Research Article

Enhancement of Ketoprofen and Ibuprofen Solubility and Dissolution by Lyophilized Milk

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ABSTRACT

This work was performed to improve the solubility and dissolution of the poorly water soluble ketoprofen (KP) and ibuprofen (IBU) using lyophilized milk (LM). The physical mixture (PM) and lyophilized solid dispersions (LSDs) of drugs were prepared using LM in different concentrations. The solubility and dissolution of KP and IBU in distilled water was investigated as a function of the solubilizer concentration (0-4 parts) in the prepared physical mixtures (PMs) and lyophilized solid dispersions (LSDs). In a concentration of 3%w/w solubilizer, the solubility and dissolution rate of both KP and IBU were improved dramatically with LM. Dissolution was found to be a function of solubility. Results were confirmed by DSC, IR and XRPD which suggested solid- solid transition of KP, IBU when formulated with LM. The results suggested that LM as a natural solubilizer added promising results in enhancing the solubility and dissolution of the poorly water soluble drugs as KP,IBU and application in the field of dosage form design in digestive therapy.

Keywords: Freeze-Drying, Ibuprofen, Ketoprofen, Physical mixture, Solid dispersion.

INTRODUCTION

KP and IBU are nonsteroidal anti-inflammatory drug which have good analgesic properties, but these drugs have low solubility in water so that it can cause problems in formulating and limiting the bioavailability.[1] The improvement of their solubilities thereby their oral bio-availability remains one of most challenging aspects of drug development process especially for oral drug delivery system. These in vivo and in vitro characteristics and the difficulties in achieving predictable and reproducible *in vivo/in vitro* correlations are often sufficiently difficult to develop formulation on many newly synthesized compounds due to solubility issues.[2,3] One way to increase the solubility of poorly soluble drugs is through the formation of solid dispersion. Numerous solid dispersion systems have been demonstrated in the pharmaceutical literature to improve the dissolution properties of poorly water-soluble drugs.[4] Other methods, such as salt formation.[5] Complexation with cyclodextrins[6-10] enhances solubilization of drugs in solvents[11,12] and particle size reduction[13] have also been utilized to improve the dissolution properties of poorly water-soluble drugs; however, there are substantial limitations with each of these techniques. On the other hand, formulation of drugs as solid dispersions offers a variety of processing and excipient options that allow for flexibility when formulating oral delivery systems for poorly water soluble drugs.

In this study natural and synthetic solubilizers have been used to enhance the solubility through inclusion complex and channeling effect. Thus, the study opens the chances of preparing such solid dispersion formulations of poorly water soluble drugs with natural solubilizers which adds a promising technique for enhancing solubility and dissolution.

MATERIALS AND METHODS

Materials

Ketoprofen (KP), Ibuprofen (IBU), absolute alcohol were purchased from Sigma Chemical Co., St.Louis, Freeze-dried milk. All water used was distilled and de-ionized. All other chemicals were of reagent grade and used as received.

Methods

Preparation of Lyophilized Solid Dispersion

The drugs and LM (0-4 parts) were dissolved in absolute alcohol. Alcohol was evaporated using rotary evaporator (Rotavapor RII, Buchi, Switzerland).The solid dispersion obtained was dispersed in a suitable amount of water then transferred to a freezer at −22°C and kept for 24 h. The frozen solid dispersions (SDs) were placed in a lyophilizer for 24 h using a Novalyphe-NL 500 Freeze Dryer (Savant Instruments, Holbrook, NY) with a condenser temperature of −45°C and a pressure of 7 × 10−2 mbar. The lyophilized solid dispersion (LSD) were kept in a desiccators over calcium chloride (0% relative humidity) at room temperature until further used.

Preparation of Physical Mixture

KP and IBU were uniformly mixed with LM in concentrations used in the LSDs using a mortar and pestle. The prepared mixtures were kept in desiccators until used. The quantitative amounts of different formulations are illustrated in table 1.

