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Compatibility studies between isosorbide mononitrate and selected excipients used in the development of extended release formulations

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Abstract

Techniques of thermal and isothermal stress testing (IST) were used to evaluate the compatibility of isosorbide mononitrate (IMN) with selected excipients used in the development of extended release formulations. In the first phase of the study, differential scanning calorimeter (DSC) was used as a tool to detect any interaction. In the next phase, excipients defined in the prototype formula were tested for their compatibility with IMN using IST. Based on the results, cellulose acetate and MCC were found to show interaction with IMN. Results of IST demonstrated incompatibility between IMN and cellulose acetate. All the excipients defined in the prototype formula were found to be compatible with IMN. Using the excipients that were found to be compatible with IMN, formulations were optimized. The optimized formulation was found to be stable after 3 months of storage at accelerated stability conditions (40 °C and 75% RH). In conclusion, tools of DSC, and IST were successfully employed to evaluate the compatibility of IMN with selected excipients.
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Keywords: Drug–excipient interaction; Dissolution; Extended release; Incompatibility; Isosorbide mononitrate; Stability

1. Introduction

Drug–excipient interaction study at an early stage of product development is an important exercise in the development of a stable dosage form. However, no universally accepted protocol is available for evaluating the compatibility of drug with different excipients. Some of the reported methods have poor predictive values and few of them are labor intensive and time consuming. For example, differential scanning calorimeter (DSC) has been proposed as a rapid method for evaluating the drug–excipient interaction [1–6]. Though it has certain advantages, such as requirement of small sample size and fast results, there are certain limitations also. This is because of exposure of drug–excipient mixture to high temperatures

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(up to 300 °C or more), which, in real situations, is not experienced by the dosage form. Therefore, the DSC results should be interpreted carefully, as the conclusions based on the DSC results alone can be often misleading and inconclusive [3,5].

Isothermal stress testing (IST) involves storage of drug–excipient blends with or without moisture at high temperature for a specific period of time (normally 3–4 weeks) to accelerate drug ageing and interaction with excipients. The samples are then visually observed and the drug content determined quantitatively [3,7,8]. Although more applicable, the disadvantage with this method is that it is time consuming and requires quantitative analysis using HPLC. Ideally, the techniques of DSC and IST should be used in combination for the selection of excipients.

In the present study, for the development of extended release formulations of isosorbide mononitrate (IMN), DSC and IST were used to select excipients. IMN, an organic nitrate, is mainly indicated for the treatment of stable and unstable angina pectoris, acute myocardial infarction, and heart failure [9]. It offers several therapeutic advantages over other organic nitrates, such as good oral absorption, long elimination half-life (4–5 h) in comparison to other nitrates [10], and absence of first pass metabolism [11]. In the first phase, DSC was used to study the compatibility of IMN with selected excipients. Those excipients that were defined in the prototype formula were tested using IST. Finally, the developed formulations were evaluated after 3 months of storage at accelerated stability conditions (40 °C and 75% RH).

2. Experimental

2.1. Materials

IMN (99.9% purity), a gift sample from JP Fine Chemicals, India, was characterized against the working standard of IMN (99.8% pure), which was obtained as gift sample from Sifa Chemicals, Switzerland. Following chemicals and excipients were purchased from commercial sources and used as such.

Cellulose acetate (Fluka, Switzerland), ethyl cellulose (Ethocel 10cps, Dow, USA), colloidal silicon dioxide (CSD, Aerosil 200, Degussa AG, Germany), lactose (Flowlac-100, Meggle, Germany), sorbitol (Sigma, USA), microcrystalline cellulose (Avicel PH-112, FMC, USA), sodium chloride AR (Loba Chemie, India), polyvinyl pyrrolidone (Plasdone K-29/32, ISP, USA), HPMC (Methocel E-15, Dow, USA), and magnesium stearate (Mallinckrodt, USA). Methanol used for the preparation of mobile phase was of HPLC grade (Ranbaxy, India) and water used throughout the HPLC analysis was prepared by reverse-osmosis (Ultra Pure water system, ELGA, UK).

2.2. Differential scanning calorimetry

For thermal analysis of drug and drug–excipient mixtures, a differential scanning calorimeter (DSC 821^e, Mettler Toledo, Switzerland) was used. Individual samples (drug and excipients) as well as physical mixtures of drug and selected excipients (all passed through BSS 60-mesh) were weighed directly in the pierced DSC aluminum pan (Table 1) and scanned in the temperature range of 25–300 °C (at the heating rate of 10 °C/min) under an atmosphere of dry nitrogen.

