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Characterization of polymeric dispersions of dimenhydrinate in ethyl cellulose for controlled release

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Abstract

Granulations of dimenhydrinate (DMH) were prepared using various concentrations of ethyl cellulose (EC) by the solid dispersion technique. Characterization was done using thermal analysis, powder X-ray diffraction, infrared spectroscopy, optical microscopy and dissolution studies. Humidity studies were performed to investigate the effect of moisture on the drug and solid dispersions. It was seen that the crystalline drug was converted into its amorphous form in all the granulations. There was no chemical interaction between the DMH and EC. The thermal decomposition of drug in the granules was not affected. Dissolution studies revealed that the drug release from the granulations was significantly reduced as compared to the pure drug. As the amount of ethyl cellulose increased, the drug release rate decreased and the drug release kinetics showed a better fit to zero-order kinetics. Humidity studies showed that the drug and granulations remained stable in conditions not exceeding 70%RH. At high humidity of 100%RH, there was formation of the hydrate crystal forms of the drug in the pure drug samples and granules with 1:1 DMH–EC content whereas the granules with higher polymer content did not show any significant changes indicating better drug stability in the granules.

Keywords: Dimenhydrinate; Ethyl cellulose; Controlled-release; Solid dispersion; Characterization; Humidity

1. Introduction

Ideally a dosage form should deliver the drug in an amount sufficient to maintain the therapeutic drug level over an extended period for optimum therapeutic action. Dimenhydrinate is the diphenhydramine salt of 8-chlorotheophylline (Martindale, 1977). It is an antihistaminic used for the prevention and treatment of nausea, vomiting, dizziness, and vertigo associated with motion sickness (Drug Facts and Comparisons, 2005). It has also been used for postoperative vomiting and drug induced vomiting (Martindale, 1977). The duration of action is 3–6 h (Genc et al., 1999) which necessitates repeated administration. Thus, a controlled release formulation of dimenhydrinate would be helpful so as to provide the necessary drug release over a longer period of time and reduce dosing frequency. The use of controlled release technology in the formulation of pharmaceutical product has become increasingly important in the last few years (Khan, 2001). A controlled release system offers advantages such as improved patient compliance due to reduced dosing frequency, decreased incidence and/or intensity of side effects, greater selectivity of pharmacological activity, a more constant or prolonged therapeutic effect and an increase in cost effectiveness (Wise, 2000). In recent years much attention has been paid to the use of polymeric matrices in the development of controlled drug delivery systems since their production has generally become more simple and cheaper. Chewing-gum formulations of dimenhydrinate have been reported by Varshosaz et al. (2002). Genc et al. used polymers such as MC, HEC, Carbopol 934, Eudragit RLPM and Eudragit NE 30D to obtain tablets using the direct compression and wet granulation techniques. Controlled-release capsules containing dimenhydrinate (II) and Ca phosphate were reported by Krishnamurthy (1993). Ethyl cellulose is a hydrophobic polymer used extensively as a coating material, as a tablet binder, in microcapsules and microspheres and in the preparation of matrix-type controlled release tablets (Iqbal et al., 2002). The application of the solid disper-

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sion technique has proved be a valuable method in controlling the drug release rate (Iqbal et al., 2002; Shaikh et al., 1987; Sadeghi et al., 2003; Pignatello et al., 2001). However, no studies have been reported where ethyl cellulose was used to prepare oral granulations of dimenhydrinate using the solid dispersion technique.

The main objectives of the present study were:

- to prepare granulations of dimenhydrinate with ethyl cellulose by the solid dispersion technique,
- to determine compatibility between the drug and polymer,
- to investigate the effect of polymer concentration on the drug dissolution rate,
- to determine the drug release mechanism,
- to investigate the effect of humidity on the drug stability.

2. Materials and methods

2.1. Materials

Dimenhydrinate was obtained from Spectrum Chemical Mfg. Corp., New Jersey. Ethocel, Standard 10FP Premium was obtained from The Dow Chemical Company, Michigan; 190 Proof, 95%, ethyl alcohol from Pharmco Products Inc., Connecticut was used. Sodium hydroxide was obtained from Fisher Scientific, New Jersey.

2.2. Methods

2.2.1. Sample preparation

To investigate the effect of ethyl cellulose content on the drug release of dimenhydrinate, three different ratios of drug–polymer, namely 1:1, 1:3 and 1:5 (w/w), were used. Solid dispersions (SD) were prepared by the solvent evaporation technique. The drug and ethyl cellulose were mixed to get a homogenous mixture. Ethyl alcohol was preheated to about 60 °C and then gradually added to the drug–ethyl cellulose mixture to dissolve the blend while continuously heating the mixture on a hot plate and slowly evaporating the solvent. The mixture was then poured on to glass plates and dried in an oven at 60 °C to constant weight. The dried material was then ground, screened and the 0.42–0.84 mm fraction of granules were used for analysis. A 1:1 homogenous mixture of drug–polymer was used for the physical mixture analysis.

2.2.2. Drug content assay

To obtain the standard curve, a known amount of the drug was dissolved in a specific volume of the dissolution medium, serial dilutions were done and a plot of absorbance versus concentration data was obtained. For the drug content, granules containing drug equivalent to 30 mg was dissolved in 100 mL dissolution medium and shaken using a mechanical stirrer for 24 h. The samples were filtered, suitably diluted and then analyzed spectrophotometrically to determine the drug content.

