Journal of Thermal Analysis and Calorimetry, Vol. 58 (1999) 29-38

STUDY OF ETHYL CELLULOSE–BENZOIC ACID INTERACTIONS IN MATRICES FOR CONTROLLED DRUG RELEASE BY DSC

R. Singhal, A. K. Nagpal and G. N. Mathur***

Department of Plastic Technology, Harcourt Butler Technological Institute Kanpur – 208 002 India

(Received March 31, 1998; in revised form December 18, 1998)

Abstract

The physical state of benzoic acid (BA) and its interaction with ethyl cellulose (EC) were examined in ethyl cellulose–benzoic acid matrices by Differential Scanning Calorimetry (DSC). The glass transition temperature (T_g) of EC of various matrices having BA in solid solution form (upto 27.7%) was reduced. The BA in matrices containing more than 38.9% drug exhibited distinct melting endotherms due to crystalline form. The peak temperatures of these endotherms were lowered and they broadened as the concentration was lowered. The solubility of BA increased at its melting point as compared to ambient temperature. The melting enthalpy of BA, when plotted as a function of its concentration yielded a straight line with intercept of 330 mg g^{-1} of matrix. This is the solubility of BA in EC at its melting temperature. Fourier Transform Infra Red Spectroscopy (FTIR) investigations confirmed that hydrogen bonding occurred between EC and BA through hydroxyl groups.

Keywords: benzoic acid, controlled release, DSC, ethyl cellulose, FTIR

Introduction

Polymeric matrix devices [1, 2] are important controlled release devices which are finding increasing usage. Matrix type controlled drug delivery devices contain drug homogeneously distributed in polymer. Part of the drug is dissolved in the polymer and the remaining fraction exists in crystal form. Determination of the amount of drug in crystalline form is crucial because it affects the rate and mechanism of drug release [2]. Theeuwes *et al.* [3] used DSC to determine the drug solubility in a polymer at the melting point of drug, the amount of drug present in the crystalline form and the heat of mixing for polydimethylsiloxane matrices. Later Van Bommel [4] used DSC to determine the percentage crystalline drug in ethyl cellulose matrices by measuring the melting enthalpies of pure drug and matrix. Similar concept has

* To whom all correspondence should be addressed.

** Director, Defence Material Stores Research and Development Establishment, Kanpur - 208 013, India.

1418–2874/99/ $ 5.00

Akadémiai Kiadó, Budapest

Kluwer Academic Publishers, Dordrecht

been also used to determine the composition of polymer blends [5]. The objective of present investigation was to evaluate the percentage of crystalline drug present in the matrices by DSC as it is a simple and rapid technique. This paper also deals with the use of DSC for determining the occurrence of secondary interactions between drug and polymer; as they lead to large deviations in controlled release behaviour of matrices.

Experimental

Materials

Ethyl cellulose (10 CP) was obtained from Aldrich Chemical Corp., USA. Benzoic acid and acetone were obtained from Ranbaxy Chemicals Ltd., India.

Preparation of matrix

Solvent casting technique which is a standard technique for producing homogeneous matrices with good reproducibility at lab scale was used for preparing matrices [1, 6]. The casting solution was prepared in acetone and contained 0, 8, 13, 16.6, 27.7, 38.9, 44.4, 50 and 54.5% benzoic acid on total solid content basis. A levelled glass plate clamped with metal strips on both sides was used as mould. The film was dried for 24 h at room temperature and then 24 h under 1 atm vacuum in order to ensure solvent evaporation. The matrices were cut in the size of 2×9 cm^2 from the dried film (thickness 110 μm) and stored in dessicator.

Differential scanning calorimetry

DSC 2910 TA Instruments was used to analyse 2–7 mg samples under nitrogen atmosphere at a heating rate of 10°C min^{-1} from 40–250°C.

Thermogravimetry

TGA 2950 TA Instruments was used to analyse samples under nitrogen atmosphere at a heating rate of 10°C min^{-1} from 40–400°C.

FTIR analysis

The infra-red spectra were recorded with Bomem MB-100 Fourier Transform Infra Red Spectrophotometer at a resolution of 4 cm^{-1}, using a deuterated triglycine sulfate (DTGS) detector. Matrices were analysed in potassium bromide pellet form and the maximum absorption in all spectra was below 0.75. The peaks were analysed by using centre of gravity method with a tolerance of 10%.

