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# FORMULATION AND *IN VITRO* CHARACTERIZATION OF IBUPROFEN-LOADED SOLID DISPERSIONS

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## ABSTRACT

The purpose of the study was to formulate solid dispersions of ibuprofen using binary mixtures of Gelucire 50/13 and HPMC by fusion and solvent evaporation methods in order to improve physical and mechanical characteristics of this drug. The dispersions were prepared with the excipients mixtures in the ratios of 1:1, 1:2, 1:4, 2:1 and 4:1 and characterized by determining the Fourier transform infra-red (FTIR) spectroscopy, solubility, entrapment efficiency (EE) and *in vitro* dissolution rate. The results showed that the EE decreased with increase in the concentrations of both Gelucire 50/13 and HPMC in the dispersions. Batch C containing Gelucire 50/13 and HPMC in the ratio 1:4 respectively showed the highest solubility for the fusion and solvent evaporation methods. Results of the FTIR spectroscopy study showed that there was no remarkable difference between the spectra of ibuprofen in the solid dispersions, physical mixtures and that of the pure sample of drug. The batches prepared by fusion method gave higher release rate in both SIF and SGF compared to those of solvent evaporation. Also, the solid dispersions showed higher release profiles than the commercial sample of ibuprofen. Thus, the Gelucire 50/13 and HPMC (ratio; 1:4, respectively) based ibuprofen solid dispersions represents a promising tool for improving of the solubility of Ibuprofen.

**KEYWORDS**: **Solid dispersion; Ibuprofen; Gelucire; HPMC (hydroxypropylmethylcellulose); Fourier transform infra-red (FTIR) spectroscopy.**

## INTRODUCTION

Drugs with poor solubility, bioavailability, permeability, rapid metabolism and elimination constitute a large percentage of the pharmaceutical market today [1]. At the pre-formulation stage of drug development, the physicochemical properties of pharmaceutical drugs present a continuing challenge. As such, extensive efforts have been mounted in the search for optimal techniques that can yield drugs with improved solubility and dissolution, and consequently, better efficacy [2, 3].

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Ibuprofen [RS-2-(4-isobutyl-phenyl) propionic acid], is one of the most potent orally active antipyretic, analgesic and non-steroidal anti-inflammatory drug (NSAIDs) used extensively in the treatment of acute and chronic pain, osteoarthritis, rheumatoid arthritis and related conditions [4]. It is characterized by a better tolerability compared with other NSAIDs [5]. Ibuprofen is a non-selective inhibitor of cyclo-oxygenase-1 (COX-1) and Cyclooxygenase-2 (COX-2) and is almost insoluble in water [4, 5]. According to the Biopharmaceutical Classification System (BCS), Ibuprofen is a class II drug and as such is practically insoluble in water (21 $mg.L^{-1}$ at 25 $^{o}C$), relatively lipophilic (log P = 4.0), with high membrane permeability, thus dissolution becomes the rate limiting step for its absorption [3, 6]. Due to its high membrane permeability, the extent of Ibuprofen absorption approaches up to 100% [7].

Various strategies have been employed to enhance the solubility and dissolution rate of poorly water-soluble drugs. Among these include complex formation [8], the use of surfactants [8], lipids and permeation enhancers [9], micronization [8, 9], salt formation [10], cyclodextrins [10], nanoparticles [11], solid dispersions (SD) [12], microencapsulation [13], pro-drug formation [14], self-emulsifying drug delivery systems [10, 13] and many other strategies. However, solid dispersion is considered the most promising method to the scientists due to the ease of preparation, ease of optimization and reproducibility of the manufacturing method [6, 15, 16]. The most common techniques of solid dispersion preparation include the fusion or melt and solvent evaporation method [17].

Solid dispersions have been previously applied in the formulation of ibuprofen using various polymeric or surfactant matrixes including hydroxy propyl methyl cellulose (HPMC) & hydroxy propyl cellulose (HPC) and sugars [6], Collodion particles [18], Tween 80 & Span 80 [19], urea [20], PEG-6000 [21]. However, despite the array of research in this direction, optimal improvement in the dissolution enhancement of ibuprofen is yet to be obtained. The aim of the research was to enhance the dissolution of ibuprofen through the formulation of its solid dispersion using a binary mixture of HPMC and Gellucire 50/13.

## METERIALS AND METHODS

### Materials

The following materials were used: Gellucire 50/13 (Gattefossé Pharma, Saint-Priest France), HPMC (Sigma-Aldrich, Steinheim, Germany), Ibuprofen (Juhel Pharmaceutical Ltd, Enugu Nigeria). All other reagents and solvents were of analytical grade and were used as supplied.

### Preparation of ibuprofen physical mixtures

Physical mixtures of ibuprofen and the excipients were prepared by mixing 100 mg of ibuprofen with HPMC and Gelucire 50/13 in a ratio of 1:1, in a glass mortar and triturating for 15 min. The resulting mixture (batch A) was sieved through a # 80 sieve and properly stored. The procedure was repeated with HPMC and Gelucire 50/13 mixed in the ratio 1:2 (batch B), 1:4 (batch C), 2:1 (batch D) and 4:1 (batch E) respectively.

### Preparation of ibuprofen solid dispersions using fusion method

The fusion method was employed in the preparation of solid dispersions. Briefly, quantities of the polymers, HPMC and Gelucire 50/13 in the ratio of 1:1 were accurately weighed and placed in a crucible on a water bath maintained at 60 $^{o}C$. The polymer mix was stirred continuously until it melted. A 100 mg quantity of Ibuprofen was then incorporated into the melted carrier with stirring until a homogenous melt was obtained. The crucible was then removed from the water bath and allowed to cool. The resulting solid dispersions were stored in a desiccator prior to further studies. The procedure was repeated with HPMC and Gelucire 50/13 in the ratios 1:2 (batch B), 1:4 (batch C), 2:1 (batch D), 4:1 (batch E) for HPMC and Gelucire 50/13, respectively.

### Preparation of ibuprofen solid dispersions using solvent evaporation method

In this method, the dispersions were prepared with 100 mg of pure ibuprofen sample and HPMC and Gelucire 50/13 combinations in the ratios 1:1 (batch A), 1:2 (batch B), 1:4 (batch B), 2:1 (batch D) and 4:1 (batch E), respectively. HPMC was dissolved in little quantity of absolute ethanol and Gelucire 50/13 in methylene chloride. The solutions of the polymers were mixed together and then the pure ibuprofen incorporated in the solution mixture while stirring vigorously for 15 min. The mixture was kept at room temperature for one week for the solvent to evaporate and the damp mass to dry to a constant weight.

