

# Compatibility studies between propafenone and selected excipients used in the development of controlled release formulations

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The objective of the present study was to evaluate the compatibility of propafenone HCl (PFH) with the selected excipients used in a controlled drug delivery system. The studies were conducted by an isothermal stress test method. The differential scanning calorimetry (DSC) and high-performance liquid chromatography techniques were used as tools to assess the compatibility of the drug with the selected excipients. Complementary techniques such as powder X-ray powder diffractometry (pXRD) and fourier transform infrared (FTIR) spectroscopy were used to assist in the interpretation of the DSC results. On the basis of the DSC results, the drug was found to be compatible with gum kondagogu (GKG), chitosan, polyelectrolyte complex of GKG and chitosan, HPMC K100M, carbopol 934P, Benecel<sup>®</sup> and A-tab<sup>®</sup>. Some degree of interaction was observed with lactose monohydrate; however, the additional studies using FTIR spectroscopy and pXRD confirmed that PFH is compatible with lactose monohydrate.

**Key words:** Chitosan, compatibility, excipient, gum kondagogu, polyelectrolyte complex, propafenone

## INTRODUCTION

Propafenone HCl (PFH), 2-(2-hydroxy-3-propylamino-propoxy)-3-phenylpropiophenone, is a class Ic antiarrhythmic agent with local anesthetic effects and a direct stabilizing action on myocardial membranes that is widely used in the treatment of ventricular and supraventricular arrhythmias.<sup>[1]</sup> PFH is supplied as prolonged-release capsules (Rhythmol XR) of 225, 325 and 425 mg for administration twice daily.<sup>[2]</sup>

The assessment of possible incompatibilities between an active drug substance and different excipients forms an important part of the preformulation stage during the development of a solid dosage form. Successful compatibility studies require a good experimental design that furnishes the required information with the minimum of experimental effort. The pharmaceutical excipients are generally considered as pharmacologically inert; however, the excipients can initiate, propagate or participate in physical or chemical interactions with the drug molecules. The

physical interactions can be studied by the differential scanning calorimetry (DSC) technique. DSC can show changes in the appearance, shift or disappearance of melting endotherms and exotherms and/or variations in the corresponding enthalpies of reaction. The chemical interactions, i.e. degradation reactions, can be studied by high-performance liquid chromatography (HPLC), liquid chromatography–mass spectrometry and nuclear magnetic resonance techniques.

The routine drug–excipient interactions can be studied by two methods, i.e. DSC and quantitative assay by HPLC after isothermal stress tests (IST). DSC allows the fast evaluation of possible incompatibilities; however, the interpretation of DSC results is not always easy. Hence, the DSC results must be interpreted carefully and some complementary techniques, such as Fourier transform infrared (FTIR) spectroscopy, microscopy or powder X-ray powder diffractometry (pXRD), can be useful in avoiding misleading conclusions.<sup>[3]</sup> The IST

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involves storage of drug–excipient blends with or without moisture at high temperature to accelerate drug ageing and interaction with excipients. The normal duration of study could be around 3–4 weeks.<sup>[4]</sup>

All the excipients used in the present study are commonly used excipients in solid dosage forms, except gum kondagogu (GKG), chitosan and polyelectrolyte complex (PEC) of GKG and chitosan. GKG (*Cochlospermum gossypium*, Family Cochlospermaceae), a tree exudate gum, is a plant growing naturally in Chittor, East Godavari districts in Andhra Pradesh and Mayurbhanj district in Orissa, India. Basically, it is a polymer of rhamnose, galacturonic acid, glucuronic acid,  $\beta$ -D-galactopyranose,  $\alpha$ -D-glucose,  $\beta$ -D-glucose, galactose, arabinose, mannose and fructose, with sugar linkage of (1-2)- $\beta$ -D-galactopyranose, (1-6)- $\beta$ -D-galactopyranose (1-4)- $\beta$ -D-Glucose, 4-O-Me- $\alpha$ -D-Glucose, (1-2)- $\alpha$ -L-Rhamnose and (1-4)- $\alpha$ -D-galactopyranose, with an average molecular weight of  $7.23 \times 10^6$  to  $8.25 \times 10^5$  g/mol determined by the static light scattering method and berry plots.<sup>[5-7]</sup> GKG was found to be safe in the 90 days sub-chronic toxicity study conducted in rats.<sup>[8]</sup> This gum is yet to be commercially exploited, as the physicochemical properties of this gum are yet to be characterized. The co-workers of our laboratory have explored the utility of GKG in the design of a controlled drug delivery system and have granted the patent.<sup>[9]</sup> Chitosan is the only natural polysaccharide with a cationic nature and chemically, it is poly- $\beta$ -(1-4)-D-glucosamine.<sup>[10]</sup> The appearance of positive charge below pH 6.3 due to protonation of the amine group makes it interact with negatively charged materials such as enzymes, polysaccharides and nucleic acids. It has shown superb biological properties such as biocompatibility, biodegradability, lack of toxicity and adsorption.<sup>[11-13]</sup> The PEC is formed by the electrostatic attractions between two oppositely charged polyelectrolytes mixed in aqueous solution. The PEC between chitosan and GKG was prepared by blending two polymer solutions at the weight ratio of 1:10 at pH 5.0.

