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Hot melt extrusion method for preparation of ibuprofen/sucroester WE15 solid dispersions: evaluation and stability assessment

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ABSTRACT

Low melting points Sucroesters (SEs) are used in hot-melt extrusion technology (HME). However, there are few literatures studying the effect of SEs on drug release and their storage stability. In this study, SE® WE15 was proposed to prepare sustained-release solid dispersions with Iburpofen (IBU), containing 60 & 30% w/w, by HME, fusion method and compared to physical mixtures. The fresh and stored samples were evaluated by a well-established release rate study (USP Apparatus IV), DSC and XRD. Results revealed that HME technique succeeded to produce sustained-release patterns for IBU. Stored samples (6 months at 40°C / 75 % RH) were unstable and showed gradual decrease in IBU release rate for both IBU loadings. HME formula (60% w/w IBU) showed an increase in the amount of drug released. Long term stability, one year at room temperature, showed a marked increase in IBU release rate for both drug loadings. Only HME containing 30% w/w IBU gave stable form among others. DSC and XRD suggested that increase of SE content led to almost complete IBU dissolved in this carrier, and considerable decrease in IBU release rate. This has been proven by DSC and XRD data analysis for IBU and SE (enthalpy and counts).

INTRODUCTION

Solid dispersions (SDs) technique has attracted substantial interest as an efficient mean of improving the dissolution rate as well as the bioavailability of a wide range of poorly aqueous soluble drugs (Hasnain and Nayak, 2012). Also, SDs can be used to sustain the drug release by selecting an appropriate polymer (Craig, 2002; Serajuddin, 1999). The two major processes of preparing SDs are melting (fusion) and solvent evaporation methods (Van den Mooter, 2006; Vilhelmsen *et al.*, 2005; Won *et al.*, 2005). Other various approaches include co-evaporation (Hong *et al.*, 2011), hot spin mixing (Dittgen *et al.*, 1995), roll-mixing or co-milling (Breitenbach, 2002), freeze-drying (Sekikawa *et al.*, 1983), spray drying (Caron *et al.*, 2011), and supercritical fluid processing (SFP) (Gong *et al.*, 2005). In the 1980s, hot melt extrusion (HME) was used for the first time in the formulation of pharmaceuticals (Stanković *et al.*, 2013). The advantages of HME over the conventional approaches are: economical process, short production time, continuous operation with few processing steps and ease of scaling-up (Maniruzzaman *et al.*, 2012). During HME of pharmaceutical dosage forms, a blend of active ingredient, thermoplastic polymeric carrier, and other processing aids (plasticizers and antioxidants) is heated and softened inside the extruder and then pressurized through a die into granules, cylinders, or films (Zhang and McGinity, 2000). Sucrose esters (SEs) are applied in HME technology as promising carriers, because of their low melting points and their surfactant properties, but the information available on these carriers is not sufficient and further investigations are needed (Szűts *et al.*, 2008).

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Ibuprofen (IBU) is widely used as a safe non-steroidal anti-inflammatory drug (NSAID) for the treatment of pain, inflammation, arthritis and dysmenorrhea (Higgins *et al.,* 2001). IBU has a short elimination half-life (2-3 hours), thus frequent dosing is necessary to maintain therapeutic plasma levels (Higgins *et al.,* 2001). Therefore, preparation of sustained-release formulations of IBU will decrease the frequency of administration; reduce the exposure time of the gastrointestinal tract (GIT) to drug; maintain the required therapeutic plasma level, decrease side effects, thus, increase the patient's compliance (Higgins *et al.,* 2001).

It is well known that polymeric carriers used in HME typically require a plasticizer in order to reduce the glass transition temperature (Tg) and viscosity of the polymers during pharmaceutical HME (Aharoni, 1998). The plasticizing effect can be attributed to the increase of free volume, the decrease of friction between polymer chains and the consequent improvement of chain mobility of polymer, resulting in reducing the drug and polymeric carrier degradation and improve the stability profile of the active compound (Aharoni, 1998). IBU, a low melting point drug (78 °C), with a known plasticizing effect, and higher IBU loading led to subsequent increase in its plasticizing effect as reported previously with different polymers such as Kollidon® SR (De Brabander *et al.,* 2002; Kidokoro *et al.,* 2001; Özgüney *et al.,* 2009). Therefore, IBU is considered a good candidate for HME technologies.

Previous literature had discussed various preparations of IBU/ SDs for improving its dissolution using different carriers (Dabbagh and Taghipour, 2007; Esnaashari *et al.,* 2005; Islam *et al.,* 2010; Newa *et al.,* 2007; Newa *et al.,* 2008a; Newa *et al.,* 2008b; Newa *et al.,* 2008c; Park *et al.,* 2009; Xu *et al.,* 2007). SDs prepared by fusion method was used to enhance the solubility, dissolution rate and absorption of IBU using PEG 6000 (Gawai *et al.,* 2013), mixture of tween 80 & span 80 (Shahrin and Huq, 2012) and polyethylene glycol (PEG) 8000 (Ofokansi *et al.,* 2016). However, very limited reports are available up till now for preparation of sustained-release SDs of IBU using HME technique. Özgüney *et al*. (2009) developed IBU/SDs using Kollidon® SR. Other studies prepared sustained-release extrudates of IBU with ethyl cellulose and xanthan gum (De Brabander *et al.,* 2003; Verhoeven *et al.,* 2006). Kidokoro *et al*., 2001 developed IBU/Eudragit RS PO tablets prepared by hot melt processing. Also IBU was used with combination of microcrystalline waxes and starch derivatives to prepare SDs (De Brabander *et al.,* 2000).

Our previous work was done to prepare IBU/HME pellets using SE®WE15 as an extrudable carrier (Emara *et al.,* 2014). The prepared pellets were in vitro evaluated, for the first time in literature, by flow through cell dissolution tester (FTC, USP Apparatus IV) using different operational conditions to select the most appropriate method for proper discrimination between formulations containing different IBU loading ratios. That study investigated the effect of different cell sizes (large and small), flow conditions (turbulent and laminar) and pellets loading into the FTC (Emara *et al.,* 2014). The FTC method reported the optimum conditions for drug release from different formulations, solved the problems of unreliable release data due to spreading of pellets to undefined sites of the cell and thereby, eliminated the resulting errors in the release rate data and thus, achieved the highest reproducibility of results (Emara *et al.,* 2014). This FTC design was chosen as an alternative to the conventional USP I & II apparatuses, where in a previous study using a modified paddle method, no differences in drug release profiles between the 60% & 40% w/w IBU loading was noticed (De Brabander *et al.,* 2000). Therefore, for *in vitro* dissolution testing, validation of the method selected is very critical to monitor any change in product performance which could affect its bioavailability.

