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Research Article

ENHANCEMENT OF SOLUBILITY AND RELEASE OF IBUPROFEN FROM WITEPSOL W35 SUPPOSITORY BASE BY INCLUSION WITH LYOPHILIZED SKIMMED MILK

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ABSTRACT

Objective: The aim of this study is to enhance the solubility and dissolution of a poorly water soluble ibuprofen(IBU).

Methods: To achieve this purpose, physical mixture (PM) and inclusion complex (IC) of IBU and lyophilized skimmed milk(LSM) were prepared and investigated.

Result: Results obtained showed that the solubility of IBU in IC was about twenty two times higher than the plain drug.Data from the dissolution rate determination have also revealed that IC of IBU with LSM was also improved the dissolution rate when compared to the PM and plain drug. Differential scanning calorimetry (DSC), X-ray powder diffraction(XRPD) and infrared spectroscopy(IR) techniques depicted the formation of IC of drug with LSM. IBU was formulated into different suppository bases. Witepsol W35 depicted the highest drug release (18.89%) in 60 minutes when compared to other suppository bases.

Conclusion: The results obtained from solubility, dissolution, DSC, XRD and IR suggest the enhancement of the solubility and dissolution were attributed to formation of IC and presence of mixed micelles in milk. The drug released from its inclusion complex(IC) with LSM depicted a superior solubility and dissolution rate which candidate it in formulation of poorly soluble drugs in rectal suppositories.

Keywords: Ibuprofen, Physical mixture, Inclusion complex, Solubility, Dissolution rate, Witepsol H15

INTRODUCTION

Among all non-steroidal anti-inflammatory drugs (NSAID), Ibuprofen can be well-mentioned for its wide usage in the treatment of mild to moderate pain and fever [1].

In the case of poorly water-soluble drugs, dissolution is the rate-limiting step in the process of drug absorption. Potential bioavailability problems are prevalent with extremely hydrophobic drugs (aqueous solubility less than 0.1 mg/ml at 37°C), due to erratic or incomplete absorbtion from GIT[2]. Thus rapid ibuprofen absorption could be a prerequisite for the quick onset of its action [3]. Enhancing solubility and dissolution rate of poorly water-soluble drugs like ibuprofen is one of the striking areas of research in pharmaceutical field [4]. To overcome the problems associated with oral absorption and bioavailability issue, various strategies have been utilized including hydrotrpes [5], complexation [6], microcapsulation [7], the use of surfactants, permeation enhancers, micronization, salt formation, cyclodextrines, nanoparticles, solid dispersions, self emulsifying drug delivery system [8-11] etc. However ahead of all, inclusion complex with the natural agents like lyophilized milk is the most promising method to the scientists due to the ease of preparation, ease of optimization, safety of these agents and reproducibility of the manufacturing method. Drug administration via mucosal membranes, including the vaginal and rectal membranes, has the advantage of by passing the hepatogastrointestinal first pass metabolism associated with oral administration. [12]. Consequently, rectal administration of ibuprofen in suppository form may offer an advantage over its oral administration to increase its bioavailability. Studies have shown that the release properties of many suppositories depend considerably on the physicochemical properties of the drug, suppository base and formulation adjuvants [13-16] and a lot of formulation work is normally required to optimize the properties of suppository preparations.

The aim of this study was to prepare different formulations of Ibuprofen by physical mixing of drug with lyophilized milk, lyophilizing of drug with lyophilized milk to obtain the most promising formula which subsequently used in formulation of rectal suppositories in the selected suppository base.

MATERIALS AND METHODS

MATERIALS

Ibuprofen ; witepsol W35 ; suppocire AP ; suppocire AT; suppocire AM ; suppocire BM ; cacoa butter absolute alcohol were purchased from Sigma Chemical Co., St. Louis, MO ; skimmed lyophilized milk. All water used was distilled de-ionized water. All other chemicals were of reagent grade and used as received.

METHODS

Preparation of skimmed milk powder

The skimmed milk was transferred to a deep freezer and kept at -21°C for 48 hours. The frozen skimmed milk was lyophilized for 72 hours at -45°C to reduce moisture content.

Preparation of the physical mixture(PM).

Drug was uniformly mixed with different concentrations of lyophilized milk using a mortar and a pestle. The qualitative amounts are illustrated in table I.