To the best of our knowledge, there is not much data available in the literature for the drug–excipient compatibility of PFH. Hence, the PFH was chosen in the present investigation. The objective of the present study is to evaluate the compatibility of PFH with the selected excipients used in the controlled drug delivery system.

## MATERIALS AND METHODS

### Materials

PFH was received as a gift sample from Ajanta Pharma Ltd., Mumbai, India. The following excipients were purchased from commercial sources and used as such: lactose mono hydrate (Signet Chemical Corporation Pvt. Ltd., Mumbai, India), carbopol 974P (Signet Chemical Corporation Pvt. Ltd., Mumbai, India), HPMC K 100M (Signet Chemical Corporation Pvt. Ltd., Mumbai, India), A-tab® (dibasic

calcium phosphate anhydrous, granular; Signet Chemical Corporation Pvt. Ltd., Mumbai, India), magnesium stearate (S.D. Fine Chemicals, Mumbai, India), Benecel® (Ashland India Pvt Ltd, Mumbai, India) chitosan (Sigma-Aldrich, Bangalore, India) and gum kongagogu (grade-1, M/s. Girijan Co-Operative Corporation, Visakhapatnam, India). The HPLC-grade solvents such as acetonitrile and methanol were purchased from Rankem, Faridabad, India, and chemicals potassium dihydrogen orthophosphate GR and ammonium acetate GR were purchased from Loba Chemicals, Mumbai, India.

## Methodology

### Isothermal stress testing

The drug and the different excipients of interest were weighed directly in 8 ml glass vials ( $n = 2$ ) and the vials were mixed on a vortex mixer for 2 min. To each vial containing the drug–excipient blend, approximately 10% w/w water was added and mixed further with a glass capillary, and the capillary was left inside the vial to prevent any loss of material. All the vials were sealed using a teflon-lined screw cap. Three set of vials were prepared as per the procedure outlined above. One set of vials were control samples and stored at 2–8°C. The second sets of samples were analyzed immediately after preparation. The third sets of samples were stored at 50°C, and removed after 4 weeks. The samplers were analyzed by DSC and HPLC. When important modifications of the drug thermal profile were observed in DSC traces of the mixtures, pXRD and FTIR spectroscopy were used as complementary techniques to assist in the interpretation of the DSC results.

### DSC analysis of samples

DSC analysis was performed on a TA Instruments Q 2000 DSC, New Castle, USA. Temperature calibration was performed using indium as the standard. Approximately 5–10 mg of the samples were weighed directly in the pierced DSC aluminum pan and scanned in the temperature range of 25–250°C at a heating rate of 10°C/min under constant purging of dry nitrogen at 30 ml/min. Before charging the samples, initial DSC thermograms were recorded and used as reference to evaluate the charged samples.

### FTIR spectroscopy

Infrared transmission spectra were obtained using a FTIR spectrophotometer (FTIR-8300, Shimadzu, Japan). Two percent (w/w) of the sample, with respect to a potassium bromide disk, was mixed with dry potassium bromide (KBr). The mixture was ground into a fine powder using a mortar and then compressed into KBr disks in a hydraulic press at a pressure of 10,000 psi. The characteristic peaks were recorded in the wave number of 4000–500/cm.

