

Formulation and Evaluation of a Flash Ibuprofen Emulsified Tablet Using Freeze-Drying Technique

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ABSTRACT

The aim of this work was to develop an ibuprofen tablet (IBU) which dissolves-rapidly in the mouth, therefore, needing not be swallowed. The solubility and dissolution rate of poorly water-soluble ibuprofen (IBU) was improved by preparing a flash tablet (FT) of IBU using freeze-drying technique (LT) and /or emulsified lyophilized tablets (ELT). The LT was prepared by dispersing the drug in an aqueous solution of highly water-soluble carrier materials consisting of gelatin, glycine, and sorbitol and / or dispersing nanoparticles of drug prepared by microemulsion and lyophilization techniques in the same aforementioned carrier materials. The mixture was dosed into the pockets of blister packs and then was subjected to freezing and lyophilization. The saturation solubility and dissolution characteristics of IBU from the LT and ELT were investigated and compared to the plain drug and the physical mixture (PM). Results obtained showed that the increase in solubility of IBU from ELT and LT matrices, nearly four and three times respectively greater than the solubility of the plain drug, was due to supersaturation generated by amorphous form of the drug. Results obtained from dissolution studies showed that ELT and LT of IBU significantly improved the dissolution rate of the drug compared with the PM and the plain drug. More than 98% and 96% of IBU in ELT and LT dissolved within 3 and 4 min respectively compared to only 50 % of IBU plain drug dissolved during 60 min. Initial dissolution rate of IBU in ELT and LT were almost tenfold and ninefold respectively higher than that of IBU powder alone. Crystalline state evaluation of IBU in ELT and LT were conducted through infrared spectroscopy (FTIR), x-ray powder diffraction (XRPD), differential scanning calorimetry (DSC), and to denote eventual transformation to amorphous state during the process. Scanning electron microscopic (SEM) analysis was performed and results suggest reduction in IBU particle size.

KEYWORDS: Ibuprofen, Freeze-Drying, micro-emulsion, nanoparticles.

1. INTRODUCTION

IBU, a phenyl propionic acid derivative, is widely used as first line non-steroidal anti-inflammatory, analgesic, and antipyretic agents with a half-life of 1.8-2 hours^(1,2). It is poorly aqueous soluble and its oral absorption is dissolution rate limited, which leads to a potential bioequivalence problem^(3,4). Thus, the improvement of IBU dissolution for its immediate release is desirable for rapid IBU absorption, which is prerequisite for quick onset of its pharmacological actions.

Oral bioavailability of a drug depends on its solubility and/or dissolution rate, and dissolution may be the rate-determining step for the onset of therapeutic activity. Therefore, poorly aqueous soluble drugs such as IBU are usually characterized by a low bioavailability due to less absorption, which is a major concern of pharmaceutical industries worldwide. Various approaches available to improve drug solubility as well as drug dissolution of poorly aqueous soluble drugs include micronization⁽⁵⁾, formation of inclusion complexes with cyclodextrins⁽⁶⁾, formation of amorphous drugs⁽⁷⁾, and formation solid dispersions of drugs using various hydrophilic carriers⁽⁸⁻¹⁰⁾, fast dissolving applying freeze-drying and self-emulsification techniques⁽¹¹⁾.

Orally fast dissolving tablets (OFDT) offer several advantages over other dosage forms like effervescent tablets and chewing tablets, which are commonly used to enhance patient's compliance. Administering effervescent tablets/granules involve unavoidable preparation that include the intake of water. Elderly patients cannot chew large pieces of tablets or gums and sometimes experience the bitter or unpleasant taste of the drug in the dosage form if the taste masking coat ruptures during mastication. FDT also provide the benefit of liquid medication in the form of solid preparation. Additionally, more rapid drug

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absorption from the pre-gastric area i.e. mouth, pharynx and oesophagus which may produce rapid onset of action⁽¹⁰⁾

Various manufacturing techniques have been applied to manufacture fast dissolving tablets such as lyophilisation, moulding, cotton candy process, spray drying, sublimation. Freeze-drying (also known as lyophilisation, lyophilization or cryodesiccation) is a dehydration process typically used to make the material more convenient for transport and storage. Freeze-drying works by freezing the material and then reducing the surrounding pressure to allow the frozen water in the material to sublime directly from the solid phase to the gas phase, leaving behind the drug in a fluffy cake that is rapidly dissolves when come in contact with aqueous medium. This technique forms the basis of Zydis, Quicksolv and Lyoc technologies which are used to manufacture fast dissolving/fast disintegrating tablets

Among the three mentioned techniques, Zydis technology, which is a patented technique^(10,12-14) had been widely used for drugs like famotidine, loperamide, piroxicam, oxazepam, lorazepam, domperidone, brompheniramine, olanzepine, ondansetron and rizatriptan. Thirteen products are currently available in the market, which had been manufactured using this technology^(15, 16).

Many approaches have been investigated to improve the drug solubility and consequently bioavailability. Among these approaches is particle size reduction (micronization/nanosizing), complexation with cyclodextrins, salt formation, solubilization based on co solvent and surfactant, freeze drying (lyophilization) and microemulsion. Micro emulsions are isotropic, thermodynamically stable transparent (or translucent) systems of oil, water and surfactant, frequently in combination with a co-surfactant with a droplet size usually in the range of 20-200 nm. They can be either oil-in-water (o/w), water-in-oil (w/o) or bicontinuous systems depending on their structure and are characterized by ultra low interfacial tension between oil and water phases. These versatile systems are currently of great technological and scientific interest to the researchers because of their potential to incorporate a wide range of drug molecules (hydrophilic and hydrophobic) due to the presence of both lipophilic and hydrophilic domains. Microemulsion is capable of protecting the drug against oxidation, enzymatic hydrolysis and improve the solubilization of lipophilic drugs and hence enhance their bioavailability⁽¹⁷⁾