2.3. Isothermal stress testing

For preparation of samples for IST, drug and different excipients (Table 2) were weighed directly in 4 ml glass vials ($n = 2$). After mixing on a vortex mixer for 2 min, 10% (w/w) water was added in each of the vials, subsequent to which the drug–excipient blend was further mixed with a glass capillary. To prevent any loss of material, capillary (both the ends of which were heat sealed) was broken and left inside the vial. The vials, after sealing with a teflon-lined screw cap, were stored at 50 °C (Hot air oven, Universal, Narang Scientific, India). Drug–excipient blends without added water and stored in refrigerator served as controls. The drug–excipient blends were periodically examined for any unusual color change. Samples were quantitatively analyzed using HPLC [12] after 3 weeks of storage at above conditions.

The sample preparation involved addition of 2 ml of mobile phase in each of the vials. The mixture was vortexed and transferred to 100 ml volumetric flask. All the vials were rinsed twice with the mobile phase and the volume made up. The samples were centrifuged and the supernatant filtered through nylon membrane

Table 1
Peak temperature and enthalpy values of IMN in various drug–excipient mixtures

Sample	Ratio (drug–excipient)	T_{onset} (°C)	T_{peak} (°C)	$\Delta H_{f\,corr}$ (J/g)[a]
IMN	–	90.42	91.08	125.32
IMN + cellulose acetate	1:1	68.01	74.82	34.10
IMN + colloidal silicon dioxide	4:1	89.10	91.09	69.22
IMN + ethyl cellulose	1:1	89.24	93.35	131.48
IMN + HPMC	1:1	87.55	89.88	71.51
IMN + lactose	1:1	89.10	92.39	123.48
IMN + MCC	1:1	73.40	80.91	73.03
IMN + magnesium stearate	1:1	88.98	91.50	89.65
IMN + PVP	1:1	53.17	71.41	140.53[b]
IMN + sodium chloride	1:1	89.45	92.00	128.24
IMN + sorbitol	1:1	87.25	92.89	253.67[c]

[a] $\Delta H_f = \Delta H_{f\,obs}/\%\text{drug in sample} \times 100$; from reference [2].
[b] Total value (IMN melting + polymer dehydration).
[c] Total value (IMN melting + excipient melting).

filters (0.45 μm pore size). After appropriate dilutions, samples were analyzed using HPLC and drug content determined from the calibration curve prepared within the expected range (15–75 μg/ml). The method was found to be linear within the studied range (R^2: 0.998) [12].

For the HPLC analysis, Shimadzu HPLC system equipped with LC-10 AT VP pump, DGU-14 AM on-line degasser, SIL-10 AD VP autoinjector, CTO-10 AS VP column oven, and SPD-10 AVP UV-VIS detector was utilized. For peak purity testing, SPD-M 10 A VP PDA detector was used. Shimadzu CLASS-VP software (Version 5.03) was used for data acquisition and mathematical calculations. Chromatographic separation was performed on a C_{18} Spherisorb column (4.6 mm × 250 mm, 5 μm particle size) at 25 °C. The optimized mobile phase composition was water–methanol (80:20, (v/v)) at a flow rate of 1 ml/min. Detection was performed at 220 nm using a UV detector.

2.4. Formulation development and stability studies

The details of the formulation development can be found elsewhere [13]. In brief, core tablets of IMN (Table 3) having an average weight of 300 mg were prepared by direct compression using a single stroke tablet-punching machine fitted with 9 mm round

Table 2
Results of analysis of IST samples after 3 weeks of storage at stressed conditions

Sample	Ratio (drug–excipient)	%Drug remaining[a]	
		Control samples[b]	Stressed samples[c]
IMN	–	101.98 ± 2.09	99.80 ± 1.26
IMN + cellulose acetate	1:1	102.18 ± 0.99	104.88 ± 1.43[d]
IMN + colloidal silicon dioxide	4:1	102.11 ± 1.98	103.21 ± 1.35
IMN + ethyl cellulose	3:2	101.32 ± 2.09	100.33 ± 1.23
IMN + lactose	1:4	100.25 ± 2.98	98.37 ± 1.93
IMN + magnesium stearate	3:2	103.12 ± 1.84	101.22 ± 0.40
IMN + PVP	1:1	100.78 ± 2.58	98.99 ± 1.05
IMN + sodium chloride	1:4	103.29 ± 1.07	104.19 ± 0.16

[a] Values expressed as average ± standard deviation.
[b] Drug excipient blends without added water and stored in refrigerator.
[c] Drug excipient blends with 10% (w/w) added water and stored at 50 °C for 3 weeks.
[d] Yellow color formation in the samples after 3 weeks of storage at stressed conditions.

Table 3
Composition of core tablets of IMN

Ingredients	% (w/w)
IMN	20.00
Lactose	34.18
Sodium chloride	33.32
PVP	10.00
Magnesium stearate	2.00
Colloidal silicon dioxide	0.50

standard concave punches. The tablets were coated in an automated perforated coating pan (GAC-250, Ganscoater, India) with a coating solution shown in Table 4. Sufficient coating solution was applied until desired weight gain (10 ± 0.5%) was obtained. The tablets were dried in an oven for 16 h at 50 °C before being stored or evaluated.