### pXRD

Powder X-ray diffractometer, Rigaku (Dmax-2200, Texas, USA), was used for diffraction studies. The studies were performed

on the samples by exposing them to  $\text{CuK}_\alpha$  radiation (40 kV, 30 mA) and scanned from 2 to 32°, 2 $\theta$  at a step size of 0.030° and step time of 1.0 s.

#### HPLC analysis of the samples

The chromatography separation was performed on an Agilent 1200 liquid chromatography system. The instrument was equipped with a G1330B pump, a G1315D diode array detector and variable UV/visible detector, a G1329 auto sampler injector and Agilent Chemstation chromatography workstation (Agilent, Santa Clara, USA). The chromatography separations were carried out on a Agilent eclips plus C-8 (4.6 mm  $\times$  75 mm, 3.5  $\mu\text{m}$ ) column. The gradient mobile phase consist of 10 mM ammonium acetate and acetonitrile; initially, the run was started with 100% aqueous solution and reached to 100% organic phase in 5 min, then 100% organic phase for 3 min followed by 100% aqueous phase in 2 min and followed by 4 min stabilization with 100% aqueous phase. The flow rate was 1.0 mL/min with detection at 254 nm and the injection volume was 10  $\mu\text{L}$ .

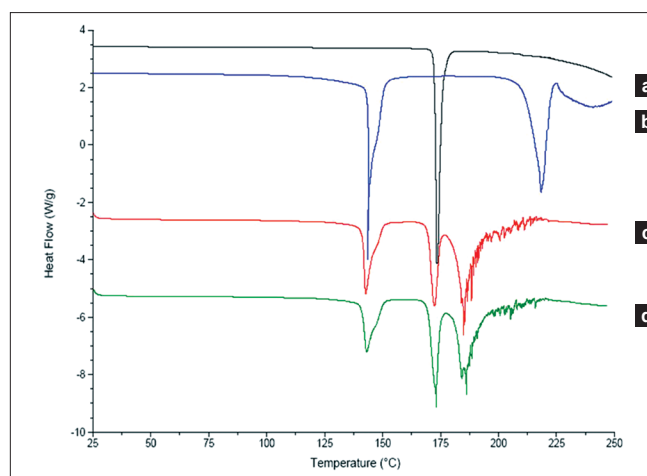
## RESULTS AND DISCUSSION

The drug–excipient compatibility studies were performed with some of the pharmaceutically relevant excipients such as lactose monohydrate (LMH), A-tab, Benecel, HPMC K100M, carbopol 934P and magnesium stearate. Chitosan, GKG and PEC were also included in the study. The drug to excipient ratio was 1:1 for all the excipients, except magnesium stearate, where the ratio was 2:1.

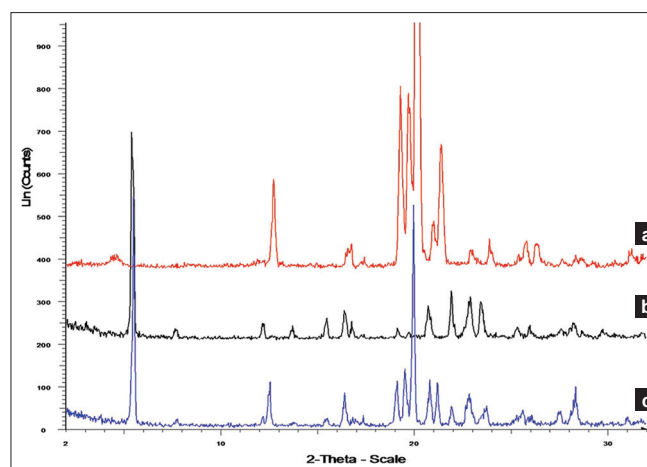
#### PFH-LMH mixture

The DSC overlay for PFH, LMH, PFH-LMH initial and PFH-LMH charged sample is shown in Figure 1. The DSC of the PFH showed a sharp single melting endothermic event with the onset of 172.5°C (enthalpy of fusion [ $\Delta H$ ]: 146 j/g). The DSC thermogram of lactose showed a sharp endothermic peak at 145.4°C due to loss of the bound water,<sup>[14]</sup> followed by its melting endotherm at around 220°C. The endothermic peak of PFH was well retained in the DSC trace of initial PFH-LMH mixture with little shift of drug peak toward the lower temperature. The endothermic peak (at 145.4°C), which was observed in case of pure LMH due to loss of bound water, was present in PFH–LMH mixture. The DSC profile of the charged sample (after 4 weeks at 50°C) of PFH-LMH was similar to the initial profile, and there was no change in the enthalpy of fusion of PFH [Table 1]. However, the melting endotherm of LMH disappeared and an additional endotherm was observed in the initial sample itself at 182°C, and the same pattern was observed in the charged sample.