Micro emulsions have been widely studied to enhance the bioavailability of the poorly soluble drugs. They offer a cost effective approach in such cases. The very low surface tension and very small droplet size resulted in high absorption and permeation through biological membranes. Interest in these flexible carriers is increasing and their applications have been expanded to various administration routes in addition to the conventional oral route. This can be attributed to their unique solubilization properties and thermodynamic stability which has drawn attention for their use as novel vehicles for drug delivery. The results obtained have been indeed very promising. Microemulsion formulation made the bioavailability and plasma concentration profiles of the drug more reproducible which is clinically important in the case of drugs showing serious adverse effects. This is a significant step forward in the delivery of poorly soluble drugs. Microemulsion systems are also now being increasingly investigated for transdermal⁽¹⁸⁻²⁰⁾, nasal⁽²¹⁾, pulmonary⁽²²⁾, vaginal⁽²³⁾ and intravenous drug delivery⁽²⁴⁾

In our study a fast-dissolving ELT and LT of IBU were prepared by freeze-drying using several excipients. Lyophilized fast-dissolving tablets which dissolve instantaneously in the mouth has been developed to large scale production in recent years and many are approved for marketing. The increasing need for such dosage forms in the market is mainly due to the ease and the convenience of administration. This type of dosage form usually improves the overall clinical performance of drugs by reducing the incidence of noncompliance especially among pediatric and geriatric patients and those patients who find it difficult to swallow tablets and capsules. 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 side effects are also expected to be reduced by formulating such dosage forms. In this work the solubility and dissolution characteristics of IBU in the prepared ELT and LT were evaluated. Differential scanning calorimetry (DSC), XRPD, IR and SEM analysis were performed to determine the physicochemical properties of the ELT, LT and the PM in comparison with the plain drug.

MATERIALS AND METHODS

Materials

Ibuprofen, micronized gelatine, glycine, sorbitol, oleic acid, propylene glycol, polysorbate-40 were purchased from Sigma Chemical Co., St. Louis. Water used was distilled de-ionized. All other chemicals were of reagent grade and used as received.

Methods

Solubility studies(SS)

IBU (100 mg), its ELTs, LTs and PMs equivalent to 100 mg IBU were placed in glass stoppered flasks and 100 mL water was added to each flask. The flasks were shaken in a water bath at 25°C for 15 h (USP XIX). The solutions were filtered through a membrane filter (0.45 µm) and the dissolved drug was measured spectrophotometrically at 221 nm. This experiment was done in triplicate.

Preparation of fast dissolving oral tablets(FDOT)

1-Preparation of fast dissolving tablets by lyophilization technique(LT)

A 2% w/v solution of gelatin in water was prepared by first soaking the gelatin in water until complete hydration. The hydrated gelatin was stirred using a magnetic stirrer until a clear solution was obtained. Different weights of glycine and sorbitol were added to the gelatin solution while stirring until completely dissolved. Glycine (used to prevent shrinkage of the tablet during manufacturing) and sorbitol (used to impart crystallinity, hardness, and elegance to the tablet) are well-known and acceptable materials used in preparing freeze-dried tablets. The percentage excipient used was optimized during the formulation process to result in a strong and elegant tablet that could be handled with ease. An accurately weighed amount of IBU powder (10 % w/v) was then dispersed in the aqueous solution of gelatin, glycine, and sorbitol. One milliliter of the resulting suspension was poured into each of the pockets of a tablet blister pack to result in IBU dose of 100 mg in each tablet. The tablet blister packs, each containing 10 tablets, were then transferred to a freezer at -22°C and kept in the freezer for 24 h. The frozen tablets were placed in a lyophilizer for 24 h using a Novalyphe-NL 500 Freeze Dryer (Savant Instruments, Holbrook, NY) with a condenser temperature of -52°C and a pressure of 7×10^{-2} mbar. The LTs were kept in a desiccators over calcium chloride (0% relative humidity) at room temperature until further used. Four blister packs containing a total of 40 tablets were produced in each run. Eight randomly selected tablets (two from each pack) were assayed for drug content uniformity. The mean % drug content was found to be $94.1\% \pm 1.20$. The quantitative amounts of ingredients used in the preparation of LT are tabulated in table I

Table(I) :Qualitative Amounts of the Ingredients Used in the Preparation of LT

Ingredients	%w/v
Ibuprofen	10
Gelatin	2.5
Sorbitol	1, 1.5, 2
Glycine	1,1,1

2-Preparation of emulsified lyophilized tablets(ELT)⁽¹¹⁾

IBU was dissolved in oleic acid, nonionic surfactant (polysorbate 40), and cosurfactant (propylene glycol), then an appropriate amount of water was added to the mixture dropwise and the microemulsion containing IBU was obtained by stirring the mixtures at ambient temperature using magnet stirrer. Initially, addition of water produced slight turbidity, however after sonication a clear microemulsion was formed. Finally, pH was adjusted with triethanolamine in the range of 6.5 to 7.5. The qualitative quantities of microemulsion are listed in table (I). The resulting O/W microemulsion was preweighed to be able to obtain the required weight of nanoparticles. The resulting micro-emulsion was lyophilized, the lyophilized nanoparticles produced were kept in a desiccators until use. A weight of lyophilized nanoparticles having an equivalent weight of IBU were dissolved in afore-mentioned solution of gelatin, glycine and sorbitol to obtain 100mg/ml. The emulsified lyophilized tablets(ELT) were prepared according to the previous lyophilization technique. ELT were kept in a desiccators until use. Eight randomly selected tablets (two from each pack) were assayed for drug content uniformity. The qualitative amounts of the ingredients used in preparation of ELT are tabulated in table II

Table(II) :Qualitative Amounts of the Ingredients Used in the Preparation of ELT

Ingredients	Ratio
Propylene glycol	1
Polysorbate-40	1
Oleic acid	0.22

Preparation of physical mixture(PM)

IBU and / or emulsified lyophilized IBU nanoparticles were uniformly mixed with gelatin, glycine and sorbitol in the same percentage used in the LT using a mortar and pestle. The prepared mixtures were kept in a desiccator until used.