Table 1: Qualitative amounts of KP, IBU and lyophilized milk

Formulation	KP (mg)	IBU (mg)	LM (mg)
Fkp	60	-	-
FIBU	-	200	-
Formulations Prepared by Lyophilization			
F1	60	-	60
F2	60	-	120
F3	60	-	180
F4	60	-	240
F5	-	200	200
F6	-	200	400
F7	-	200	600
F8	-	200	800
Formulations Prepared by Physical Mixing			
F9	60	-	60
F10	60	-	120
F11	60	-	180
F12	60	-	240
F13	-	200	200
F14	-	200	400
F15	-	200	600
F16	-	200	800

Drug content

An amount of LSD and PM equivalent to a theoretical KP, IBU contents of 25 and 200 mg respectively were accurately weighed and allowed to disintegrate completely in 100 ml of absolute alcohol. After filtration, the solution was assayed spectrophotometrically for drug content at 262 and 221 nm for KP and IBU respectively.

Differential scanning calorimetry studies (DSC)

Samples weighing approximately 5 mg were sealed in aluminum pans and analyzed using a Shimadzu DSC-60 (Kyoto, Japan). The samples were heated in an atmosphere of nitrogen and thermograms were obtained by heating at a constant heating rate of 50°C/min in the range of 50–300°C.Thermograms for KP, IBU and their LSDs (1:3drug/LM), were obtained.

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 KP, IBU, and their LSDs (1:3 drug/LM) were obtained.

Infrared spectroscopy (FTIR)

IR spectra were determined using infrared spectrophotometer (Shimadzu IR-345-U-04, Japan. An amount of 2-3mg KP, IBU and their LSDs(1:3drug/LM) were mixed separately with 400 mg dry potassium bromide powder, compressed into transparent discs and their IR spectra were recorded.

Solubility studies

Excess KP, IBU, their LSDs and PMs were placed in stoppered glass flasks. 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 262 and 221 nm, for KP and IBU respectively. This experiment was done in triplicate.

Dissolution studies

The dissolution profiles of KP, IBU and their LSDs, PMs 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± 0.5°C with a paddle rotation speed at 50 rpm. The amount of drug used was equivalent to 25 and 200 mg for KP and IBU respectively. After specified time intervals, samples of dissolution medium were withdrawn, filtered, and assayed for drug content spectrophotometrically at 262 and 221 nm for KP and IBU respectively after appropriate dilution with distilled water. The experiment was repeated in triplicate.

Kinetic analysis

The release data of plain drugs, LSDs and PMs were subjected to kinetic analysis according to zero order, first order kinetics and Higuchi diffusion model.

RESULTS AND DISCUSSION

Drug content

The value of the experimental drug content of KP and IBU was very close to the theoretical one for all prepared LSDs and PMs.

Differential scanning calorimetry Studies (DSC)

DSC studies were performed on KP and IBU powders and their lyophilized formulations (with 3% LM) as shown in figure 1. The thermogram of KP showed sharp endothermic peaks at nearly 90°C. Whereas that of IBU was at 87.8°C corresponding to their melting transition points. The thermogram of the LSDs prepared with 3%w/w LM showed the endothermic peak of KP shifted to the left at melting transition point at 66°C indicating reduction in crystalline state of KP. Whereas a little changes in melting point of IBU, this indicated a minor change in crystalline properties of IBU (figure 1).

X-ray powder diffraction analysis (XRPD)

The results obtained with DSC were further confirmed by x-ray diffraction studies (Figure 2).The x-ray diffraction pattern of the pure KP and IBU exhibit their characteristic diffraction peaks at various diffraction angles indicating the presence of crystallinity. The diffraction study of drugs with 3%w/w LM and prepared by lyophilization

showed the peaks corresponding to the crystalline drug molecules present in the mixture, although their intensity was lower due to the high solubilizer–drug ratio employed. The diffraction pattern of the LSD of drugs showed absence, broadening, and reduction of major KP and IBU diffraction peaks indicating that mostly an amorphous form (disordered state) existed These results could explain the observed enhancement of solubility and rapid dissolution of KP and IBU in LSDs.