Preparation of inclusion complex (IC)

Drug was uniformly mixed with different concentrations of lyophilized milk, the mixure was suspended in a few milliliters of water.The mixture was frozen in a deep freezer for 48 hours and then lyophilized for 72 at -45°C. IC was sieved through 250 um mesh sieves. The qualitative amounts are illustrated in table I.

Table 1: Qualitative Amounts of IBU with LSM in PM and IC

Drug/LSM Ratio					
PM			IC		
F1	F2	F3	F4	F5	F6
1:1	1:2	1:3	1:1	1:2	1:3

Drug content

An amount of PM and IC equivalent to a theoretical IBU content of 200 mg was accurately weighed and allowed to disintegrate completely in 100 ml of absolute alcohol. After filteration, the solution was assayed spectrophotometrically for drug content at 221 nm.

Solubility studies

IBU (200 mg), its PMs and ICs equivalent to 200 mg 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.

Dissolution studies

The dissolution profiles of IBU plain drug(200 mg), amounts of PMs and ICs containing the equivalent to 200 mg IBU 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. 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.

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 IBU, PMs, and ICs 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 IBU, PMs, and ICs were obtained.

Infrared spectroscopy (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 their IR spectra were recorded.

Preparation of ibuprofen Suppositories

Preparation of ibuprofen suppositories using different suppository bases

Suppositories(each weighing 2g and containing 200 mg IBU) were prepared adopting the creamy melting technique[17] using different suppository bases namely, witepsol W35, suppocire AP, suppocire AT, suppocire BM, and cacao butter. Drug displacement in the used bases was first determined [18] and the amount of IBU required was calculated.The prepared suppositories were left for 24 hours at 25°C before testing.

Preparation of ibuprofen suppositories using PM(F2) and inclusion complex(F5)

Suppositories (each weighing 2 g) containing the equivalent amount of 200 mg from F2 and F5 were prepared with witepsol W35 as suppository base using the aforementioned technique.

In-vitro release of ibuprofen from different suppository bases

Adult suppositories prepared with different suppository bases (each weighing 2g and containing 200 mg IBU) were tested for drug release using the dissolution medium and the conditions stated before.

In-vitro release of ibuprofen from selected suppository base and the commercially available products

Adult witepsol W35 suppositories(each weighing 2g) were prepared with PM(F2) and IC(F5) each containing the equivalent amount of 200 mg IBU were tested for the drug release and compared with two commercially available products in the market (FA and FB) using aforementioned dissolution medium and the stated conditions.

RESULTS AND DISCUSSION

Drug content

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

Solubility studies

The solubilities of IBU, IBU in PMs and ICs in water were depicted in figure 1.The used LSM improved the solubility by virtue of its dual effect.First, surface activity property enhanced the wettability of the hydrophobic drug, thus resulted in improved drug

solubility.This increase in drug solubility could be attributed to the micellar solubilization of a large amount of the unionized drug in the hydrophobic interior of the micelles present in milk[19]. Second, the inclusion effect in which non polar molecule or the non polar region of one molecule (known as guest) inserted into the cavity of another molecule or group of molecules (known as host) [20].The increase in solubility of IBU in PMs and ICs was due to the dual effect of mixed micelles and inclusion.Solubilities of F2 and F5 were found to be 15 and 22 times higher than the plain drug.The increased solubility of IC (F5) over that of PM(F2) was due to aforementioned effects moreover the larger surface area in contact with solvent resulting from nano sizes of lyophilized particles.Solubilities in F1 and F4 were lower than in F2 and F5.This may be due to the insufficient amount of LSM required to form a complex with the whole drug.Whereas F3 and F6 depicted no significant increase in solubility.This may be due to increased concentration in LSM which increases the viscosity of the medium.