### Determination of percent yield

The percent yield of ibuprofen from the various formulations was calculated using the following equation [22, 23]:

$$\text{Percent yield} = \frac{weight\ of\ prepared\ solid\ dispersions}{weight\ of\ drug + carriers} \times 100 \quad \ldots. 1$$

### Determination of encapsulation efficiency (EE)

A 5 mg quantity of each formulation of ibuprofen solid dispersions prepared by various techniques was weighed and dissolved in 100 ml of absolute ethanol and filtered through a Millipore filter (pore size 0.45 µm). A 10 ml volume of the filtrate was diluted to 50 ml with absolute ethanol and the absorbance taken at 234.5 nm. The encapsulation efficiency (EE) was calculated using the formula below [24]:

$$\% \text{ EE} = \frac{\text{actual drug content}}{\text{theoretical drug content}} \times \frac{100}{1} \quad \ldots. 2$$

### Solubility determination

An excess amount of each formulation of ibuprofen prepared by various techniques (about 100 mg) was poured into 25 ml of phosphate buffer saline (pH 7.4). The sample was shaken for 24 h at 37±1 ˚C using a horizontal shaker and filtered through a Millipore filter (pore size 0.45 µm). Then 0.5 ml of the filtrate was diluted 50 folds and assayed for ibuprofen using UV-VIS spectrophotometer at 272 nm. All experiments were performed in triplicates.

### Characterization of the prepared solid dispersion by FTIR

FT-IR spectra analysis of the pure sample of ibuprofen, physical mixtures of ibuprofen, HPMC and Gelucire 50/13 and the solid dispersions were carried out in the region of 4000-400 $cm^{-1}$ using FT-IR spectrophotometer (8400s, Shimadzu Industries, Japan). A 5 mg quantity of each sample was mixed with IR grade dry potassium bromide and compressed at 10 tonnes in a hydraulic press for about 5 min to form discs. The discs were then subjected to FT-IR spectroscopy to obtain the spectra of the samples.

### *In vitro* dissolution analysis

The dissolution rate of ibuprofen from the formulations was studied in simulated intestinal fluid (SIF) [25] and simulated gastric fluid (SGF) [26], using the dialysis *in vitro* release method. The dialysis membrane (MW 6000-8000, Spectrum Laboratories, Strasbourg, France) was placed in the dissolution medium for 24 h to hydrate prior to the commencement of the procedure. A 200 ml volume of the dissolution medium (SIF, pH 7.4) maintained at 37 ±1 ◦C by means of a thermostat with agitation provided by a magnetic stirrer at 100 rpm was employed. A 20 mg quantity of solid dispersion of ibuprofen was weighed out and transferred into the dialysis membrane containing 2 ml of SIF. The other end of the dialysis membrane was then tied and it was immersed into the dissolution medium. Samples (5 ml aliquots) were withdrawn from the dissolution medium and was replaced with 5 ml of fresh SIF at intervals of 10, 20, 30, 40, 50, 60, 70, 80, 90 and 120 min and analyzed for the drug content using UV-VIS spectrophotometer at 272 nm. This was performed for all the batches of ibuprofen solid dispersion, physical mixtures as well as the commercial sample. The procedure was also repeated using SGF (pH 1.2) at 245 nm.

## RESULTS

### Percentage yield of solid dispersions

The percent yield of Ibuprofen solid dispersions ranged from 84-98, 76-89 and 88-96 % for batches prepared by fusion, solvent evaporation and physical mixtures respectively (Figure 1). Batch C prepared by fusion method gave the highest yield (98 %) while D prepared by solvent evaporation gave the lowest yield (76 %).

### Encapsulation efficiency (EE)

The EEs of the solid dispersions (Figure 2) were high for all the batches, with values ranging from 54 to 98 %. It was observed that the EE decreased as the concentration of Gelucire 50/13 increased, with batch C prepared by fusion having the lowest EE value (54%). It was also observed that an increase in the concentration of HPMC brought about an increase in EE value of the formulations with the batch E prepared by solvent evaporation method having the highest EE value (98%).

### Solubility studies

The solubility profiles of ibuprofen in the various formulations and the pure sample in phosphate buffer saline (pH 7.4) at 37±1 ˚C are shown in Table 1. It was observed that the solubility of ibuprofen increased with increase in the concentration of Gelucire 50/13. Batch C formulated by fusion method had the highest solubility (39.7 mg/ml) in the medium and when compared to the pure drug sample (12.6 mg/ml), increased solubility of ibuprofen approximately 3.15-fold.

