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Research Article

PREPARATION AND CHARACTERIZATION OF NEW ORAL LYOPHILIZATES CONTAINING A NON STEROIDAL ANTI INFLAMMATORY DRUG

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ABSTRACT

The purpose of this project was to develop diclofenac sodium oral lyophilizates and their controls. The oral lyophilizate dissolves rapidly in the mouth, needing not to be swallowed. The oral lyophilizates were prepared by dissolving the drug in a suspension of the mannitol in an aqueous solution of PVP K-30 and aspartame. The mixture was poured into the pockets of blister packs and then was lyophilized. Several formulas containing different proportions of mannitol and PVP K-30 were prepared. The time of disintegration, hardness, friability, residual humidity and dissolution profiles of the several prepared oral lyophilizates were investigated. Results showed that the oral lyophilizates which contains the higher proportion of mannitol and the lower proportion of PVP K-30 showed the best characteristics. Crystalline state evaluation of diclofenac sodium and mannitol was conducted through differential scanning calorimeter and X-ray diffraction to investigate eventual transformation during the process. The results showed that diclofenac sodium transformed partially to the amorphous state. Several cycles of lyophilization were conducted on the formulation and were compared. The results showed that the longer cycle was preferable as it produces oral lyophilizate with low residual humidity. Concerning the other characteristics, all the results were good and comparable to that of some marketed products.

Key words: Oral lyophilizate, Crystallization, Freeze drying, Residual humidity, diclofenac sodium.

INTRODUCTION

Diclofenac sodium is the sodium salt of o (2, 6 dichlorophenyl-amino) phenyl acetic acid. It is a representative non-steroidal anti-inflammatory drug (NSAID) [1]. The primary action of this drug is associated with inhibition of cyclo-oxygenase (COX) activity, which in turn prevents the production of prostaglandins, just like other NSAIDs, and is thus widely used for pain control and treatment of Rheumatic diseases. Although diclofenac sodium is one of the best tolerated NSAIDs, severe side effects including gastrointestinal (GI) ulcers and renal damage upon administration limit its use [2]. Diclofenac sodium is subject to first pass metabolism, since only 50–60% of the drug reaches the systemic circulation in the unchanged form [3]. Therefore, exploration of new drug delivery systems to avoid risks for serious GI complications associated with NSAIDs and to improve the bioavailability of these drugs would be relevant. The preparation of freeze dried tablets seems to be an adequate dosage form usually used in order to improve the overall clinical performance of drugs by reducing the incidence of non-compliance especially among pediatric and geriatric patients and those patients who have difficulty swallowing tablets and capsules [4]. It is estimated that 50% of population is affected by this problem which results in a high incidence of non-compliance and ineffective therapy [5].

The bioavailability of some drugs, especially those suffering from a high first pass metabolism, can be improved due to pre-gastric absorption and local gastro-intestinal and their side effects are also expected to be reduced by formulating such dosage forms.

Fast dissolving tablets offer the combined advantages of performance, convenience [6], rapid onset of action, patient compliance and allow administration of an oral solid dosage form in the absence of water or fluid intake [7]. When placed on the tongue, it disintegrates instantaneously, releasing the drug which dissolves or disperses in the saliva [8]. They are prepared by techniques such as tablet molding, spray drying, lyophilization, sublimation, or addition of disintegrants [9]. Because of the high porosity, oral lyophilizates (named freeze dried tablets) disintegrate in oral cavity faster than other systems.

Pharmaceutical formulators often face the challenge of finding the right combination of formulation variables that will produce a product with optimum properties. Oral lyophilizates consist of a drug enclosed in a water soluble matrix made of a hydrophilic structure-forming polymer and filler. Other ingredients of the tablets may be sweetening agents, taste-masking additives and preservatives [10].