Infrared analysis(FTIR)

IR spectra were determined using infrared spectrophotometer(Shimadzu IR-345-U-04, Japan . An amount of 2-3 mg IBU , PMs and ICs were mixed separately with 400 mg dry potassium bromide powder, compressed into transparent discs and IR spectra of plain drug , ELT,LTand PM were recorded.

X-ray Powder Diffraction Analysis(XRPD)

X-ray diffraction experiments were performed in a Scintag x-ray diffractometer (USA) using Cu K α radiation with a nickel filter, a voltage of 45 kV, and a current of 40 mA. Diffraction patterns for ELT, LT, and PM were obtained.

Differential scanning calorimetry(DSC)

Samples were placed in Al pan and heated at rate of 50°C/min with indium in the reference pan , in an atmosphere of nitrogen up to a temperature of 300°C . The DSC studies were performed for IBU and its ELT, LT and PM .

Scanning Electron Microscopic Analysis(SEM)

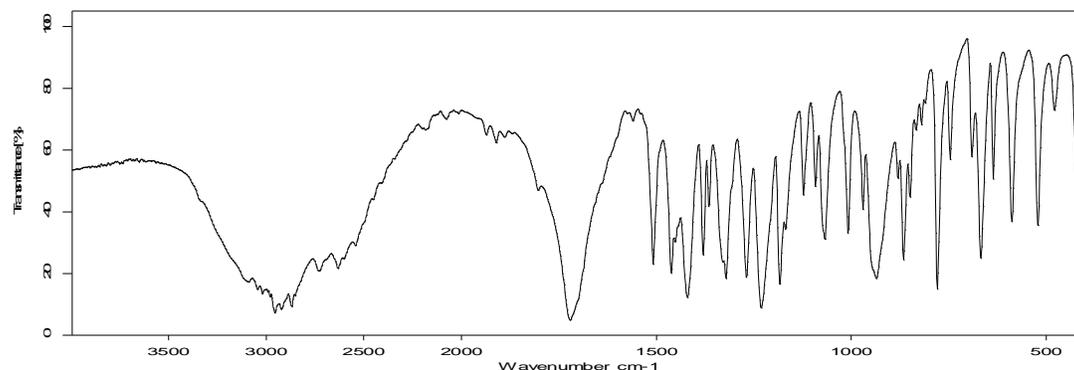
Surface morphology of IBU, its ELT, LT as well as PM, was examined by SEM (Jeol JSM-6400, Tokyo, Japan). Cross-sections of the ELT and LT were made to study their inner structure. Photographs were taken at magnification of 1000.

Dissolution studies(DS)

The dissolution profiles of ELT, LT and PM, compared with the plain drug, were determined in a dissolution tester (VK 7000 Dissolution Testing Station, Vankel Industries, Inc., NJ) following the USP paddle method. All tests were conducted in 900 mL of distilled water maintained at 37 \pm 0.5°C with a paddle rotation speed at 50 rpm. The amount of drug used was equivalent to 100 mg. After specified time intervals, samples of dissolution medium were withdrawn, filtered, and assayed for drug content Spectrophotometrically at 221 nm after appropriate dilution with water.

RESULTS**Table III:Solubility of Ibuprofen as a Plain Drug, in ELT, LT and PM in Distilled Water at 25°C**

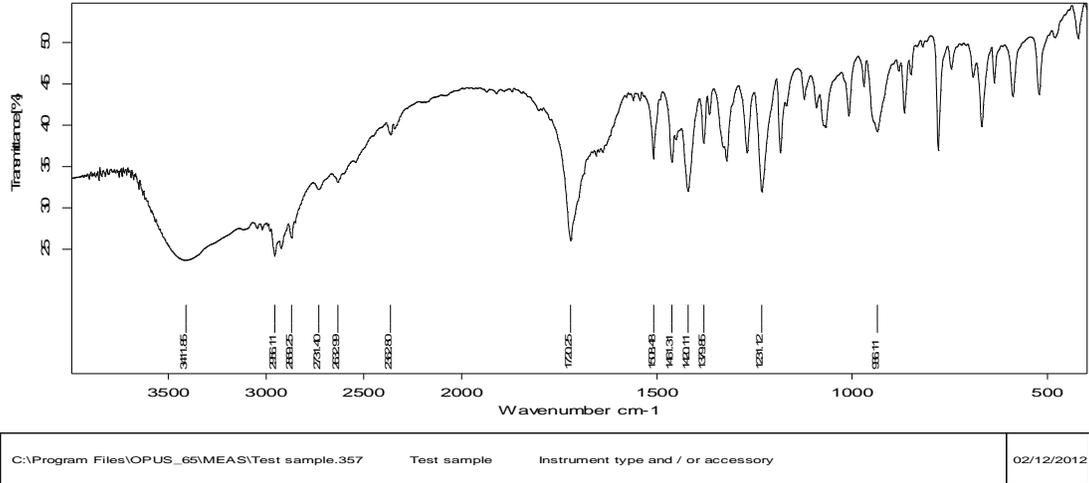
Ibuprofen (mg)	Form of drug	Solubility(mg/ml)
100	ELT	0.85
100	LT	0.61
100	PM	0.37
100	Pain drug	0.24



