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Preparation and Evaluation of Directly Compressible Tablets of Ibuprofen Crystals

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Crystallization; Mechanical strength; Pharmacotechnical parameters; Direct compression technique; Dissolution.

ABSTRACT: The goal of present study was to prepare the directly compressible tablets of Ibuprofen crystals prepared by crystallization technique using saccharin sodium as an excipient. The prepared tablets were evaluated for the improvement in drug release of Ibuprofen as compared to the pure drug. The crystal formation of Ibuprofen lead to improve the compressibility and mechanical strength of the drug which can be easily converted to directly compressible tablets. The *In-vitro* dissolution profile demonstrates 3.96 fold increment in the drug release rate from tablets of Ibuprofen crystals compared to the pure drug after one hour. The characterization was done by Powder X-Ray Diffractometry (pXRD), and Headspace Gas Chromatography (HSGC) Study of Ibuprofen treated crystals illustrates the improvement in manufacturability and pharmacotechnical parameters of the drug.

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INTRODUCTION

Ibuprofen is a potent non-steroidal anti-inflammatory drug (NSAID) in inflammation, pain, fever, and swelling. It has antipyretic action by acting on the hypothalamus leading to an increased peripheral blood flow, vasodilation, and subsequent heat dissipation. Ibuprofen is of BCS Class II drug which has poor aqueous solubility [1-3] with high permeability. According to the classification of powder rheology, Ibuprofen is classified as a powder with poor flow property and compressibility [2-4] and hence it is not directly converted into tablet dosage form by direct compression technique.
Ibuprofen crystals can showed improvement in mechanical strength, compressibility and tensile strength which lead to formulate directly compressible tablets of Ibuprofen crystals.

Directly compressible tablets of pure drug, its control batch, and Ibuprofen loaded crystals

Improvement in the mechanical and processing parameters like flowability, packability, compactibility, and compressibility of samples under investigation enables to employ direct compression process of Ibuprofen crystals prepared by crystallization technique [5]. Hence tablets containing the pure drug, its control batch and an equivalent amount of Ibuprofen containing treated crystals are prepared by direct compression process by using different formulation excipients. Samples used for tableting should have a similar size range of particles. The weighed quantity of ingredient for each tablet (containing an equivalent amount of API) is introduced into the die manually and compressed into the tablet form.

Dissolution Study

***In-Vitro* drug release study of directly compressible tablets of pure drug, its control batch, and Ibuprofen loaded crystals**

Directly compressible tablet dosage form of Ibuprofen loaded crystals can be done without addition of any amount of directly compressible diluent during the tablet formulation while such type of directly compressible diluent is required to

be added for the preparation of directly compressible tablet dosage form of pure drug and its control batch which clearly implies that there is an improvement in the flowability, packability, compactibility, and compressibility of API loaded crystals which enable to form directly compressible tablet dosage form.

In-vitro drug release study of directly compressible tablets of pure drug, control batch and Ibuprofen loaded crystals is carried out and compared to determine the improvement, if any, in the amount of drug released from the tablet dosage form of treated crystals compared to the compressed tablets of pure drug and its control batch after scheduled time intervals which furnish an idea about the effect of compression on the samples under investigation from their dissolution behavior.

Dissolution parameter study of directly compressible tablets of Ibuprofen loaded crystals

In-vitro drug release study of Ibuprofen loaded crystals in powder form is carried out to determine the amount of drug released after 5, 10, and 60 minutes in order to evaluate the dissolution percent and dissolution efficiency respectively and compared with the *in-vitro* drug release study of pure drug, and control batch at the same time interval which enable to find the improvement in the dissolution rate, dissolution percent and dissolution efficiency of the treated crystals compared to the pure drug and its control batch.

Dissolution Parameters

The dissolution data were analyzed by model independent parameters calculated at different time intervals, such as dissolution percent (DP), dissolution efficiency (%DE) and time to release 50% of the drug ($t_{50\%}$). DP at a different time interval and $t_{50\%}$ can be obtained from percent dissolution Vs time profile/data [6].