Most of freeze dried products contain several components in addition to the drug or active ingredient. These excipients are intended to serve a specific function, normally related to stability or process, and may constitute the major fraction of the freeze dried solid. In oral lyophilizates, bulking agents are used to provide product elegance as well as to provide sufficient cake mechanical strength. The most commonly used bulking agents are mannitol, lactose, sorbitol, hydroxyethylstarch, glycine, and the most commonly compound used as binder are PVP, xanthan gum and gelatin

In this study, a new oral dosage form of diclofenac sodium has been developed using freeze-drying technique and optimized oral lyophilizates have been obtained. To the best of our knowledge, there is no published study about the preparation of oral lyophilizates containing diclofenac sodium.

MATERIALS AND METHODS

Materials

Diclofenac sodium was purchased from Sigma Aldrich (France), D mannitol and aspartame were obtained from Cooper (France), PVP K-30 was provided by Ludwigshafen (Germany). Phosphoric acid, methanol and mono basic sodium phosphate were purchased from Merck (Germany). All other reagents and chemicals were of analytical grade.

Methods

Preparation of diclofenac sodium oral lyophilizates

Various oral lyophilizates were prepared. The composition of the different formulations is presented in tables 1 and 4. A solution of PVP K-30 in water was prepared, and was stirred using a magnetic stirrer until a clear solution was obtained. Various quantities of mannitol and aspartame were added to PVP K-30 solution while stirring. The concentration of excipients used was optimized during our study to result in a strong and elegant tablet that could be easily handled. After the optimization of the oral lyophilizate's cake, an accurately weighed amount of diclofenac sodium powder (5%w/v) was dispersed in the excipient mixture. One milliliter of the resulting preparation was poured into each of the pockets of a tablet blister

pack to result in a diclofenac sodium dose of 50 mg in each oral lyophilizate. The tablet blisters were then transferred to a freeze dryer (Usifroid SMH 45, France) and the lyophilization was carried out according to the parameters that are presented in table 2. The oral lyophilizates were kept in a desiccator over particles of silica-gel.

Thermal analysis

The glass transition temperature of maximally cryo-concentrated suspension (T'_g) of the optimized formula with drug substance was measured by a differential scanning calorimeter (TA Instrument, U.S.A). A heating rate of 10°C/min was applied throughout the analysis in the temperature range of - 80°C to 30°C.

Freeze drying cryostage

The collapse temperature (T_{col}) was determined for the suspension that prepared by the optimized formula with drug substance by a freeze drying microscope (Linkam, England) equipped by a video camera and a computer to capture the collapse image.

Optimization of freeze drying process

Four cycles of freeze drying have been performed on the optimized formula using the conditions presented in table 5.

Characterization of the oral lyophilizates

Oral lyophilizates disintegration time

Disintegration times of oral lyophilizates were determined on six oral lyophilizates in distilled water using a disintegration tester (Erweka, Germany) at 20 ± 0.5°C according to European Pharmacopeia specifications. All results are presented as mean value (n = 6).

Residual humidity analysis

The oral lyophilizates were analyzed for their residual humidity content after lyophilization using a Karl Fisher titration (Metler Toledo titrator DL 38, Swiss) using methanol as a sample solvent (n=3).

Hardness test

The crushing strength of the tablets (n=3) was measured using a hardness tester (D.R. Schleuniger, Germany**)**

Dissolution studies

The dissolution profiles of optimized diclofenac sodium oral lyophilizates were determined in a dissolution tester (Erweka Dt 12 R., Germany). All tests were conducted in 500 ml of distilled water maintained at 37±0.5°C with a paddle rotation speed at 50 rpm. After specified time intervals (5, 10, 15, 20, 25 and 30 min), samples of dissolution medium were withdrawn (5ml), filtered and assayed for drug content spectrophotometrically at 276 n.m. using Shimadzu spectrophotometer (Japan) (n=3). The percentage of drug dissolved in the preparations was calculated using calibration equations.

Differential Scanning calorimeter studies on diclofenac sodium and oral lyophilizates

Samples weighing approximately 5 mg were sealed in aluminium pans and analyzed using a T.A. Instrument DSC. The samples were heated in atmosphere of nitrogen and thermograms were obtained by heating at a constant heating rate of 10°C /min in the range of 20°C to 350°C. Thermograms for diclofenac sodium and the optimized oral lyophilizate were obtained.