To address the slight shift in the melting point of PFH toward a lower temperature in the presence of LMH, the charged sample of the PFH–LMH mixture was further analyzed by pXRD and FTIR spectroscopy. The pXRD overlay is shown in Figure 2. The pXRD of the pure PFH powder showed



**Figure 1:** DSC thermogram of (a) PFH, (b) LMH, (c) initial sample of PFH and LMH mixture and (d) charged sample of PFH and LMH



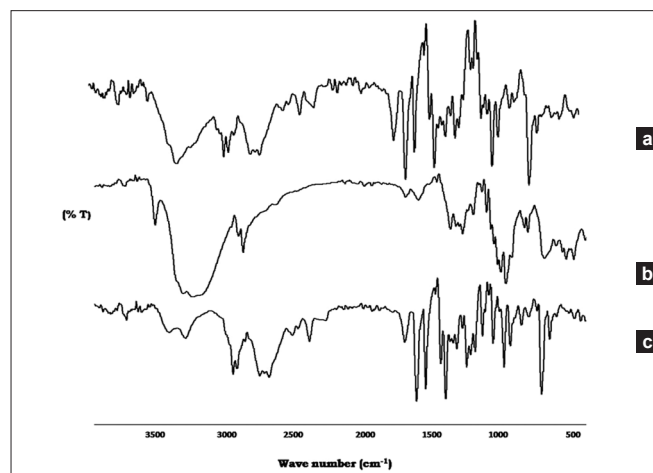
**Figure 2:** pXRD overlay of (a) LMH, (b) PFH and (c) charged sample of PFH and LMH mixture

significant reflections in the 2 $\theta$  values at about 3.0, 5.4, 7.6, 12.2, 13.7, 15.4, 16.4, 16.7, 17.3, 17.4, 19.1, 19.7, 20.7, 21.9, 22.9, 23.5, 25.3, 25.9, 27.6, 28.0, 28.3, 28.7, 29.7 and 31.8°. The pXRD of the charged sample was compared with the pure drug to determine the solid state stability. All the crystalline peaks of PFH appeared in the charged sample at the same 2 $\theta$  as that of the pure PFH, and also the characteristic crystalline peaks of LMH. Therefore, the pXRD data indicates that there was no change in the solid form of PFH. The FTIR overlay is shown in Figure 3. The major functional groups present in the FTIR spectrum of PFH were 3310/cm due to -OH stretching, 1657/cm corresponding to stretching of the carbonyl groups (-C=O), 1592/cm due to phenyl ring stretching and the asymmetric and symmetric stretching of the ether group (C-O-C) at 1239/cm and 1030/cm, respectively. The FTIR spectroscopy data showed all the characteristic peaks of PFH in the charged sample indicate that PFH is intact. The HPLC assay of the PFH–LMH mixture after 4 weeks was around 98.6% [Table 1], indicating that there was no degradation of PFH. The DSC and pXRD data

indicated that there was no physical interaction between PFH and LMH, the slight shift in melting endotherm of PFH could be due to solid–solid interaction, but not necessarily an incompatibility.

#### PFH-GKG mixture

The GKG showed a broad endotherm at 109.4°C, which may be attributed to desorption of moisture [Figure 4].<sup>[15]</sup> The melting endothermic peak of PFH appeared at 171.4°C ( $\Delta H$ : 52.1 j/g) in the DSC traces of the initial physical mixture of PFH–GKG. The endothermic peak (at 109.4°C), which was observed in case of pure GKG due to loss of bound water, was present in the PFH–GKG mixture, but little shift of peak to lower temperature (around 89°C) was observed. There was no change in the DSC profile of the charged sample of the PFH–GKG mixture after 4 weeks of storage at 50°C, and the melting endothermic peak of PFH appeared at 171.4°C ( $\Delta H$ : 53.8 j/g) and also the broad endothermic peak of GKG at 89°C. The HPLC analysis of the charged sample of the PFH–GKG mixture showed 99.97% assay [Table 1]. Based on the above results, the PFH is compatible with GKG.