The optimized formulation of IMN (IMNOP-4/8) was packed in strips of 0.04 mm thick aluminum foil laminated with PVC coating and stored in ICH certified stability chambers (WTC Binder, Germany) maintained at 40 °C and 75% RH. The samples were withdrawn periodically and subjected to assay and dissolution studies.

For assay, one accurately weighed tablet ($n = 5$) was dissolved in 100 ml of methanol. The samples were sonicated (Ultra sonic water bath, 3510, Branson, USA) for 30 min, after which they were filtered through nylon membrane filter (0.45 μm pore size). The filtered solutions, after appropriate dilution with the mobile phase, were analyzed by a validated HPLC method [12].

Drug release testing of the formulations ($n = 6$) was carried out using USP-I dissolution apparatus (TDT-06P, Electrolab, India) at 100 rpm. Simulated intestinal fluid, pH 6.8 (900 ml) maintained at 37 ± 0.5° C was used as dissolution medium. The samples (10 ml) were withdrawn at predetermined time and replaced with an equivalent amount of fresh medium. The samples were filtered through nylon membrane filter (0.45 μm pore size) and analyzed by HPLC. The cumulative percent drug release was plotted against time to determine the release profile.

Table 4
Coating composition for the core tablets of IMN

Ingredients	% (w/w)
Ethyl cellulose	2.74
PVP	1.52
Propylene glycol	0.73
Ethanol	38.00
Dichloromethane	57.00

For the comparison of release profiles of stability samples, "difference factor", f_1 and "similarity factor", f_2, were calculated [14]. The difference factor (f_1) measures the percent error between the two curves over all time points and was calculated as follows:

$$f_1 = \frac{\sum_{j=1}^{n} |Rj - Tj|}{\sum_{j=1}^{n} Rj} \times 100 \quad (1)$$

where n is the number of sampling points, R_j and T_j are the percent dissolved of the reference and test products at each time point j. The two release profiles are considered to be similar, if f_1 value is lower than 15 (between 0 and 15).

The similarity factor (f_2) is a logarithmic transformation of the sum of squared error of differences between the test T_j and the reference products R_j over all time points. It was calculated using the following equation:

$$f_2 = 50 \times \log \left\{ \left[\left(1 + \frac{1}{n} \right) \sum_{j=1}^{n} w_j |R_j - T_j|^2 \right]^{-0.5} \times 100 \right\} \quad (2)$$

where w_j is an optional weight factor and other terms are as defined earlier. The two dissolution profiles are considered to be similar, if f_2 value is more than 50 (between 50 and 100). For the calculation of f_1 and f_2 values, only one data point was taken into consideration after 85% of the drug was released.

3. Results and discussion

3.1. Drug–excipient compatibility testing

In the first phase of the study, compatibility of IMN with different excipients was tested using DSC. Different formulation trials were taken to optimize the formulations. Finally, the excipients defined in the prototype formula were tested using the techniques of IST.

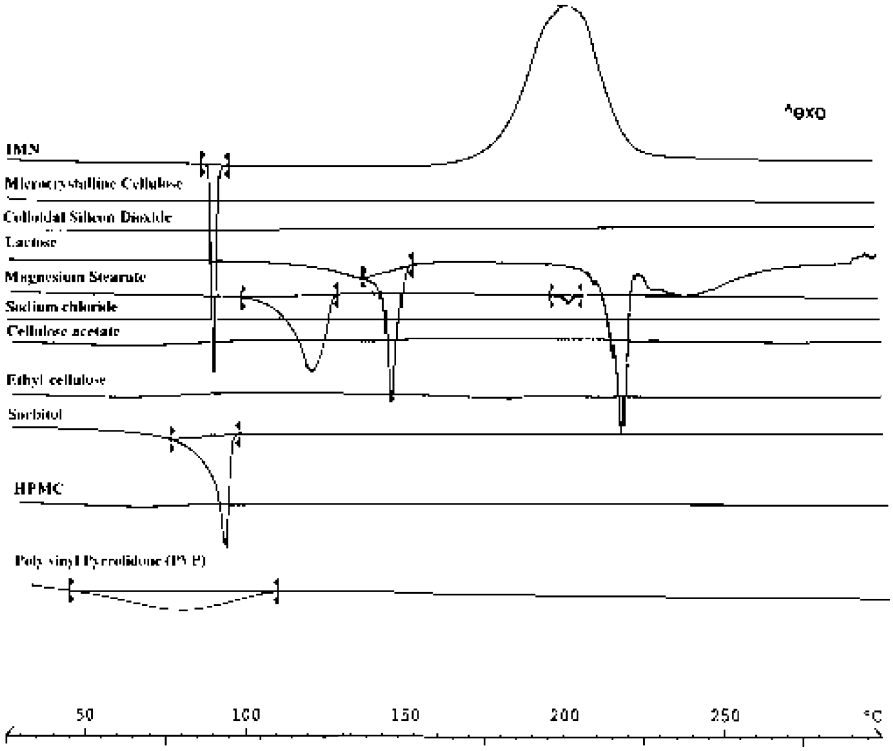

Fig. 1. DSC thermogram of IMN and different excipients.