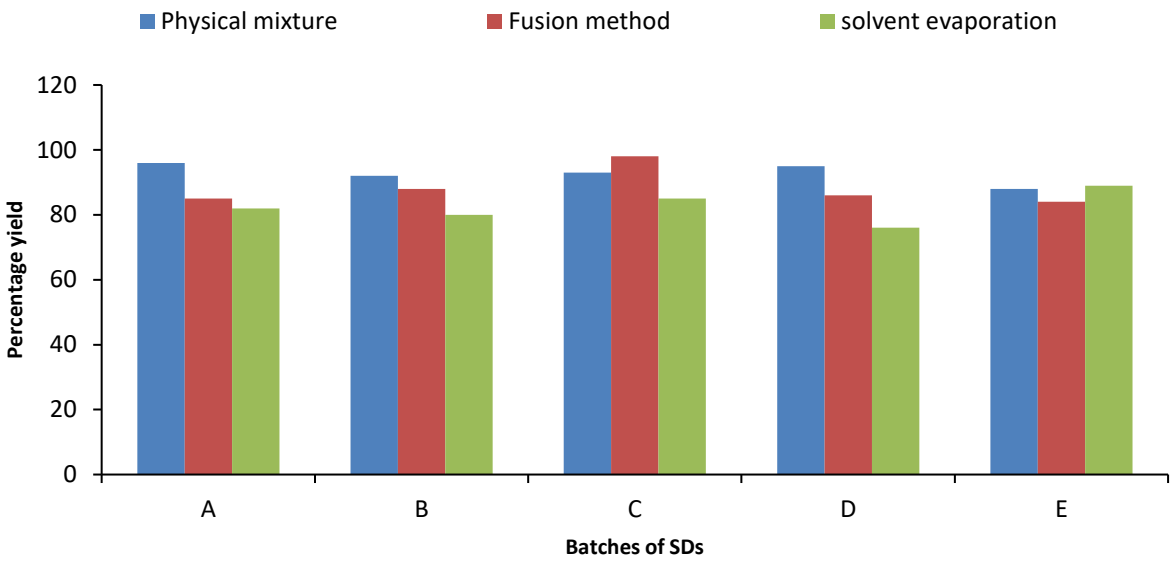



**Figure 1: Percentage yield of ibuprofen solid dispersion and physical mixtures.**

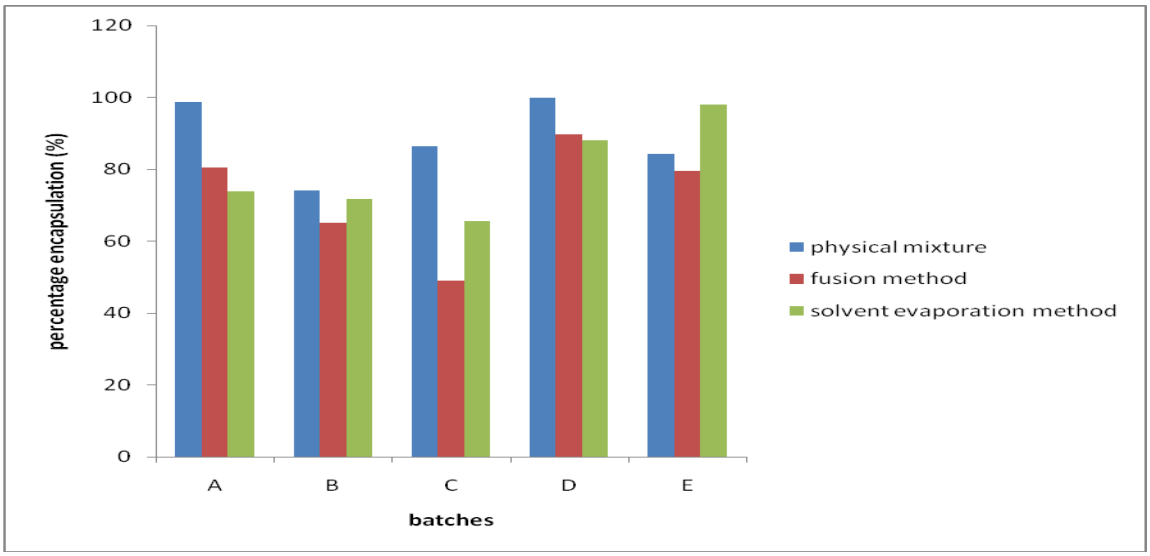
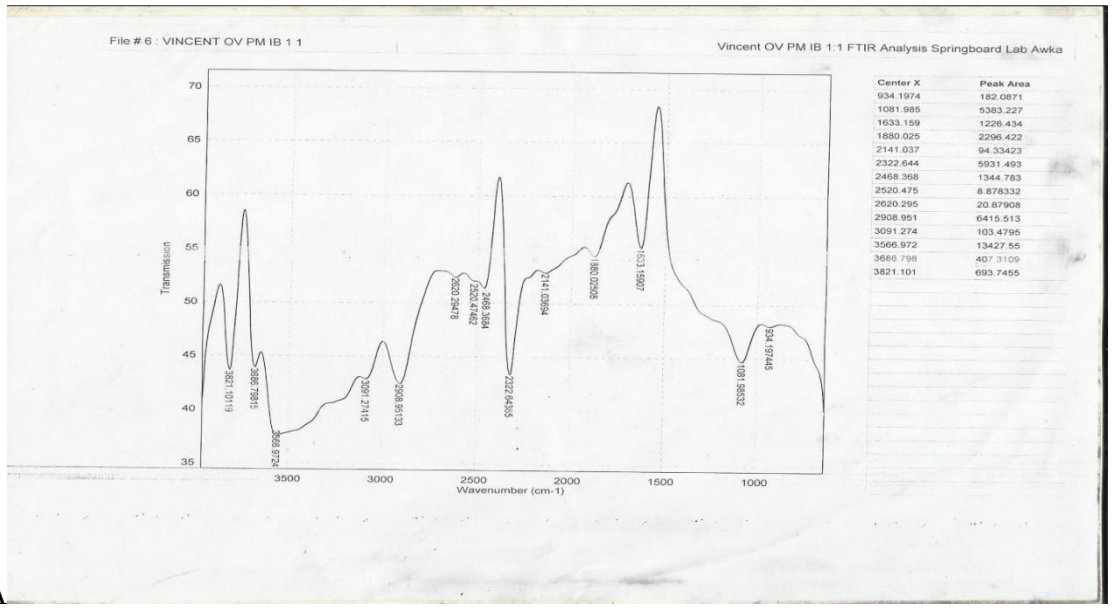


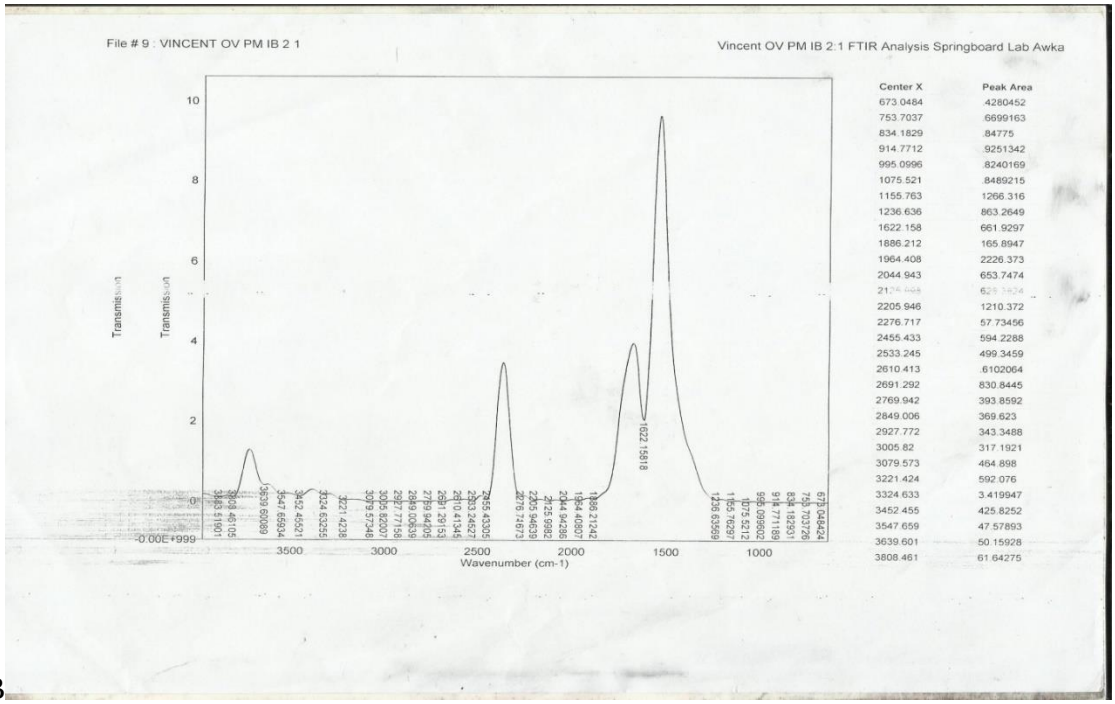

**Figure: 2. Encapsulation efficiency of ibuprofen solid dispersions and physical mixtures.**

**Table 1: Saturation solubility of ibuprofen solid dispersions in phosphate buffer (pH 7.4)**

| | SOLUBILTY (MG/ML) ± SD (N=3) | | | | |
|---|---|---|---|---|---|
| **BATCHES** | A | B | C | D | E |
| **FUSION** | 22.14 ±0.21 | 30.05 ± 0.03 | 39.7 ± 0.04 | 16.4 ± 0.22 | 17 ± 0.31 |
| **SOLVENT EVAPORATION** | 22.14 ± 0.11 | 21.30 ± 0.02 | 30 ± 0.05 | 20.33 ± 0.06 | 14.6 ± 0.03 |
| **PHYSICAL MIXTURE** | 13.00 ±0.13 | 15.30 ± 0.21 | 21 ± 0.09 | 14 ± 0.13 | 13 ± 0.03 |
| **PURE IBUPROFEN** | 12.60 ±0.04 | _ | _ | _ | _ |