2.2.3. Differential scanning microscopy (DSC)

A DSC 822e with a TS0801RO robotic sampler (Mettler-Toledo, Inc., Columbus, OH) with the STARe® ver 8.10 software for data analysis was used. A 7–10 mg sample was placed in a 100 μL aluminum pan, weighed on a Mettler MT 5 microbalance and crimped with a lid containing a pinhole and placed in the DSC unit along with a similar pan as a reference. The sample was heated at a rate of 10 °C/min from 25 to 160 °C. Nitrogen was used as a purge gas with a flow rate of 50 mL/min. The DSC was calibrated using indium (melting point, 156.6 ± 0.2 °C) and zinc (melting point, 419 ± 0.3 °C) as standards.

2.2.4. Powder X-ray diffraction (PXRD)

A PAN analytical X-Pert Pro ver 1.6 with Cu as the anode material and a BB004 flat stage was used. The sample was powdered finely and placed in a plastic sample holder of 1 in. square. Data were collected at 45 kV and 40 mA. Samples were scanned from 5 to 35 °C at step size of 0.0084 and scan rate of 0.0026°/s. The X-Pert Data collector ver 2.1 was used to analyze the data.

2.2.5. Infrared spectroscopy (IR)

IR studies were done using the Digilab FTS 6000. The drug was dispersed in dry KBr, ground well in a mortar and pestle and the drug–KBr disc was prepared. The disc was placed in FT-IR sample holder and purged with nitrogen gas for 5 min and reading taken. The scan range was from 4000 to 400 cm^{-1}. The results were analyzed using the Digilab Win-IR PRO 3.4 software.

2.2.6. Optical microscopy

Crystal images were taken using an Optical Microscope (Nikon SMZ 1500) with Nikon Coolpix 990 (3.34 MPixel) digital camera. The sample was mounted on a glass slide, viewed under normal light and pictures taken.

2.2.7. Dissolution testing

The dissolution studies were carried out using a Vanderkamp 600, six-spindle apparatus. The dissolution medium consists of 900 mL of reverse osmosis water. The temperature was maintained at 37 ± 1 °C and the number of paddle rotations was adjusted to 50 rpm. Aliquots of 5 mL were taken at specific intervals and an equal amount of fresh dissolution medium was added to maintain a constant volume of the dissolution medium. Whatman No. 2 filter papers were used. Filtered portions of the aliquots were then analyzed by a spectrophotometer. A Beckman DU 640 B Spectrophotometer was used to measure the absorbance at a λ_{max} of 276 nm.

2.2.8. Humidity studies

Samples of the drug, polymer and granules were placed in plastic trays, weighed and kept in glass humidity chambers. Aqueous solution of 100 mL volume containing a specific concentration of sodium hydroxide was placed at the bottom of each humidity chambers to obtain the desired relative humidity conditions. The samples were exposed to relative humidity conditions of 40%, 70% and 100% for 7 days. The humidity chambers were sealed using petroleum jelly and Parafilm® to prevent moisture entry or escape. After seven days the samples were removed and analyzed to determine any possible effects of water sorption.

Table 1
Drug content of the various DMH granules

DMH:EC ratio	Actual % drug content
1:1	100.00 ± 2.01
1:3	99.97 ± 1.81
1:5	97.68 ± 1.27

2.2.9. Statistical analysis

The SAS version 9 from SAS Institute Inc., Cary, NC, USA was used as the statistical program to analyze the results obtained from the dissolution studies. The analysis was done using one-way ANOVA. The results were interpreted at the significance level of $\alpha = 0.05$.

3. Results and discussion

3.1. Drug content of granulations

The actual amount of dimenhydrinate (DMH) in the various granules has been summarized in Table 1. It was seen that the actual drug content of the granules prepared using the 1:1 and 1:3 drug:polymer ratio was almost 100%. Thus, there was good process efficiency in obtaining the granules with the solid dispersion technique within this drug:polymer range. However, with a 1:5 drug–polymer ratio, the drug content in the granules reduced.

3.2. Differential scanning calorimetry

The DSC runs for dimenhydrinate, ethyl cellulose, physical mixture and various granules are shown in Fig. 1. The DSC curve for dimenhydrinate showed a sharp melting endotherm at 104 °C. The DSC curve for ethyl cellulose showed no peaks signifying the complete amorphous nature of ethyl cellulose. The physical mixture showed no shift in the melting endotherm for dimenhydrinate indicating that there is no chemical interaction between the dimenhydrinate and ethyl cellulose in the physical mixture. All the solid dispersion (SD) granules exhibited no endothermic peak corresponding to the melting of dimenhydrinate indicating that the drug is dispersed amorphously in the EC matrix (Makhija and Vavia, 2002).

3.3. Powder X-ray diffraction studies

The X-ray diffraction patterns for pure dimenhydrinate, pure ethyl cellulose, the physical mixture and various granules are depicted in Fig. 2. The pure drug showed numerous sharp peaks demonstrating the crystalline nature of the drug whereas, ethyl cellulose showed diffused peaks indicating the amorphous nature of the polymer. The characteristic crystalline peaks of dimenhydrinate were also seen in the XRD pattern for the physical mixture which supported the DSC results that there was no interaction between the drug and ethyl cellulose. This also reflected no change in the crystal form of the drug in the presence of ethyl cellulose in the physical mixture. All the SD granules showed diffused peaks indicating that the drug is dispersed at the molecular level in the polymer matrix and hence, no crystals were found in the granules (Agnihotri and Aminabhavi, 2004).