Selected DSC scans of drug and drug–excipient mixtures are shown in Figs. 1–4. Peak melting temperature and enthalpy values of IMN in various excipient mixtures are summarized in Table 1.

DSC trace of pure IMN showed a sharp endothermic peak at 91.08 °C corresponding to its melting point (Fig. 1), followed by a broad exotherm due to drug decomposition at around 200 °C [15]. The melting endotherm of the drug was well preserved in majority of cases. However, there were slight changes in the peak shape with little broadening or shifting towards the lower temperature, which could be attributed due to the mixing process that lowers the purity of each component in the mixture [6,16–18].

In case of MCC (Avicel PH-112), no peak was observed in the range of 25–300 °C (Fig. 1). In Fig. 2, the DSC trace of IMN–MCC mixture showed the endothermic peak of IMN, which, however, was broadened and shifted to lower temperature (80.91 °C). There was also a significant reduction in the enthalpy value (Table 1). The above incidents point towards a possible solid–solid interaction, but not necessarily an incompatibility. It is suggested that before using this excipient in the formulation, its compatibility should be confirmed by utilizing the techniques of IST.

In the DSC thermogram of colloidal silicon dioxide, no peak was observed in the range of 25–300 °C (Fig. 1). The endothermic peak of IMN was well retained in the DSC trace of IMN–CSD mixture (Fig. 2) with a slight change in the enthalpy value. Based on the results, it was concluded that IMN is compatible with CSD.

The thermogram of lactose showed a sharp endothermic peak at 145.36 °C due to loss of bound water [19], followed by its melting endotherm at around 220 °C (Fig. 1). The endothermic peak of drug was well retained in the DSC trace of IMN–lactose mixture (Fig. 2) with little change in the enthalpy value (Table 1). The endothermic peak (at 145.36 °C), which was observed in case of pure lactose due to loss of bound water, is present in IMN–lactose mixture. However, melting endotherm of lactose seemed

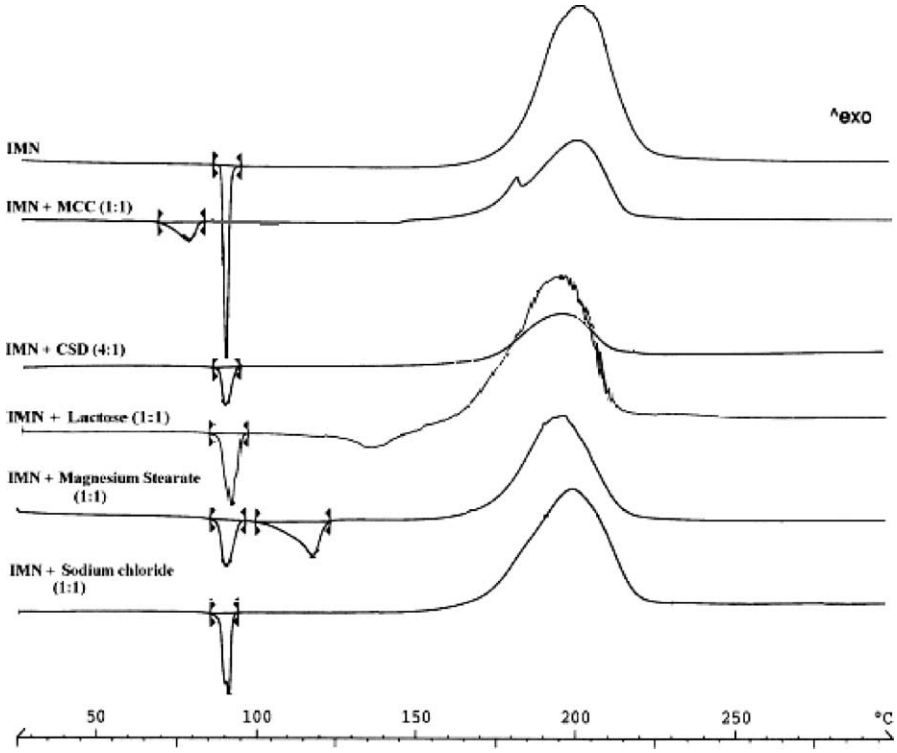

Fig. 2. DSC thermogram of IMN and physical mixtures of IMN with different excipients.

to merge with the exothermic peak of drug. It was concluded that IMN is compatible with lactose.