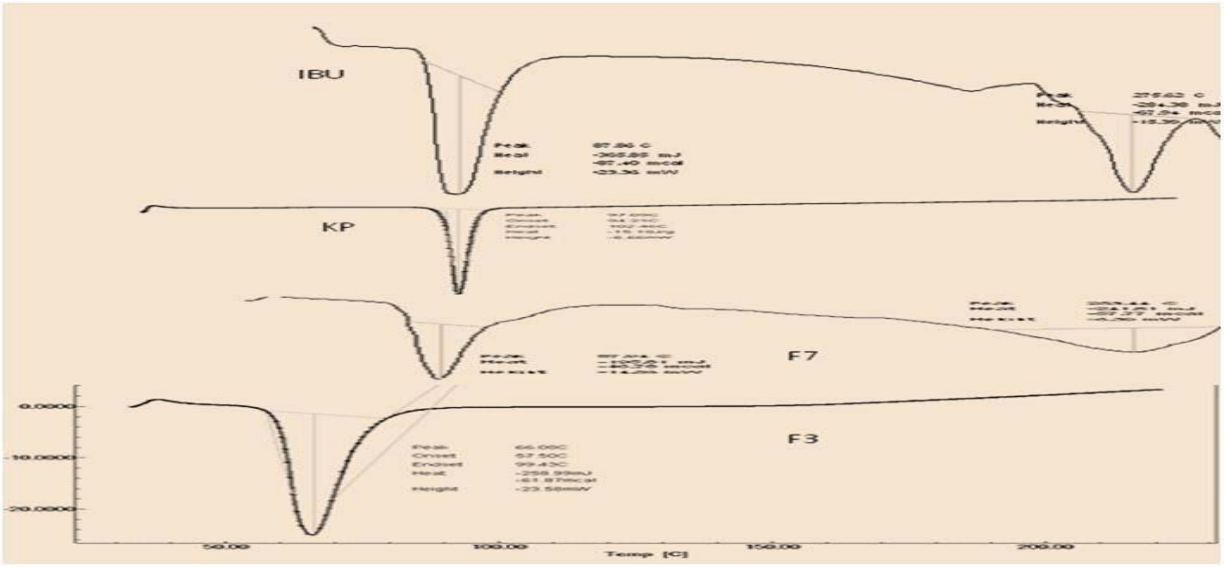

Figure 1: DSC of KP, IBU, F3 and F7

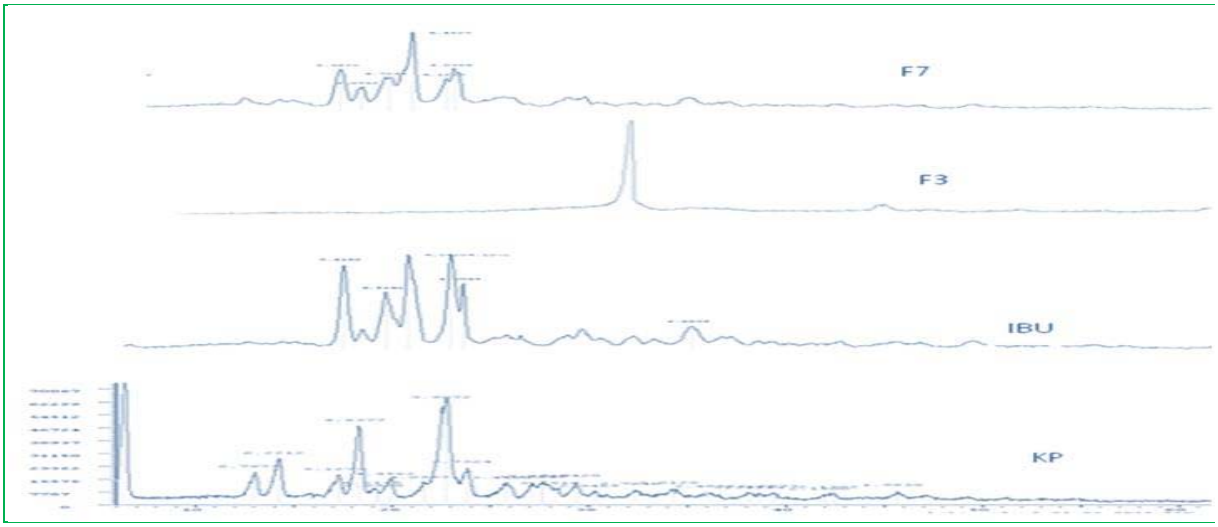

Figure 2: XRPD of KP, IBU, F3 and F7

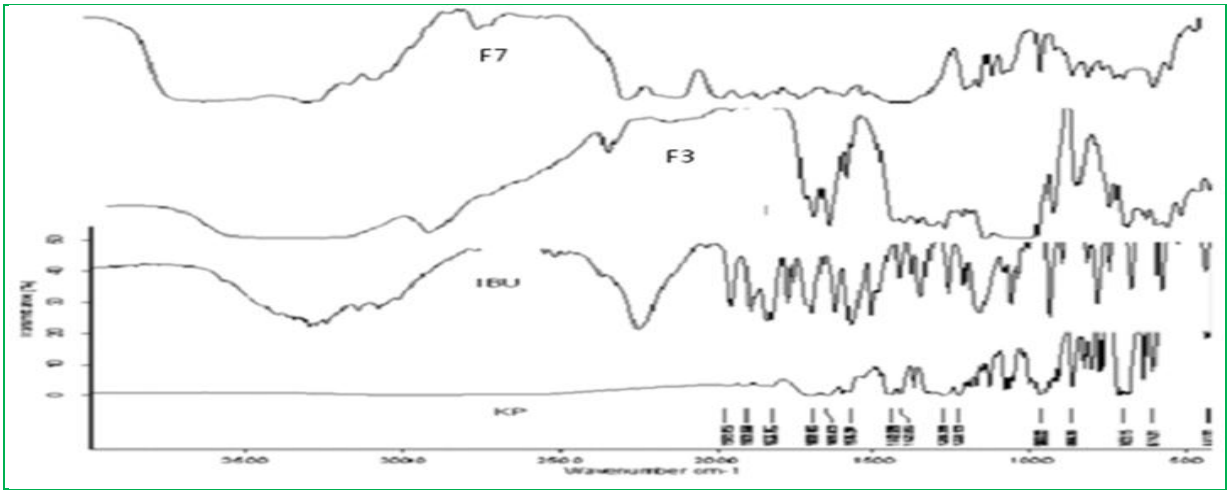

Figure 3: FTIR of KP, IBU, F3 and F7

Infrared spectroscopy (FTIR)

Infrared spectroscopy was used to study the interactions between the drug and the solubilizers. Both KP and IBU depicted their specific bands in functional group region. When their LSDs prepared with 2%w/w LM no change in functional group region. This indicates the absence of chemical interaction between KP, IBU and lyophilized milk whereas their fingerprint regions are not superimposed. This is due to the change in physical characters of the drug; this was confirmed by DSC and XRPD.

Solubility studies

The solubility of KP and IBU using different concentrations of LM in water is shown in tables 2. LM enhances the wetting properties of the hydrophobic drugs. Thus resulted in improved drug solubility. The difference in the solubilities of the two drugs may depend on a specific interaction between KP, IBU and matrix of the LM. Formulation of drugs in 1:3 ratio depicted maximum solubility. This may be due to complete incubation of drug molecules by LM molecules, after this concentration an excess in LM concentration approximately had no effect on the solubility of the drugs (figure 4).