X-ray diffraction analysis

X-ray diffraction experiments were performed in an X-ray diffractometer (Bruker D 8 Advance, Germany), operated with Cu K α x radiation at 40 k V and 30 mA. The scans were conducted in the 20 range from 3◦ to 35◦. Diffraction patterns for diclofenac sodium, mannitol and for the optimized oral lyophilizate were obtained. Identification of the samples was carried out by comparing the diffraction pattern of the samples with library data in the powder diffraction file (diffract plus software).

Drug content in the oral lyophilizates

Quantitative determination of diclofenac sodium was performed by an HPLC system consisting of a liquid chromatograph (Shimadzu SPD 20AV, Japan). The apparatus was equipped with a U.V. detector and a computer integrating apparatus. Analyses were performed at 254 nm with a 4.6 mm - 25 cm column (Restek, U.S.A) that contains packing L7 (end –capped). The mobile phase, a mixture of 70% methanol and 30% phosphate buffer pH=2.5 (v/v), was delivered at a flow rate of 1 ml/min. Samples (20µl) were injected. The standard solution of diclofenac sodium (0.5 mg/ml) was prepared by dissolving the drug in the diluent solution consisting of methanol 70% /water 30% (v/v). The samples were prepared by dissolving an optimized diclofenac sodium oral lyophilizate in 100ml of the diluent solution. Samples preparation and analyses were performed at room temperature.

RESULTS AND DISCUSSION

Oral lyophilizate can be considered an interesting oral dosage form. The effectiveness of a piroxicam fast dissolving dosage form based on lyophilization has been reported from years [11]. The oral lyophilizates has been developed to large scale production in recent years and many are approved for marketing.

In this study, a new formula of oral lyophilizates of diclofenac sodium has been developed using excipients widely known in freeze drying. Mannitol has been used as bulking agent, PVP K-30 has also been used as binder. Aspartame has been added as sweetener, whereas the oral lyophilizates would disintegrate in the mouth and it should have a sweet taste.

Influence of the excipients on oral lyophilizates characteristics:

In the first step of the study, different formulations (formulation 1, 2 and 3) have been prepared using different percentages of mannitol and PVP, in order to formulate oral lyophilizates of suitable characteristics (Table 1). The resulting oral lyophilizates were broken for mannitol and PVP of 5% and 10% with unacceptable aspect and having low hardness corresponding respectively to 10N and 12N (Table 1). These primary formulations had fast disintegration (less than 12 seconds). However, the formulas have been excluded on basis of the incorrect appearance and the multiple broken units.

Table 1: The primary formulations and their characterizations

	1	2	3	IA	IB	IC	4P	5P	6P	8P	10P
Mannitol	5	10	20	20	40	60	5	5	5	5	5
PVP K-30	5	10	20	5	5	5	4	5	6	8	10
Aspartame	0.05	0.1	0.02	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Distilled water (ml) QSF for	100	100	100	100	100	100	100	100	100	100	100
Tablet hardness (N)	10	12	17	16	20	38	*	*	*	*	*
Disintegration time (s)	2	10	12	12	15	35	*	*	*	*	*
Visual aspect	-	-	+	+	+	+++	- -	- -	- -	- -	- -

N.B.: These formulations have been prepared without drug substance. - - Most of them crashed, - Some of them crashed, + Acceptable aspect, +++ Very good aspect, * not determined

Table 2: The parameters of lyophilization cycle

	Rate (°C/min)	Temperature (°C)	Hold for (min)	Pressure (µbar)
Freezing step	1	-40	120	-
Primary drying step	1	-20	720	100
Secondary drying step	1	25	360	50

Effect of the concentration of mannitol on oral lyophilizates charactertics

In order to improve the oral lyophilizates properties, others formulas (formulations IA, IB, IC) have been prepared using higher concentrations of mannitol (20, 40 and 60%) with a fixed concentration of PVP K-30 (5%) and aspartame (0.05%) (Table 1). Previous work has studied the role of formulation's excipients in the development of lyophilized fast disintegrating tablets and founded that Disintegration times of lyophilized fast disintegrating tablets are best within a mannitol concentration window of 20–50% [12].