The DSC trace of magnesium stearate showed an endothermic peak at 121.11 °C (Fig. 1). A small peak was also present at 203.83 °C, which might be due to palmitate impurity [4,5]. Fig. 2 shows that the melting endotherm of IMN was well retained in the IMN–magnesium stearate mixture (91.50 °C) along with the peak of magnesium stearate (118.53 °C). It was concluded that IMN is compatible with magnesium stearate.

No peak was observed in the DSC trace of sodium chloride in the temperature range of 25–300 °C (Fig. 1). The melting endotherm of the drug was retained in the DSC trace of IMN–sodium chloride mixture (Fig. 2) with a little change in the enthalpy value (Table 1). Based on the results, any incompatibility between IMN and sodium chloride was ruled out.

In the DSC thermogram of cellulose acetate (Fig. 1), no peak was observed in the range of 25–300 °C. In case of IMN–cellulose acetate mixture, drug peak was shifted to 74.82 °C (Fig. 3). There was also a drastic reduction in the enthalpy value (Table 1), which suggested an incompatibility.

In case of ethyl cellulose, there was no peak in the region of 25–300 °C. DSC trace of IMN and ethyl cellulose mixture showed the endothermic peak of drug at 93.35 °C (Fig. 3), thus ruling out any incompatibility.

The DSC trace of sorbitol shows a melting endothermic peak at 95.33 °C. In the thermogram of IMN–sorbitol mixture, melting endotherm of IMN appeared to be merged with that of sorbitol and the peak was present at 92.89 °C (Fig. 3). The enthalpy value (Table 1) also confirms the additive effect of drug and sorbitol. Thus, it is very unlikely that there is an incompatibility between IMN and sorbitol.

In case of HPMC, no peak was observed in the range of 25–300 °C. In the DSC trace of IMN–HPMC mixture (Fig. 3), the melting endotherm of the drug was well retained at 89.88 °C, indicating that the drug is compatible with HPMC.

The DSC trace of PVP showed a broad endotherm at 81.62 °C (44.44–113.53 °C), probably because of loss of adsorbed moisture (Fig. 1). The thermogram

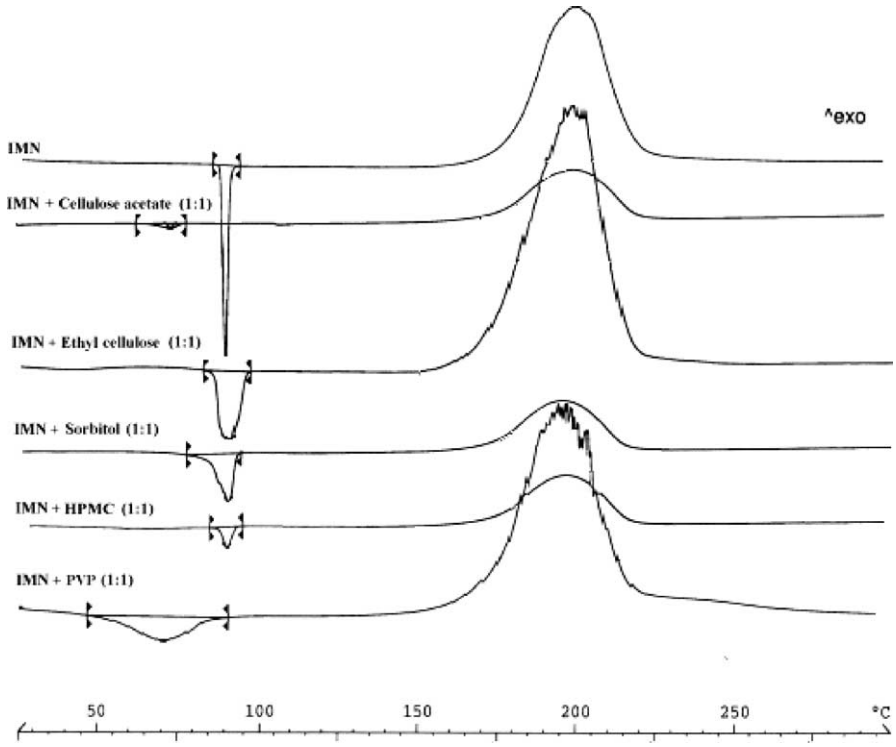

Fig. 3. DSC thermogram of IMN and physical mixtures of IMN with different excipients.