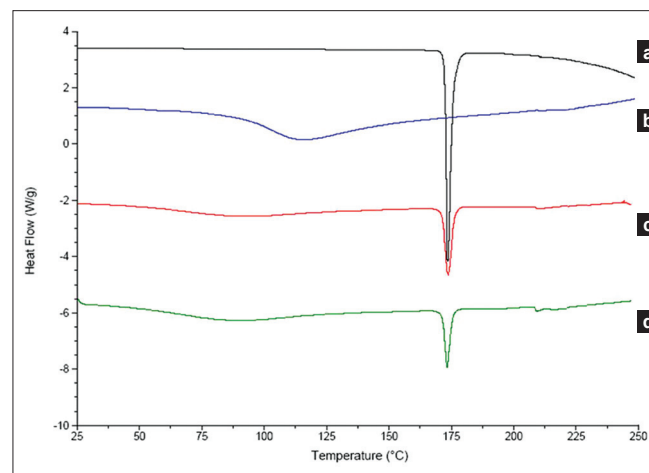
**Figure 3:** FTIR overlay of (a) charged sample of PFH and LMH (b) LMH and (c) PFH

#### PFH–chitosan mixture

The DSC traces of chitosan showed a broad endothermic event at 95.4°C, which could be due to loss of the associated water molecules from the structure of chitosan [Figure 5]. The DSC traces of the initial PFH–chitosan mixture showed shifting of the melting endothermic peak of PFH from 172.5°C to 169.7°C ( $\Delta H$ : 59.4 j/g), and also broadening of the drug peak was observed. The endothermic peak (at 95.4°C), which was observed in the case of pure chitosan due to loss of water, was present in the PFH–chitosan mixture, but there was a small additional sharp endotherm observed at 90°C, which was absent in the pure chitosan. The DSC profile of the charged sample of the PFH–chitosan mixture after 4 weeks of storage at 50°C was exactly similar to that of the initial DSC thermogram of the PFH–chitosan mixture and also there was no change in the enthalpy value of PFH. The assay of PFH in the charged sample of PFH–chitosan was 98.2% [Table 1]. Based on the data, the PFH is compatible with LMH.

#### PFH–PEC mixture

The DSC data is shown in Figure 6. The DSC traces of PEC showed a broad endothermic event at 109°C, which could



**Figure 4:** DSC thermogram of (a) PFH, (b) GKG, (c) initial sample of PFH and GKG mixture and (d) charged sample of PFH and GKG mixture

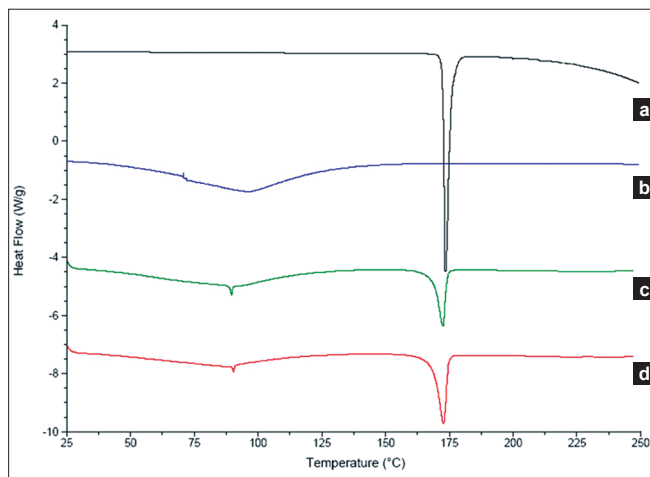
**Table 1: The percentage of drug remaining and the DSC results of PFH in various drug–excipient mixtures**