Results and discussion

The matrices having 8 and 13% drug loading were clear and colourless in the appearance, while drug crystals were visible by the naked eye in the matrices containing higher drug loading. The drug crystallization phenomena in various matrices

Fig. 1 Scanning Electron Micrograph of matrix surface containing 27.7% BA

were studied by Scanning Electron Microscopy [6] and drug crystal size was maximum at 27.7% drug loading (Fig. 1). The results of DSC investigations of matrices containing 8–54.5% BA are as follows.

Moisture endotherm

The DSC scans indicate a broad endothermic event in the temperature range of 50–100°C for matrices containing 8 to 54.5% BA. However, such an event was absent or negligible in the case of pure EC matrix or powder, respectively. The total heat absorbed varies between 13–18 J g^{-1} for various matrices. In order to investigate the nature of endotherm, the DSC run was carried out for 13% BA containing matrix upto 140°C at a programmed heating rate of 10°C min^{-1}. (At 140°C no degradation occurs in EC.) An endotherm was observed in this DSC scan in the temperature range of 50–100°C. The DSC cell was allowed to cool upto 40°C. The matrix was reheated to 140°C at the same heating rate and no endotherm was observed. It indicated that the endotherm might be caused by the evaporation of water or residual solvent i.e. acetone.

For further verification TG of various matrices were carried out and there was no appreciable mass loss in the temperature range of 55.5–56.5°C which is the boiling point of acetone. This eliminated the possibility that this endotherm was caused by residual solvent. However rapid mass loss occurred above this temperature indicating that the exchanged volatile could be water. The mass loss from 1.86 to 5.1% was observed at the temperature range of 40–100°C for various drug containing matrices. The mass loss and heat absorbed varied in an arbitrary fashion for various matrices. Such moisture endotherms had been reported earlier for EC films used in tablet coating reservoir devices by Sakellariou *et al.* [7] and Dubernet *et al.* [8]. It was also noted that moisture endotherms were enhanced in drug loaded matrices as compared to pure polymer indicating some sort of interaction between BA and EC leading to enhanced moisture absorption.

Glass transition temperature

The DSC scan (Fig. 2) of EC film confirmed that EC is an amorphous polymer in accordance with previous findings [4, 7] as it did not show a melting endotherm corresponding to melting of crystalline phase. The T_g of EC matrix exhibited a slightly

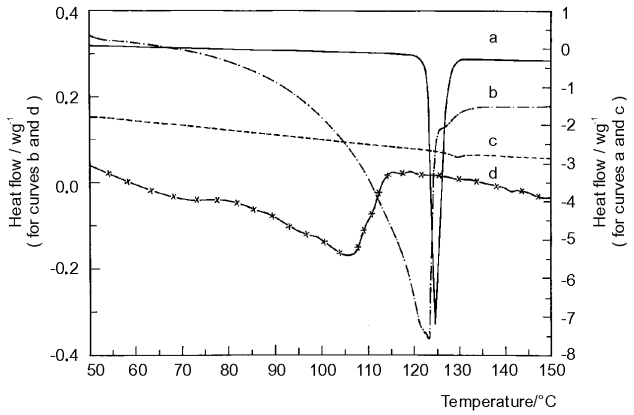

Fig. 2 DSC scan of (a) pure BA (b) physical mixture of EC and BA in equal ratio (c) plain EC matrix (d) matrix containing equal amounts of BA and EC

lower value of 126.4°C than for pure EC 130°C possibly due to acetone incorporation during matrix preparation.

The T_g was reduced from 126.4 to 94°C as drug loading was increased from 0 to 27.7% (Table 1); while matrices with higher loadings did not exhibit a clear T_g. The depression of T_g shows that incorporation of drug was plasticizing the drug containing matrices as reported in Table 1 similar to earlier results [4, 9, 10]. The results indicated that plasticization occurred only when the drug was in dissolved state as the matrices were having homogeneous structure. For matrices carrying drug in crystalline form the drug crystals hinder the movement of polymer chains and nullify the plasticization effect even though drug was present at molecular level. The matrices with higher drug loadings did not exhibit a clear T_g because the endotherm corresponding to melting of drug crystals hindered in exactly determining T_g.