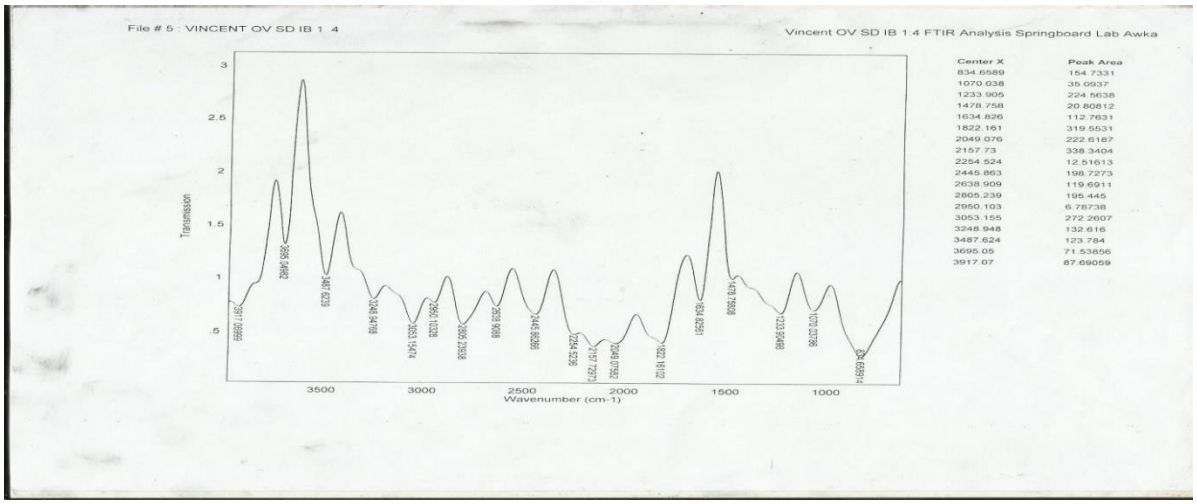

A



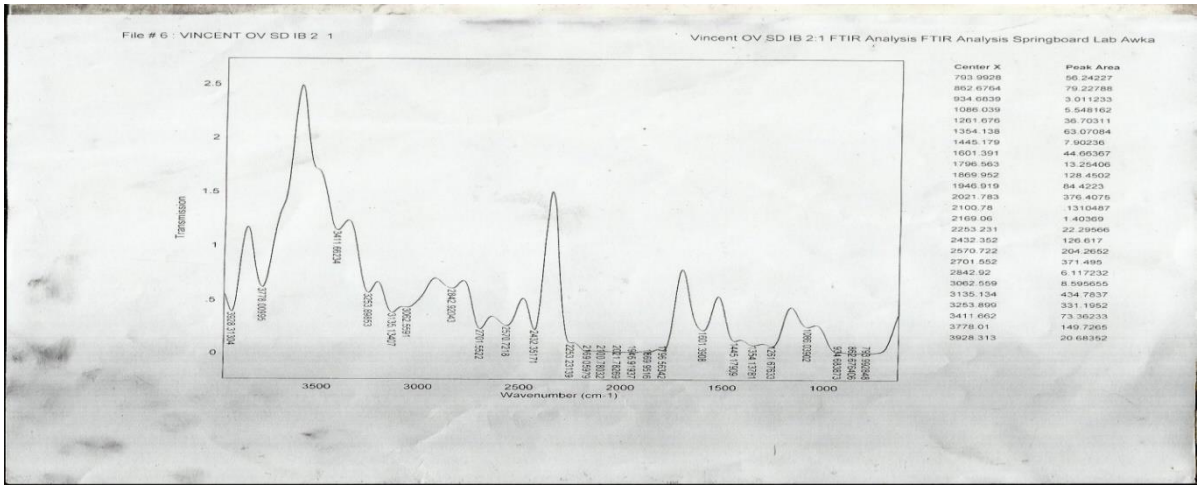

B

**Figure 3a. FT-IR spectra of physical mixtures of ibuprofen (A and B).**

**C**




D




E

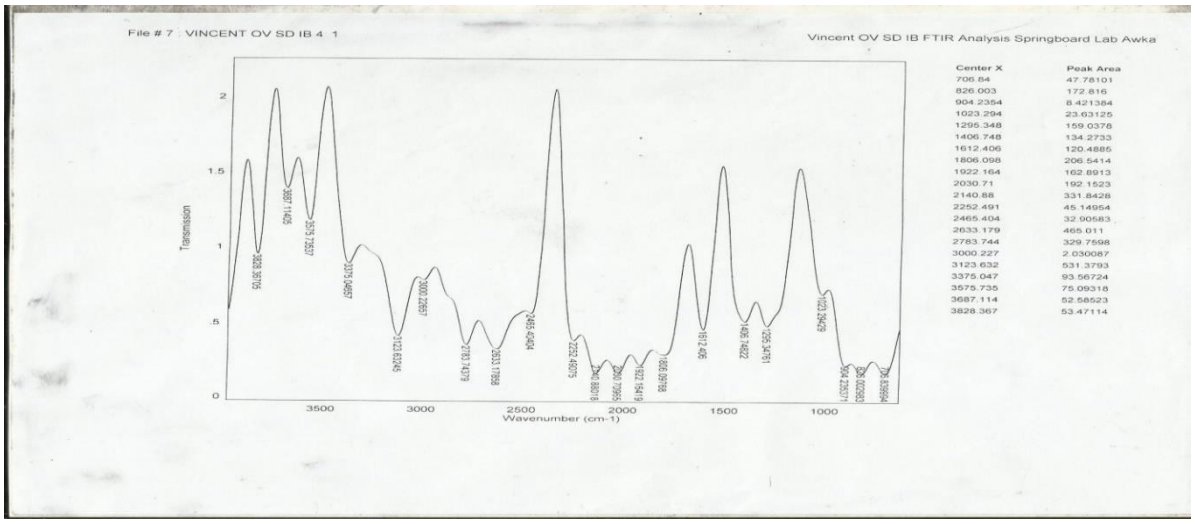
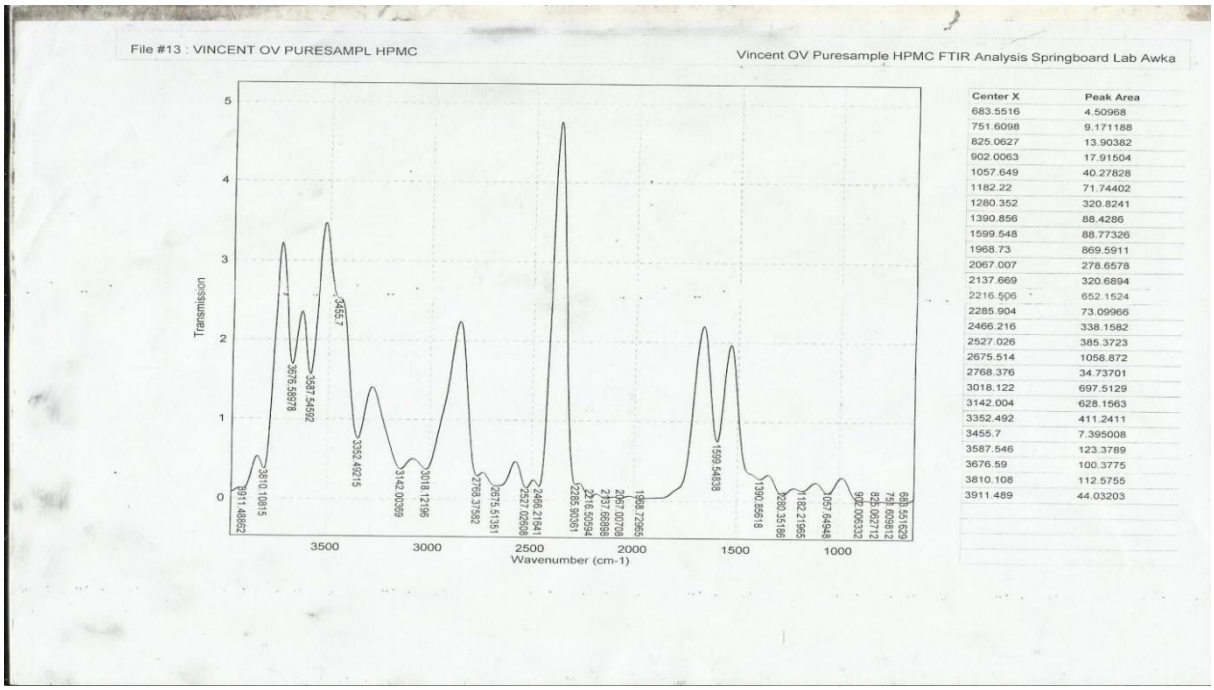