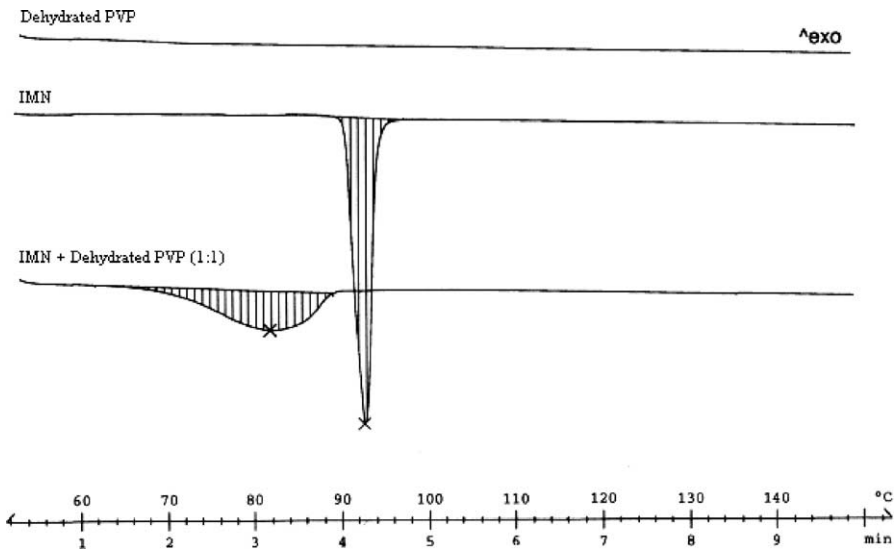

Fig. 4. DSC thermogram of dehydrated PVP, IMN, and their 1:1 physical mixture.

of IMN–PVP mixture in Fig. 3 showed an endotherm at 71.41 °C (53.17–86.10 °C) with an anomalous enthalpy value (Table 1). The reason for this behavior could be because of shifting of IMN peak to lower temperature, which could have merged with the moisture loss peak of PVP [1]. Another possibility included that the water, which emerged from PVP (in the temperature range of 44.44–113.53 °C) resulted in dissolution of drug (high water solubility of drug coupled with the temperature increase during DSC experiment), because of which drug peak disappears. To confirm this hypothesis, PVP was dehydrated (by drying at 50 °C for 24 h) and thermal data obtained. By looking at the DSC curve of dehydrated PVP (Fig. 4), it is evident that there is no endothermic peak due to loss of adsorbed moisture. On the other hand, DSC trace of physical mixture of IMN with dehydrated PVP (1:1 ratio) shows endothermic peak of drug at 81.56 °C (T_{onset}: 69.25 °C; $\Delta H_{f\,corr}$: 90.36 J/g). The reason for shifting of drug peak at lower temperature could be because of mixing with the excipients that lowers the purity of each component and the peak shifts to lower temperature [6,17]. Finally, based on the DSC results, it can be concluded that IMN is compatible with PVP.

On the basis of DSC results alone, MCC and cellulose acetate were found to exhibit interaction with IMN. However, no definitive conclusions were drawn based on the results of DSC results alone. Based on the results of formulation trials [13,20], following excipients were defined in the prototype formula: sodium chloride, cellulose acetate, ethyl cellulose, lactose, PVP, and magnesium stearate. These excipients were tested using the technique of IST and the quantitative results are shown in Table 2. As seen from the table, there is little change in the drug content after storage of drug–excipient blends under stressed conditions.

In the developed formulations, lactose was used as a diluent. Based on DSC results, any incompatibility between IMN and lactose was ruled out. Results of IST studies showed little change in the drug content after 3 weeks of storage under stressed conditions (Table 2). Based on the results of DSC and IST, it was concluded that both IMN and lactose are compatible with each other.

Sodium chloride was included in the developed formulations as an osmagent [13]. Based on the results of DSC and IST (Table 2), it was concluded that there is no incompatibility between IMN and sodium chloride.

PVP was added as a dry binder in the developed formulations. DSC results showed absence of incompatibility between IMN and PVP. IST results showed little change in the drug content after 3 weeks of storage under stressed conditions, thus ruling out any incompatibility between IMN and PVP.

Magnesium stearate was used as a lubricant in the formulations. Results of DSC ruled out any possible incompatibility between IMN and magnesium stearate. After 3 weeks of storage under stressed conditions, the drug content was within limits, which demonstrated that both are compatible with each other.

In the developed formulations, CSD was used as glidant. Results of DSC showed absence of any potential incompatibility between the two. Results of IST studies (Table 2) confirm the results and finally, it can be concluded that both IMN and CSD are compatible with each other.

Cellulose acetate was used as a rate-controlling polymer in the developed formulations of IMN. DSC results suggested an incompatibility between IMN and cellulose acetate. When IST samples (IMN–cellulose acetate mixture) were observed after 3 weeks of storage under stressed conditions, yellow coloration was observed. The samples were analyzed by HPLC and when the chromatograms were compared, a new peak at around 4.8 min was found in stressed samples of IMN–cellulose acetate mixture (Fig. 5). This new peak was not present in the control samples, suggesting some chemical interaction in the samples stored under stressed conditions. On the basis of above results, it was concluded that there is a chemical incompatibility between IMN and cellulose acetate. However, no attempts were made to characterize the interaction and cellulose acetate was not pursued further in the formulation development.