Although SEs are widely used in HME technique, yet, no published data are available on the applicability of SEs prepared by HME on the dissolution behavior and physical stability of drug /carrier system after storage under different conditions.

The aim of the present study was the development of sustained-release IBU/ SDs using HME technique with SE® WE15 as an extrudable carrier. Moreover, SDs prepared by the traditional fusion method (FM) as well as their respective physical mixtures (PM) were also prepared for comparisons. The most important target was to test the stability of the proposed SDs, to select a promising formula for *in vivo* testing. The system stability was done by studying the IBU content by HPLC, release rate by a properly designed FTC, DSC as well as XRD.

MATERIALS AND METHODS

Materials

Pure Ibuprofen (IBU) was kindly donated from Sigma pharma, Cairo, Egypt. Sucroester® WE15 (SE® WE15)(HLB=15) was obtained from Gattefose S.A., France. Sodium hydroxide pellets and potassium dihydrogen orthophosphate were purchased from Laboratory Rasayan, India. HPLC grade acetonitrile and Sodium dihydrogen phosphate (NaH2PO4) were purchased from Merck, (Germany). Milli-Q purified water (Millipore Corp., Billerica, MA, USA) was used to prepare the dissolution medium.

Methods

Preparation of solid dispersions by hot melt extrusion

SDs of IBU/ SE®WE15 was processed using HME with two different IBU loading ratios, i.e. 60% and 30% w/w for HME-1 and HME-2, respectively. Extrusion was performed using ¼ inch single screw extruder with a single rod die (Randcastle Microtruder RC-025, Randcastle Extrusion Systems, Inc., USA). The four zones of the extruder were heated to the required temperatures ranges from 55 – 65 °C and screw rotation was set at 30 rpm. The extrusion conditions and steps required to form the final product was previously discussed (Emara *et al.,* 2014) with slight modification. The prepared hot melt extrudates were cut manually into pellets with the following dimensions: length equals to 1 ± 0.1 mm and width equals to 0.6 ± 0.1 mm. Equivalent dose of IBU in each formula was 400 mg.

Preparation of solid dispersions by fusion method

SDs of IBU/ SE®WE15 was prepared by melting the required amount of drug and carrier for each formula in a hot plate on a water bath maintained at the specified temperature (65°C) for 10 minutes till complete melting. The fused mixture was cooled at room temperature, kept in vacuum oven overnight to solidify. The solidified mass was ground in a mortar, sieved to obtain particle size ranges of 850 µm – 710 µm and < 450 µm. The fusion mixtures were coded as FM-1 (60/40%w/w) and FM-2 (30/70 %w/w) for two different ratios of IBU / SE®WE15, respectively.

Preparation of physical mixtures

Physical mixtures (PM-1 & PM-2) of IBU and SE®WE15 in the same weight ratios as the SDs were prepared by thoroughly mixing the appropriate amount of IBU and carrier in a mortar by trituration for 15 minutes, and then sieving through a 60 mesh sieve. Granules of 850 µm to 710 µm were then prepared by dry granulation.

Determination of percent drug content by HPLC

An accurately weighed amount of PM and SDs, each equivalent to the amount of IBU in each formula were dissolved in acetinitrile, volume was adjusted to 25 mL, vortexed and filtered (Millex, 0.45 um). The filtrate was further diluted with mobile phase consisting of a mixture of acetonitrile/phosphate buffer (60:40, v/v, pH 7.0) and analyzed for drug content by an HPLC/UV method as described previously (Battu and Reddy, 2009). The HPLC apparatus consists of Waters 600 E Multi Solvent Delivery System Controller equipped with Rheodyne injector P/N 7725i, and Waters 2487 Dual λ Absorbance Detector coupled to Millennium 32 computer program. Chromatographic separation was achieved using a Symmetry C18 column (5 µm, 3.9X150, Waters Assoc., USA) protected by a guard pack precolumn module with Symmetry C18, 5 µm inserts (Waters Assoc., USA). The flow rate was adjusted to 0.8 mL/min with UV detection at 260 nm and the column was kept at room temperature. The adopted method was selective and sensitive with LOD and LOQ equal to 10 ng/mL and 25 ng/mL, respectively. Each formulation was tested in triplicates.

***In vitro* drug release studies**

In vitro drug release studies of IBU powder, PM and the prepared SDs were carried-out as described previously in details (Emara *et al.*, 2014); using the closed loop setup of flow through cell (FTC) dissolution apparatus (USP IV, a Dissotest CE-6 equipped with a CY 7-50 piston pump, Sotax, Switzerland) in phosphate buffer pH 7.2. The dissolution studies were done in triplicate and the mean value was calculated.

The FTC design selected to perform the dissolution studies had proven its efficacy to achieve the optimum conditions for IBU release from the proposed formulations; also it was able to discriminate between formulations containing different IBU loading ratios (Emara *et al.*, 2014).

Stability Studies

Stability studies were conducted as stated by ICH guidelines, 2003 on the prepared SDs along with PM to assess their stability with respect to DSC, XRD, chemical stability by HPLC and drug release characteristics. The prepared formulae were placed in a tightly closed glass container and subjected to accelerated stability study using thermostatically controlled oven adjusted at 40 ℃ ± 0.5 ℃ with RH of 75% (maintained using a saturated solution of NaCl) for 6 months as well as storage at room temperature ranged from 18 °C to 33 ℃ for 12 months.

Differential Scanning Calorimetry (DSC)

Thermal behavior of the powdered IBU, SE®WE15, PM and the prepared SDs were examined by differential scanning calorimetry (DSC-50, Shimadzu, Japan) to investigate the state of drug and carrier in the different tested samples and to assess incompatibility if any in the prepared samples. DSC analysis was performed for fresh samples as well as samples stored at different conditions. The thermograms were performed using an automatic thermal analyzer (DSC-50). Accurately weighed samples (5 mg) were placed directly into pierced aluminum pans and the thermal analysis was carried - out using heating ramp from 25 to 300 °C at 10 °C/min scale up rate. A nitrogen purge (20 mL/min) was maintained throughout the run.