Sample	DSC results of PFH in the sample					
	Assay (%)		Initial sample		Charged sample	
	Initial sample	Charged sample	T <sub>onset</sub> (°C)	$\Delta H$ (j/g)	T <sub>onset</sub> (°C)	$\Delta H$ (j/g)
PFH	100.2	99.8	172.5	147.9	172.6	149.3
PFH + LMH	99.4	98.7	168.9	64.0	169.5	59.5
PFH + A-Tab	98.7	99.1	171.4	54.5	172.2	55.6
PFH + HPMC	99.0	100.1	171.7	62.5	171.9	69.1
PFH + carbopol	102.0	101.2	171.4	65.6	171.4	64.9
PFH + Benecel	99.0	98.7	171.8	66.8	171.9	67.0
PFH + GKG	100.0	99.9	171.4	52.1	171.4	53.8
PFH + chitosan	99.6	98.2	169.7	59.4	168.8	65.5
PFH + PEC	100.2	101.3	171.9	61.6	171.9	61.6
PFH + magnesium stearate	98.5	100.1	170.6	120.2	171	127.4

be due to loss of water molecules associated in the PEC. In the DSC traces of the initial PFH-PEC mixture, the melting endothermic peak of PFH appeared at 171.9°C ( $\Delta H$ : 61.6 j/g). The DSC profile of the PFH-PEC mixture after 4 weeks of storage at 50°C was exactly similar to that of the initial DSC thermogram of the PFH-PEC mixture. The HPLC analysis of the PFH-PEC mixture showed a 101.35% assay of PFH after the 4-week study period [Table 1]. Thus, there is no incompatibility between PFH and PEC.

#### PFH-HPMC mixture

The melting endothermic peak of PFH at 171.7°C ( $\Delta H$ : 64 j/g) and also the characteristic broad endothermic event of HPMC at 78°C registered in the DSC traces of the initial PFH-HPMC mixture [Figure 7]. No change in the DSC profile was observed in the charged sample. The assay of PFH in the charged sample of the PFH-PEC mixture was 100.12% assay [Table 1]. The DSC and HPLC assay data indicate that PFH and HPMC are compatible.



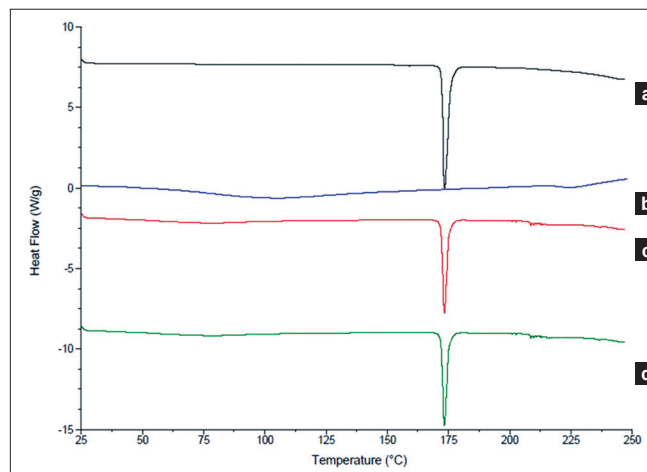
**Figure 5:** DSC thermogram of (a) PFH, (b) chitosan, (c) initial sample of PFH and chitosan mixture and (d) charged sample of PFH and chitosan

#### PFH-A-tab mixture

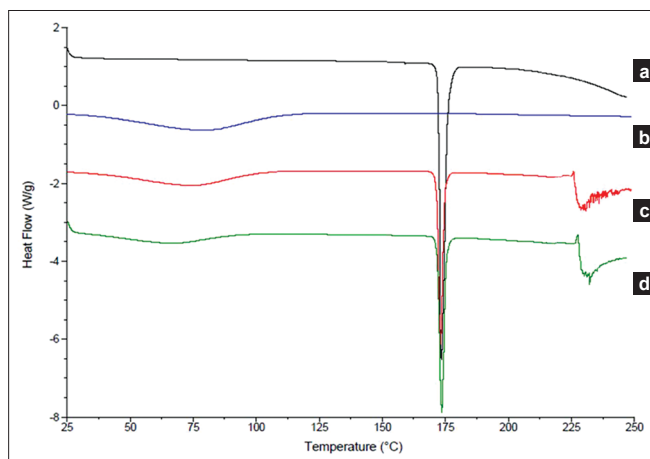
In the DSC scan of A-Tab, no peak was observed in the temperature range of 25–250°C [Figure 8]. The DSC profile of the initial and charged samples of the PFH-A-Tab mixture was similar and the melting endothermic event of PFH appeared at 171.4°C ( $\Delta H$ : 56 j/g). The HPLC assay of the charged sample was 99.12% [Table 1] of PFH. The results suggested that PFH is compatible with A-Tab.