Dissolution efficiency is a measure of the determination of *in-vitro* drug release data. Dissolution efficiency is defined as the area under the curve (AUC) up to a certain time 't' determined as the percentage of the area of rectangle described by 100% drug release in the same time [7].

$$\%DE = \int_0^t \frac{y \cdot dt}{y_{100}\, t} \times 100 \quad \text{.....[1.1]}$$

Statistical analysis of the dissolution profiles of directly compressible tablets of Ibuprofen loaded crystals [8]

Model independent mathematical approach proposed by Moore and Flanner, 1996 [9] for calculating a similarity factor f_2 was used for comparison between dissolution profiles of different samples.

The similarity factor f_2 is assessed by determining the similarity in the percentage drug released between two dissolution profiles and is evaluated by the following equation:

$$f_2 = 50 \times \log\left[\left(1 + \left(\frac{1}{n}\right)\sum_{t=1}^{n} w_t (R_t - T_t)^2\right)^{-0.5} \times 100\right] \quad \text{.....[1.2]}$$

Where n is the number of withdrawal points, R_t is the percentage drug released of the reference sample at the time point t and T is the percentage drug released of the test sample at the time point t. Similarity factor (f_2) value 100% shows the test and reference sample profiles are identical. Therefore, values between 50 and 100 indicate the dissolution profiles are identical while values less than 50 indicate an increase in dissimilarity between drug release profiles.

MDT reflects the time for the drug to dissolve and is the first statistical moment for the cumulative dissolution process that provides an accurate drug release rate. It is an accurate expression of drug release rate. A higher MDT value indicates greater drug retarding ability.

The difference in drug release rate of pure drug and prepared formulations can be evaluated by putting the drug release data into the following equation.

$$MDT_{in\text{-}vitro} = \frac{\sum_{i=1}^{n} t_{mid}\ \Delta M}{\sum_{i=1}^{n} \Delta M} \quad \text{.....[1.3]}$$

Here, i is the number of samples, n is number of drug release times, t and t_{mid} is time at the midpoint between the time t_i and t_{i-1}, and ΔM is the amount of drug released (mcg) between the time t_i and t_{i-1}. MDT represents the time required for the drug to release which expresses an accurate drug release rate at the specific time of dissolution. It also represents the first statistical moment for the cumulative drug release process. Higher the value of MDT represents the greater drug retarding ability.

Characterization parameters of Ibuprofen loaded crystals

Powder X-Ray Diffractometry (pXRD) Study

The pXRD study is performed to determine the intensities of pure drug, control batch, excipient, physical mixture of Ibuprofen and excipient, and Ibuprofen loaded crystal formulation at different 2θ values to characterize the crystalline behavior of respective samples and compare them to analyze the change in crystallinity in the final treated crystal formulation. The crystalline or amorphous form of the samples under investigation can be carried out by pXRD study.

Headspace Gas Chromatography (HSGC) Study [10, 11]

Analysis of residual solvents (Volatile Organic Compounds or VOCs) as well as the volatile terpene constituents of the sample can be best achieved using GC with Headspace (HSGC) sampling. HSGC technique heats the sample in a sealed vial such that all of the volatile components are vaporized into the vial headspace, above the sample, from which the sample is drawn for analysis. This results in the analysis of only the volatile components of the sample,

minimizing the effects due to other complex matrix components.

Headspace gas analysis provides itself to automation for quality control or sample screening. This is made possible by modern instrumentation through which highly reproducible samples can be prepared in an efficient and accurate manner. Complex sample matrices, which may be difficult to analyze directly or would otherwise require sample extraction or preparation, are ideal candidates for headspace since they can be placed directly in a vial with little or no preparation which saves both time and money.

MATERIALS AND METHODS

Materials

Ibuprofen (IBU) was gifted by Marksans Pharma Limited, Goa. Potassium dihydrogen phosphate (KH_2PO_4) and Disodium hydrogen orthophsophate dihydrate (Na_2HPO_4) were purchased from SDFCL, Mumbai. Sodium Hydroxide (NaOH) and Sodium acetate trihydrate were procured from Rankem, New Delhi, India. Saccharin sodium dihydrate (SAC-Na) was gifted by Pure Chem. Pvt. Ltd., Ankleshwar, Gujarat. All other solvents, excipients and chemicals used were of analytical and HPLC grade (Merck Pvt. Ltd., Mumbai, India).