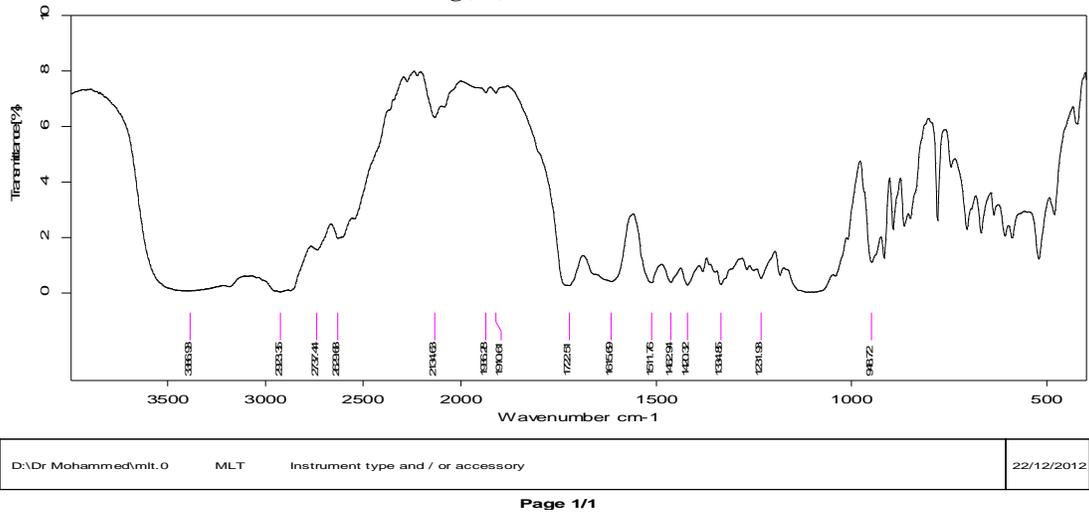
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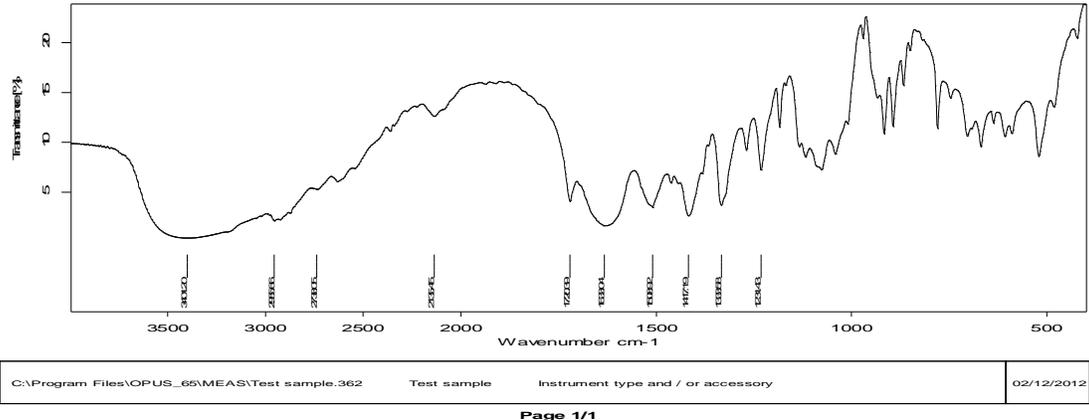
Fig(1a):FTIR of IBU



