH, and MET look quite similar with long thin slab-looking or long wire-like crystals. The relative polarities of solvents used are as follows:

Chloroform = 0.259, Dichloromethane = 0.309, Ethanol = 0.654, Methanol = 0.762For the mixed solvent, chloroform/ethanol = 4/1, the relative polarity will be $0.8 \times 0.259 + 0.2 \times 0.654 = 0.338$. Since 0.309 and 0.338 are close, this explained why the crystalline morphology in DCM and C-ETH look very similar after solvents evaporated. The polarity of dichloromethane, 4/1 ratio chloroform/ethanol, and methanol is higher than chloroform, and the better solubility of drugs in polar solvent favors crystallization, therefore, crystals were seen in DCM, C-ETH, and MET, while no such drug crystals were observed in CHL.

Spherulite-looking crystals with beautiful impinged boundaries were observed in B-CHL. This is unambiguously because of the drug

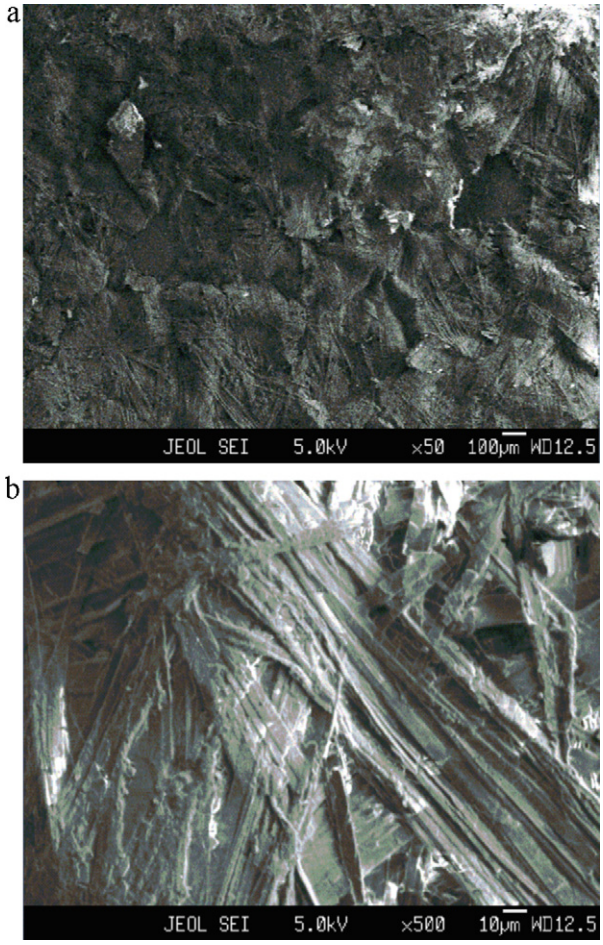

Fig. 2. (a) Scanning electron micrograph of transdermal film prepared using dichloromethane as casting solvent (DCM) at 50x magnification. (b) Scanning electron micrograph of transdermal film prepared using dichloromethane as casting solvent (DCM) at 500× magnification.