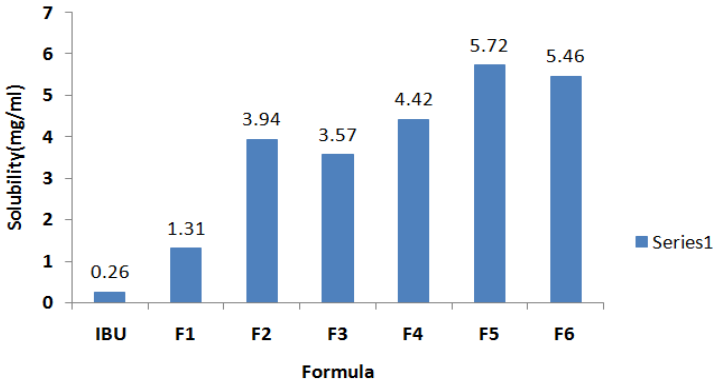

Fig. 1: Histograms of solubility of IBU in PM, IC and plain IBU

Dissolution studies

Figure (2) reveals a very slow dissolution rate for the plain drug, due to its low inherent solubility in aqueous medium.By reviewing the results of the solubility studies, it is clear that, the dissolution of IBU in its PMs and ICs is a function of the solubility.Increased LSM concentration can improve IBU dissolution by increasing the saturated solubility of the drug and/or by increasing surface area of the powder via improved wetting and inclusion effect [19, 20]. IBU in F2 and F5 was immediately dispersed and almost completely dissolved in 40 and 20 minutes respectively. Initial dissolution rate of IBU in the F5 increased markedly nearly six times when compared to IBU powder alone. The dissolution rate was also higher and faster in F5 than in F2. The percentage of IBU dissolved from F2 for 20 min (69.9%) increased approximately four fold compared to IBU powder alone (16.7%).

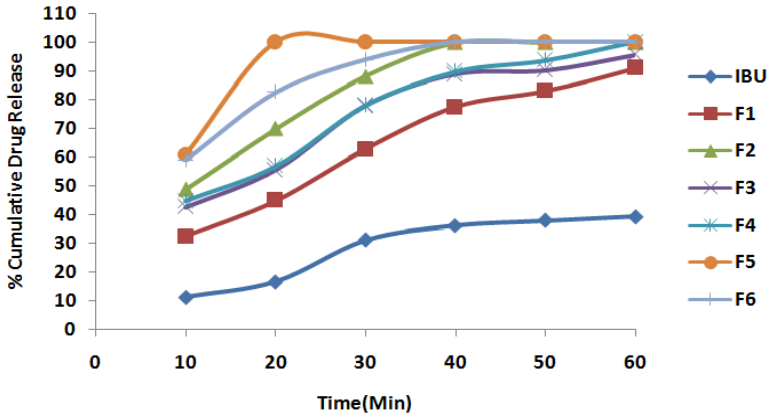

Fig. 2: Dissolution pattern of different formulations of ibuprofen with LSM in distilled water at 37°C.

Differential scanning calorimetry studies (DSC)

Figure (3) depicted the DSC thermograms of IBU, F2(Fig 3B) and F5(Fig3C). 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 F2 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(151.17°C), indicating that the crystalline state is reduced in the PM(F2). However, in F5 the decomposition endotherm was nearly disappeared on the DSC thermogram suggesting the presence of inclusion complex between LSM and IBU.