It can be noticed according to table (1) that the increase of mannitol concentration (mannitol 20, 40 and 60%) resulted in increased hardness (16, 20 and 38N respectively). The same effect could be observed for the disintegration times (12, 15 and 35 sec for the prepared formulas with mannitol 20, 40 and 60 % respectively). On basis of the results in table (1), the formula IC which composed of mannitol 60%, PVP K-30 5% and aspartame 0.05% was chosen as the best formula as all its characteristics are good and within the target specifications (hardness 38N, disintegration time 35 sec and a very good aspect). It can be conclude that an increase the proportion of mannitol has a positive effect on the characteristics of the oral lyophilizates, especially for aspect and hardness.

Effect of the concentration of PVP K-30 on oral lyophilizates characteristics

In order to assess the impact of PVP K-30 on the oral lyophilizates characteristics, different formulas (formulations 4P, 5P, 6P, 8P, 10P) have been prepared containing various percentages of PVP K-30 (4, 5, 6, 8 and 10%) and fixed percentages of mannitol (5%) and aspartame (0.05%) (Table 1).

It could be noticed that the increasing of proportion of PVP K-30 didn't improve the aspect of oral lyophilizates nor the characteristics, as most of the oral lyophilizates were broken (Figure 1).

Fig. 1: Photos of crashed oral lyophilizates prepared using the formulas 4P, 6P, 8P and 10P.

Furthermore, the percentage of PVP had a negative impact on the residual humidity which doubled (from 5.23 to 10.18 %) with the increasing of PVP K-30 percentages (from 5 to 10%) as shown in table 3.

Table 3: The residual humidity in the prepared oral lyophilizates of the formulas 5P, 6P, 8P, 10P

	5P	6P	8P	10P
RH (%)	5.23	8.604	11.61	10.18

This interesting finding can be explained by the hygroscopic nature of PVP [13]. The results indicate that mannitol has an important impact on the properties (aspect and hardness) of the prepared oral lyophilizates. It is well known that mannitol has a crystalline structure after freeze drying giving the required hardness and an elegant cake [10]. For this reason, the higher concentration of mannitol (60%) was selected and several formulas (4M, 6M, 8M, 10M) have been prepared with changing the concentration of PVP K-30 (4, 6, 8 and 10 %) (Table 4).

It could be noted that the resulting oral lyophilizates have a good aspect with the absence of any break or crash, but there were excessive increasing in the hardness with the increasing of the proportion of PVP K-30 in presence of 60% mannitol (table 4).

Similar results have been founded by Corveleyn et al [14]. They studied the influence of different formulations and process parameters on the characteristics of hydrochlorothiazide oral lyophilizates and reported that the mechanical strength of the oral lyophilizates depended on xanthan gum concentration using as binder.

However, there was difficulty in getting diclofenac sodium oral lyophilizates out of blisters with the formulations containing the highest concentrations of PVP K-30 (8, 10%). Furthermore, the residual humidity has increased (1.1 to 2.38 %) confirming our previous findings. Therefore, the formulation (4M) has been selected as the best formula, which contains the largest percentage of mannitol (60%) and the lowest percentage of PVP K-30 (4%), figure (2).

Table 4: Formulations with a constant concentration of mannitol (60 %) with different concentrations of PVP K-30, and their characterizations.

	4M	6 M	8 M	10M
Mannitol (w/v%)	60	60	60	60
PVP K-30 (w/v%)	4	6	8	10
Aspartame (w/v%)	0.05	0.05	0.05	0.05
Distilled water (ml) QSF for	100	100	100	100
Tablet hardness (N)	36	60	95	82
Disintegration time (s)	27	30	27	31
RH%	1.1	1.63	1.91	2.38

N.B.: These formulations have been prepared without drug substance.

Fig. 2: Acceptable oral lyophilizates prepared by the optimized formula (4M) (mannitol 60%, PVP K-30 4% and aspartame 0.05%).