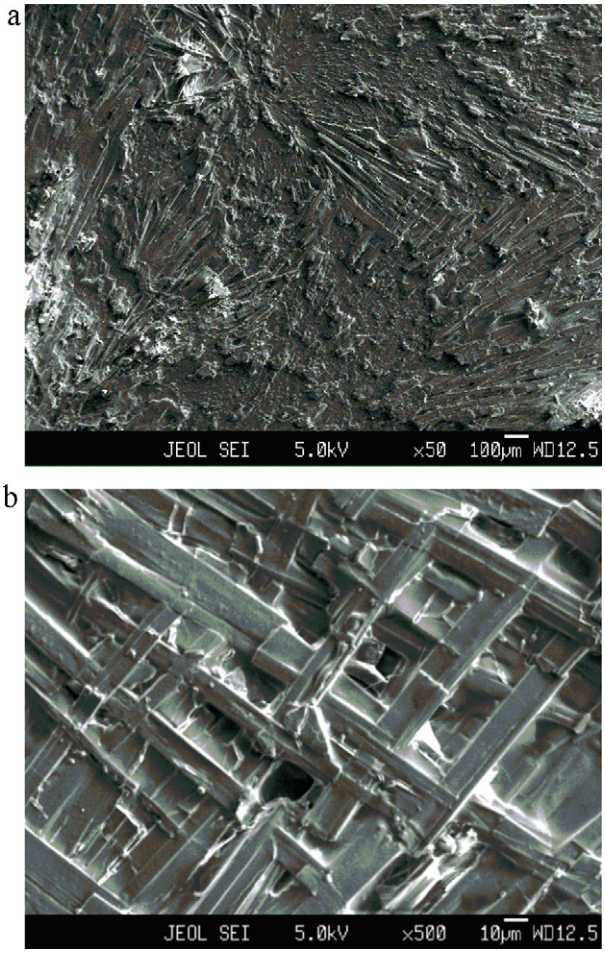

Fig. 3. (a) Scanning electron micrograph of transdermal film prepared using mixture of chloroform and ethanol as casting solvent (C-ETH) at 50× magnification. (b) Scanning electron micrograph of transdermal film prepared using mixture of chloroform and ethanol as casting solvent (C-ETH) at 500× magnification.

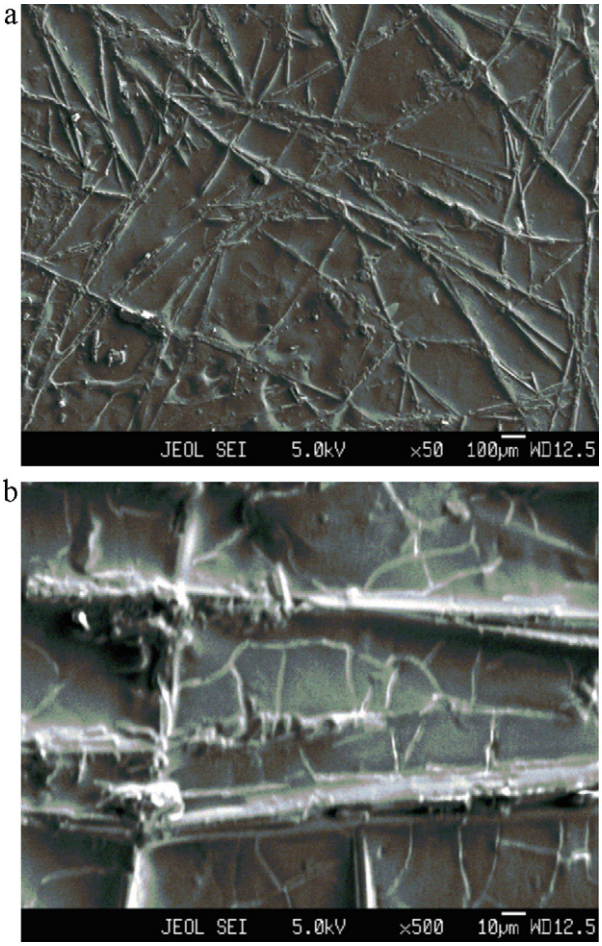

Fig. 4. (a) Scanning electron micrograph of transdermal film prepared using methanol as casting solvent (MET) at 50× magnification. (b) Scanning electron micrograph of transdermal film prepared using methanol as casting solvent (MET) at 500× magnification.