**Figure 3b. FT-IR spectra of ibuprofen solid dispersions (C, D and E).**

**F**




**G**

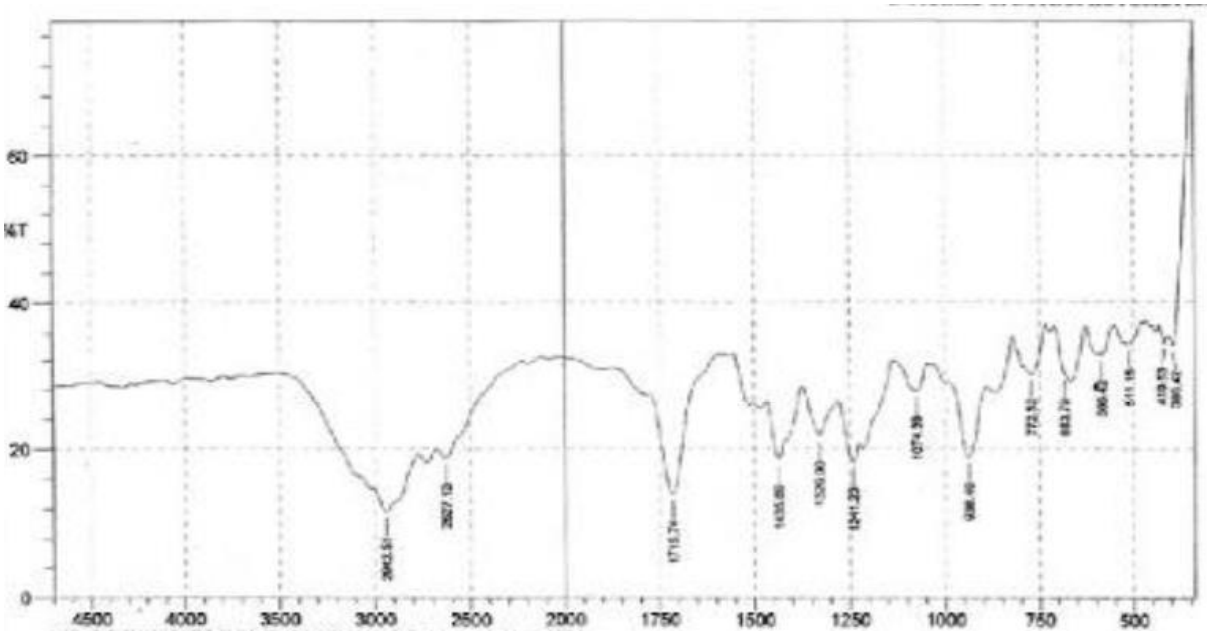



**Figure 3c. FT-IR spectra of HPMC (F) and ibuprofen (G).**

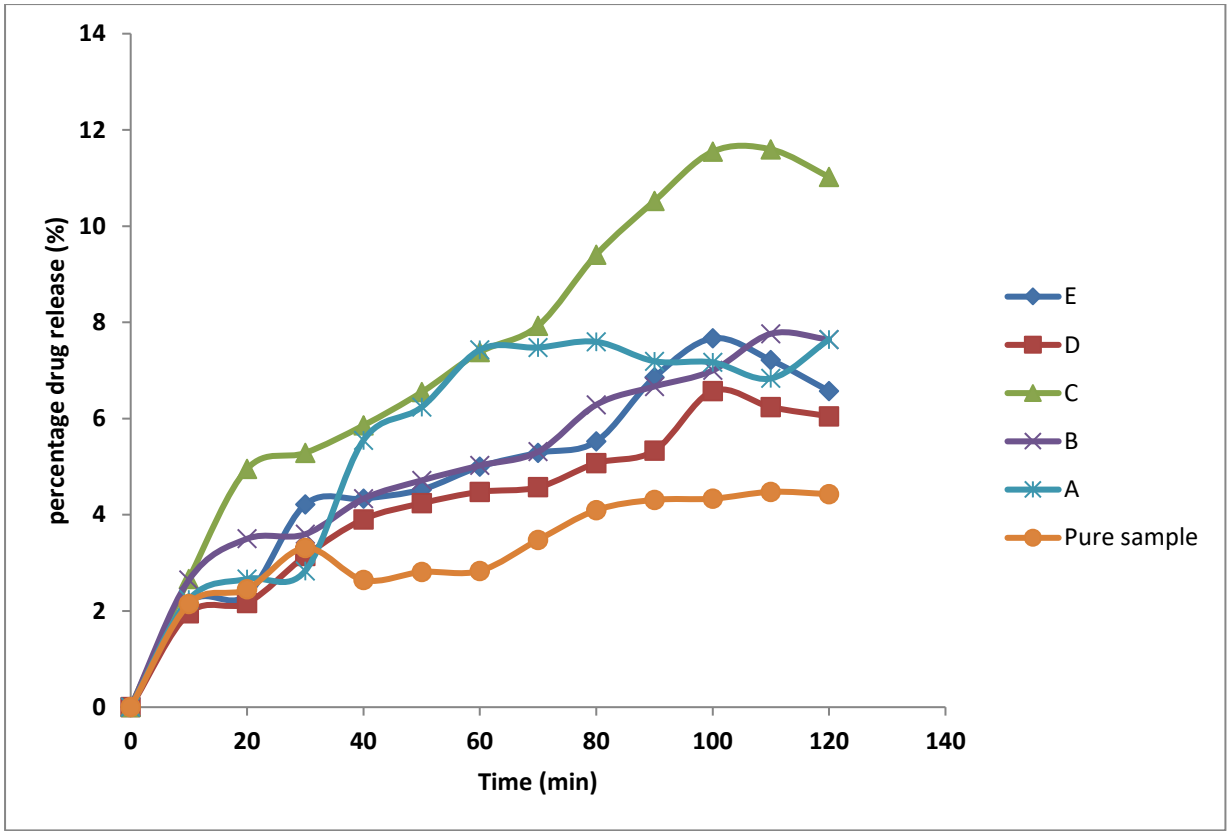



**Figure 4: Dissolution profile of Ibuprofen from the solid dispersions prepared by solvent evaporation method in SIF.**

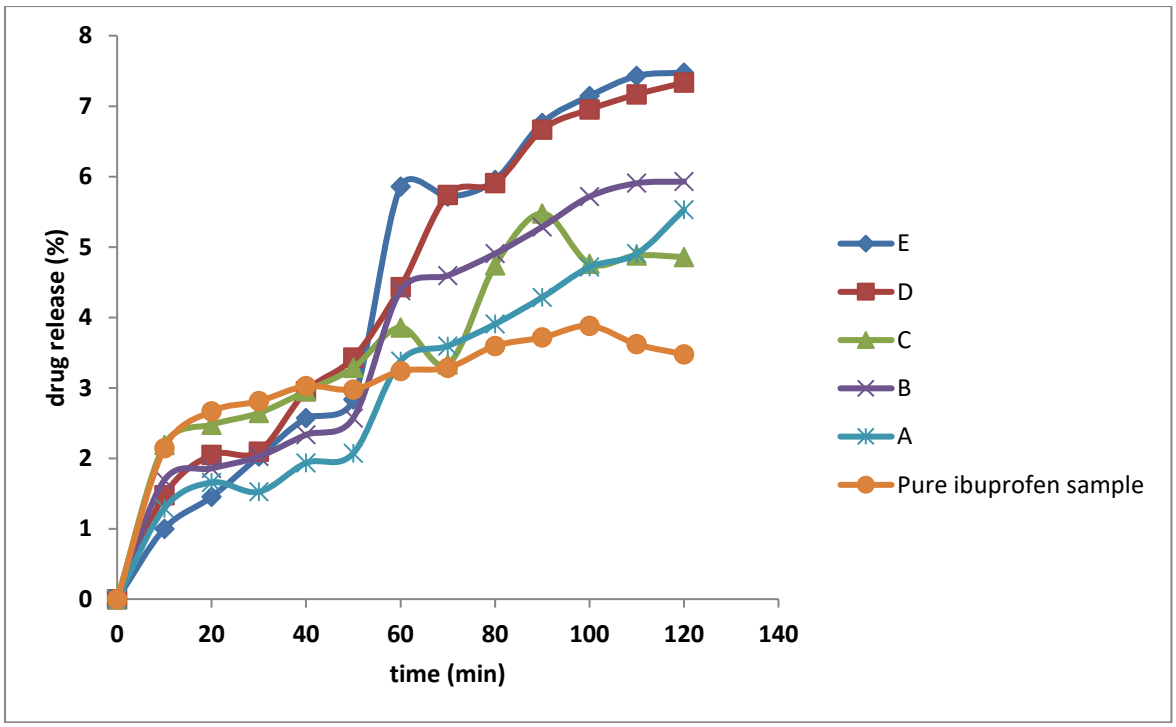



**Figure 5: Dissolution profile of ibuprofen from the solid dispersions prepared by solvent evaporation method in SGF.**

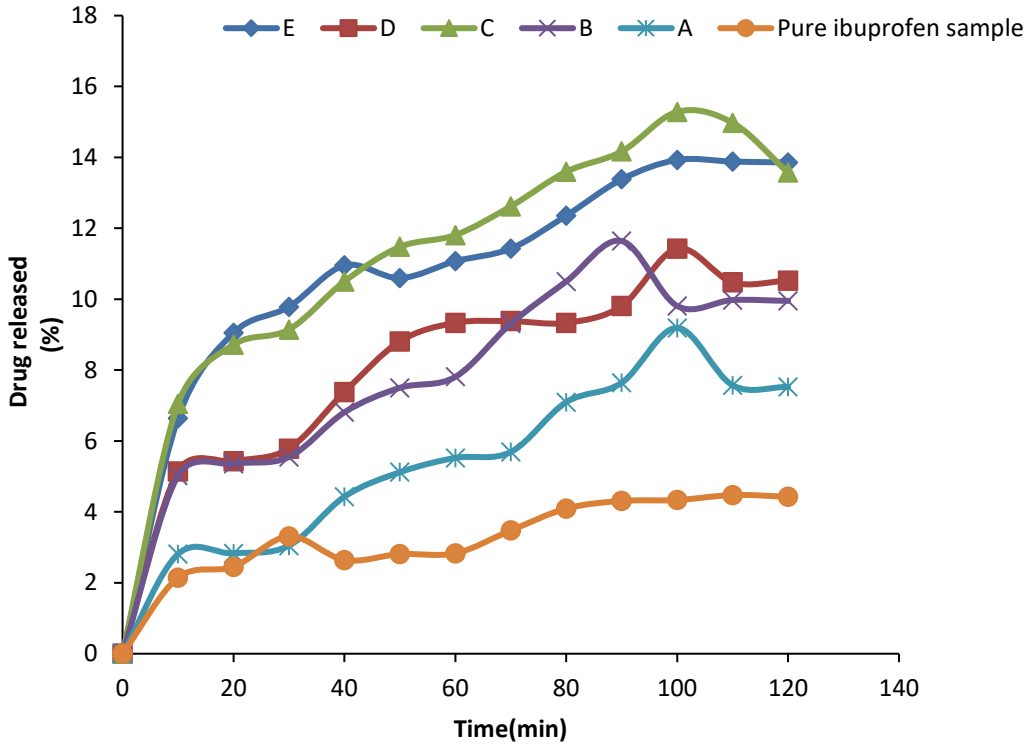



**Figure 6: Dissolution profile of Ibuprofen from the solid dispersions prepared by fusion method in SIF.**

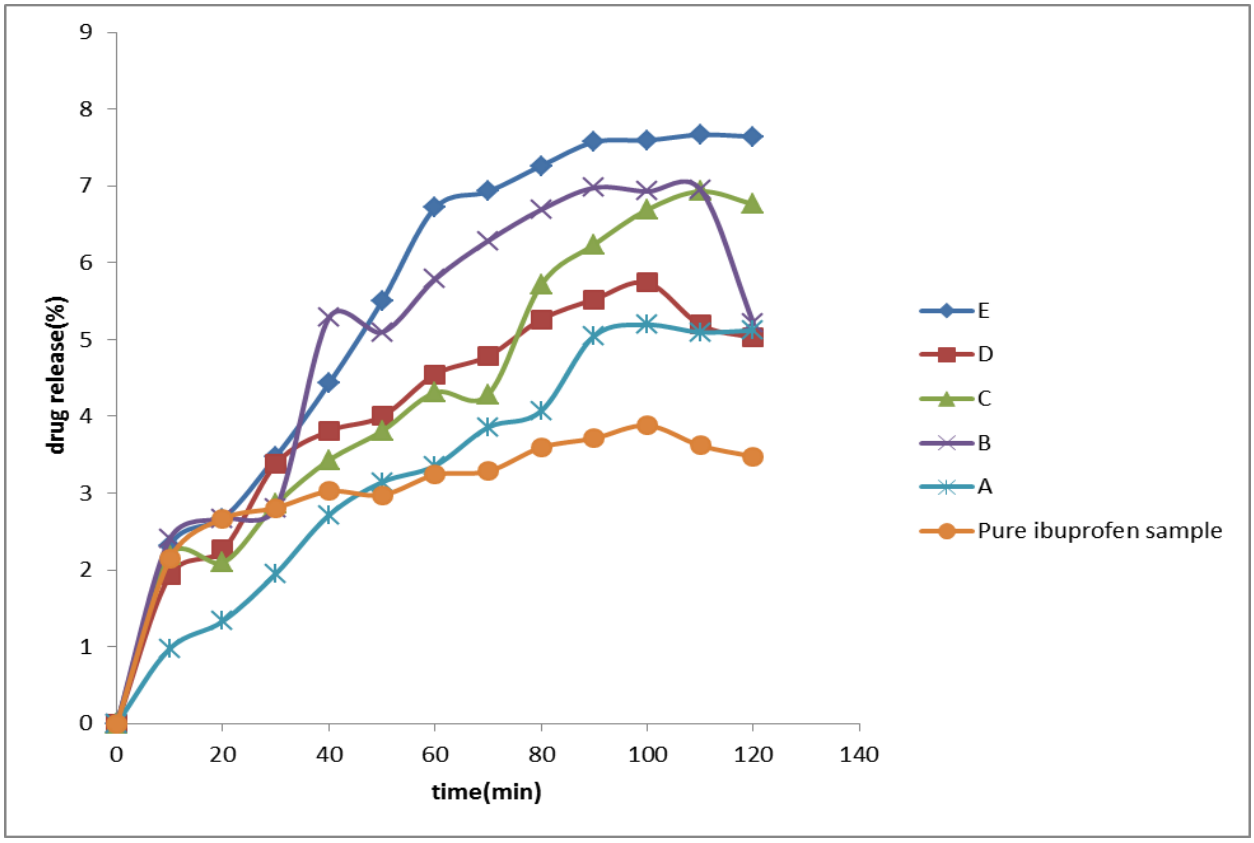



**Figure 7: Dissolution profile of Ibuprofen from the solid dispersions prepared by fusion method in SGF.**

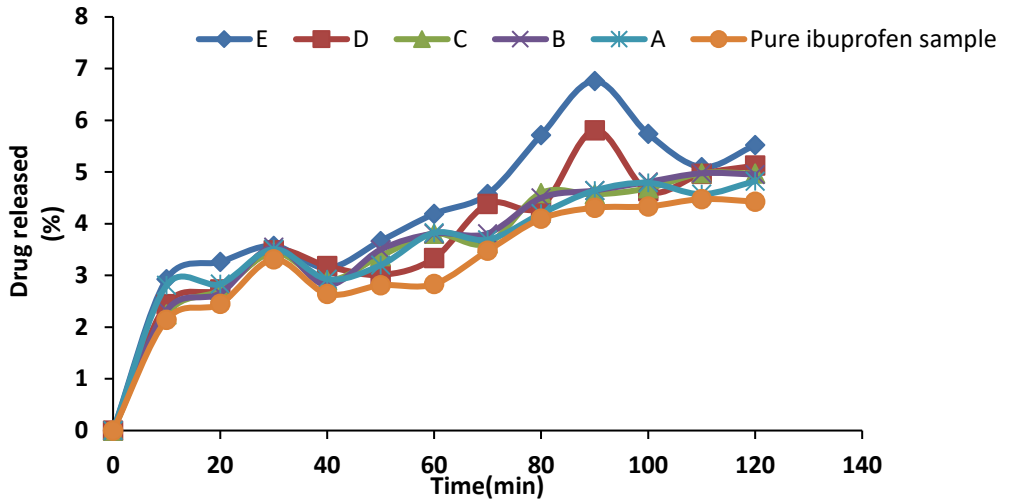



**Figure 8: Dissolution profile of Ibuprofen from the physical mixtures in SIF.**

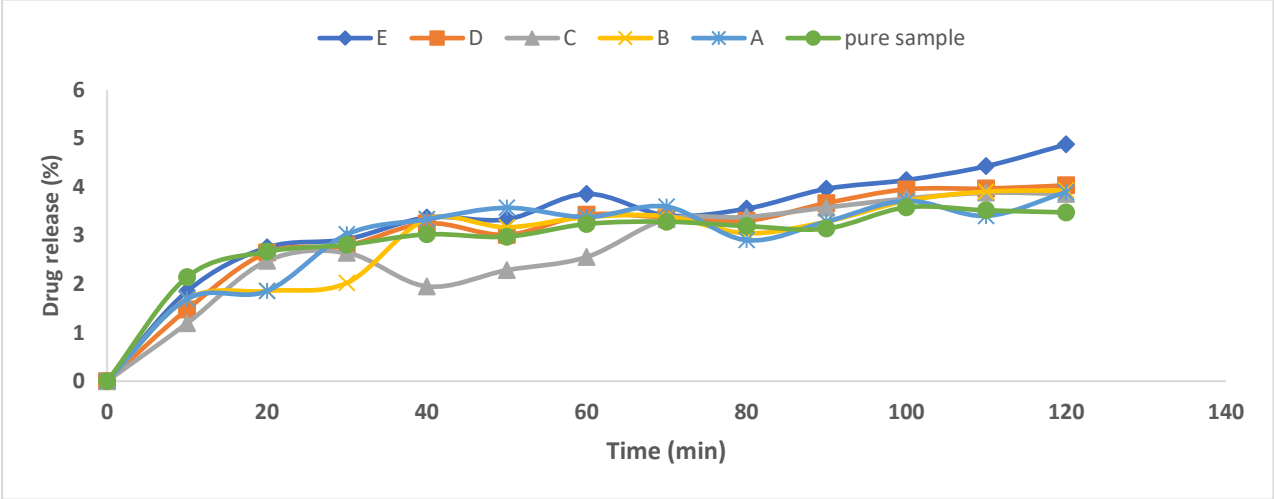



**Figure 9: Dissolution profile of Ibuprofen from the physical mixtures in SGF.**

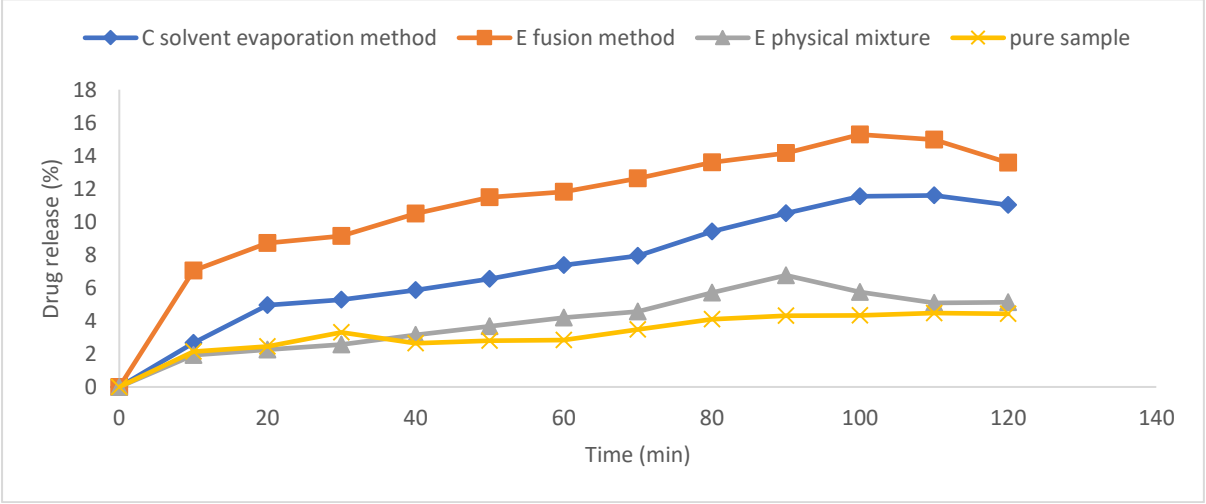



**Figure 10: Comparison of the dissolution profile of Ibuprofen prepared by various techniques in SIF.**

### Fourier transform infra-red (FTIR) spectroscopy

The spectra for the various formulation batches showed major peaks for ibuprofen at wave numbers 3629, 3528 and 3377 $cm^{-1}$ (free O—–H stretching vibrations); 3157 and 3023 (free C——H stretching vibrations); 1611, 1413 and 1300 $cm^{-1}$ (carboxylic acid and carbonyl functional group stretching vibrations); 902 and 780 $cm^{-1}$ (stretching vibrations for C——C single bonds) were retained in both the physical mixtures and solid dispersions (Figure 3).

### *In vitro* release studies

It was observed from the *in vitro* release studies that the solid dispersions and the physical mixtures showed improved dissolution of ibuprofen over that of the pure sample (Figures 4 -10). It was also observed that all the batches of solid dispersions showed significantly ($p<0.5$) faster release rate in SIF than SGF with the batch E prepared by fusion method having the highest release rate in both SIF and SGF (13.8 % and 7.6 % as seen in Figures 6 and 7) compared to those prepared using solvent evaporation method (batches C, 11.6 % in SIF and E, 7.4 % in SGF as seen in Figures 4 and 5.