As an alternative, ethyl cellulose was tried as a rate-controlling polymer. DSC results ruled out any incidence of incompatibility between IMN and ethyl cellulose. IST results showed little change in the drug content, thus substantiating the claim that both IMN and ethyl cellulose are compatible with each other.

3.2. Formulation development and stability studies

Excipients defined in the prototype formula were used for formulation development. Various core and membrane variables were varied to optimize the

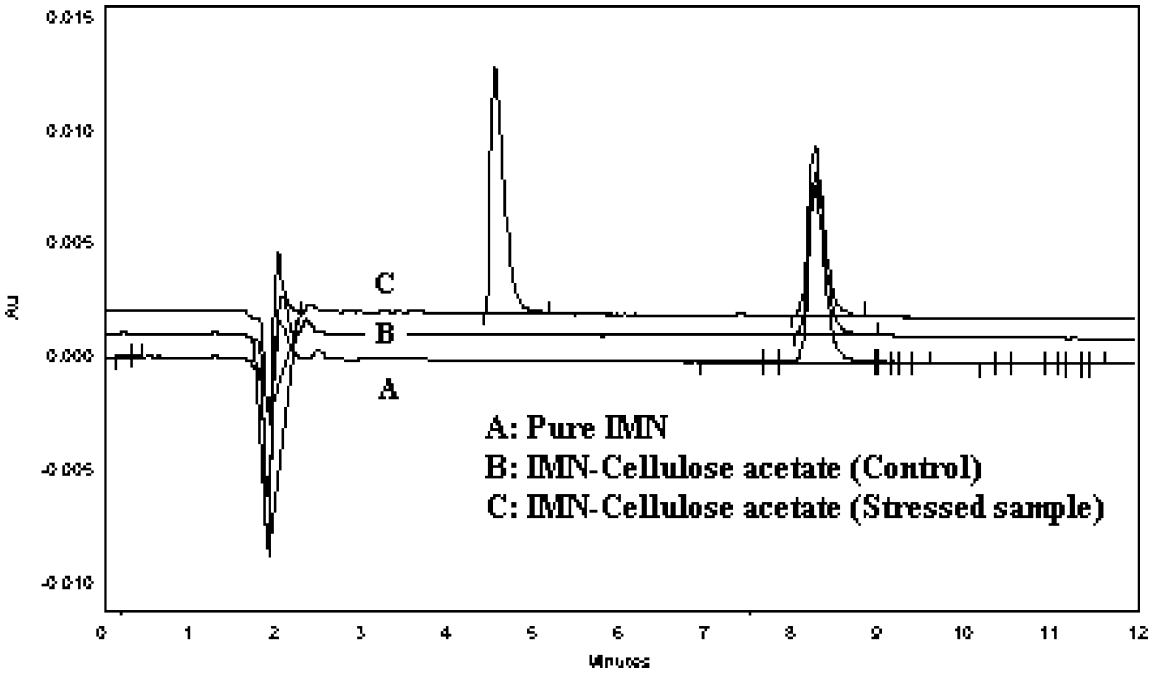

Fig. 5. HPLC chromatogram of IMN with cellulose acetate.

prototype formula [13]. The optimized formulation (IMNOP-4/8), packed in strips of 0.04 mm thick aluminum foil laminated with PVC, was evaluated after 3 months of storage at accelerated stability conditions (40 °C and 75% RH), results of which are shown in Table 5 and Fig. 6. It is evident that the formulation is having good stability in terms of both drug content and dissolution stability. There was little change in the drug content after 3 weeks of storage at accelerated stability conditions (Table 5). Drug peak was found to be pure, when tested using PDA detector. Release profile was similar after stability studies as shown by the f_1 (less than 15) and f_2 values (more than 50). Based on the results, it can be concluded that the formulations are sta-

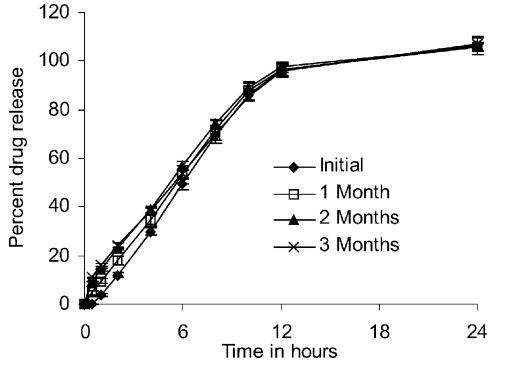

Fig. 6. Dissolution stability of optimized IMN formulations after 3 months of storage at accelerated stability conditions. Key to symbols: (◆) initial; (□) 1 month; (▲) 2 months; and (×) 3 months stability sample.