3.4. Thermogravimetric analysis

The TG curves for pure dimenhydrinate, ethyl cellulose, physical mixture and various granules are given in Fig. 3. Dimenhydrinate and ethyl cellulose showed a significant mass loss with an extrapolated onset temperature of decomposition around 240 and 344 °C, respectively. The physical mixture shows an extrapolated onset temperature of decomposition of about 241 °C. As the decomposition onset temperature of the physical mixture was not lower than that of the pure drug, it indicated the decom-

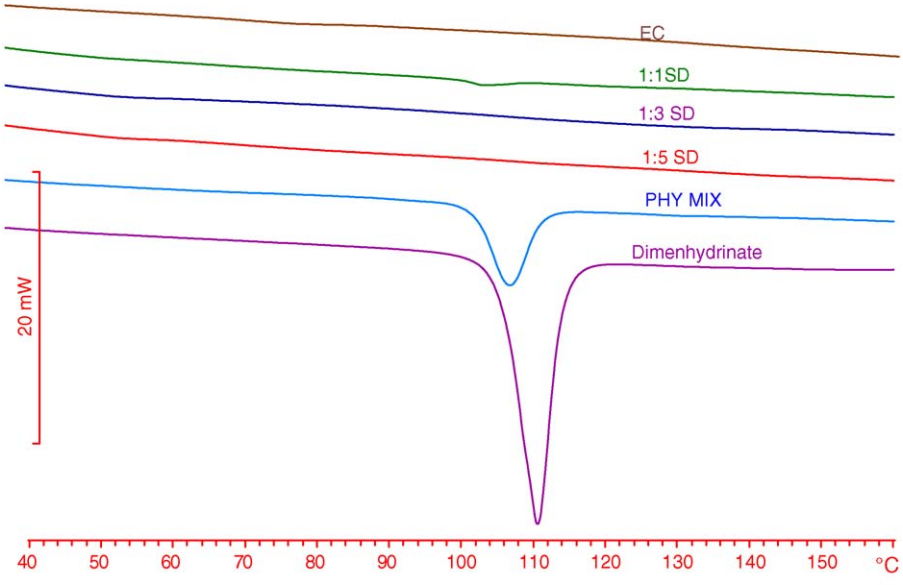

Fig. 1. DSC curves of DMH, EC, physical mixture and the various granules.

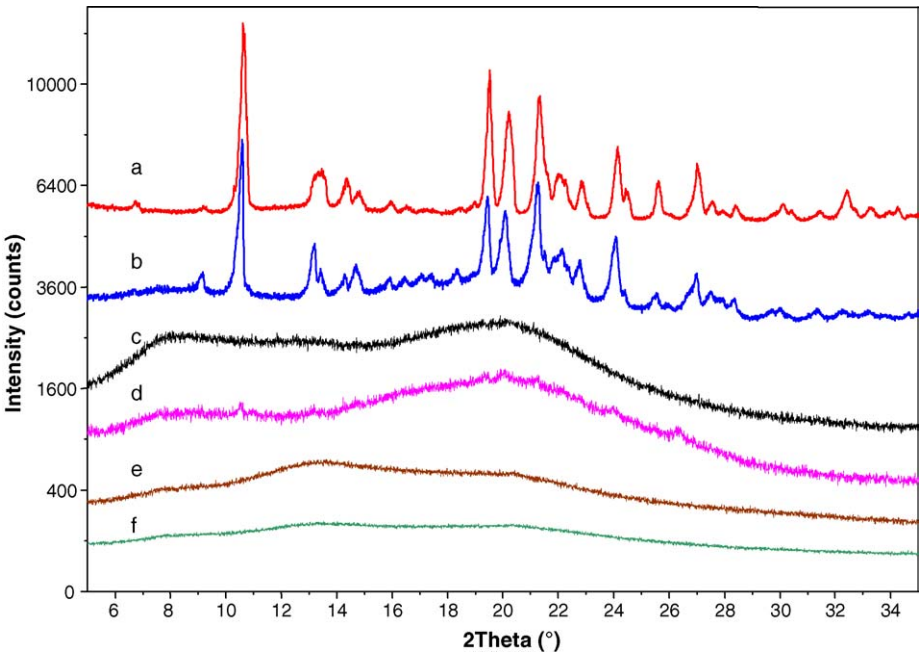

Fig. 2. XRD patterns of (a) DMH, (b) physical mixture, (c) EC, (d) 1:1 SD, (e) 1:3 SD, (f) 1:5 SD.

position of the drug is not influenced by the presence of ethyl cellulose (Medeiros et al., 2001). All the granules showed a decomposition onset temperature greater than that of the pure drug indicating that decomposition of the drug in the granules was not affected by the preparation techniques. Thus, the thermal stability of the drug was maintained even in the granules.