## DISCUSSION

The high percentage yield values obtained (Fig. 1), showed that the methods employed in the formulation of the solid dispersions were very efficient [27] and the losses incurred might have occurred during weighing, mixing, transference or other processes involved in the preparation process [27, 28].

It was observed that although the EE value for the various batches was high (54 -98%), it decreased as the concentration of Gelucire 50/13 increased while the reverse was the case with HPMC (Fig 2). This suggests that when Gelucire 50/13 is used as matrix the drug is tightly entrapped. It could also suggest that ethanol is not a very good solvent to extract the drug from the matrix. Also, it was observed that fusion method yielded lower EE than solvent evaporation method which in turn gave lower values than that of the physical mixtures, suggesting that the drug is more molecularly dispersed in fusion method than in the other two methods [28, 29].

The results showed that the solid dispersions were useful in improving the solubility of poorly soluble ibuprofen as they were able to increase the solubility of ibuprofen approximately 3.15-fold. This could be as a result of the fact that when the solid dispersions came in contact with the medium, the polymer particles were hydrated rapidly into solutions thereby increasing the wettability of the drug particles [30].

The IR spectrum of a compound is unique and characteristic of the compound and as such could detect difference in the energy distribution of interactions between the drug and the matrix [27]. The analysis was therefore carried out to rule out any strong interaction between the drug, ibuprofen and the polymers, HPMC and Gelucire 50/13 used. All major peaks observed for ibuprofen at wave numbers 3629, 3528 and 3377 $cm^{-1}$ (free O—–H stretching vibrations); 