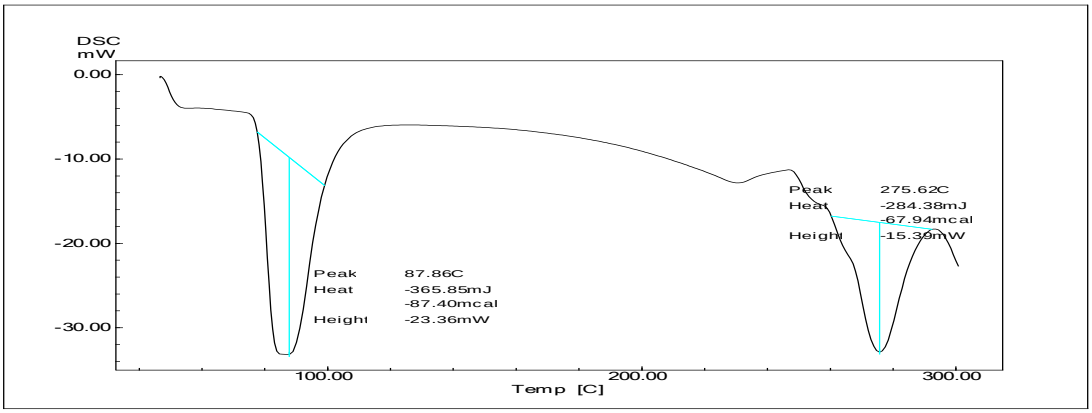

Fig. 3A: DSC of IBU

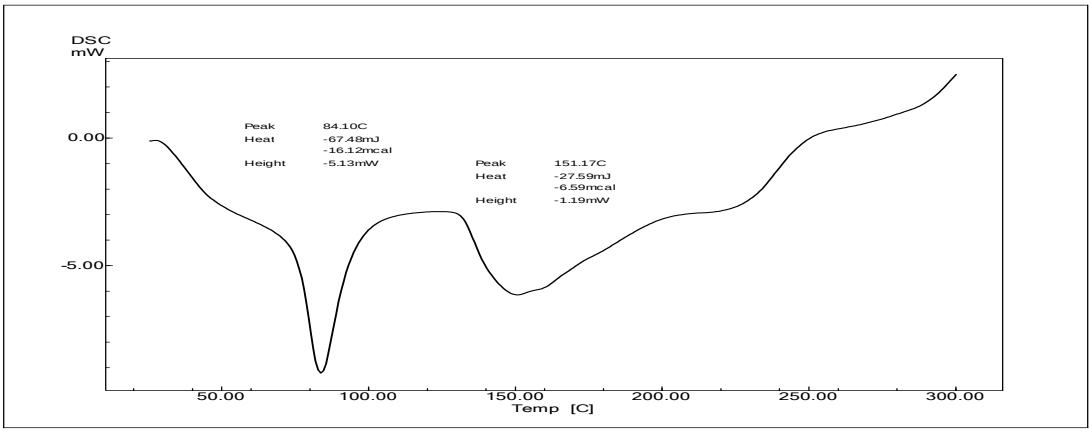

Fig. 3B: DSC of F2

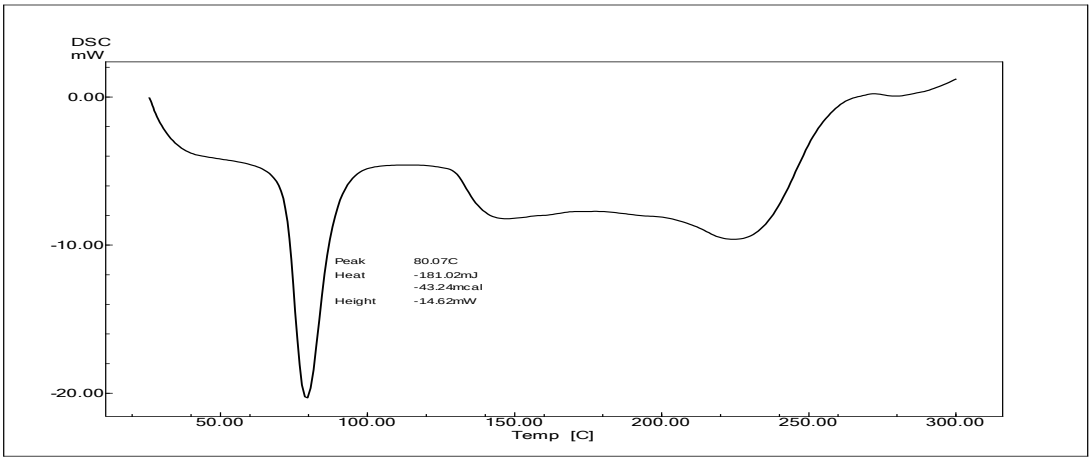

Fig. 3C: DSC of F5

X-ray powder diffraction analysis(XRPD)

These results were further confirmed by x-ray diffraction studies (Fig. 4).The x-ray diffraction pattern of the pure drug exhibits its characteristic diffraction peaks at various diffraction angles indicating the presence of crystallinity(Fig 4A). The diffraction study of F2 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(F4B). The diffraction pattern of F5 showed absence, broadening, and reduction of major IBU diffraction. Peaks indicating that mostly an amorphous form (disordered state) existed(F4C).These results could explain the observed enhancement of solubility and rapid dissolution of IBU.

Infrared spectroscopy (FTIR)

Figure (5) revealed IR spectra of IBU(Fig 5A, F2(Fig 5B) and F5(Fig 5C). The IR spectra revealed no significant change in functional group region of drug when formulated with F2 and F5 whereas the fingerprint region of IBU are not superimposed the other regions in F2 and F5.This indicates the change in physical properties of drug only. This was in accordance with the results obtained with solubility, dissolution, DSC and XRPD.