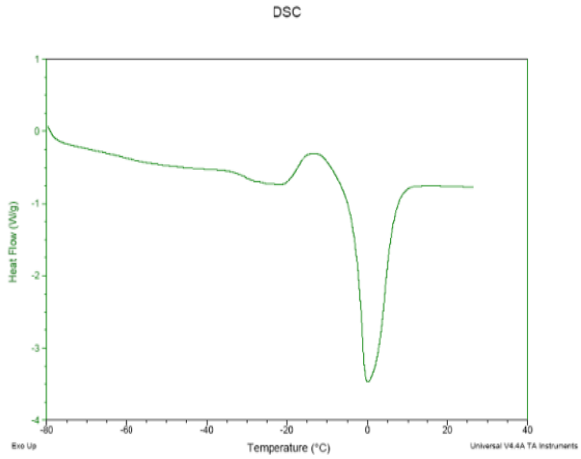

Fig. 3: DSC thermogram of a suspension containing (diclofenac sodium 5%, mannitol 60%, PVP K-30 4% and aspartame 0.05%).

Glass transition and collapse temperatures determination

The glass transition temperature of maximally cryo-concentrated suspension (T'_g) of the optimized formula (4M) with drug substance was measured by DSC and it was about - 25°C (Figure 3).

The collapse temperature (T_{col}) was determined by freeze drying microscope and it was about -15°C (Figure 4).

This difference between T'_g and T_{col} can be explained by the presence of mannitol with a crystalline structure in high concentration (60%) and this led to increased collapse temperature. The nature and percentage of amorphous excipients determine the value of T'_g, and the presence of some crystalline materials can modify the collapse temperature of formula [15]. The increased collapse temperature leads to high temperature of primary drying step and accelerate the lyophilization cycle.

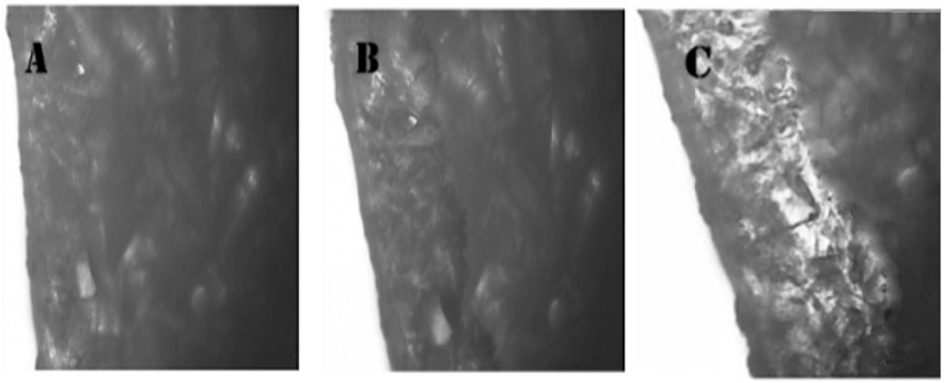

Fig. 4: Determination of collapse temperature of the formula 4M with diclofenac sodium (diclofenac sodium 5%, mannitol 60%, PVP K-30 4% and 0.05% aspartame) by freeze drying microscope. Photos at (A) -40°C , (B) -27 °C , (C) -15°C.

Impact of the drying conditions on the characteristics of the oral lyophilizate

Lyophilization is an interesting industrial drying process having many advantages. However, the main drawback is the long time of the process [16]. In order to shorten the time of freeze drying, several cycles have been applied on the optimized formula (diclofenac sodium 5%, mannitol 60%, PVP K-30 4%, aspartame 0.05%) using different times of primary drying and secondary drying (table 5). Most of the oral lyophilizates properties were within the accepted specifications in all the cycles.

The results demonstrated an increasing in the residual humidity (0.71- 1.05 and 1.17%) with the decrease of time of lyophilization steps. It could observe that the longer cycle C1 (Primary drying 12 h with secondary drying 6 h) was preferable as it produces oral lyophilizates having low residual humidity (0.71%). In the cycle C3 (primary drying 8 hours without secondary drying), the residual humidity was very high (4.8%), and even the oral lyophilizates were very wet that prevents taking them out of blisters. These results can be explained by the presence of a considerable portion of bounded water which can normally removed by secondary drying.