3157 and 3023 (free C——H stretching vibrations); 1611, 1413 and 1300 $cm^{-1}$ (carboxylic acid and carbonyl functional group stretching vibrations); 902 and 780 $cm^{-1}$ (stretching vibrations for C——C single bonds) were retained in both the physical mixtures and solid dispersions (Figure 3). The spectra revealed almost all the bands without affecting the characteristic peak positions and trends which indicates absence of formation of new compound and strong interactions between the drugs and polymers [27].

The release profile of ibuprofen from the various formulations was investigated in SGF and SIF in order to simulate the gastro intestinal environment which would aid the prediction of the release profiles from the various formulations [28]. The solid dispersions and the physical mixtures showed improved dissolution of ibuprofen over that of the pure sample (Figures 4 -10). The improved dissolution of Ibuprofen might be as a result of increased wettability and therefore improved solubility due to the higher level of hydrophilicity achieved by the use of polymers, Gelucire 50/13 and HPMC, which sterically stabilized the surface of the hydrophobic drug [28, 30]. This resulted in the drug being adsorbed on the surface of the carrier in an extremely fine state of subdivision. A decrease in particle size and subsequently an increase in the surface area could bring about increase the thermodynamic activity of the drug, which in turn could greatly enhance its dissolution compared to the pure sample [31]. Also, the observation that the solid dispersions prepared by various methods produced higher solubility of ibuprofen compared to the physical mixtures, might due to the fact that the drug is in an amorphous state unlike the physical mixtures and the pure sample, where it is present in the crystalline state [32]. Many other mechanisms such as formation of solid solution and complexes, reduction of aggregation and agglomeration, improved wetting of drug, and solubilization of the drug by the carrier of the diffusion layer have also been reported to be responsible for improving the dissolution properties of drugs in solid dispersions [33, 34].