Ibuprofen crystals prepared by solvent evaporation method [5]

Ibuprofen loaded crystals were prepared by conventional solvent evaporation technique in the molar proportion of 1M:2M using Saccharin sodium dihydrate as an excipient which form hydrogen bonding with Ibuprofen. Crystallization of Ibuprofen lead to improve mechanical strength, physicochemical, and pharmacotechnical parameters with improvement in *in-vitro* dissolution rate. A batch of control crystals was also formulated by excluding excipient and keeping all other experimental parameters same.

Procedure for the preparation of directly compressible tablets of pure drug, its control batch and Ibuprofen loaded crystals

Tablets of pure drug, its control batch and Ibuprofen loaded crystals were prepared by direct compression method. All the ingredients were separately weighed and sifted using 40# mesh. API and Mannitol were passed through a 30# mesh. Tablets containing an equivalent amount of API was mixed gently in glass mortar using a pestle with different formulation excipients of directly compressible type and finally, the blend was lubricated with Magnesium stearate and Talc. Before compression, the surfaces of punches were lubricated with 2% w/v magnesium stearate in acetone. The powder blend was directly compressed into tablets as per the formulation for the preparation of directly compressible tablets for all batches.

Directly compressible tablets of Ibuprofen loaded crystals, containing an equivalent amount of Ibuprofen, were prepared using 12 mm round concave faced punch of an eight-station rotary tablet machine to obtain tablets of required hardness and thickness. Compression force was kept constant for all formulations. The tablets were ejected and stored in screw-capped bottles for 24 h to determine possible hardening and elastic recovery. The tablets were taken for in-process and finished product evaluation tests carried out immediate after ejection and also after relaxation period of 24 h. The tablets were studied in three replicates. The same technique was applied for the preparation of tablets of the pure drug as well as of control batch of Ibuprofen.

Evaluation Parameters of Directly Compressible Tablets of Pure Drug, its Control Batch and Ibuprofen Loaded Crystals

Uniformity of Weight

The USP XXX weight variation test was carried out by weighing 20 tablets individually of each batch separately and calculating the average weight and comparing the individual tablet weight to average weight.

Thickness

The thickness was measured by digital vernier calipers (Digimatics). The thickness of tablets for each batch was measured in mm.

Hardness Test

Hardness was measured by Monsanto hardness tester. From each batch, ten tablets were tested. The force required to break the tablet is recorded. The hardness of tablets for each batch was measured in kg/cm^2.

Friability Test

Twenty tablets were weighed and placed in the Roche friabilator (Electrolab – EF 2, USP). The apparatus was rotated at 25 RPM for 4 minutes then the tablets were dedusted and weighed again. The percentage friability was measured for each batch.

In-Vitro drug release study of directly compressible tablets of Ibuprofen pure drug, its control batch and Ibuprofen loaded crystals (USP XXX)

In-vitro dissolution measurements were carried out in USP dissolution test apparatus (Electrolab Dissolution Tester TDT-06P, USP). The dissolution profile of directly compressible tablets of Ibuprofen pure drug, control batch and treated crystals were studied in 900mL of Phosphate buffer pH 7.2. The directly compressible tablets were placed in a dissolution flask containing 900 mL of the dissolution medium, thermostated at 37 ± 0.5 °C, with a paddle (USP Type II) with a rotation speed of 50 RPM for one hour.

After each time interval i.e., 5, 10, 15, 20, 30, 40, 50 and 60 minutes, the samples (5 mL) were withdrawn and replaced immediately with fresh dissolution medium. The samples were filtered and one milliliter of the filtrate was diluted with respective buffer solution till the absorbance was measured in the range of 0.2 - 0.8. All the samples were assayed similarly by measuring the absorbance spectrophotometrically at 222 nm wavelength for the dissolved drug. The dissolution experiments were conducted in triplicate and the mean of the

absorbances was calculated. After one hour of dissolution, the amount (%) of the Ibuprofen drug dissolved was calculated graphically and used as comparison parameter in dissolution studies.