#### PFH-Benecl mixture

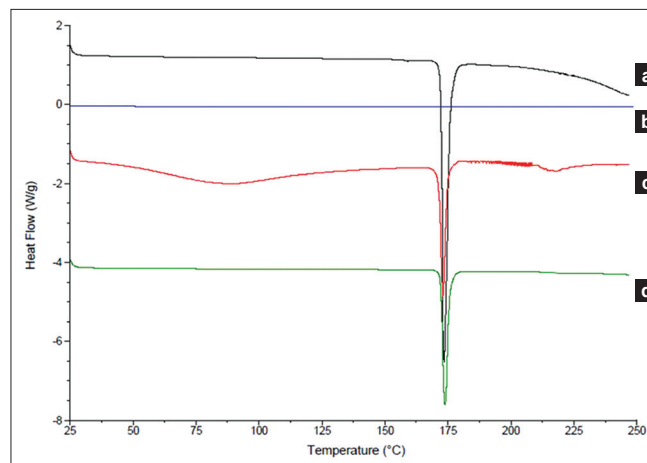
A broad endothermic peak was registered at 73°C in the DSC scan of pure Benecl. The DSC traces of the initial PFH-Benecl mixture showed a broad endothermic event at 73°C, corresponding to Benecl and the melting endothermic event of PFH at 171.8°C ( $\Delta H$ : 66.8 j/g) [Figure 9]. The DSC profile was same even in the charged sample, indicating that PFH and Benecl are compatible. The assay PFH in the charged sample was 98.71% [Table 1].



**Figure 6:** DSC thermogram of (a) PFH, (b) PEC, (c) initial sample of PFH and PEC mixture and (d) charged sample of PFH and PEC

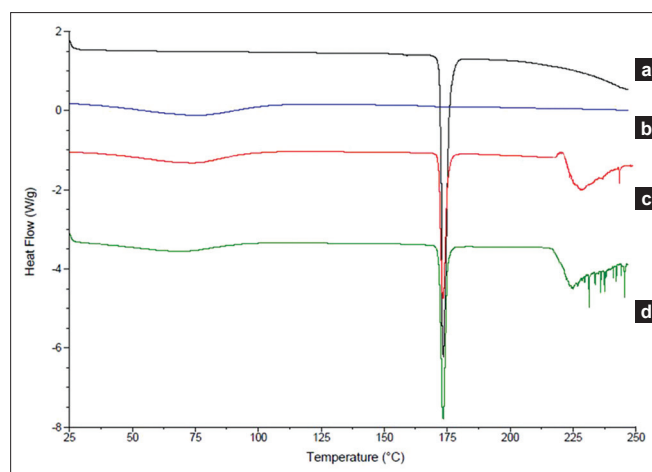


**Figure 7:** DSC thermogram of (a) PFH, (b) HPMC, (c) initial sample of PFH and HPMC mixture and (d) charged sample of PFH and HPMC

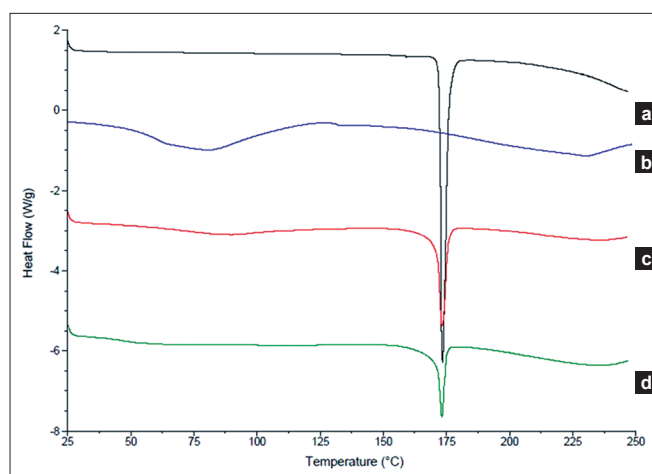


**Figure 8:** DSC thermogram of (a) PFH, (b) A-tab, (c) initial sample of PFH and A-tab mixture and (d) charged sample of PFH and A-tab