Melting endotherm corresponding to drug crystals

The DSC scans of matrices containing 8–27% drug did not show a melting endotherm while matrices containing 38.9–54.5% drug showed distinct melting endotherm. Table 1 gives the values of melting enthalpies and peak maximum temperature for these endotherms. DSC of the matrix with 27.7% drug did not show melting of drug crystals during DSC run; but it exhibited large size drug crystals at ambient conditions. Figure 1 shows the SEM of matrix surface containing 27.7% drug, which shows large size [6] drug crystals. It suggests that the solubility of BA in EC increased significantly at the melting temperature of drug as compared to ambient temperature indicating enhanced miscibility at elevated temperature. The melting point of pure BA crystals was determined by dynamic DSC scan be 124.8°C; while it lowered to 98.2°C for matrix containing 38.9% BA. It was also observed that the peak broadened and shifted more towards lower side as drug content of matrix was increased. It indicates that BA is miscible and acting as diluent for EC as the depres-

sion of melting temperature in case of polymer-diluent system is well established [11]. The melting point depression has been observed also in case of miscible polymer–polymer blends and it is used as a measure to judge the miscibility of both components [12, 13]. Negligible depression would have been observed in case BA did not act as diluent for EC or BA and EC were immiscible.

The depression in melting point was obtained by subtracting the melting point of matrix from melting point of pure drug ($124.8–t_{peak}$); and plotted *vs*. drug content. A straight line plot was obtained; which is shown in Fig. 3 which can be used to determine the drug content of matrix by measuring the shift in melting temperature by a simple dynamic DSC scan.

Figure 2 shows a sharp melting peak for pure BA crystals with peak maximum temperature 124.8°C and melting enthalpy 122.1 J g^{-1}. Figure 2 shows the scan of physical mixture of EC and BA in 50:50 ratio with melting enthalpy 98.0 J g^{-1}; while the heat absorbed by EC was calculated to be negligible. This lowering of melting enthalpy of BA from 122.1 to 98.0 J g^{-1} might have occurred due to partial solubilization of BA in EC. Figure 2 also shows the DSC scan of matrix containing EC and BA ratio indicating further lowering of melting enthalpy and melting point accompanied by considerable broadening of peak. Above observations clearly indicate drug–polymer interaction of some sort which increases in matrix form due to homogenisation of EC and BA in acetone.

Table 1 lists the results of DSC scans of various matrices and pure EC and BA. The drug content (mg of BA/g of matrix) *vs*. melting enthalpy of various drug containing matrices was plotted in Fig 4. A straight line plot was obtained, which upon extrapolation gave intercept having value 330 mg/g of matrix. It could be considered as drug solubility in polymer at the melting temperature of drug [3]. This value is equivalent to 33% drug in matrix; so it could be assumed that upto 33% BA concentration drug remains in dissolved form in matrix at its melting temperature. BA above 33% concentration exist in crystalline form in matrices and is responsible for the melting endotherm corresponding to melting of drug crystals. The values of BA concentration in dissolved and crystalline form were calculated and reported in Ta-

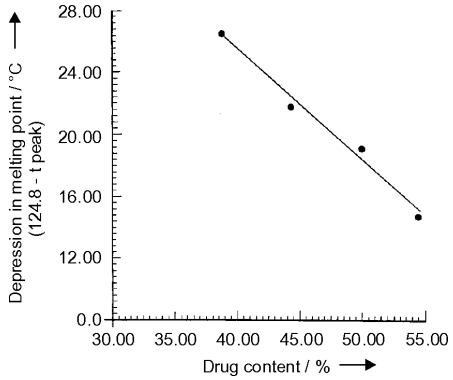

Fig. 3 Plot of depression in melting point *vs*. drug content for EC matrices containing various amount of BA

Table 1 Parameters derived from endotherms of melting of EC-BA matrices observed during DSC experiments

BA concentration based on total solid content		Enthalpy of melting endotherm/ $J\ g^{-1}$	Peak maximum/ °C	BA concentration in		Glass transition temperature/ °C
Percentage	mg of BA/g of matrix*			dissolved form/%	crystalline form**/%	
0.0	0.0	–	–	0.0	0.0	126
8.0	80.0	–	–	8.0	0.0	120
13.0	130.0	–	–	13.0	0.0	114
16.6	166.6	–	–	16.6	0.0	–
27.7	277.7	–	–	27.7	0.0	94
38.9	389.0	7.47	98.2	33.0	5.9	–
44.4	444.4	16.1	103.0	33.0	11.4	–
50.0	500.0	19.9	105.7	33.0	17.0	–
54.5	545.4	29.0	110.0	33.0	21.54	–
100.0	–	122.1	124.8	–	100.0	–

* mg of BA per g of matrix $= \frac{BA\%}{100} 1000$

** concentration of BA in crystalline form = total percentage of BA – 33.00

ble 1. For EC/BA matrices this value is quite high in comparison to 35 and 6 mg/g of matrix observed for cholesterol and progesterone in silicone rubber matrices [3]. All the results indicate some sort of secondary interaction occurring in between EC and BA which resulted in miscibility between the two.