X-ray Diffraction (XRD)

X-ray diffraction patterns of the fresh and stored SDs, compared with pure drug and carrier were recorded by using Empyrean diffractometer. Samples were irradiated with monochromatized Cu Kα radiation, and analyzed between 2 θ of 3° and 80°, with step size 0.026°. The voltages, current and time per step were 45 kV, 30 mA, and 18.87 s, respectively.

Statistical Analysis

In vitro drug release of stored samples was compared with fresh samples by employing the similarity factor (f_2) as proposed by Moore and Flanner, 1996, according to the following equation:

$$f_2 = 50 \bullet \log \{[1+ (1/n) \Sigma_{t=1}^{n} (R_t - T_t)^2]^{-0.5} \bullet 100\}$$

Where, n is number of time points, R_t and T_t are cumulative percentage releases at the selected n time point of the reference and the test product, respectively.

The similarity factor (f_2) is a measure of the similarity between two dissolution curves and its value ranges from 0 and 100. FDA suggests that two dissolution profiles are considered similar if the similarity factor f_2 is between 50 and 100 (US-FDA, 1997).

RESULTS AND DISCUSSION

Drug Content

The percentages drug content of various IBU/ SDs as well as their corresponding PM were within the range of 97.76 ±

8.08 % to 107.94 ± 7.64 % which complied with the accepted pharmacopoeial limits (British Pharmacopoeia, 2007).

***In vitro* release study for fresh samples**

Our previous study on IBU/SE®WE15 sustained-release pellets using HME technique containing different drug concentrations were evaluated using specific operational conditions of the FTC dissolution apparatus (Emara *et al*., 2014). These specific features of the FTC were selected in order to develop a sensitive *in vitro* method to precisely discriminate between different formulations, ensure high reproducible *in vitro* results and to detect even minor differences which might occur after storage (Emara *et al.*, 2014). SDs of different particle sizes prepared by fusion method showed the same release rate results. Therefore, the particle size range of 850 – 710 um was selected for further studies.

SDs of IBU was previously prepared by different techniques and compared with its physical mixtures for better understanding of the effect of different methods on the physicochemical characteristics of the drug. IBU/SDs were previously prepared by the solvent and fusion-solvent methods using different carriers and compared with the physical mixtures (Dabbagh and Taghipour, 2007). *In vitro* dissolution results showed that SDs containing Eudragit or HPMC resulted in retardation of the dissolution of IBU, while SDs containing PEG gave faster dissolution rates than the physical mixtures (Dabbagh and Taghipour, 2007). Also, IBU/SDs was prepared by melt dispersion technique using macrogol 4000 and 6000 as carriers (Al Masum *et al.*, 2012). The results showed that the prepared SDs enhanced the dissolution of IBU relative to physical mixtures.

Figure 1 showed the release profiles of different preparations of IBU/ SE®WE15 SDs (containing 60% and 30% w/w IBU) prepared by HME & FM, the prepared PM and comparing the results with pure IBU powder.

Aggregation and agglomeration of PM were observed during dissolution study. The results showed that the physical mixtures (i.e. PM-1 & PM-2) and SDs prepared by fusion method (i.e. FM-1 & FM-2) did not cause any pronounced change in the amount of IBU released (Figures 1 A&B) compared to the observed sustained-release effect detected with hot melt extrudates (i.e. HME-1 & HME-2). In case of 60% w/w IBU, PM-1 and FM-1 showed the same release profiles, while HME-1 significantly slowed the release rate (Figure 1A & Table 1).

Figure 1B & Table 1 also showed that both PM-2 and FM-2 containing 30% w/w IBU, gave comparable release patterns with pure drug, while HME-2 showed the slowest release rate. These results clearly identify the advantages of HME technique over the other conventional methods as it provides uniform and intimate dispersion and/ or mixing of all ingredients by the high shear extruding forces. Thereafter, SDs prepared by different methods can have differences in product release properties, which might affect its performance based on a case by case study.

After 8 hours release study, 64.65 % and 47.09 % of IBU were released from HME-1 (60% IBU) and HME-2 (30% IBU), respectively (Table 1). This might be due to possible solid-state interactions and the higher content of SE® WE15 in HME-2 sample, resulting in more intimate distribution and entrapment of IBU within the SE structure. This result could be used to tailor the required release profile by increasing the percentage of SEs in the formula.

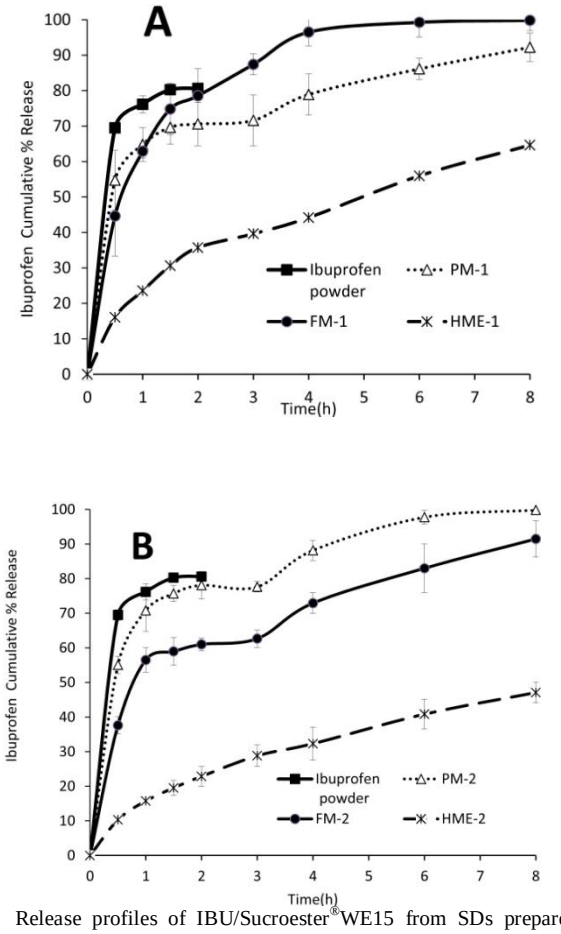

Fig. 1: Release profiles of IBU/Sucroester®WE15 from SDs prepared by fusion method (FM) and hot-melt extrusion (HME) with their respective physical mixture (PM) at: (A) 60% drug loading; (B) 30% drug loading. (Mean ±SD, *n*=3).