Table 5: Influence of lyophilization cycle parameters on disintegration time, residual humidity (RH %), hardness and percentage of drug released.

Cycle of freeze drying		*C1	*C2	*C3	*C4
Primary drying step (min)		720	360	480	480
Secondary drying step (min)		360	360	**	180
Residual humidity (%)		0.71±0.29	1.05±0.1	4.8±1.9	0.8±0.54
Disintegration time (s)		38.9±8.13	40.3±4.1	-	33.8±1.6
Tablet hardness (N)		55.3±6.80	43.7±7.1	-	51.3±4.5
Drug content (%)		103.2±0.6	102.2±1.6	-	100.8±1.3
Drug released%	10 min	84.6±0.45	85.5±0.68	-	83.5±0.93
	20 min	96.4±0.37	97±0.90	-	96.4±0.71

All values present the mean ± standard deviation.

* For all the cycles the constant parameters are presented below:

Freezing step was the same for all cycles: T = - 40°C, ramp 1°C/min, hold for 120 min

Primary drying T = - 20°C, ramp 1°C/min, Pressure = 100µbar

Secondary Drying T = 25°C, ramp 1°C/min , Pressure = 50µbar

** secondary drying was not applied

The dissolution rates of diclofenac sodium from the oral lyophilizates were rapid in all cycles (C1, C2, C4), figure (5). The fast dissolution rates of diclofenac sodium from the oral lyophilizates (drug released%: 84.6, 85.5, 83.5 in 10 min from the diclofenac sodium oral lyophilizates that prepared by the lyophilization cycles C1, C2, C4 respectively) suggest that these dosage forms might have a rapid oral absorption following disintegration in the mouth and dissolution in the saliva after oral administration. A previous research compared the pharmacokinetic of piroxicam freeze drying tablet with that of piroxicam capsule. It has been founded that the administration of piroxicam as freeze drying tablet gave a much faster absorption rate of piroxicam than the capsule formulation [17]. Furthermore, comparable results have been reported, El Samaligy M.S., et al. conducted that the percentage relative bioavailability of diclofenac sodium from buccoadhessive discs and from tablets was 147.31%, they concluded that the buccoadhessive discs of diclofenac sodium can be a good way to bypass the extensive hepatic first pass metabolism and is expected to be less irritant to gastric mucosa [18]. Similar results can be expected for diclofenac sodium from the oral lyophilizates.

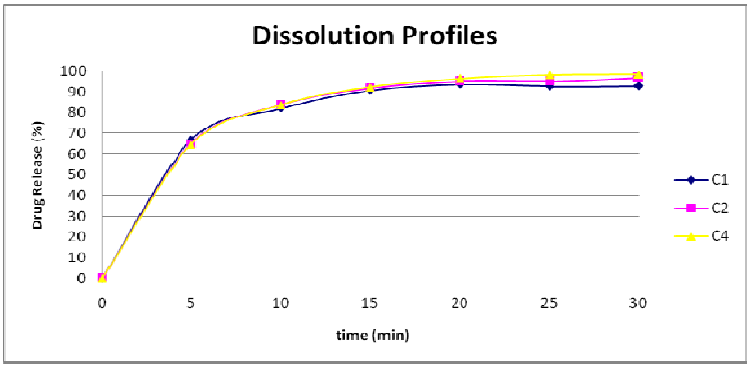

Fig. 5: Dissolution profiles of oral lyophilizates prepared by the optimized formula 4M with diclofenac sodium (diclofenac sodium 5%, mannitol 60%, PVP K-30 4% and aspartame 0.05%) using lyophilization cycles C1, C2 and C4.

Studying the crystalline state of diclofenac sodium before and after freeze drying by DSC and X-ray diffraction

The X-ray diffraction pattern of the pure drug exhibits its characteristic diffraction peaks at various diffraction angles, indicating the presence of crystalline structure. The diffraction study of optimized diclofenac oral lyophilizate showed absence of major drug diffraction peaks indicating that mostly an amorphous form existed in the oral lyophilizate, figure (6).