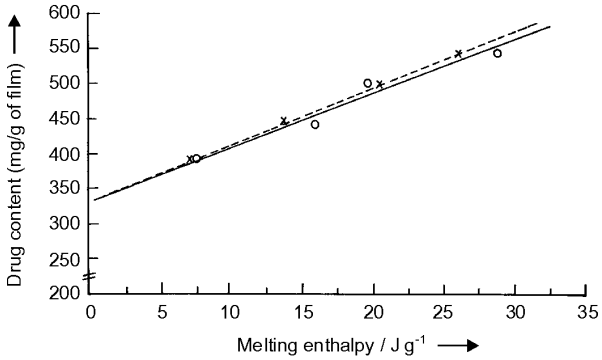

Fig. 4 Plot of melting enthalpy (both observed and calculated) *vs.* drug content for EC and BA matrices; o – observed, x – calculated

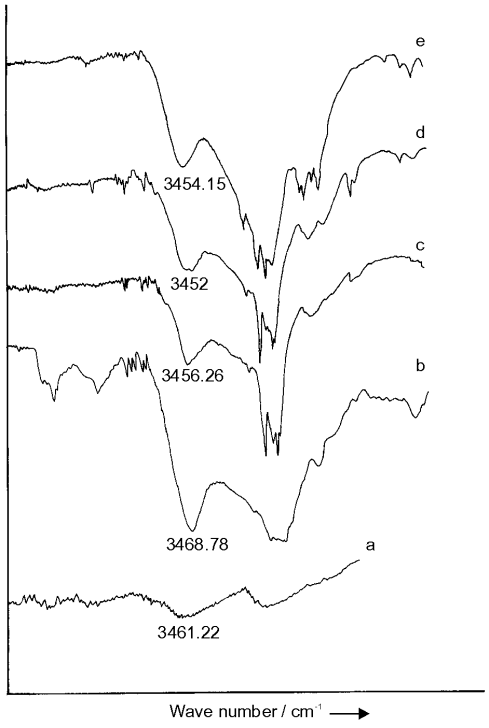

Fig. 5a Peak positions for hydroxyl group in (a) plain EC; (b) 13% BA; (c) 27.7% BA; (d) 38.9% BA and (e) 50% BA containing EC matrices

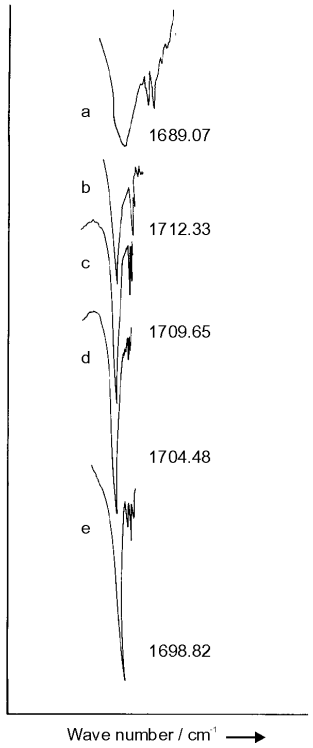

Fig. 5b Peak positions for carboxyl group in (a) pure BA; (b) 13% BA; (c) 27.7% BA; (d) 38.9% BA and (e) 50% BA containing EC matrices

The heat required to melt the crystalline portion of drug in matrix can be calculated by using the drug solubility in matrix obtained by Fig. 4. Following simple relationship is proposed and tested to calculate the heat required to melt the crystalline portion of BA in matrix by considering the heat of mixing zero or negligible.

$$q_t = (m_t - m_s)\, q_d$$

where, q_d – melting enthalpy of pure drug (J g^{-1}); m_t – total drug concentration (g of drug/g of matrix); m_s – solubility of drug in polymer at the melting point of drug (g of drug/g of matrix). Here m_s is found to be 330 mg g^{-1} of matrix.

In order to verify the validity of above equation the values were calculated and plotted as shown in Fig. 4 by dotted line. The values of melting enthalpies obtained experimentally and calculated by the equation agree within experimental error confirming its validity. The difference between observed and calculated values of q_t lies in the range of 0.85 to –2.7 and would be due to heat of mixing or other thermal effects. It is also reported that heat of mixing should be zero or negative in case of occurrence of secondary interaction between two components [14]; affirming the suspicion of secondary interactions between EC and BA.