While, SE® WE15 succeeded to sustain the IBU release rate up to 8 hours from hot melt extrudates, however, it was used previously to enhance the release of poorly soluble compounds: 17-Estradiol (Hülsmann *et al.*, 2000) and Nifedipine (Badr, 2006). Szűts *et al.*, 2008 used the melt technology (i.e. fusion method) to prepare melts of two different drugs (i.e. Meloxicam and Diclofenac Sodium) with three SEs having wide range of HLB values (1 – 16). Their results showed that Meloxicam release rate was increased by the presence of SEs having high HLB compared to plain powder, while, no change in the dissolution rate of Diclofinac Sodium was observed. On the other hand, low HLB values slowed the release rates for both drugs (Szűts *et al.*, 2008). These results revealed that SDs prepared by the same SE can behave differently according to the physicochemical property of each drug. Thus, to be able to understand and estimate the pattern of drug release, it is necessary to evaluate the material properties,

as well as the possible interactions between the drug and the carrier. Also, the physicochemical properties of drugs might give different performances with the same carrier.

Stability Results:

No information available in literature regarding the stability of IBU/SDs prepared by HME using SEs as an extrudable carrier. Thus, for final judgment of product selection prior to *in vivo* testing, stability of IBU/SE® WE15 preparations was carried -out for full investigation of the impact of different storage conditions on drug release using a sensitive and well-established *in vitro* release method. As the system stability will be anticipated to be changed due to physical transformation of drug from the amorphous to the crystalline structure.

Chemical Stability by HPLC:

Results showed no changes in color and / or appearance of the prepared formulae observed upon storage. The content of different IBU/SE® WE15 was investigated by HPLC and results showed that the drug content in all stored samples ranged between 99.01 and 103.04%, which indicated that IBU was chemically stable with no trace of degradation or weight loss during the whole period of storage. Each formulation demonstrated uniform drug content with relative standard deviation ranging between 0.5 and 3.86% for samples stored for 6 months (at 40 °C and 75% RH) and 12 months at room temperature,which indicated excellent content uniformity with high chemical stability.

***In vitro* release study for stored samples**

The comparative release profiles of stored samples were compared with initial data of freshly prepared ones by employing the similarity factor(f_2), and the results were summarized in Table 1 and Figure 2. For samples stored for 6 months at 40 °C/75 % RH; Figure 2 and Table 1 showed that the percentage of IBU released after 8 hours prepared by physical mixture (i.e. PM-1 & PM-2) and fusion method (i.e. FM-1 & FM-2) were drastically and significantly decreased, as depicted by $f2$ values (i.e. $f2 < 50$). This decrease might be due to recrystallization of IBU during storage or some physical changes which might take place in SEs. On the other hand, percent IBU released from hot melt extrudates behaved differently. Where a considerable increase in release rate was observed with high IBU content (HME-1), while HME-2 (30% w/w IBU) stored for 6 months at 40 °C/75 % RH showed a decrease in IBU release rate as shown in Table 1 and Figure 2. All the tested samples were found to be unstable upon storage for 6 months at 40 °C/75 % RH as depicted by similarity factor ($f2$ values < 50; cf. Table 1).

On the other hand, HME samples subjected to long term stability study (12 months) at room temperature revealed that only formula (HME-2) was stable as depicted by the dissolution similarity factor ($f2$ value = 50; cf. Table 1). These results might be due to the presence of high SEs content in this formula (i.e.70% w/w SE® WE15 in HME-2) which prolonged the system stability at room temperature.

The current results clearly confirmed the superiority of HME for preparation of IBU / SDs over other conventional methods with respect to its sustained-release properties and the stability of the final product. Also, these results highlight the need of elaborative work for studying the performance and stability of different SDs of IBU / SE® WE15 prepared by HME technique. To understand the possible reasons for the changes observed before and after storage, DSC and XRD were carried-out.

Table 1. Effect of different Storage Conditions on the Cumulative Release % (Q 8 hours) of IBU from different samples.

Storage Conditions	Cumulative IBU Release % (Q 8 hours)					
	PM-1	**PM-2**	**FM-1**	**FM-2**	**HME-1**	**HME-2**
Fresh	92.23 (± 3.96)	99.83 (±1.18)	99.28 (± 2.96)	91.48 (± 5.25)	64.65 (± 0.12)	47.09 (± 2.98)
***6 months**	65.27 (± 4.98)	69.13 (± 4.95)	73.80 (± 1.05)	58.90 (± 2.59)	99.98 (± 1.73)	24.72 (± 1.73)
Similarity Factor (f_2)	35	22	27	43	30	43
****12 months**	ND	ND	ND	ND	99.87 (± 4.95)	62.83 (± 5.76)
Similarity Factor (f_2)	NA	NA	NA	NA	38	50

*6 months (40 °C / 75 % RH).
**12 months at Room Temperature.
ND: Not done.
NA: Not applicable.