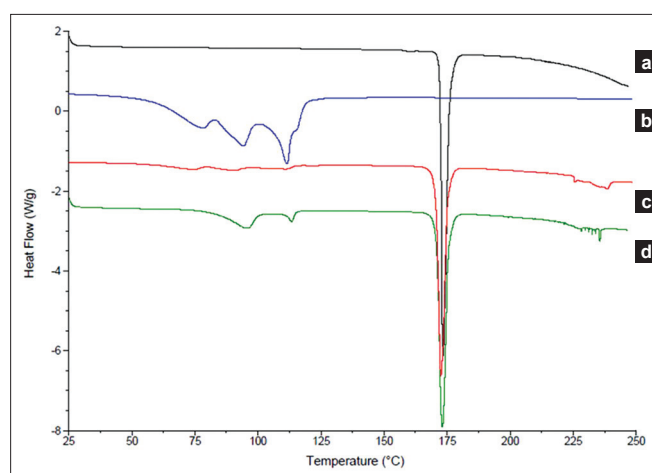




**Figure 9:** DSC thermogram of (a) PFH, (b) Benecel, (c) initial sample of PFH and Benecel mixture and (d) charged sample of PFH and Benecel



**Figure 10:** DSC thermogram of (a) PFH, (b) Carbopol, (c) initial sample of PFH and Carbopol mixture and (d) charged sample of PFH and Carbopol



**Figure 11:** DSC thermogram of (a) PFH, (b) magnesium stearate, (c) initial sample of PFH and magnesium stearate mixture and (d) charged sample of PFH and magnesium stearate

#### *PFH–carbopol mixture*

A broad endothermic event was observed at 80°C in the DSC scan of carbopolol [Figure 10]. The DSC traces of the PFH–carbopol initial mixture showed a characteristic broad endothermic event of carbopol at 80°C and also the melting endothermic event of PFH at 171.4°C ( $\Delta H$ : 65.6 j/g). The DSC profile of the charged sample was well matched with the initial sample of PFH and carbopol mixture. The HPLC analysis of the PFH–carbopol mixture showed 101.23% assay of PFH after a 4-week study period [Table 1]. Based on the DSC and HPLC data, PFH is compatible with carbopol.

#### *PFH–magnesium stearate mixture*

The DSC trace of magnesium stearate showed three endothermic events at 77, 93 and 111°C [Figure 11]. The melting endotherm of PFH appeared at 170.6°C ( $\Delta H$ : 120.2 j/g) and also three endothermic events were recorded at 77, 93 and 111°C, which were characteristic to pure magnesium stearate. The DSC profile of the PFH–magnesium stearate mixture after 4 weeks of storage at 50°C matched with the initial DSC thermogram of the PFH–magnesium stearate mixture. The melting endothermic peak of PFH appeared at 171.0°C ( $\Delta H$ : 122.4 j/g), and also the endothermic events corresponding to magnesium stearate. The HPLC analysis of the PFH–magnesium stearate mixture showed 100.12% assay [Table 1] of PFH after 4 weeks of the study period. Based on the DSC and HPLC data, PFH is compatible with magnesium stearate.

## CONCLUSION

As a part of the research work on the development of controlled release formulations of PFH, the drug–excipient compatibility studies were conducted with the excipients of interest. The DSC and HPLC were used as a technique to evaluate the compatibility of excipients with the compound. A shift in the melting endotherm of PFH toward lower temperature was observed in the DSC traces of the PFH–LMH mixture. The pXRD data of these mixtures showed all the characteristic peaks of pure drugs at the same  $2\theta$ , indicating that there was no evidence of physical instability. The HPLC analysis results of those mixtures were evident of chemical stability of PFH as the assay was within the acceptable range. Based on the DSC, pXRD, FTIR-spectroscopy and HPLC results, any possible pharmaceutical incompatibility between PFH and lactose was ruled out.

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- Only the references from journals indexed in PubMed will be checked.
- Enter each reference in new line, without a serial number.
- Add up to a maximum of 15 references at a time.
- If the reference is correct for its bibliographic elements and punctuations, it will be shown as CORRECT and a link to the correct article in PubMed will be given.
- If any of the bibliographic elements are missing, incorrect or extra (such as issue number), it will be shown as INCORRECT and link to possible articles in PubMed will be given.