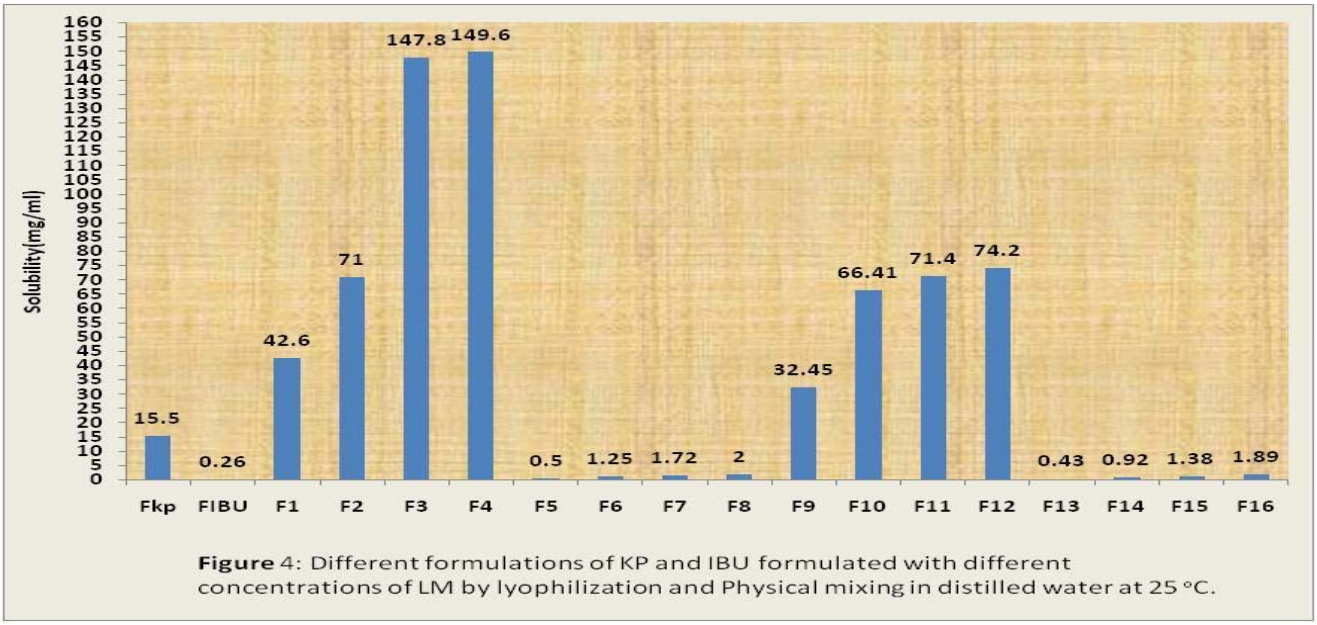

Figure 4: Different formulations of KP and IBU formulated with different concentrations of LM by lyophilization and Physical mixing in distilled water at 25 °C.

Dissolution studies

Figures 5 and 6 revealed the slow dissolution rate of both KP and IBU, due to their low inherent solubility in aqueous medium. By reviewing the results of the solubility studies it is clear that, the dissolution of KP and IBU in their different formulations is a function of the solubility. Increased LM concentration improved the dissolution rate of KP and IBU especially in ratio (1:3 & 1:4). This may be due to formation of inclusion complex between lyophilized milk beside the wetting properties of surfactants present and their mixed micelles solubilizing effect [14]. KP depicted a higher dissolution rate in all formulations compared to IBU. This is due to solid-solid transition of KP from crystalline to amorphous state when formulated with LM. The transition in case of IBU is lower compared to KP. The formulations prepared by lyophilization depicted dissolution rate greater than those prepared by physical mixing.

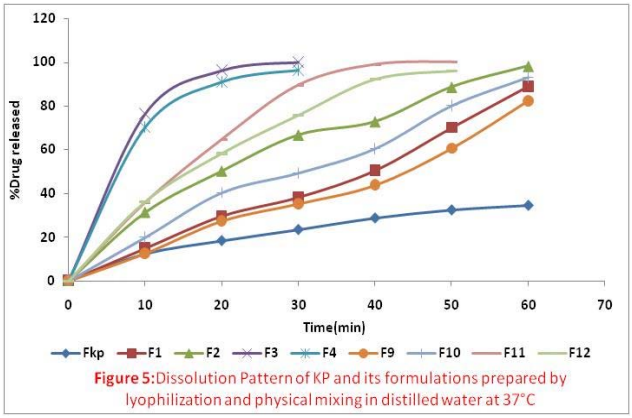

Figure 5: Dissolution Pattern of KP and its formulations prepared by lyophilization and physical mixing in distilled water at 37°C