3.5. FT-IR studies

Since the drug and ethyl cellulose were present in the amorphous form in most of the granules, FT-IR studies were performed to aid in the evaluation of any possible chemical interactions in the amorphous state. The FT-IR spectrum for the pure drug and ethyl cellulose is presented in Fig. 4. The FT-IR spectrum for ethyl cellulose shows a distinct peak at 3500 cm^{-1} which is due to the –OH groups present on the closed ring structure of the polymer's repeating units. The same also represents the intra- and intermolecular hydrogen bonding due to the –OH groups (Ravindra et al., 1999). The asymmetric peak seen around 2950–2850 cm^{-1} may be due to –CH stretching. The peak at 1375 cm^{-1} is due to $-CH_3$ bending and the small peak near 1450 cm^{-1} is due to $-CH_2$ bending. The broad distinct peak near 1100 cm^{-1} may be due to the C–O–C stretch in the cyclic ether. The FT-IR spectrum for dimenhydrinate shows a distinct peak of the C–Cl stretching around 700–750 cm^{-1}. The peaks at around 1675 and 1650 cm^{-1} may be due to C=O

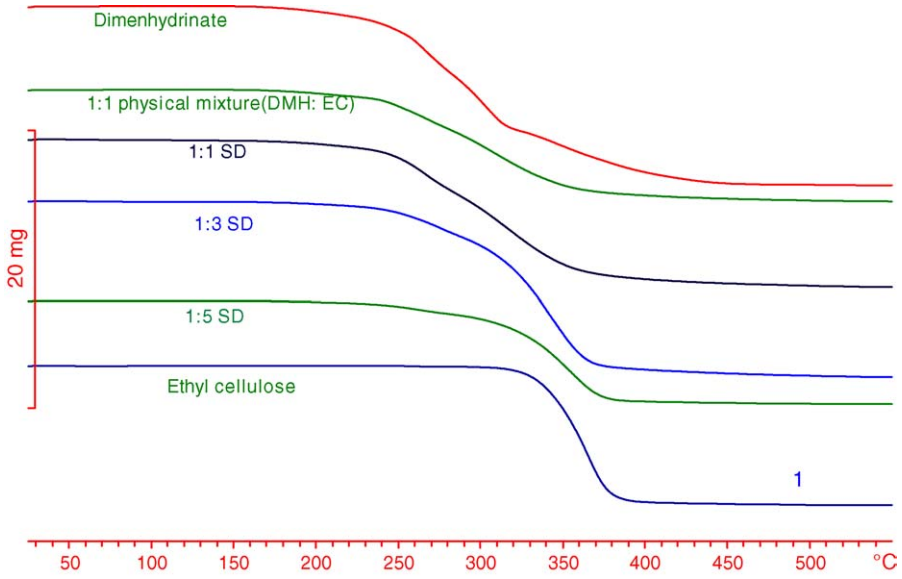

Fig. 3. TG curves of DMH, EC, physical mixture and the various granules.

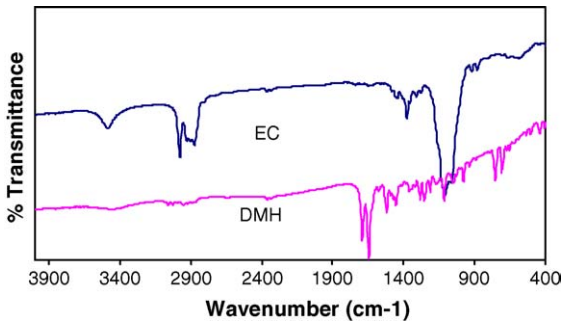

Fig. 4. FT-IR spectrum of dimenhydrinate and ethyl cellulose.

and a C=C peak, respectively (Lambert et al., 1998). The FT-IR spectra for the various granules are given in Fig. 5.

If the drug and the polymer would interact, then the functional groups in the FT-IR spectra would show band shifts and broadening compared to the spectra for the pure drug and polymer (Silverstein et al., 1991). The FT-IR spectra obtained from the various granules showed peaks which were a summation of the characteristic peaks obtained with the pure drug and pure ethyl cellulose. This showed that there was no chemical interaction of the drug with ethyl cellulose even in the amorphous state when the granules were prepared by the solid dispersion method. An increase in the polymer content also did not initiate any drug polymer interactions.

3.6. Optical microscopy studies

Optical photomicrographs examined the morphology of the granules. The granules were further ground and passed through # 80 sieve so as to obtain granules that could be distinctly seen by the microscope. Photomicrographs of samples of pure dimenhydrinate, ethyl cellulose and the various ratio granules are given in Figs. 6–10. From the optical images, it was seen that pure dimenhydrinate is a highly crystalline material with flat rod, plate like crystals whereas ethyl cellulose is completely amorphous in nature. The change in crystalline nature of the drug in the granulations can be easily seen in the photomicrographs. The solid dispersion granules show non-spherical granules with the drug dispersed in the ethyl cellulose matrix. Moreover, as the ethyl cellulose content increased, the granules appeared denser.

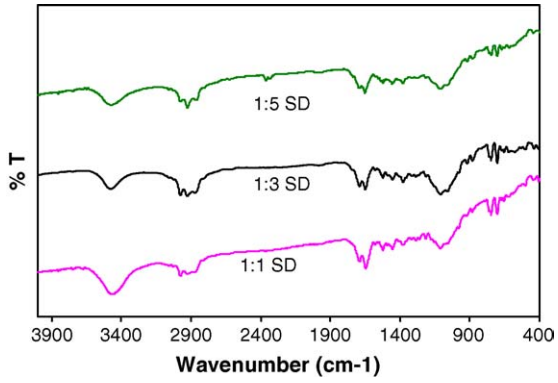

Fig. 5. FT-IR spectrum of the various ratio SD granules.