Characterization parameters

The prepared Ibuprofen loaded crystals and control batch were characterized by comparing them with the pure drug for the following attributes:-

Powder x-ray diffractometry (pXRD) study

The crystalline state of pure drug, Saccharin sodium excipient, physical mixture of drug and excipient, control batch and Ibuprofen loaded crystals was confirmed with powder X-ray diffractometry (pXRD) using CuKα radiation. The instrument was operated in 2θ scale with an angular range of 10° to 80.0064° at a scan rate of 0.0499°. The intensity of samples was compared at different diffraction patterns of 2θ values to characterize the crystalline behavior of the respective samples using a wide angle X-ray diffractometer.

Headspace gas chromatography study (HSGC)

Preparation of blank solution

Blank solution was prepared by transferring 5 ml of diluent [water:DMF (50:50)] into a headspace vial. The Polytetrafluoroethylene (PTFE) butyl septa was closed and sealed with aluminium crimp cap.

Preparation of standard solutions

Standard solution of Ethanol (1000 ppm) was prepared by accurately measuring ethanol (5 µL) and diluted it up to 5 mL with diluent [Water:DMF (50:50)] while second standard solution of Ethanol (2000 ppm) was prepared by accurately measuring ethanol (10 µL) and diluted it up to 5 mL with diluent [Water:DMF (50:50)] for quantitative determination of ethanol in standard solution. This solution was transferred into a headspace vial. The PTFE butyl septa was closed and sealed with aluminium crimp cap.

Preparation of sample solution

Sample solution equivalent to 502 mg of Ibuprofen crystals, was used after dilution up to 5 mL with diluent [Water:DMF (50:50)] and then transferred accurately into headspace vial. The PTFE butyl septa was closed and sealed with aluminium crimp cap.

Procedure for gas chromatography

As per the above cited procedure, 1 vial for a blank solution, 2 vials for standard solutions (1000 ppm and 2000 ppm), and 1 vial for sample solution, were prepared. These sealed vials were placed in the sample magazine and headspace analyzer was started to run. Peaks were measured and chromatograms were recorded. The concentration of ethanol (volatile organic component) in the sample can be calculated as [12-14]:

$$\text{Amount of organic solvent (ppm)} = \frac{A}{C} \times \frac{W_s}{W_t} \times 1{,}000{,}000$$

…….....[2.1]

Here, A and C are the average peak area responses of solvent in the sample and standard preparation, respectively. W_s and W_t are weight in mg of standard and test sample, respectively.

Method parameters of HSGC for Ibuprofen loaded crystals

Instrument: Perkin Elmer Clarus 500 (GC-FID)
Column: ZB-5 (30m*0.25mm*0.25µm)
Oven program

- Initial Temp: 40°C Hold 2.00 min
- Ramp: 10 °C /min to 150°C holds for 2.00 min
- Total run time: 15.00 min
- Split ratio: 20:1
- Detector: 200°C
- Injector temperature: 150°C
- Carrier Gas: N2
- Pressure : 10 psi

RESULTS AND DISCUSSION

Formulation of directly compressible tablets of Ibuprofen pure drug, its control batch and Ibuprofen loaded crystals [15, 16]

Formulation for the preparation of directly compressible tablets of Ibuprofen pure drug, control batch and treated crystals is shown in the **Table 1**.

Preparation of directly compressible tablets of Ibuprofen pure drug, its control batch and Ibuprofen loaded crystals

By comparing the formulation of the preparation of directly compressible tablet of Ibuprofen pure drug, its control batch and Ibuprofen loaded crystals, it was found that 12% of Microcrystalline Cellulose (MCC), a directly compressible diluent, was required to be added for the preparation of directly compressible tablets of Ibuprofen pure drug and its control batch while it was not added for the preparation of directly compressible tablets of Ibuprofen loaded crystals which clearly stated that there was a considerable improvement in the properties of drug for making directly compressible form.

Therefore, it was revealed that the packability, compactibility, and compressibility of Ibuprofen loaded crystals were better than the Ibuprofen pure drug and its control batch as well. Hence Ibuprofen loaded crystals could be easily converted into conventional and most acceptable directly compressible tablet dosage form as per the formulation is shown in the above **Table 1**. As per the IP 2010, Vol.III, daily intake of Saccharin sodium should not be more than 5 mg/kg of body weight. In the above formulation, Table 1, of directly compressible tablet dosage form of Ibuprofen loaded crystals contain 200 mg Ibuprofen and 4.77 mg Saccharin sodium excipient and hence the amount of Saccharin sodium (SAC-Na) was not beyond the acceptable limit.