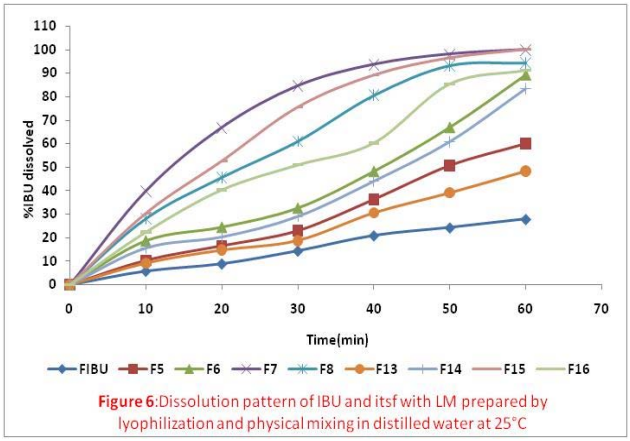

Figure 6:Dissolution pattern of IBU and itsf with LM prepared by lyophilization and physical mixing in distilled water at 25°C

Kinetic analysis

Table 2 illustrates the kinetics of drug release. The drug dissolved in all formulations, followed zero order, first order kinetics and diffusion model.$T_{50\%}$ clarifies the variations present between the different formulations of drug, its PMs and LSDs in the solubility and dissolution rate.

Table 2: Kinetic analysis of release data of Ketoprofen, ibuprofen and their different formulations

Formula	Model	R^2	Slope	Y-Intercept	$T_{50\%}$ (min)	Mechanism of Release
Fkp	Zero First Diffusion	0.941 0.991 0.994	0.551 -0.002 5.020	4.932 1.962 -3.601	114	Diffusion
FIUB	Zero First Diffusion	0.998 0.986 0.975	0.466 -0.002 5.097	0.713 1.998 -12.O40	81.8	Zero
F1	Zero First Diffusion	0.981 0.845 0.943	1.436 -0.016 15.49	1.626 2.196 -39.76	33.7	zero
F2	Zero First Diffusion	0.981 0.846 0.993	1.302 -0.028 14.420	22.38 2.294 -14.300	19.9	Diffusion
F3	Zero First Diffusion	0.846 0.998 0.913	1.140 -0.073 10.410	67.800 2.084 45.360	5.5	First
F4	Zero First Diffusion	0.897 0.995 0.937	1.305 -0.045 11.470	59.700 1.905 35.670	1.6	Diffusion
F5	Zero First Diffusion	0.977 0.945 0.932	1.090 -0.007 11.160	-3.526 2.061 -30.860	49.1	Zero
F6	Zero First Diffusion	0.946 0.803 0.884	1.240 -0.016 15.030	-2.988 2.206 -39.060	42.7	Zero
F7	Zero First Diffusion	0.855 0.970 0.929	1.152 -0.033 13.210	40.210 2.136 5.153	12.1	First
F8	Zero First Diffusion	0.960 0.954 0.979	1.407 -0.024 15.640	17.800 2.196 -22.17	21.3	Diffusion
F9	Zero First Diffusion	0.967 0.847 0.927	1.006 -0.012 14.07	2.000 2.130 -36.620	47.7	Zero
F10	Zero First Diffusion	0.988 0.878 0.976	1.316 -0.019 15.480	7.880 2.203 -31.200	32.0	Zero
F11	Zero First Diffusion	0.795 0.928 0.592	1.245 -0.058 23.130	37.920 2.564 -97.880	15.5	First
F12	Zero First Diffusion	0.918 0.977 0.967	1.279 -0.030 14.450	31.490 2.178 -6.162	16.7	First
F13	Zero First Diffusion	0.979 0.958 0.935	0.798 -0.005 8.590	-1.226 2.030 -22.270	64.2	Zero
F14	Zero First Diffusion	0.948 0.832 0.882	1.357 -0.013 14.400	-5.333 2.164 -40.030	40.8	Zero
F15	Zero First Diffusion	0.921 0.967 0.968	1.408 -0.032 8.900	24.700 2.263 11.700	18.5	Diffusion
F16	Zero First Diffusion	0.977 0.913 0.966	1.393 -0.018 15.24	9.586 2.168 0.966	29.0	Zero

$T_{50\%}$: Time required for 50% Drug Release

CONCLUSION

The results of this work revealed that the used LM enhanced the solubility by dual effects, mixed micelle and incubation of drugs. This finding would rationalize the use of such natural substance as promising additives for the development of optimal formulation conditions of poorly water soluble drugs.

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