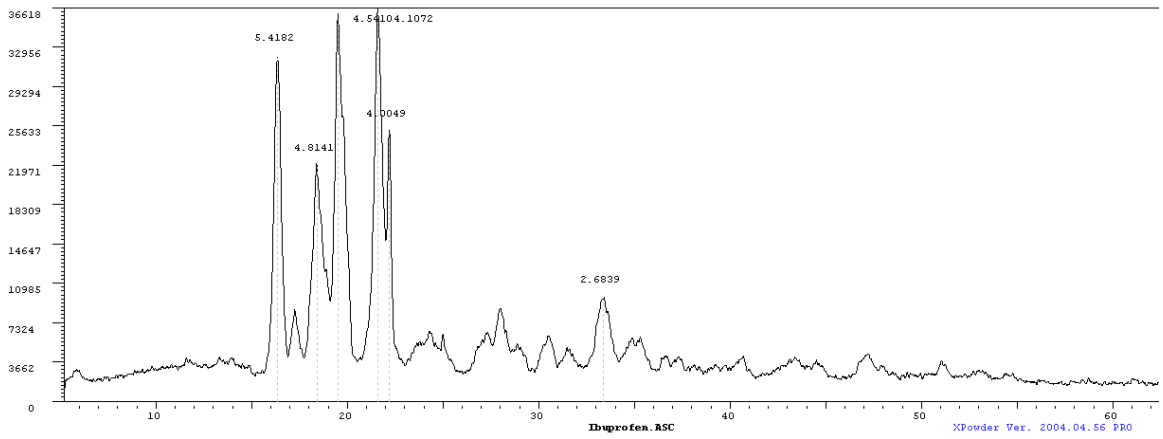

Fig. 4A: XRPD of IBU

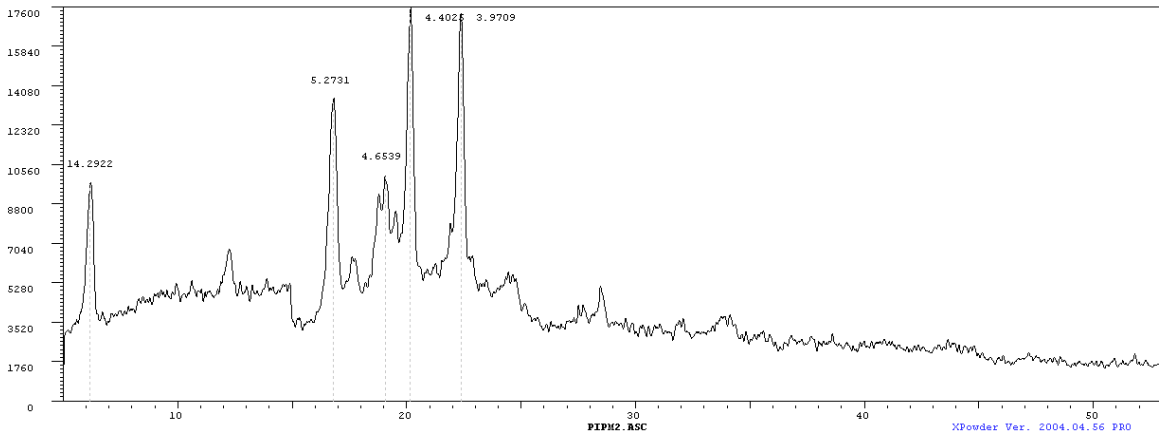

Fig. 4B: XRPD of F2

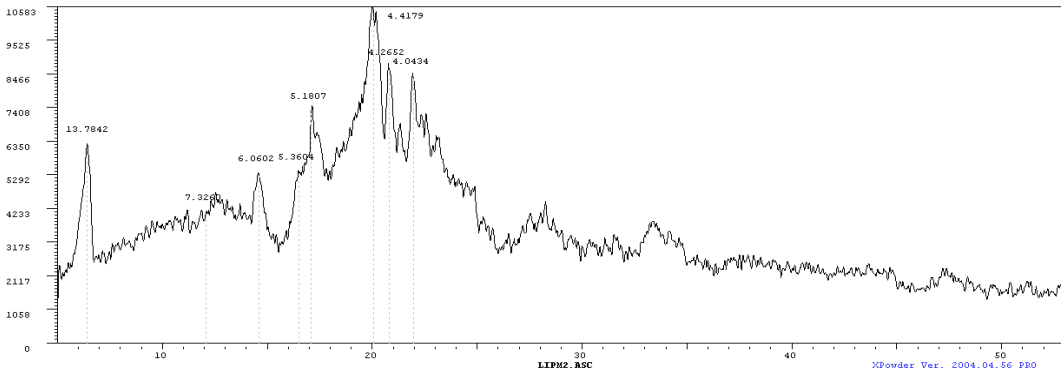

Fig. 4C: XRPD of F3

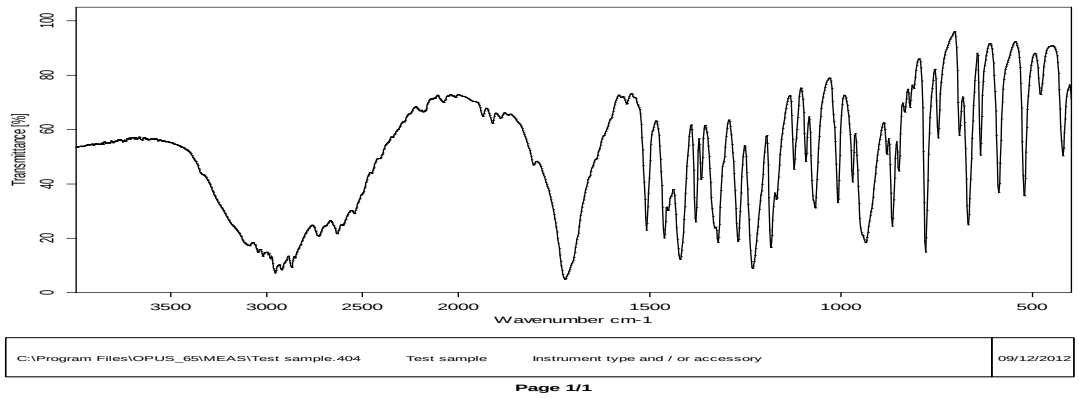

Fig. 5A: IR Spectrum of IBU

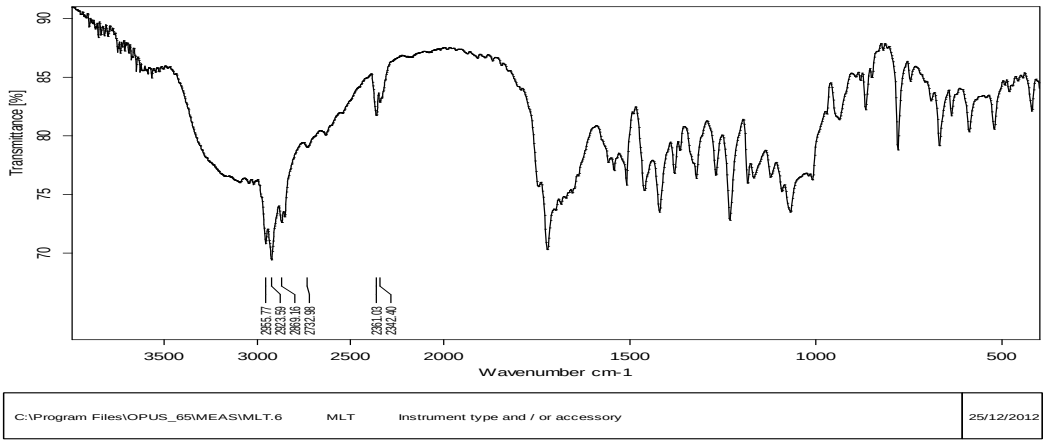

Fig. 5B: IR Spectrum of F2

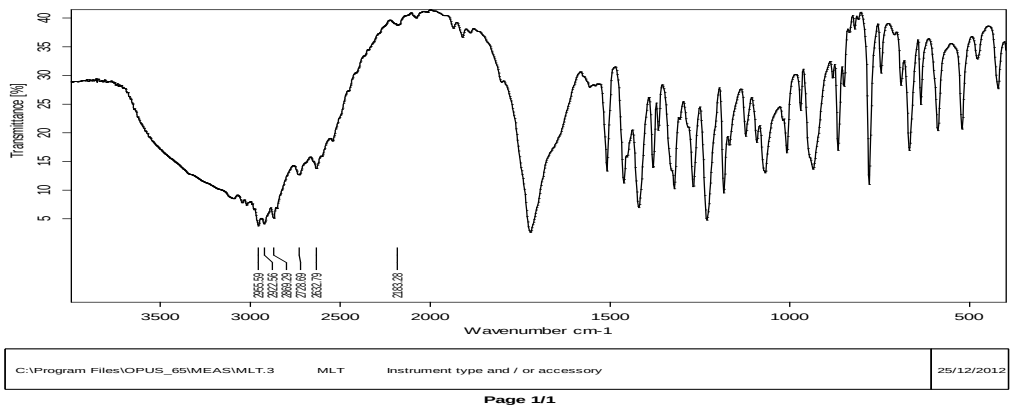

Fig. 5C: IR Spectrum of F5

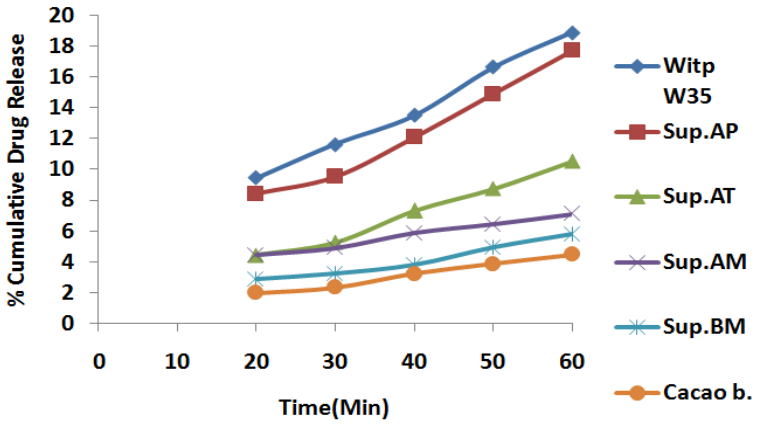

Fig. 6: In Vitro Release of ibuprofen from different suppository bases in distilled water at37°C

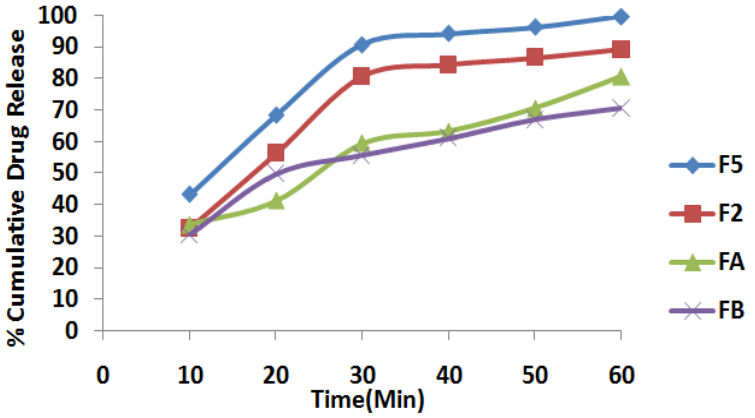

Fig.7: In vitro release of ibuprofen from different suppository formulations in distilled water at 37°C

In-vitro release of ibuprofen from different suppository bases

Fig(6) depicted the in vitro release of the drug from different suppository bases.The ranking order of drug release from different suppository bases was as follow: witepsol W35>suppocire AP >suppocire AT> suppocire AM >suppocire BM > cacao butter. The highest drug release from witepsol W35 may be attributed to its good emulsifying properties and pores formed in the base by penetrating solution into the suppository [21].

In-vitro release study from witepsol W35 suppository base

Figure (7) depicted the release of IBU from the selected formulae (F2 and F5) and the two commercial products(FA and FB) available in the market. The release pattern of F5 was significantly higher than the other formulations.This is due to the superior characteristics of IC mentioned before.

CONCLUSION

The drug released from its inclusion complex(IC) depicted the superior solubility and dissolution rate which candidate it in formulation of poorly soluble drugs in rectal suppositories with small doses.

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