Table 5
Evaluation of IMNOP-4/8 formulation in 0.04 mm thick aluminum foil after 3 months of storage at 40 °C and 75% RH

Parameter	Initial	1 month	2 months	3 months
Drug content (%)[a]	93.47 ± 2.47	92.56 ± 4.34	96.14 ± 3.01	100.94 ± 4.57
Hardness (kp)[a]	9.79 ± 0.53	7.24 ± 0.66	6.80 ± 0.43	7.46 ± 0.41
f_1 value[b]	–	8.60	14.97	14.70
f_2 value[b]	–	66.71	53.74	54.49

[a] Values expressed as average ± standard deviation.
[b] Initial sample (0 month) was taken as reference to calculate f_1 and f_2 values.

ble after 3 months of storage at accelerated stability conditions.

4. Conclusions

As a part of an ongoing project on the development of extended release formulations of IMN, different excipients were tested for their compatibility with IMN. Present study has demonstrated the successful utilization of techniques of DSC and IST to assess the compatibility of IMN with the excipients used in the development of extended release formulations.

Based on the results of DSC alone, majority of the excipients were found to be compatible with IMN. However, results showed that there might be some interaction between IMN and cellulose acetate and MCC. Results of IST confirmed that there is some chemical interaction between IMN and cellulose acetate. All the excipients that were defined in the prototype formula were found to be compatible with IMN. Using the results of this study, extended release formulations were developed using the compatible excipients. The optimized formulation was packed in strips of aluminum foil and was found to be stable after 3 months of accelerated stability studies. In conclusion, DSC and IST were successfully used to select the excipients for extended release formulations of IMN and the developed formulation were found to be stable after accelerated stability studies.

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References

[1] E.C.V. Tonder, A.P. Lotter, S.A. Botha, Drug Dev. Ind. Pharm. 16 (1990) 2125–2133.
[2] S. Venkataram, M. Khohlokwane, S.H. Wallis, Drug Dev. Ind. Pharm. 21 (1995) 847–855.
[3] R. Kandarapu, V. Grover, H.P.S. Chawla, S. Garg, S.T.P. Pharm Sci. 11 (2001) 449–457.
[4] P. Mura, A. Manderioli, G. Bramanti, S. Furlanetto, S. Pinzauti, Int. J. Pharm. 119 (1995) 71–79.
[5] P. Mura, M.T. Faucci, A. Manderioli, G. Bramanti, L. Ceccarelli, J. Pharm. Biomed. Anal. 18 (1998) 151–163.
[6] S.A. Botha, A.P. Lotter, Drug Dev. Ind. Pharm. 16 (1990) 673–683.
[7] A.T.M. Serajuddin, A.B. Thakur, R.N. Ghoshal, M.G. Fakes, S.A. Ranadive, K.R. Morris, S.A. Varia, J. Pharm. Sci. 88 (1999) 696–704.
[8] L. Gu, R.G. Strickley, L. Chi, Z.T. Chowhan, Pharm. Res. 7 (1990) 379–383.
[9] J.D. Parker, J.O. Parker, New Eng. J. Med. 338 (1998) 520–531.
[10] U. Abshagen, G. Betzien, R. Endele, B. Kaufmann, Eur. J. Clin. Pharmacol. 20 (1981) 269–275.
[11] U.E. Jonsson, Drugs 33 (1987) 23–31.
[12] R.K. Verma, S. Garg, J. Pharm. Biomed. Anal. 30 (2002) 583–591.
[13] R.K. Verma, A.M. Kaushal, S. Garg, Int. J. Pharm. 263 (2003) 9–24.
[14] J.W. Moore, H.H. Flanner, Pharm. Technol. 20 (1996) 64–74.
[15] K. Uekama, K. Oh, T. Irie, M. Otagiri, Y. Nishimiya, T. Nara, Int. J. Pharm. 25 (1985) 339–346.
[16] A. Smith, Anal. Proc. 19 (1982) 559–561.
[17] T. Durig, A.R. Fassihi, Int. J. Pharm. 117 (1993) 161–170.
[18] C.E.P. Malan, M.M. Villers, A.P. Lotter, J. Pharm. Biomed. Anal. 15 (1997) 549–557.
[19] A.A.S. Araujo, S. Storpirtis, L.P. Mercuri, F.M.S. Carvalho, M.S. Filho, J.R. Matos, Int. J. Pharm. 260 (2003) 303–314.
[20] R.K. Verma, Development and evaluation of novel osmotically controlled oral drug delivery systems for glipizide and isosorbide mononitrate, Ph.D. thesis, Department of Pharmaceutics, NIPER, SAS Nagar, India, 2002