In general, all the batches of solid dispersions showed significantly ($p<0.5$) faster release rate in SIF than SGF with the batch E prepared by fusion method having the highest release rate in both SIF and SGF (13.8 % and 7.6 % as seen in Figs 6 and 7) compared to those prepared using solvent evaporation method (batches C, 11.6 % in SIF and E, 7.4 % in SGF as seen in Figs 4 and 5). It was also observed that that the solid dispersions improved the *in vitro* release property of the ibuprofen. There was increase in the release rate as the concentration of Gelucire 50/13 decreased except for the batches prepared by solvent evaporation which had batch C show the highest release rate in SIF.

*In vitro* drug release is generally affected by the nature and design of the delivery system, as well as the medium used in the release study [30]. A drug with low solubility and high permeability will likely be present in the intestine for a long time. The intestinal luminal contents and the intestinal membrane change along the intestine; this brings about variations in pH and constituent [30, 34]. It is known that pH is a very important factor in the *in vitro* dissolution of a drug; consequently, the rate of dissolution of a drug *in vitro* or *in vivo* will be determined by the pKa of the drug. Weak acids tend to be more soluble at higher pH while weak bases are more soluble at lower pH because of the possibility of ionization in the corresponding media [28]. Other factors such as agitation, viscosity and temperature of the medium, can also affect the release of the drug [28].

## CONCLUSIONS

The study showed that the ibuprofen solid dispersions prepared using binary blends of Gelucire 50/13 and HPMC were able to increase the solubility and the *in vitro* dissolution properties of ibuprofen. As such, this could represent a promising tool for improving the solubility and consequently, oral bioavailability of the poorly soluble, BCS class II drug, ibuprofen.

## ACKNOWLEDGEMENTS

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