As mentioned earlier DSC analysis clearly indicated an interaction between EC and BA. Donbrow and Friedman [5] suspected hydrogen bonding occurred between EC and BA during sorption and permeability studies. This was supported by substantial enhancement in uptake of BA by EC films during sorption experiments as compared to other compounds [15]. To exactly determine the nature of interaction, FTIR of matrices with 0, 16.6, 27.7, 38.9 and 50% were done. Hydrogen bonding is characterized by broadening and lowering of peak positions of corresponding functional groups in IR spectrum [16]. On analysis of the spectra, changes in peak positions of only hydroxyl and carboxyl groups were observed (Fig. 5a and 5b). Figure 5a showed considerable increase in the intensity of hydroxyl group of EC and peak position shifted from 3468.78, 3456.26, 3452.00 and 3454.15 cm^{-1} for 13, 27.7, 38.9 and 50% drug containing matrix, respectively. The considerable shifting in peak position indicated a hydrogen bond of reasonably high strength.

For pure BA the carbonyl peak was broad and lowered to 1689.07 cm^{-1} from usual 1740 cm^{-1}, due to acid dimerization [16]. Another bond characteristic of the dimeric acid species arises from the O–H out of plane deformation vibration which appeared at 921.51, 921.22, 927.7, 931.6 and 928.97 cm^{-1} for 13, 27.7, 38.9, 50% BA containing matrix and pure BA, respectively [16]. The intermolecular hydrogen bonding is favoured when the hydrogen atom is attached to an electronegative atom (such as oxygen). For EC such oxygen is available in unsubstituted 'CH_2OH' group as degree of substitution was in between 2.4–2.5. As carbonyl group is shifting to higher side, it can be concluded that 'H' from BA is making hydrogen bond with unsubstituted 'CH_2OH' of EC.

Conclusions

Melting of BA in EC matrix was characterized by lowering of melting point and considerable broadening of peak. The drug solubility at the melting point of drug was determined to be 330 mg/g of matrix by measuring the melting endotherm of BA for various drug level containing matrices; which was unusually high. Good miscibility of BA in EC, as evident from lowering of BA's melting point and high solubility in EC indicated secondary interactions such as hydrogen bonding which was confirmed by FTIR studies. It can be concluded from the study that DSC can be used as a quick scanning technique for controlled release matrix devices for determining moisture, plasticization of matrix by drug, drug solubility, drug content and hydrogen bonding between polymer and drug making it valuable for preformulation investigations.

References

1 A. F. Kydonieus, Controlled Release Technologies, Method, Theory and Applications, Vol. 1 & 2, CRC Press Inc. Florida, 1980.
2 J. Heller and R. W. Baker, in R. Baker (ed.), Controlled Release of Bioactive Materials, Academic Press New York, 1980.
3 F. Theeuwes, A. Hussain and T. Higuchi, J. Pharm. Sci., 633 (1974) 427.

4 E. M. G. Van Bommel, Ph. D. Thesis, Utrecht, The Netherland 1989.
5 R. L. Blaine, Application Brief, Dupont Co., No. TA 36.
6 R. Singhal and G. N. Mathur, J. Polymer Materials, 13 (1996) 139.
7 P. Sakellariou, R. C. Rowe and E. F. T. White, Int. J. Pharm., 27 (1985) 267.
8 C. Dubernet, J. C. Rouland and J. P. Benoit, Int. J. Pharm., 64 (1990) 99.
9 C. M. Klech and X. Li, J. Pharm. Sci., 79 (1990) 999.
10 M. R. Jenquin, S. M. Liebowitz and R. E. Sarabia, J. Pharm. Sci., 79 (1990) 811.
11 J. P. Runt, in H. R. Mark, N. M. Bikales, C. G. Overberger and G. Menges (Eds.), Encyclopedia of Polymer Science and Eng.. Vol. 4, Wiley 1986, p. 482.
12 M. Kimura, R. S. Porter and G. Salee, J. Polym. Sci., Polym. Phys. ED., 21 (1983) 367.
13 V. M. Nadkarni, V. L. Shingakuli and J. P. Jog, J. Appl. Polym. Sci., 46 (1992) 339.
14 D. R. Paul, J. W. Barlow and H. Keskkula in H. F. Mark, N. M. Bikales, C. G. Overberger, G. Menger, J. I. Kroschwitz (Eds.), Encyclopedia of Polymer Science and Eng., Vol. 12, Wiley New York, p. 399.
15 M. Donbrow and M. Friedman, Pharm. Pharmac., 27 (1975) 633.
16 O. Vogel, Textbook of Practical Organic Chemistry, Revised by B. S. Furniss. A. J. Hannaford, P. W. G. Smith, A. R. Tatchell, Longman Singapore Pub. Pvt. Ltd. Singapore, 1994.