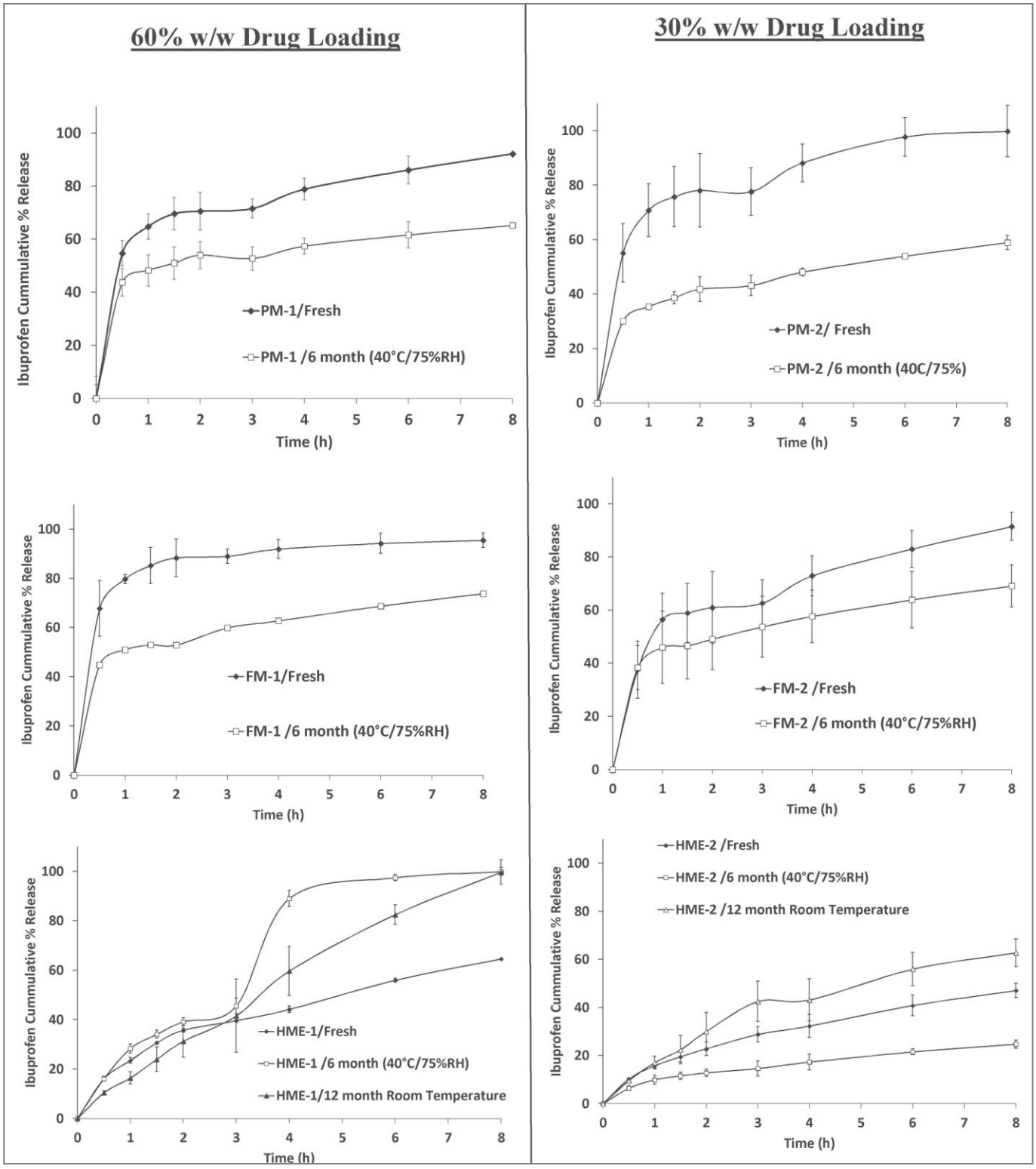

Fig. 2: Effect of different storage conditions on the release profiles of IBU/Sucroester®WE15 from SDs prepared by fusion method (FM) and hot melt extrusion (HME) compared with physical mixture (PM) (Mean ±SD, *n*=3).

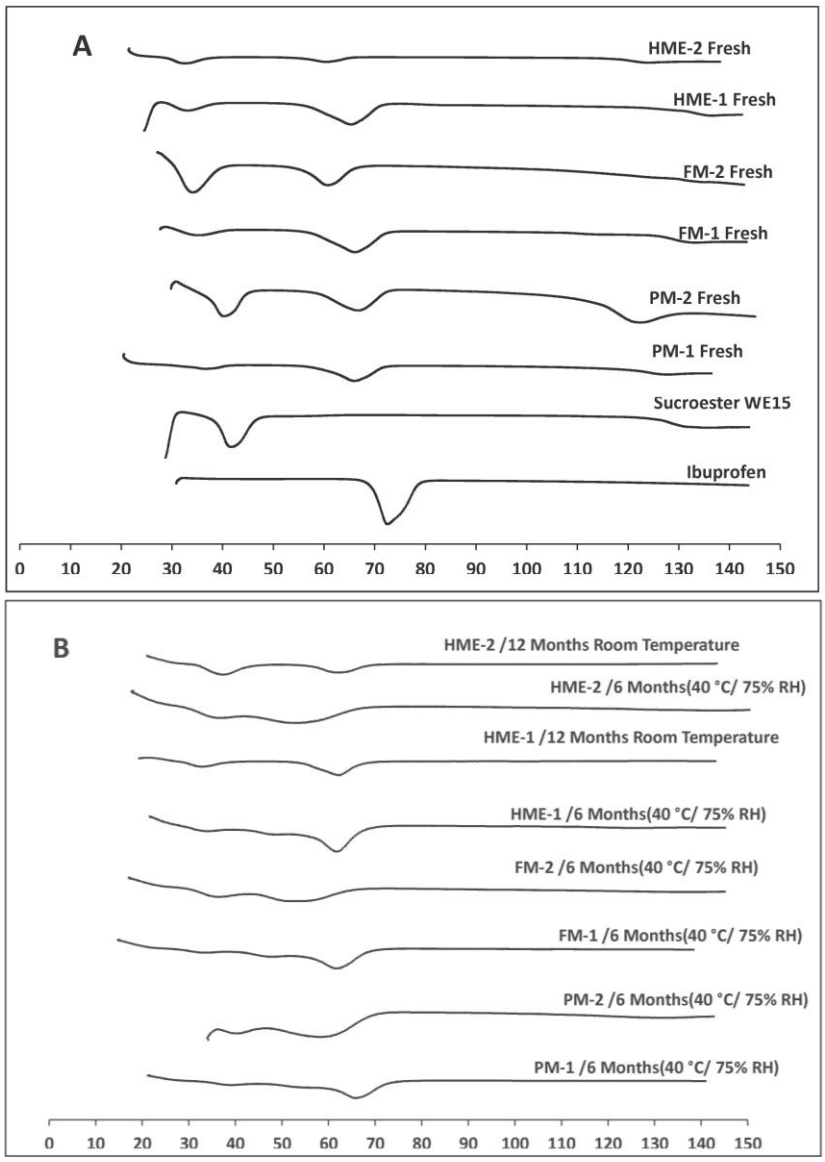

Fig. 3: DSC thermograms of IBU and Sucroester® WE15 in pure forms, PM and SDs: (A) Fresh samples; (B) Stored samples.