Evaluation parameters of directly compressible tablets

Evaluation of directly compressible prepared tablets of Ibuprofen pure drug, its control batch and Ibuprofen loaded crystals were performed and the results obtained are reported in the **Table 2**.

Table 1. Formulation for the preparation of directly compressible tablets of Ibuprofen pure drug, control batch and Ibuprofen loaded crystals

Sr. No.	Ingredients	Amount per tablet		
		Ibuprofen pure drug (mg)	Control batch (mg)	Treated Crystals of Ibuprofen (mg)
1	Ibuprofen	200	200	200
	Saccharin Sodium (SAC-Na)	---	---	4.77
				204.77 (equivalent to 200 mg Ibuprofen)
2	Microcrystalline cellulose (MCC)	60	60	---
3	Crospovidone	25	25	25
4	Polyvinyl Pyrrolidone (PVP K30)	15	15	15
5	Aspartame	10	10	10
6	Magnesium Stearate	10	10	10
7	Talc	5	5	5
8	Mannitol	175	175	230.23
	TOTAL	**500**	**500**	**500**

Table 2. Comparison of general parameters of directly compressible tablets of pure Ibuprofen, control batch and Ibuprofen loaded crystals

Sr. No.	Parameters	Pure Ibuprofen [IBU]	CONTROL [C]	IBU:SAC-Na (1M:2M)
1	Weight Variation (mg) ± SD*	506.43 ± 1.38	505.47 ± 1.45	504.58 ± 1.58
2	Thickness (mm) ± SD*	3.7 ± 0.07	3.5 ± 0.07	3.2 ± 0.06
3	Hardness (Kg/cm^2) ± SD*	5.3 ± 0.16	5.3 ± 0.26	5.5 ± 0.21
4	Friability (% loss) ± SD*	0.22 ± 0.06	0.20 ± 0.09	0.18 ± 0.07
	* Results are mean ± SD of three observations			

Table 3. In-Vitro dissolution profile of directly compressible tablets of Ibuprofen pure drug, control batch and Ibuprofen loaded crystals

Time (Minutes)	Cumulative % Drug Released		
	IBU ± SD*	CONTROL [C] ± SD*	IBU:SAC-Na (1M:2M) [B] ± SD*
0	0	0	0
5	1.28 ± 6.12	1.87 ± 5.23	12.34 ± 6.54
10	1.82 ± 4.88	3.70 ± 5.84	20.97 ± 5.33
15	2.34 ± 6.90	9.88 ± 6.58	29.79 ± 6.34

20	3.78 ± 5.36	14.37 ± 5.97	36.66 ± 5.67
30	10.33 ± 6.74	19.39 ± 4.08	47.90 ± 4.67
40	16.34 ± 5.88	23.08 ± 5.80	69.73 ± 5.39
50	20.74 ± 5.93	30.66 ± 4.77	84.67 ± 6.55
60	23.96 ± 5.75	34.71 ± 6.85	94.88 ± 4.59
* Results are mean ± SD of three observations			

Table 4. Dissolution parameters for directly compressible tablets of Ibuprofen loaded crystals

Sample	% DE_{10}	DP_{5min}, %	t_{50}, min
	Tablet formulation	Tablet formulation	Tablet formulation
Ibuprofen pure drug	1.821	1.282	---
Control batch	3.703	1.873	---
Treated crystals	20.97	12.337	31

Table 5. Value of f2 and MDT for directly compressible tablets of Ibuprofen crystals

Sample	f_2	MDT, min
	Tablet formulation	Tablet formulation
Ibuprofen pure drug	---	39.847
Control batch	39.795	23.508
Treated crystals	22.94	14.024