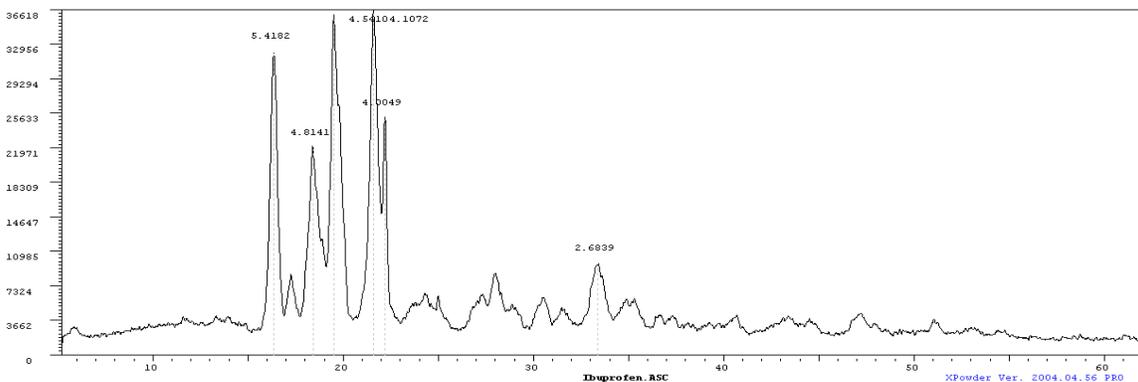
Fig(1b): FTIR of PM



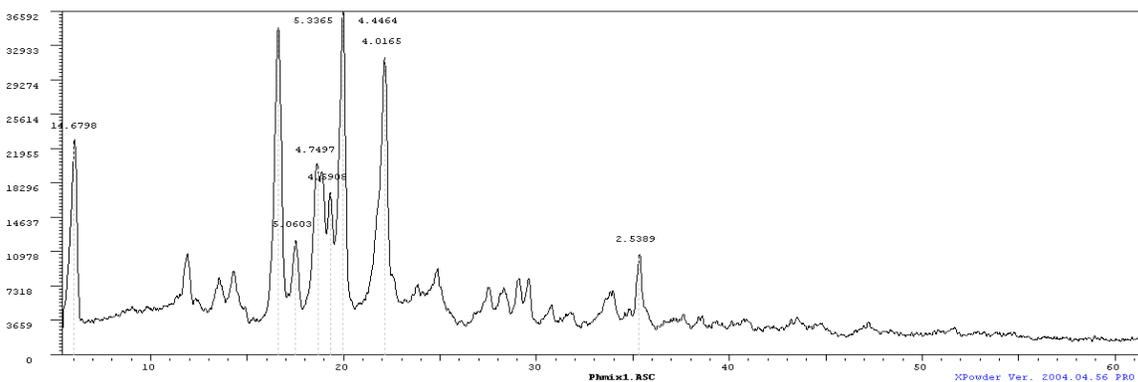
Fig(1c): FTIR of ELT



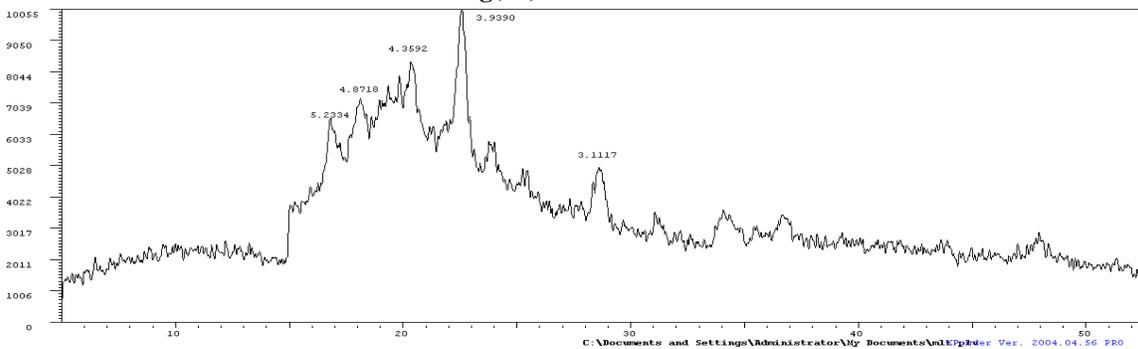
Fig(1d): FTIR of LT



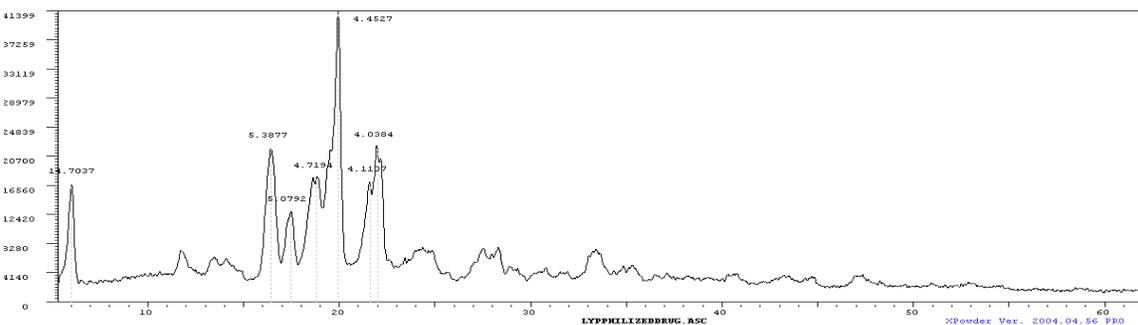
Fig(2a):XRPD of IBU



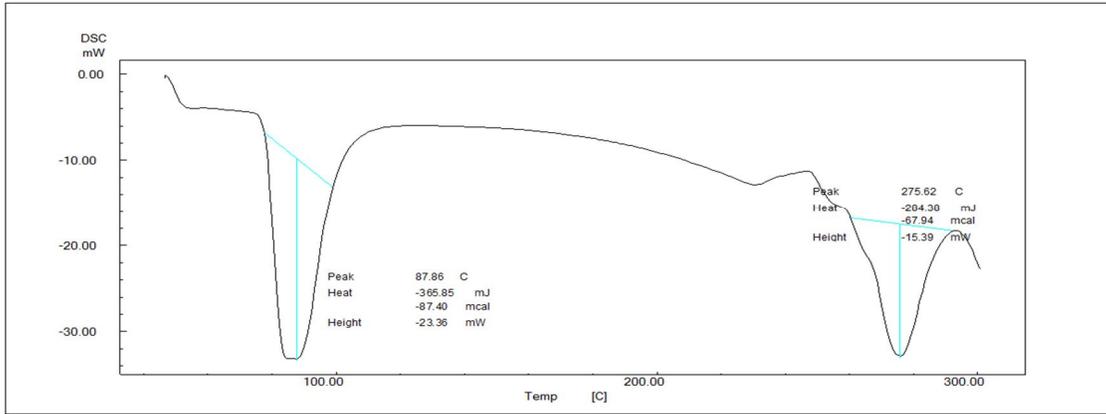
Fig(2b):XRPD of PM