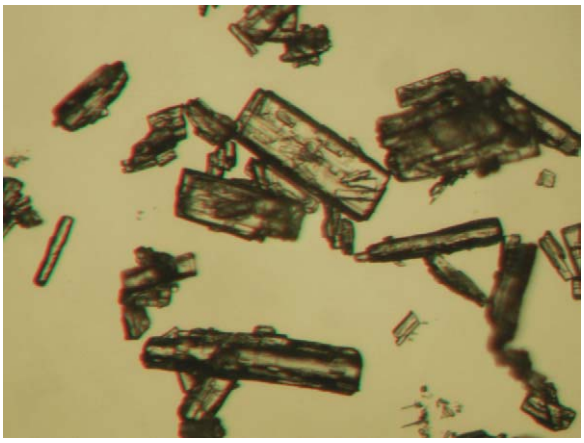

Fig. 6. Optical microscopy image of dimenhydrinate.

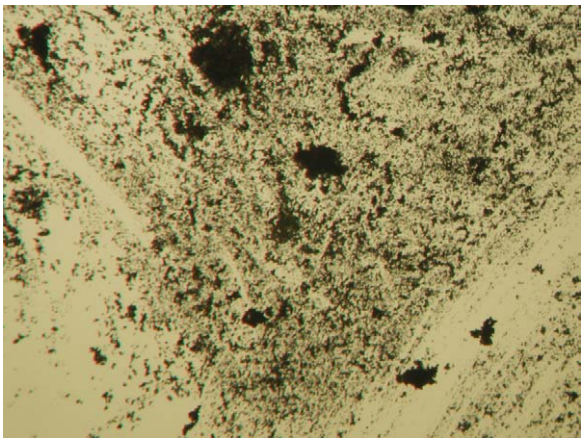

Fig. 7. Optical microscopy image of ethyl cellulose.

This would have an influence on the bulk properties, flow properties and compressibility of the granules.

3.7. Dissolution studies

The drug release from the various granules as compared to the pure drug is shown in Fig. 11. It was seen that the pure drug

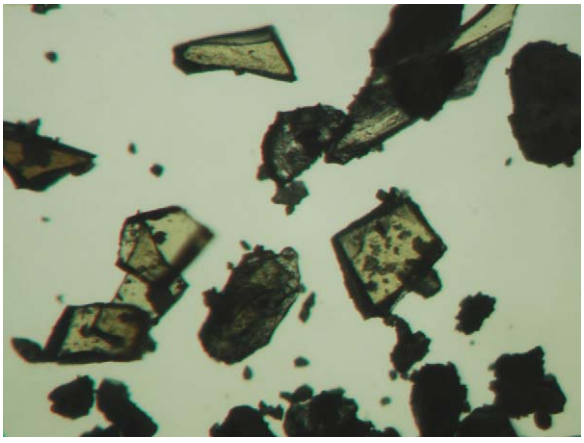

Fig. 8. Optical microscopy image of 1:1 SD granules.

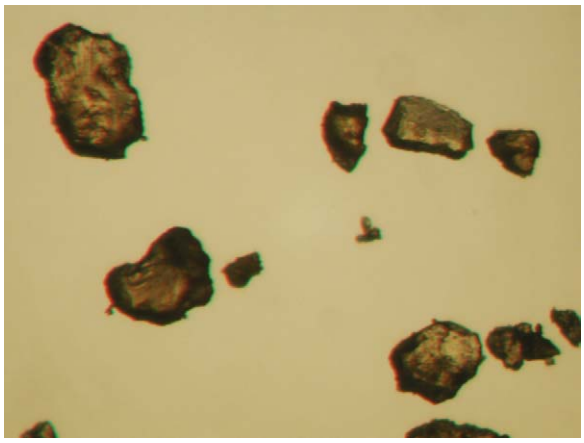

Fig. 9. Optical microscopy image of 1:3 SD granules.

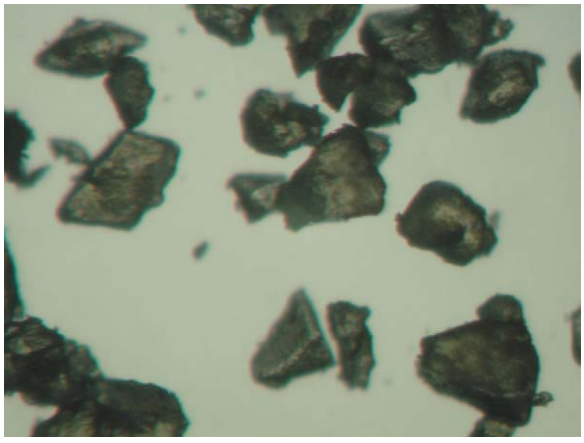

Fig. 10. Optical microscopy image of 1:5 SD granules.

crystals showed a faster dissolution giving about 100% release within 40 min. The dissolution rate for the pure drug was significantly different from the release rate for all three sustained release granulations. The reduction in the drug release is due to the hydrophobic nature of ethyl cellulose, whereby the diffusion of the drug is reduced. Fig. 12 shows a comparison of the amount of drug released from granules after 4 h. It was observed that as the amount of ethyl cellulose increased, the drug release rate reduced correspondingly. This is due to a greater reduction in drug diffusion into the medium. There was a significant difference in the drug release rate from all three solid dispersion granules.