Table 6. Data Analysis of Ibuprofen Crystals by HSGC

Sr. No.	Name of Sample mixed with Diluent	Peak of EtOH at	Any other peak observed	Observation of EtOH peak	Inference
1	Blank (Only Diluent without EtOH)	---	Peak of Diluent is observed at 6.84	EtOH peak not observed	EtOH is absent in Blank sample
2	Standard1 (EtOH 1000)	3.05	Peak of Diluent is observed at 6.85	EtOH peak observed	EtOH is present in Standard1 sample
3	Standard2 (EtOH 2000)	3.04	Peak of Diluent is observed at 6.84	EtOH peak observed	EtOH is present in Standard2 sample
4	Ibuprofen crystals (1M:2M)	---	Peak of Diluent is observed at 6.84	EtOH peak not observed	EtOH is absent in the Ibuprofen crystals

From the results shown in the **Table 2**, it was found that all the parameters of tablets were good in acceptance criteria.

***In-Vitro* drug release study of directly compressible tablets of Ibuprofen loaded crystals**

Drug release profiles of directly compressible tablets of Ibuprofen pure drug, its control batch and Ibuprofen loaded crystals were studied and the results obtained are illustrated in the **Table 3**.

In-vitro drug release data (**Table 3**) and profile (**Figure 1**) depicted that there was a significant difference in the CPR of directly compressible tablets of Ibuprofen pure drug, its control batch and treated crystals. The CPR of the directly compressible tablets of Ibuprofen loaded crystals after one hour was maximum 94.88% with 3.96 fold while control batch

tablets showed 34.71% with 1.45 fold drug release compared to Ibuprofen pure drug shown 23.96% drug release within one hour.

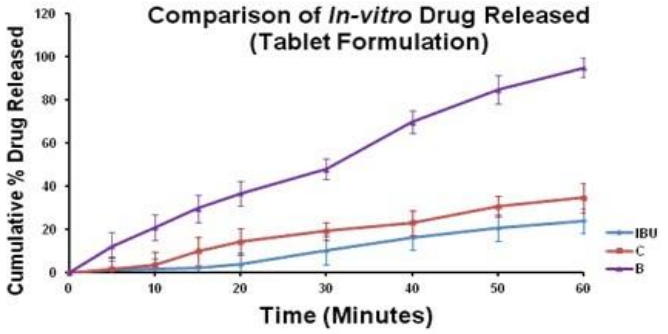

Figure 1. Comparison of In-Vitro Drug Release Profile in Phosphate Buffer pH 7.2 at 37 °C ± 0.5 °C. Directly Compressible Tablets of Ibuprofen Pure Drug (IBU), Control Batch (C) and Ibuprofen Loaded Crystals [1M:2M] (B)

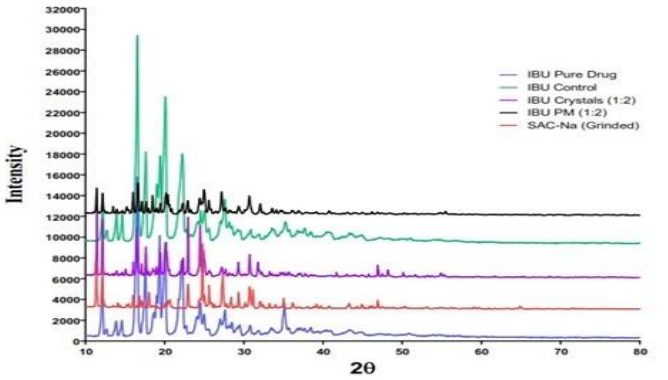

Figure 2. Comparison of pXRD pattern of Ibuprofen, Saccharin sodium, Control batch, Physical mixture and Ibuprofen loaded crystals

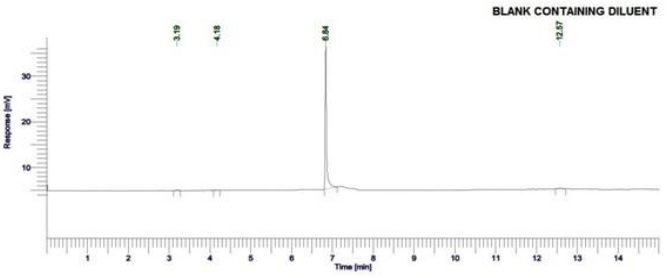

Figure 3. Chromatogram of Blank Sample Containing Diluent, Water:DMF (50:50), by HSGC

The results clearly revealed that the physical properties of Ibuprofen pure drug were improved by the crystal engineering approach as there was a remarkable increase in the aqueous solubility of directly compressible tablet dosage form which was further in a correlation with the drastic increase in dissolution rate of the drug. It was also depicted that there was an improvement in the mechanical properties and compressibility of Ibuprofen loaded crystals compared to its pure drug.