Furthermore, the same characteristic peaks of mannitol were observed on the X-ray diffraction patterns of both the pure β mannitol sample and oral lyophilizate, indicating the preservation of the same crystalline state of β mannitol after freeze drying.

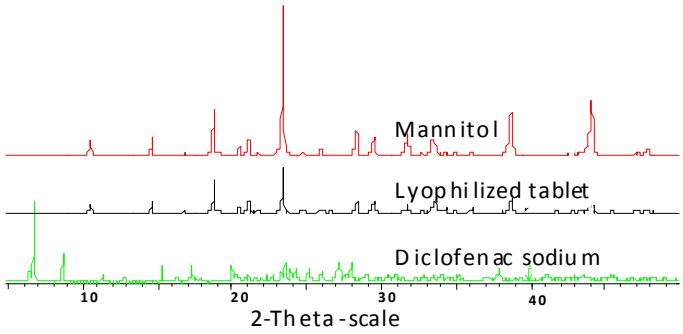

Fig. 6: X-ray diffraction analysis of mannitol, diclofenac sodium and oral lyophilizate prepared using the optimized formula (4M) with diclofenac sodium (diclofenac sodium 5%, mannitol 60%, PVP K-30 4% and aspartame 0.05%) using cycle C1.

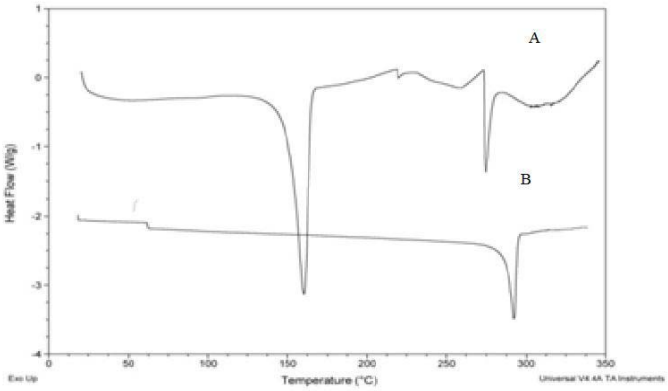

Fig. 7: DSC thermograms of an oral lyophilizate prepared by the optimized formula 4M with diclofenac sodium (diclofenac sodium 5%, mannitol 60%, PVP K-30 4% and aspartame 0.05%) using cycle C1(A), and diclofenac sodium (B).

To confirm the results of X-ray diffraction study, DSC analysis were performed on diclofenac sodium powder and its oral lyophilizates. The DSC thermogram of diclofenac sodium powder showed a sharp endothermic peak at about 290°C, corresponding to its melting point. However, DSC thermogram of diclofenac sodium oral lyophilizate showed a sharp endothermic peak at about 275°C, corresponding to the melting point of diclofenac sodium .figure (7).
It could be conclude from the results of DSC and X-ray diffraction that diclofenac sodium in the oral lyophilizates is partially crystallized. This partially crystallized diclofenac sodium was not detected by X-ray diffraction as the sensitivity of the test was less than that of DSC. Partially crystallized diclofenac sodium may have an accelerated dissolution rate in comparison with the crystalline form as observed in previous study on ketoprofen oral lyophilizates (6). In this study, there was a transformation of the crystalline state of ketoprofen to an amorphous state and this state had enhancement solubility and a rapid dissolution rate of ketoprofen from oral lyophilizate.

CONCLUSION

In this work diclofenac sodium oral lyophilizates could be prepared successfully by freeze drying. The prepared oral lyophilizates have fast dissolution rate, fast disintegration and suitable mechanical strength. The present study shows that the amount of mannitol and PVP K-30 significantly affect the aspect, disintegration time, hardness, residual humidity of the oral lyophilizates. The existence of mannitol in crystalline state with high percentage in the formulation could give the suitable mechanical strength and the good aspect of the oral lyophilizates. Furthermore, the high concentration of mannitol could increase the collapse temperature of the formulation protecting the oral lyophilizate from the collapse during the lyophilization process and accelerates this procedure.

Further studies will be carried out in order to assess the stability of these new dosage forms, to demonstrate the reducing of the gastro-intestinal side effects and to evaluate its bioavailability.

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