DSC

DSC studies of pure IBU, pure SE®WE15, the PM and SDs were conducted to investigate the crystallinity and/ or drug-carrier interaction and the results were shown in Figure 3 and Table 2. The DSC thermograms showed pure crystalline IBU with a single, sharp endothermic peak at 74.15 °C which represent the melting of the drug with an enthalpy (ΔH) of -88.53 J/g, while, the endothermic peaks of fresh samples ranged from 63.91 to 71.17°C (Table 2). The DSC thermogram of pure SE®WE15 showed an endothermic peak at 42.62 °C with enthalpy (ΔH) of -39.61 J/g, while the endothermic peaks of fresh samples ranged from 35.31 to 41.30 ° C. As expectedly, the enthalpy values for both IBU and SE ® WE15 decreased with decreasing their contents in the fresh samples. For example, PM-1, FM-1 and HME-1 (containing 60 % IBU w/w), showed higher enthalpy values compared to PM-2, FM-2 and HME-2 which contain 30% IBU w/w (Table 2, Figure 3A). Also, the same behavior was recorded in case of SE® WE15. The results obtained from the DSC thermograms of fresh samples could be correlated with the *in vitro* dissolution results. In case of SDs prepared by fusion method (FM-1 & FM-2) and hot melt extrusion (HME-1 & HME-2);increasing SE® WE15 content in SDs (as in FM-2 and HME-2) led to a subsequent increase in its enthalpy (Table 2) resulting in a decrease in the amount of IBU released (Table 1). On the other hand, increasing IBU content in SDs (as in FM-1 and HME-1) led to a subsequent increase in the enthalpy of IBU (Table 2) and a simultaneous increase in the amount of IBU released (Table 1). All the samples stored under stress conditions for 6 months showed considerable reduction of the enthalpy (ΔH) values for SE® WE15; as depicted in Table 2. On the other hand, the changes of the enthalpy values for IBU did not show the same straight forward decrease pattern as that recorded with SE® WE15.

Table 2: DSC data of fresh and stored samples.

Formula Code	SE® WE15				IBU			
	Fresh	*6 months	**12 months			Fresh	*6 months	**12 months
Enthalpy (J/g)								
pure SE® WE 15	-39.61				pure IBU	-88.53		
PM-1	-16.28	-6.49			PM-1	-60.96	-65.8	
PM-2	-27.52	-2.14			PM-2	-22.73	-20.85	
FM-1	-22.79	-4.57			FM-1	-78.69	-32.48	
FM-2	-38.25	-10.70			FM-2	-22.95	-29.77	
HME-1	-17.14	-7.74	-31.94		HME-1	-61.53	-42.20	-61.99
HME-2	-27.25	-12.90	-38.37		HME-2	-18.06	-39.87	-36.38
Melting Peak (°C)								
pure SE® WE 15	42.62				pure IBU	74.15		
PM-1	40.69	42.59			PM-1	71.17	72.23	
PM-2	41.30	42.68			PM-2	69.27	63.66	
FM-1	37.77	41.03			FM-1	69.83	72.65	
FM-2	36.76	43.10			FM-2	64.33	60.28	
HME-1	36.73	46.14	43.71		HME-1	69.90	71.03	75.83
HME-2	35.31	41.92	44.29		HME-2	63.91	59.24	71.22
Melting Range (°C) onset - endset								
pure SE® WE 15	38.81 – 47.55				pure IBU	70.96 – 80.54		
PM-1	36.61 – 45.38	36.91 – 49.28			PM-1	64.80 – 77.25	64.57 – 80.85	
PM-2	37.24 – 45.82	40.01 – 51.10			PM-2	61.03 – 75.15	51.20 – 81.03	
FM-1	31.73– 43.19	34.34 – 48.46			FM-1	61.31 – 76.26	66.57 – 80.56	
FM-2	32.91 – 42.06	35.20 – 50.00			FM-2	59.95 – 69.75	50.30 – 80.07	
HME-1	32.17 – 41.94	40.12 – 55.77	36.95 – 50.67		HME-1	61.43 – 75.96	65.46 – 77.29	66.75 – 81.83
HME-2	32.28 – 40.05	32.28 – 40.05	38.28 – 51.41		HME-2	59.01 – 68.99	49.54 – 74.30	63.95 – 78.25

*6 months (40 °C / 75 % RH); **12 months at Room Temperature.

Table 3: XRD data of fresh and stored samples.

Formula Code	SE® WE15			IBU			
	Fresh	*6 months	**12 months		Fresh	*6 months	**12 months
Counts							
pure SE® WE15	644.9591			pure IBU	2428.4200		
PM-1	465.5429	404.8343		PM-1	1098.7638	1288.9808	
PM-2	873.5090	607.7043		PM-2	679.7487	557.0254	
FM-1	509.1560	419.0762		FM-1	1383.9128	1136.5184	
FM-2	783.6898	608.0393		FM-2	682.6544	610.1858	
HME-1	462.0656	175.9885	382.8305	HME-1	1084.2043	1191.7921	1058.2062
HME-2	746.4484	445.7935	601.0246	HME-2	682.7927	517.7523	621.1304
2Θ (°)							
pure SE® WE15	21.1611			pure IBU	16.5591		
PM-1	21.3431	21.3671		PM-1	16.5071	16.5051	
PM-2	21.3431	21.4191		PM-2	16.5591	16.5571	
FM-1	21.2651	21.5231		FM-1	16.4551	16.6091	
FM-2	21.3431	21.4711		FM-2	16.4811	16.5831	
HME-1	21.2911	21.1591	21.3149	HME-1	16.5071	16.5831	16.5569
HME-2	21.4211	21.4191	21.4709	HME-2	16.6111	16.5571	16.6349

*6 months (40 °C / 75 % RH), **12 months at Room Temperature.