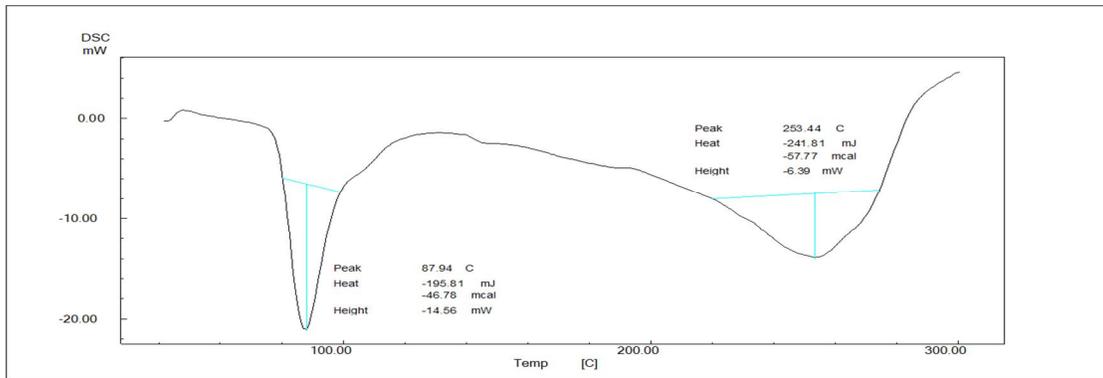
Fig(2c):XRPD of ELT



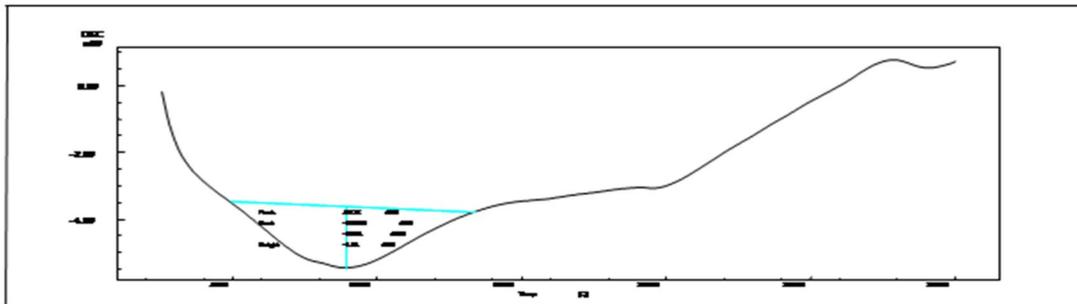
Fig(2d):XRPD of LT



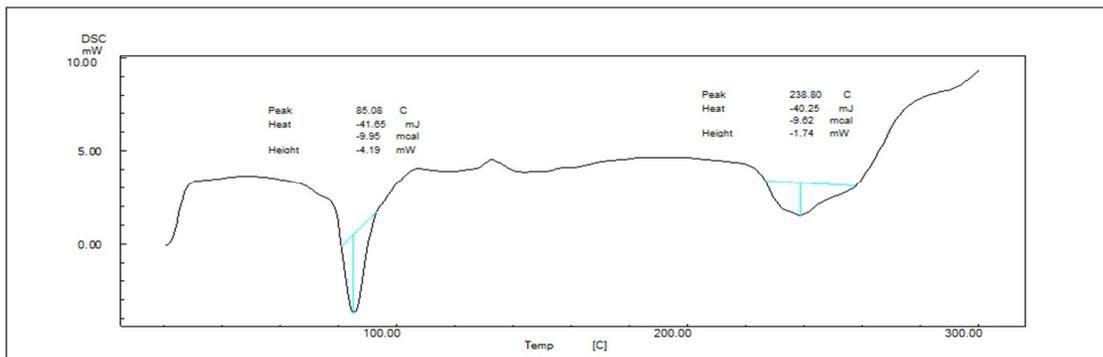
Fig(3a): DSC of Ibuprofen



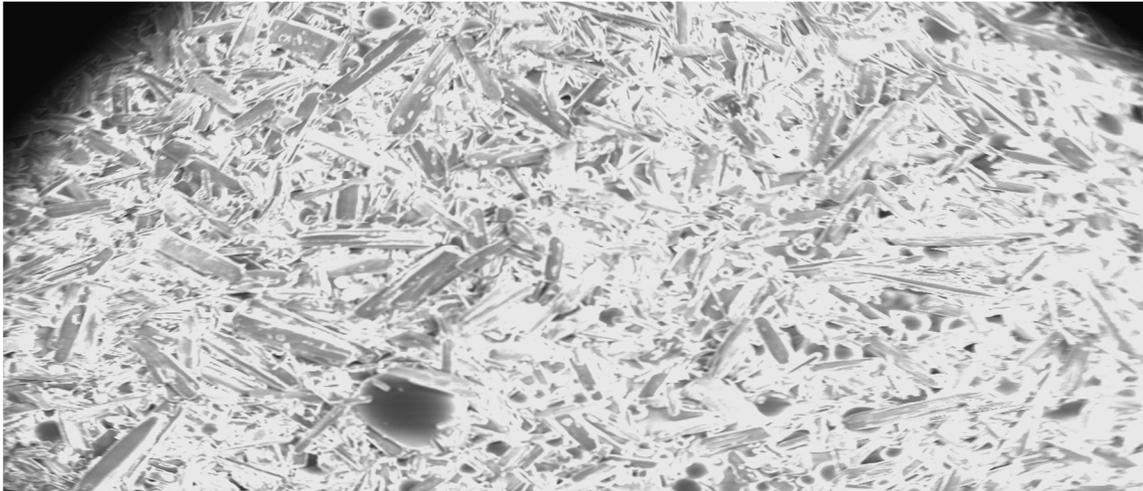
Fig(3b): DSC of PM



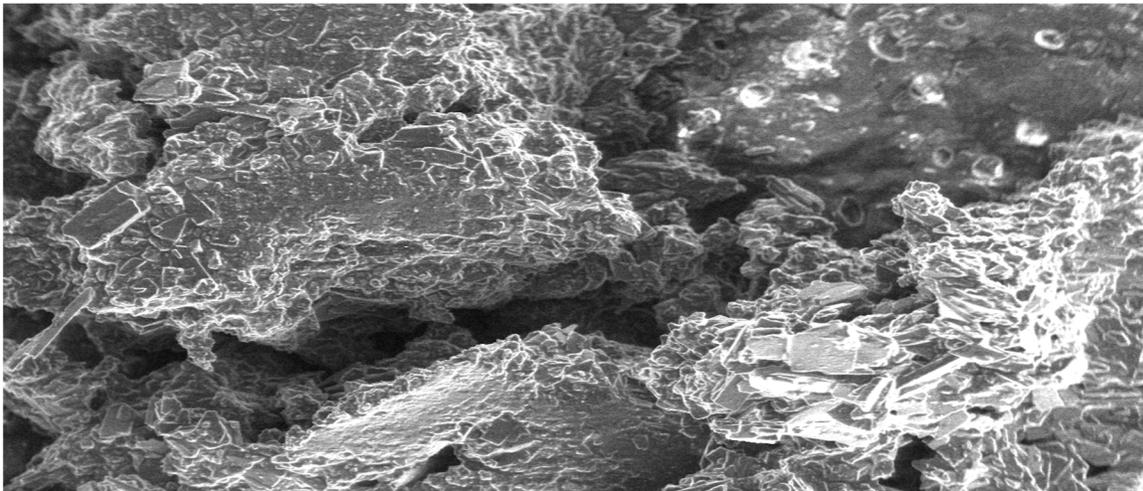
Fig(3c): DSC of ELT