Dissolution parameter study of directly compressible tablets of Ibuprofen loaded crystals

Dissolution parameters such as dissolution percent (DP_{5min}), dissolution efficiency (% DE_{10}) and time to release 50% of the drug ($t_{50\%}$) were determined in the medium of Phosphate buffer pH 7.2.

The above results showed (**Table 4**) that there was a remarkable difference in the dissolution parameters of Ibuprofen pure drug, control batch and Ibuprofen loaded crystals because Ibuprofen is practically insoluble in water while there was a noticeable improvement in the dissolution of drug from crystals probably due to the formation of hydrogen bonding between the drug and excipient. Hence, there was a significant difference in the dissolution parameters of Ibuprofen loaded crystals compared to the pure drug as well as control batch.

Statistical analysis of the dissolution profiles of directly compressible tablets of Ibuprofen loaded crystals

Similarity factor (f_2) and mean dissolution time (MDT) were determined for the comparison of dissolution profiles of Ibuprofen loaded crystals with Ibuprofen pure drug and its control batch studies at Phosphate buffer pH 7.2.

From the results of **Table 5**, it was seen that there was no any similarity ($f_2 < 50$) by comparing the dissolution profiles of Ibuprofen pure drug with Ibuprofen loaded crystals and control batch. Ibuprofen pure drug is practically insoluble in water while in case of control batch, an improvement in the dissolution was seen. In case of Ibuprofen loaded crystals, there was a drastic improvement in the dissolution of the drug. Hence, there was no any similarity by comparing the dissolution profile of Ibuprofen pure drug with its control batch as well as Ibuprofen loaded crystals.

MDT value was less for Ibuprofen loaded crystals and control batch compared to Ibuprofen pure drug because of the improvement in the aqueous solubility as well as *in-vitro* drug release study for treated crystals as well as its directly compressible tablet dosage form [8].

Characterization parameters

Powder X-Ray Diffractometry (pXRD) study

Powder X-ray diffraction pattern of Ibuprofen pure drug, Control batch, Saccharin sodium excipient, Physical mixture of Ibuprofen and Saccharin sodium in a molar proportion of 1:2 and Ibuprofen loaded crystal formulation was recorded as illustrated in the following diffraction patterns (**Figure 2**).

In case of Ibuprofen pure drug, diffractogram revealed high intensity reflections with characteristic sharp peaks at 12.1441°, 16.5319°, 17.579°, 19.3741°, 20.0721°, 22.1165°, 24.5099°, 27.6512° and 35.1305° (2θ).

Recrystallized Ibuprofen (Control batch) from ethanol (95%) showed different pXRD pattern compared to pure drug. pXRD spectra of recrystallized Ibuprofen showed a highest intense

peak at 16.5818°, which was a high intense peak with the pure drug. Moreover, the other higher intensity peaks were observed at 17.6289°, 20.0721° and 22.2162° (2θ). Theta region between 10° to 40° was almost same as a pure drug with the appearance of intense peaks at 16.5818°, 20.0721°, 17.6289°, 22.2162°, 12.1939°, 24.5597°, 25.0085° and 27.6013° (2θ). It might be an evidence of retention of crystalline nature of the drug.