Where, some samples showed reduced enthalpy values for IBU (PM-2, FM-1 & HME-1), while the rest of the samples showed the opposite behavior. Table 2 showed increased enthalpy values for both SE® WE15 and IBU for HME samples (i.e. HME-1 and HME-2) stored for 12 months at room temperature, in comparison to fresh ones. Table 2 showed that the largest differences in melting range (°C) (i.e. onset–endset) were recorded in samples containing higher content of SE® WE15 (i.e. PM-2, FM-2 & HME-2) and stored under stress conditions for 6 months. The endothermic peaks of IBU and SE® WE15 in these samples lost their sharpness and distinctive appearances (Figure 3B).

This might be due to drug inclusion complexation between the two components and/or incorporation of IBU between parts of the crystal lattice of the carrier, leading to certain physical changes and a probable drug / carrier interaction.

This wider melting range difference observed in samples stored under stress conditions might be due to the changes occurring in the crystallinity of SE® WE15 at elevated temperature (40°C) and humidity (75%).

This was proved by the remarkable decrease in the amount of IBU released in all samples stored under stress conditions for 6 months (Table 1).

XRD

Diffractograms of pure drug, carrier, and the prepared formulae were shown in Figure 4 and Table 3. There were several distinctive peaks for IBU seen at 6.047 °, 12.105°, 16.515° (the major one), 17.549°, 20.06°, 22.633° and 24.97° at angle of diffraction (2θ), which confirmed the crystalline nature of the drug.

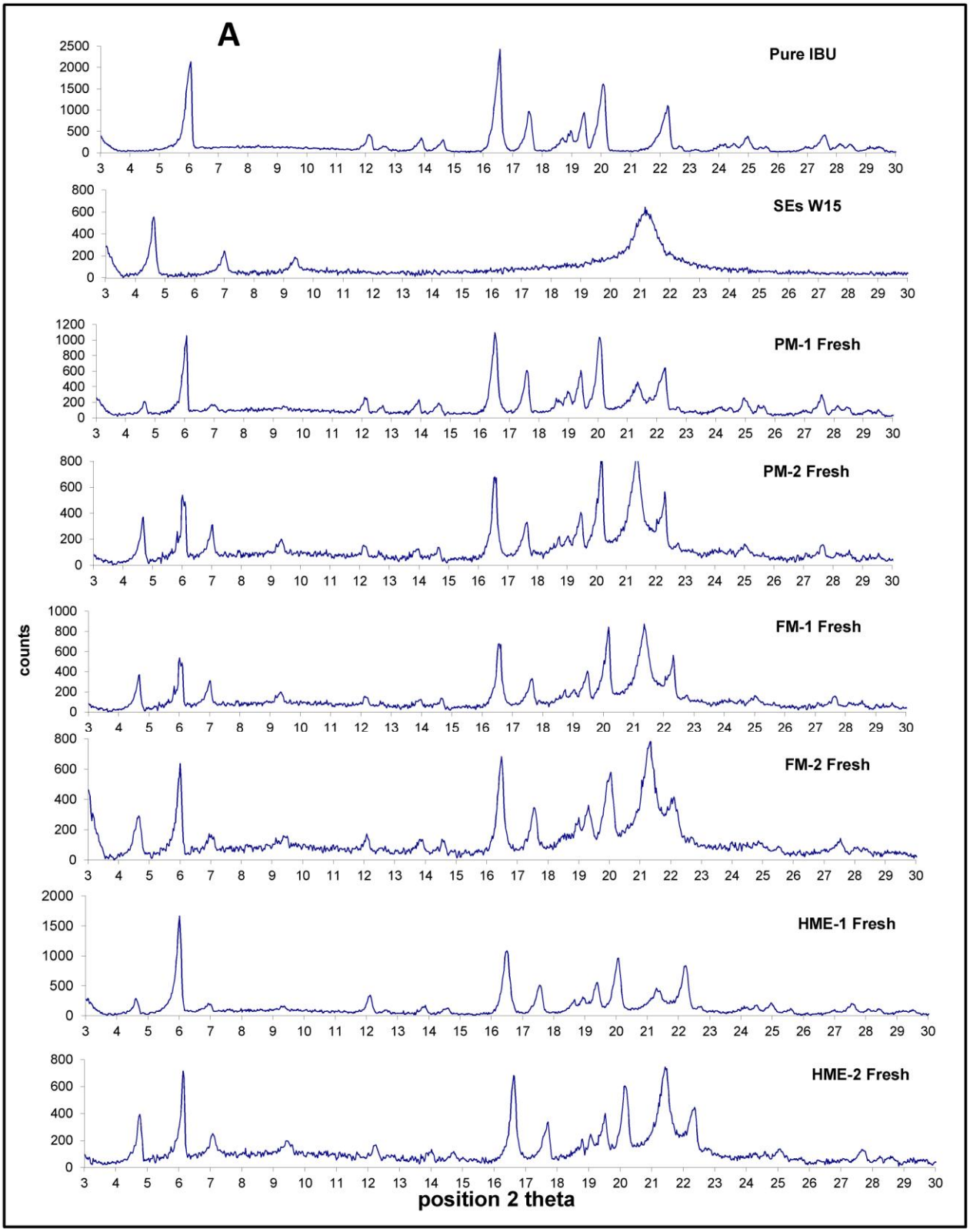

Fig. 4: XRD patterns of pure IBU, pure Sucroester®WE15, PM and SDs as a function of storage conditions (A) Fresh samples; (B) Stored samples.