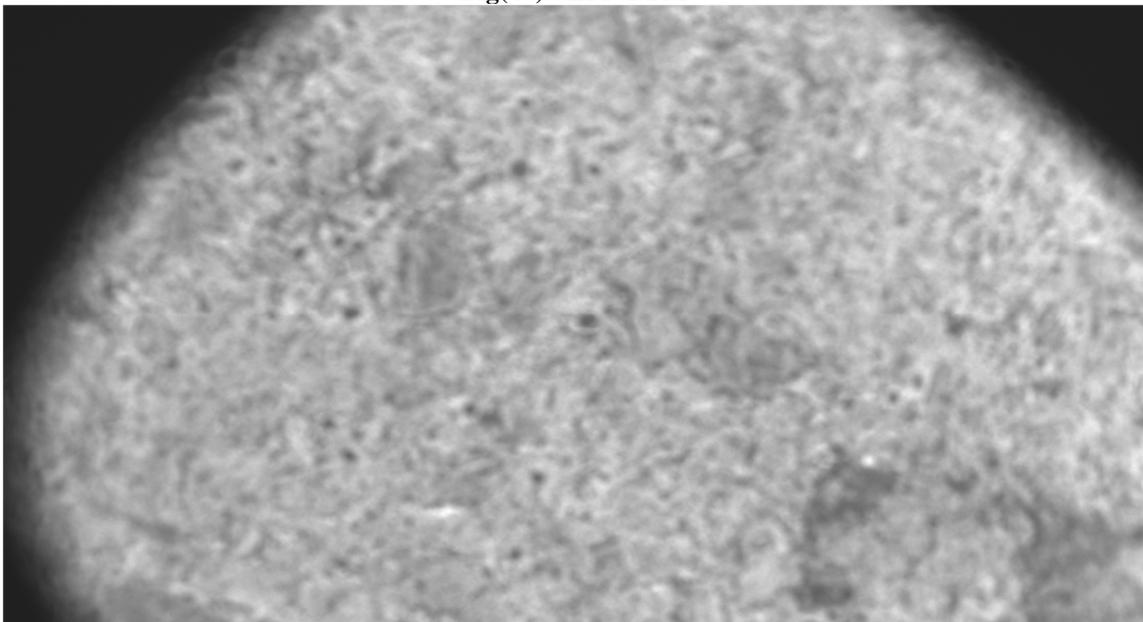
Fig(3d): DSC of LT



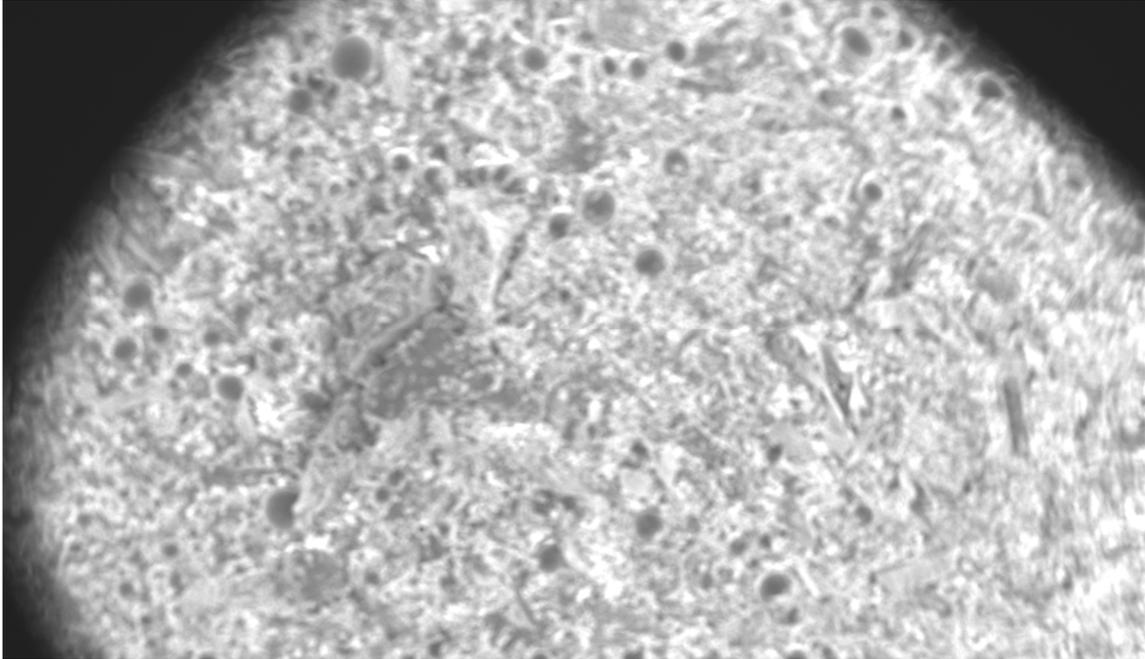
Fig(4a) : SEM of plain IBU



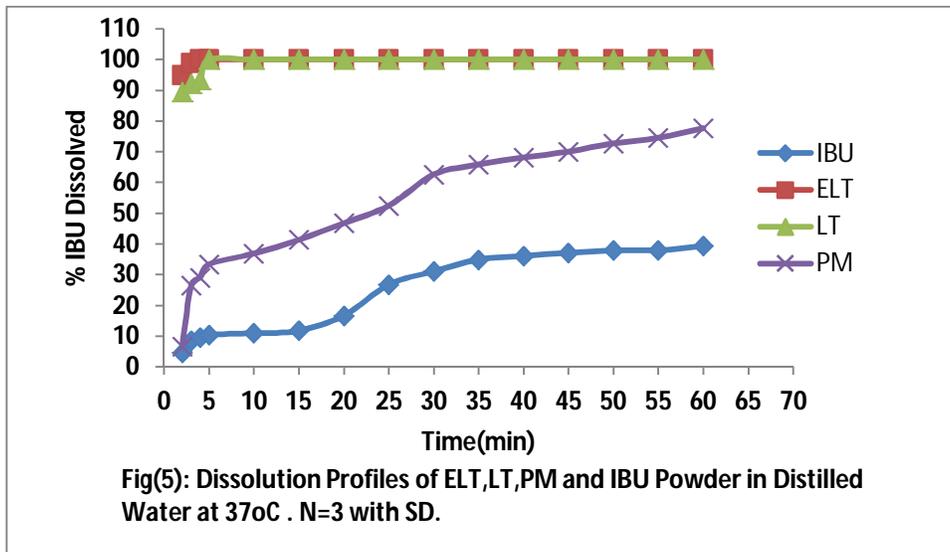
Fig(4b):SEM of PM



Fig(4b):SEM of ELT



Fig(4d):SEM of LT



Fig(5): Dissolution Profiles of ELT,LT,PM and IBU Powder in Distilled Water at 37oC . N=3 with SD.