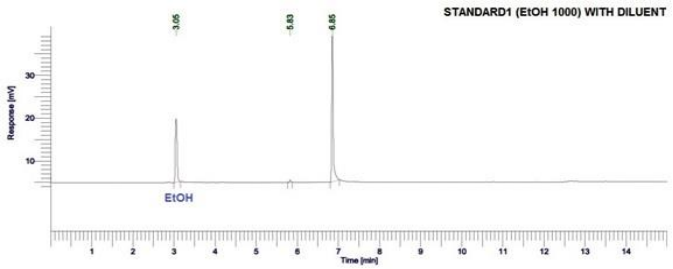

Figure 4. Chromatogram of Standard1 by HSGC

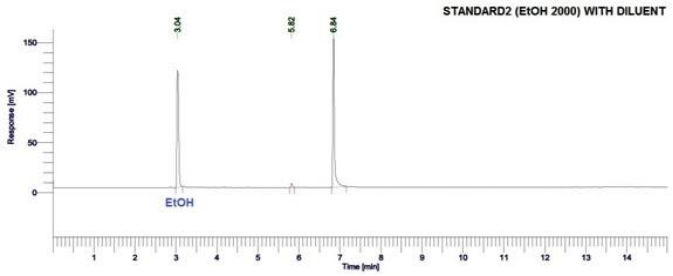

Figure 5. Chromatogram of Standard2 by HSGC

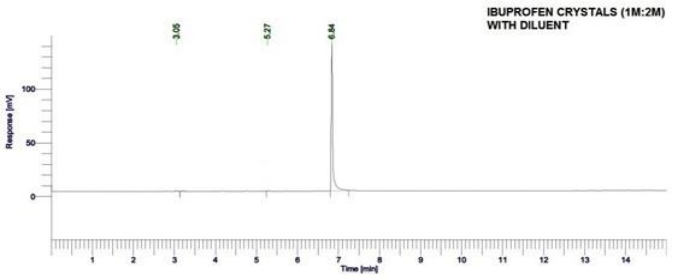

Figure 6. Chromatogram of Ibuprofen Crystals by HSGC

Saccharin Sodium diffractogram exhibited a distinct pattern with diffraction peaks at 11.3961°, 12.1441°, 16.0333°, 16.8311°, 18.0278°, 20.6705°, 22.9641°, 24.7592°, 25.6068°, 27.352°, 28.3991°, 29.3465°, 30.7426°, 31.1415°, 35.0308°, 36.1776°, 43.3079° and 46.898° (2θ). The diffractogram of physical mixture of IBU:SAC-Na in 1M:2M proportion showed the characteristic peaks of the pure components at nearby identical angles, which proved that no interactions took place during mixing.

Crystals of Ibuprofen-Saccharin Sodium from ethanol (95%) showed different pXRD pattern compared to its pure components. pXRD spectra of treated crystals showed a highest intense peak at 11.446°, which was a great shift in principal peaks compared to Ibuprofen pure drug as well as Saccharin sodium. Theta region between 10° to 60° of Ibuprofen loaded crystals was different compared to Ibuprofen pure drug and Saccharin sodium with the appearance of new intense peaks at 11.446º, 20.1719º, 24.46º, 24.9088º, 29.2966º, 31.7897º and 48.1944º (2θ).

Headspace Gas Chromatography (HSGC) study

For determining the presence and amount of Ethanol (EtOH), if any, in the treated crystals, the analysis was done by HSGC (Headspace Gas Chromatography). The following **Figures 3** to **6** and **Table 6** clearly suggested that there were no any Ethanol solvent present in the Ibuprofen loaded crystals.

CONCLUSION

Ibuprofen is a BCS Class II drug having poor flowability and manufacturability. In the present research, directly compressible tablets of Ibuprofen crystals were prepared by crystallization technique which suggested improvement in the compressibility, mechanical properties, and tensile strength of Ibuprofen crystals. For the preparation of tablets of treated crystals, there was not required to add any amount of directly compressible diluent while the same was required to be added in the preparation of tablets of control batch and pure drug to enable it into directly compressible form. The tablets of crystals shown greater improvement in the dissolution profile compared to the pure drug. The characterization parameters also suggested improvement in the physicochemical, mechanical and pharmacotechnical parameters compared to the pure drug.

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AUTHOR CONTRIBUTION

All the authors have equally contributed in conceiving this research and designing of experiments; all authors have participated in the design and interpretation of the data; experiments and analysis; writing the paper and participated in the revisions of it. All authors read and approved the final manuscript.

ETHICS STATEMENT

The authors have taken all the necessary permissions as per ethical guidelines wherever applicable. The authors will be responsible for all the technical content mentioned in the manuscript. Journal and Publisher will not be responsible for any copyright infringement and plagiarism issue.

DATA AVAILABILITY

The data used to support the research are included in the article.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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