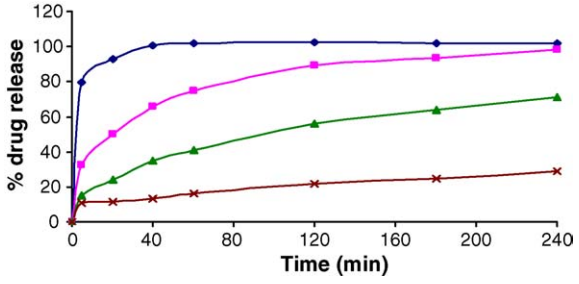

Fig. 11. Drug release from the various SD granules where dimenhydrinate (♦), 1:1 SD (■), 1:3 SD (▲) and 1:5 SD (×).

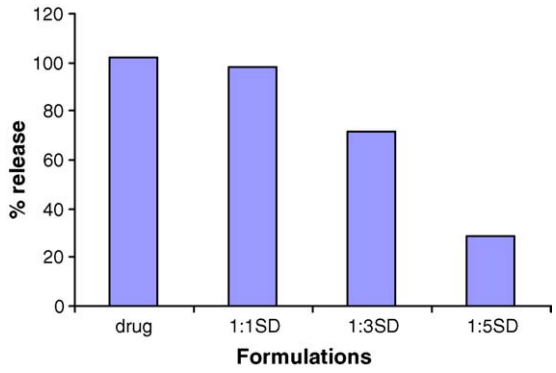

Fig. 12. Amount of drug released after 4 h.

3.8. Drug release kinetics of granulations

The kinetics of drug release from the granulations was studied by evaluating all the experimentally obtained dissolution data points for zero-order kinetics, first-order kinetics, Higuchi's square root of time equation and Hixson–Crowell's cube root equation. Linear regression was carried out and the R^2-values of the equations so obtained are given in Table 2. It can be seen that there was no specific trend in the various granules with respect to the best-fit kinetics. The drug release from the granules showed a good linear fit to first-order kinetics. As the amount of ethyl cellulose increased, the drug release showed a corresponding better zero-order kinetic fit, representing greater controlled release.

3.9. Humidity studies

As the 1:1 SD and 1:3 SD granules showed good drug recovery, they were employed for the humidity studies. The samples were weighed before and after exposure to different humidity conditions. The samples that were exposed to 40% and 70%RH did not show any significant increase in weight (<3%). However, the samples exposed to a relative humidity of 100%RH showed a significant increase in sample weight (8–14%) indicating significant absorption of moisture. Figs. 13–15 show the DSC overlay of samples exposed to 40%, 70% and 100%RH, respectively.

From the DSC curves it was seen that ethyl cellulose shows no change when exposed to the different humidity conditions. There was no effect of humidity on pure dimenhydrinate up to 70%RH. At 100%RH, the DSC curve showed three endotherms suggesting changes in crystal forms. The endotherm peak at about 101 °C corresponded to the melting point of the drug whereas the peaks at about 90 and 56 °C were due to the formation of

Table 2
R^2-values obtained from linear regression analysis of the dissolution data fitted to various kinetic models

	Zero-order	First-order	Higuchi's square root	Hixon–Crowell
1:1 SD	0.7965	0.9882	0.9309	0.9587
1:3 SD	0.9265	0.9824	0.9936	0.9678
1:5 SD	0.9849	0.9900	0.9750	0.9885

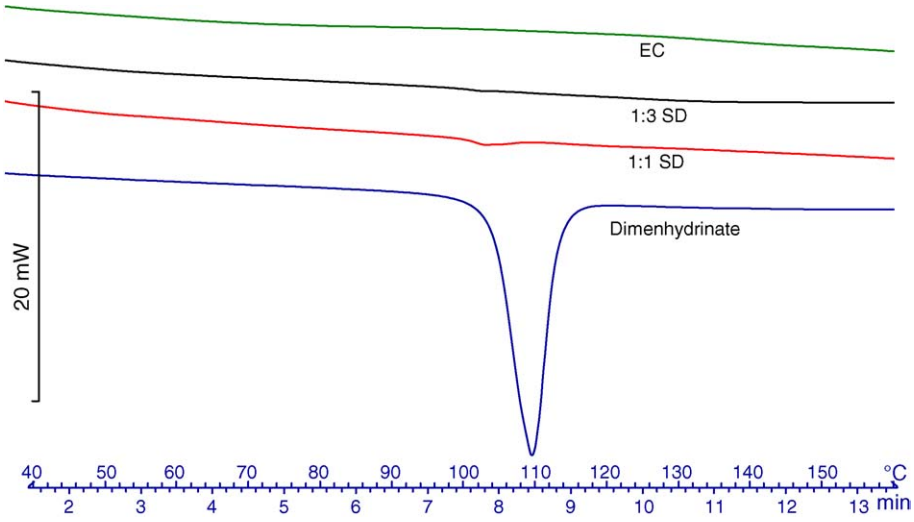

Fig. 13. DSC curves of samples exposed to 40%RH.