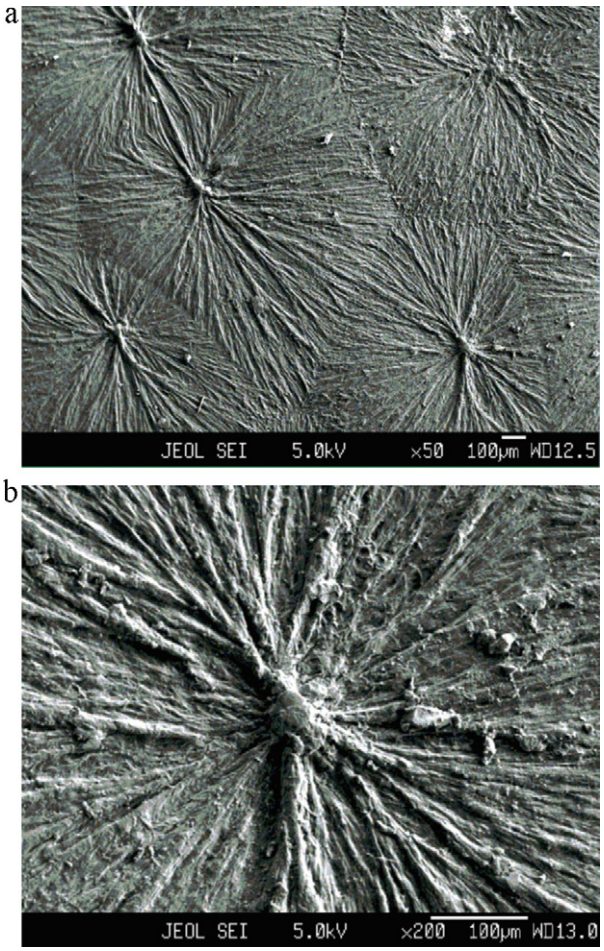

Fig. 5. (a) Scanning electron micrograph of transdermal film prepared using ondansetron base and chloroform as casting solvent (B-CHL) at 50× magnification. (b) Scanning electron micrograph of transdermal film prepared using ondansetron base and chloroform as casting solvent (B-CHL) at 200× magnification.

type used, i.e., base form as opposed to HCl salt form. The base form of drug favored its nucleation and growth in the presence relative less polar solvent (i.e., chloroform).

PVP was used as matrix forming polymer and this polymer was reportedly used successfully as anti-nucleating agent to prevent crystallization of ketoprofen, estradiol, fluocinonide, hydrocortisone acetate in transdermal systems (Megrab et al., 1995; Schwarb et al., 1999; Raghavan et al., 2001; Kim and Choi, 2002). Though a higher fraction of PVP was used for preparation of transdermal films in the present investigation, it failed to prevent crystallization in all the cases except when chloroform was used as casting solvent.

5.2. X-ray diffraction (XRD) studies

X-ray diffraction studies were undertaken to confirm the crystalline characteristics of ondansetron hydrochloride in the polymeric matrix of transdermal patches (Fig. 6). The pure ondansetron hydrochloride exhibited the diffraction peaks at 2θ values of 8.26°, 13.28°, 16.84°, 20.20°, 23.96°, 24.36°, 25.72°, 27.88°, 30.84°, etc., indicating the presence of crystalline ondansetron hydrochloride. Interestingly, there were no crystalline peaks (shoulder observed at scattering angle, 2θ value of 19.73°) of ondansetron hydrochloride in the polymeric matrix prepared using chloroform as casting solvent (CHL).

Therefore, it is presumed that the drug molecule was dispersed at the molecular level and the crystallinity of the drug was not shown by X-ray diffraction study which is in agreement with the SEM results. This result implies that ondansetron hydrochloride is present as an amorphous form in the transdermal system, CHL. On the contrary, though the intensity was found less compared to pure crystalline ondansetron HCl, crystalline peaks were observed in all other transdermal films (DCM: diffraction peaks at 2θ values – 6.68°, 10.58°, 11.21°, 12.41°, 19.97°, 22.28°, 22.67°, 25.23°, etc.; MET: diffraction peaks at 2θ values – 7.22°, 12.69°, 16.46°, 19.66°, 27.44°, etc.; C-ETH: diffraction peaks at 2θ values – 7.56°, 12.68°, 16.49°, 19.37°, 22.38°, 23.87°, 27.51°, etc.; B-CHL: diffraction peaks at 2θ values – 6.16°, 6.89°, 11.68°, 19.22°, 23.72°, 25.34°, 29.66°, etc.) fabricated using casting solvents other than chloroform (Fig. 6). Though, chloroform was used as casting solvent, it was worth noting that crystalline peaks were observed in B-CHL (ondansetron free base was used with chloroform as casting solvent) indicating the influence of initial form of drug used. This may be due to the fact that the free base form of drug favored its nucleation and growth in the presence of relative less polar solvent. This indicated that apart from the casting solvent, salt or base form of drug also influence its crystalline state in the transdermal product.

5.3. Differential scanning calorimetry (DSC) studies

The physicochemical state of drug in the formulation was assessed by DSC. Thermograms of pure ondansetron HCl (OND),