DISCUSSION

The formulation containing glycine/sorbitol in a ratio of (1:1) depicted higher drug content compared to the ratio of (1:1.5 & 1:2) , good formed tablets and the best elegance .The mean % drug content of ELT was found to be $96.1\% \pm 1.16$. Whereas drug content of LT was found to be $93.8\% \pm 1.33$.The increase in solubility of IBU from ELT matrix (0.085 % w/v), nearly four times higher when compared to the solubility of the plain drug (0.024 % w/v), and from LT matrix(0.061% w/v) , nearly three times higher than the plain drug . This indicates that the supersaturation obtained from both ELT and LT is generated by the amorphous form of the drug in the ELT and LT.The increase in solubility of IBU from the PM (0.037 % w/v), nearly one and half times higher than the plain drug, could be due to the solubilizing effect of highly water soluble carrier materials used in the formulation such as glycine and sorbitol. Solubilities are presented in Table III.

To evaluate the crystalline state of IBU in PM, ELT and LT; IR, XRPD, DSC and SEM studies were performed on IBU powder, its PM, ELT and LT. Figure(1) depicted IR spectra of IBU (fig 1a), PM (fig 1b), IBU in ELT (fig 1c) and LT (fig 1d). The IR spectra revealed no change in functional group region of drug when formulated in PM, ELT and LT whereas their fingerprint regions are not superimposed to that of drug. This indicated the change in physical properties of drug only.

These results were further confirmed by x-ray diffraction studies (Fig. 2). The x-ray diffraction pattern of the pure drug exhibits its characteristic diffraction peaks at various diffraction angles indicating the presence of crystallinity (fig 2a). The diffraction study of the PM of drug and excipients showed the peaks corresponding to the crystalline drug molecules present in the mixture, although their intensity was lower due to the high excipients–drug ratio employed (fig 2b). The diffraction pattern of the ELT and LT showed absence, broadening, and reduction of major IBU diffraction peaks indicating that mostly an amorphous form (disordered state) existed in both ELT and LT (fig c,d). These results could explain the observed enhancement of solubility and rapid dissolution of ibuprofen in ELT and LT.

The DSC curve of IBU showed two sharp endothermic peaks at nearly 87.8°C, corresponding to its melting transition point and 275.62°C corresponding to its decomposition temperature (fig 3a). The thermogram of the PM reflected the endothermic peak of IBU representing its melting transition point, and the endothermic peak representing the decomposition point appeared more broader and shifted to the left (253.44°C), indicating that the crystalline state is reduced in the PM (fig 3b). However, the decomposition endotherm was greatly shifted to right at (238.8°C) and significant broadening of drug endothermic peak respectively on the DSC thermograms of the ELT and LT, suggesting absence of crystallinity and presence of amorphous state of the drug (fig 3c,d).

Figure(4) depicted SEM micrographs of IBU, PM, ELT and LT. The results show the rod crystal shape of IBU (fig 4a). These crystals could be seen in the PM (4b) while the micrograph of ELT and LT show a matrix in which no crystals of IBU could be seen (fig 4d,c). The SEM micrograph of ELT and LT suggests that the particles of drug might have been reduced during dissolution in the gelatin–glycine–sorbitol solution. This could therefore indicate that IBU particle size has been reduced which also accelerates dissolution.

The dissolution profiles of IBU in the PM, ELT, LT, and IBU powder alone in distilled water at 37°C are shown in Fig. 1. IBU in the ELT was immediately dispersed and almost completely dissolved in 3 min. Initial dissolution rate of IBU in the ELT increased markedly (about twelve fold) compared to IBU powder alone whereas the dissolution rate of IBU in LT, PM was (about eleven fold, three fold) the dissolution rate of IBU powder respectively. The dissolution rates of ELT and LT were comparable. The percentage of IBU dissolved from its PM for 60 min (77.7%) increased approximately twofold compared to IBU powder alone (39.3%). The increased dissolution rate of IBU from its ELT and LT suggests that ELT and LT might have a rapid oral absorption following disintegration in the mouth and dissolution in the saliva since solubilized IBU is absorbed rapidly and completely from the gastrointestinal tract after oral administration. The enhancement in solubility and dissolution rate of IBU in its ELT and LT may be attributed to the formation of amorphous state in the porous lyophilized matrix of the fast dissolving carrier materials moreover the nanoparticle dispersion formed in ELT matrix.

Based on these results, it can be concluded that the freeze dried IBU tablet could be a suitable form of IBU in terms of solubility and dissolution in water. This technique provides a promising manufacturing procedure directly resulting in sublingual tablets without any other mixing or formulation steps. Moreover, the properties of the tablet are suitable.

Conclusion

We demonstrated that a lyophilized IBU tablet made of widely used, safe, water-soluble excipients is feasible for enhancing the solubility and increasing the dissolution rate of IBU. Since the technology to the production scale of manufacture is now available, we think that the formulation we developed in this work is feasible for easy industrialization, up-scaling, and manufacturing. The results obtained were attributed to the formation of an amorphous state of the drug in the porous lyophilized matrix and probably to reduction of drug particle size. Future work will be focused on investigating the physical stability of the tablets and determining the absorption rate and bioavailability of IBU from ELT and LT in human volunteers.

We suggest that the prepared ibuprofen ELT and LT might have a higher oral bioavailability due to expected rapid dissolution in the saliva than standard dosage forms; therefore, it would be possible to

formulate IBU in ELT and LT having an eventual decreased therapeutic dose resulting in reduced side-effects encountered with IBU therapy such as gastrointestinal disturbance.

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