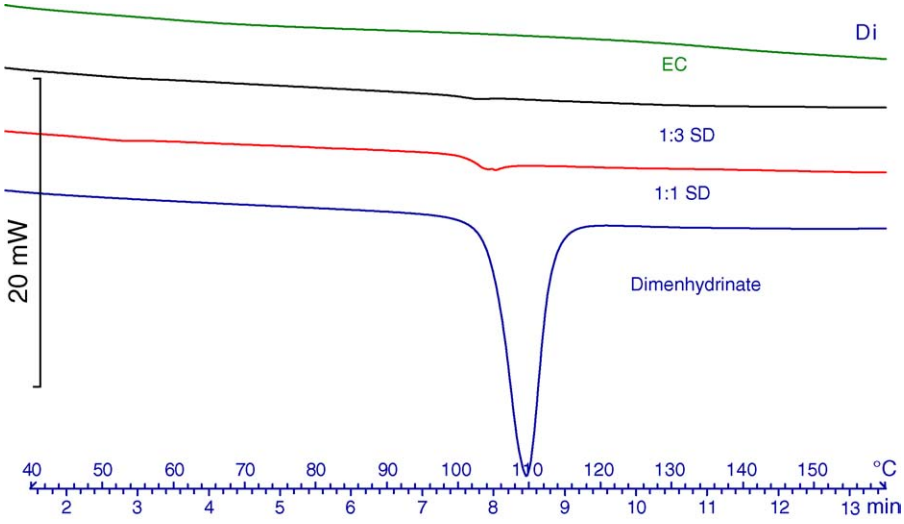

Fig. 14. DSC curves of samples exposed to 70%RH.

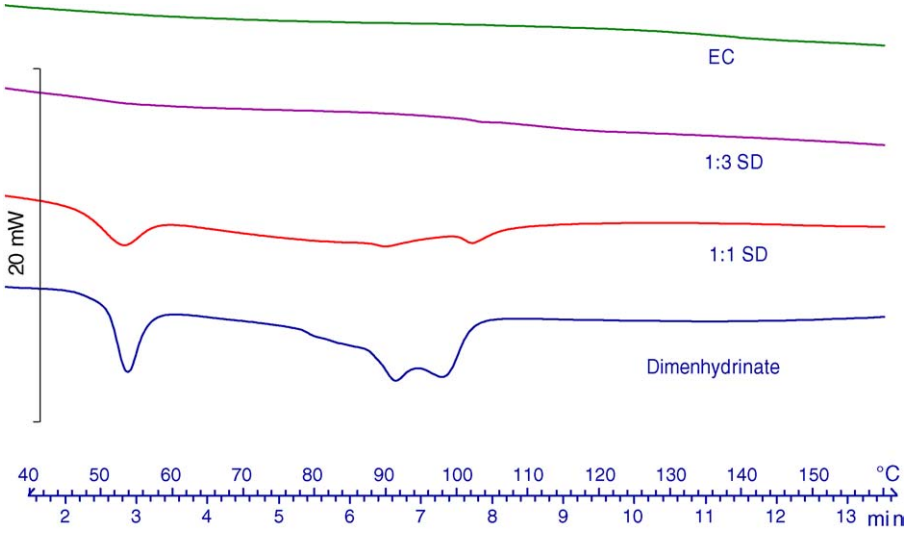

Fig. 15. DSC curves of samples exposed to 100%RH.

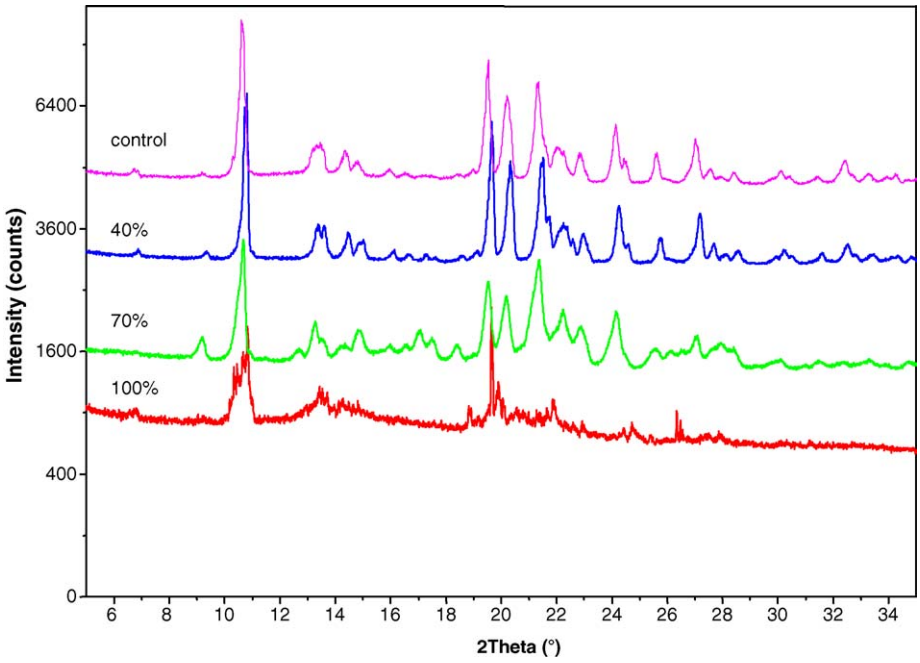

Fig. 16. XRD patterns of dimenhydrinate exposed to various humidity conditions.