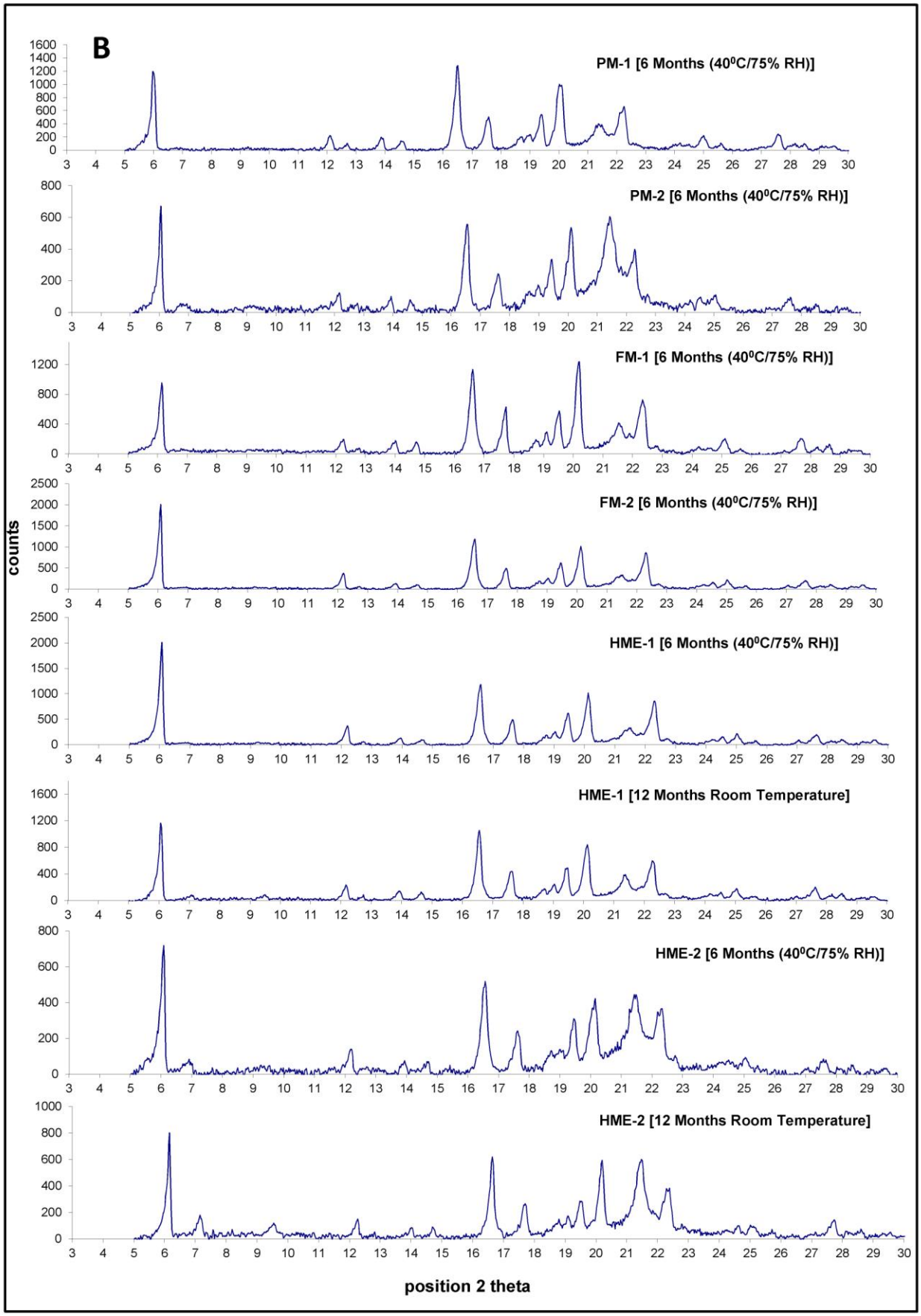

Fig. 4: XRD patterns of pure IBU, pure Sucroester®WE15, PM and SDs as a function of storage conditions (A) Fresh samples; (B) Stored samples.

The X-ray measurements showed, that the SE® WE15 displayed only one peak, at position (2θ = 21.16°). There were also some peaks at small angles in different positions, which are characteristic of the fatty acids contained in the SEs. It can be concluded, that SEs (HLB = 15) are semi-crystalline materials, with crystalline and amorphous regions (Szűts *et al.*, 2008).

The positions of the peaks of all samples and their intensities are listed in Table 3 and plotted in Figure 4. We have selected the major distinctive peaks of IBU and SE® WE15 at 16.515 (2θ) and 21.16113 (2θ), respectively, to analyze the changes occurring between fresh and stored samples (Figures 4A & B), taking into consideration that the stability of this system (IBU/SE® WE15) has not been studied before.

Although, the positions of the peaks of both IBU and SE® WE15 from fresh (Figure 4A) and stored samples (Figure 4B) were not changed considerably, however, their impact might have its meaning on the solid-state changes (crystalline-amorphous ratios and polymorphism) of both components (Table 3).

Table 3 showed that increasing the contents of either SE® WE15 (PM-2, FM-2 & HME-2) or IBU (PM-1, FM-1 & HME-1) in SDs led to simultaneous increase in their intensities for fresh and stored samples, and these XRD results coincide with the results observed in DSC thermograms for both components. For fresh samples containing 60% IBU w/w (PM-1, FM-1 & HME-1), the degree of crystallinity of IBU was decreased to about half as compared to pure drug, while it was decreased to about fifth for samples containing 30% IBU w/w (PM-2, FM-2 & HME-2).These characteristic decrease in IBU peak intensities suggested that more drug was dissolved in SE® WE15. As, the structures of the SE® WE15 continuously change after melting and solidification, probably because polymorphs are undergoing transformation.

The DSC scans and X-ray patterns of stored samples do not display the same pictures as that for the fresh ones. In consequence of the changes in structure, IBU might partially or completely assume a crystalline form, which might sustain or enhance its dissolution rate. In this regards, our results proved that as long as the enthalpy and intensity of IBU increased, which is a sign for a higher crystalline form, one would expect a decrease in its dissolution which was observed in case of PM and FM. However, the increase in these parameters, unexpectedly, led to an increase in the amount of IBU released in case of HME samples except HME-2 stored at stress conditions for 6 month.

CONCLUSION

The stability study of SE® WE15, or any other grade, was not reported till now, in spite of its importance. Without a valid, sensitive and reproducible *in vitro* release test, a misleading data could be obtained. This study highlights the use of SE® WE15, as an extrudable carrier, in HME technique, which behave extremely different than the fusion method. HME was able to sustain the IBU release rate with good stability especially with lower drug content. Moreover, IBU was an excellent candidate for preparation of SD by HME technique due to its known plastizing effect. The recorded DSC and XRD data were good tools to understand the effect of different manufacturing techniques on the system performance for both fresh and stored samples. HME-2 containing IBU in 30% w/w loading ratio was a promising formula, which add a value to this advanced technique compared to fusion method. This formula deserve to be tested *in vivo* on healthy human volunteers.

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