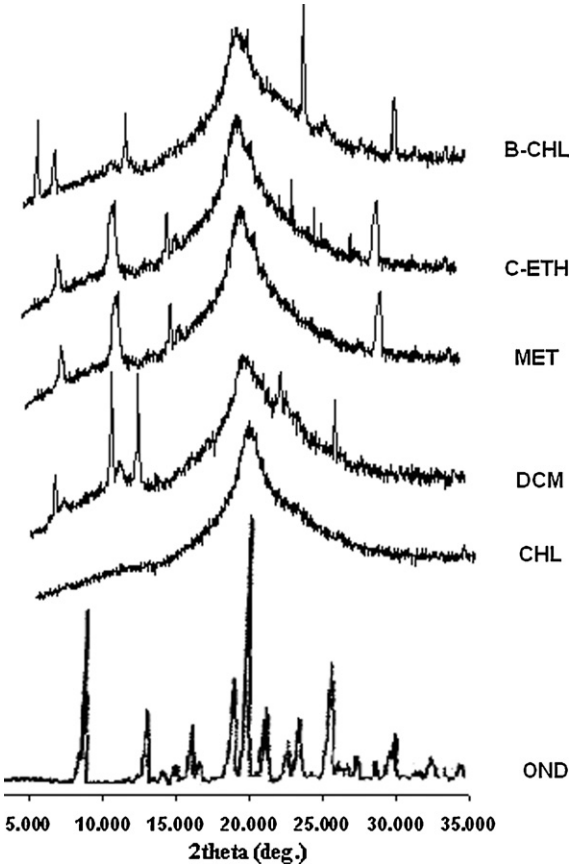

Fig. 6. X-ray diffraction pattern of ondansetron hydrochloride (OND) and transdermal films CHL (chloroform as casting solvent), DCM (dichloromethane as casting solvent), MET (methanol as casting solvent), C-ETH (chloroform/ethanol mixture as casting solvent, B-CHL (prepared using ondansetron base and chloroform as casting solvent).

physical mixture of ondansetron HCl with polymers (PM), and drug loaded transdermal patches (CHL, DCM, MET, C-ETH, and B-CHL) are shown in (Fig. 7). In the case of pure ondansetron, a sharp endotherm was observed at 182.66 °C, corresponding to the melting point of ondansetron. The comparatively larger endotherm observed at 108.06 °C corresponds to the dehydration process (dehydration from hydrated ondansetron pure drug). Similar endotherm (at around ~108 °C) in transdermal patches may be due to loss of sorbed water from films (expected due to presence of larger fraction of PVP in the films). The exothermic peaks beyond 300 °C may correspond to the decomposition process. The relatively decreased intensity of the endothermic peaks in physical mixture (PM) may be due to dilution effect. The significantly decreased intensity and sharpness of the endothermic peaks corresponding to the melting point of ondansetron in the formulations (specifically in CHL) indicated partial dissolution of ondansetron crystals in the polymeric film, i.e., the presence of ondansetron in an relatively amorphous state, dissolved or molecularly dispersed state.

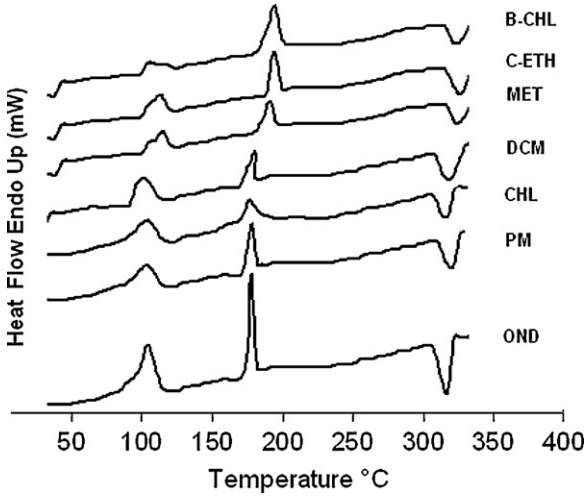

Fig. 7. DSC thermograms of pure ondansetron HCl (OND), physical mixture of ondansetron HCl with polymers (PM), and transdermal formulations (CHL, DCM, MET, C-ETH, and B-CHL).

6. Conclusions

Effects of casting solvents like, chloroform, dichloromethane, methanol and mixture of chloroform/ethanol on drug crystallinity in transdermal polymeric films were studied using SEM, XRD and DSC as analytical tools. Though a higher fraction of PVP was used for preparation of transdermal films in the present investigation, it failed to prevent crystallization in all the cases except when chloroform was used as casting solvent.

Both the analytical tools suggested chloroform as preferred casting solvent due to minimum or practically absence of drug in crystalline state. Relatively amorphous state of ondansetron in the transdermal system CHL, is technologically advantageous owing to its anticipated better bioavailability. A long term stability study is essential to assess the stability of the relatively amorphous state of ondansetron in the polymeric films because, usually, this is a thermodynamically unstable state.

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