the hemihydrate and dihydrate crystal forms of dimenhydrinate (Matoba et al., 1985). The dihydrate peak at around 56 °C was a little lower than the reported literature value of approximately 64 °C which may be due to some experimental variations. When exposed to a relative humidity of 40% and 70%RH, the 1:1 SD and 1:3 SD granules did not show any distinct peak. This indicated that the drug remained predominantly in the amorphous state in the granules. At 100%RH, the 1:1 SD granules showed a distinct peak at 55 °C and a minor broad peak at 104 °C indicating initiation of crystallization of the drug in the granules. The 1:3 SD granules however, showed no significant changes even at high humidity of 100%. To further investigate if changes in the crystalline properties occurred in the 1:3 SD granules, XRD patterns of the 1:3 SD samples exposed to humidity were compared to that of pure drug. Figs. 16 and 17 show XRD patterns of dimenhydrinate and 1:3 SD, respectively. It was observed that the drug sample shows a distinctly different XRD pattern after exposure to 100%RH, whereas no significant changes in crystalline properties were seen with 1:3 SD granules. Thus, the XRD corroborates the DSC findings that the crystalline prop-

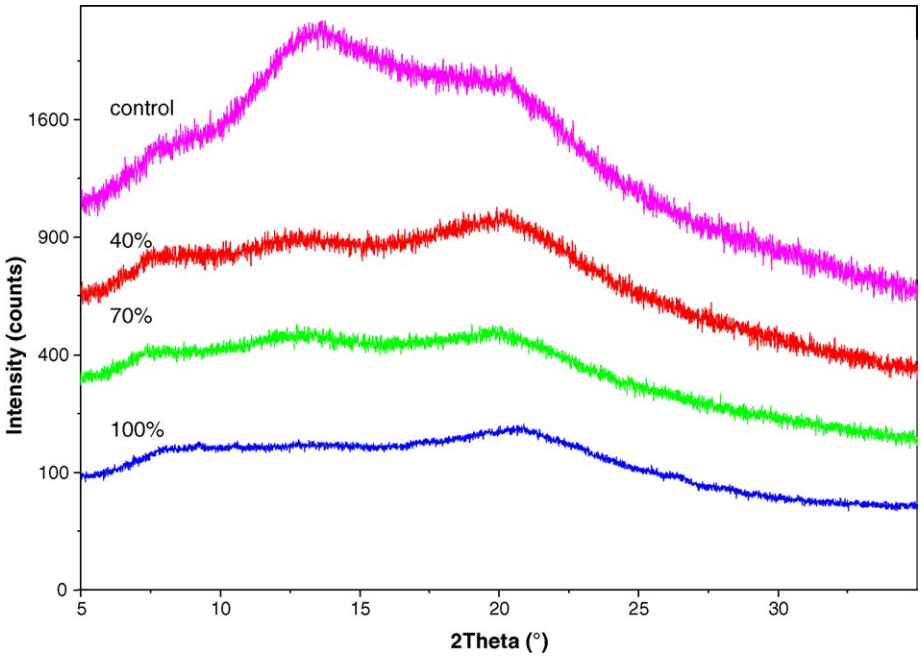

Fig. 17. XRD patterns of 1:3 SD granules exposed to various humidity conditions.

erty of the drug in the 1:3 SD granules, remained unaffected even at high humidity conditions indicating greater stability of the drug in the granules as compared to drug alone when exposed to humidity.

4. Conclusions

Application of ethyl cellulose to achieve the controlled release of dimenhydrinate using the solid dispersion technique was investigated. Granules with different dimenhydrinate: ethyl cellulose ratios, namely 1:1, 1:3 and 1:5, were prepared. Drug content was almost 100% in the granules with 1:1 and 1:3 drug:polymer content indicating good process efficiency whereas with further increase in polymer amount, the drug content reduced. From the DSC and XRD studies it was concluded that the crystalline drug was converted into its amorphous form in all the solid dispersions. The TGA studies showed that the decomposition or thermal stability of the drug was not affected when granules of drug and ethyl cellulose were prepared by the solid dispersion technique. There was no chemical interaction between the drug and polymer as inferred primarily from the FT-IR studies. The optical microscopy studies revealed that the pure drug was highly crystalline with long plate like crystals whereas the solid dispersion granules show the drug finely dispersed within the ethyl cellulose matrix. From the dissolution studies, it was seen that as the amount of polymer increased, the drug release rate gradually reduced. The drug release reduced to about 26% with 1:5 drug–polymer ratio. Studies for the kinetics of the drug release from granules showed a good fit to first-order kinetics. As the ethyl cellulose content increased, the linearity of the drug release for zero-order kinetic model increased, indicating better controlled release of the drug. Humidity studies showed that there was no significant change in the crystalline properties of the drug of the granules after exposure to 40% and 70%RH. At 100%RH, the drug and the granules with 1:1 drug:ethyl cellulose content showed the formation of the hydrates of the drug. However, granules with higher polymer content did not show any significant changes in crystalline properties indicating greater stability of the drug in the granules. Thus, ethyl cellulose proved useful as a rate controlling polymer to produce a controlled release formulation of dimenhydrinate using the solid dispersion technique.

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