International Journal of Drug Delivery 9 (2017) 52-70
http://www.arjournals.org/index.php/ijdd/index

Original Research Article

ISSN: 0975-0215

Sustained release formulation of metformin-solid dispersion based on gelucire 50/13- PEG4000: an in vitro study

Mumuni A Momoh*[1], Calister E Ugwu[2], Tenderwealth Clement Jackson[3], Ngumezi C Udodiri[1]

***Corresponding author:**
Mumuni A Momoh
[1]Drug Delivery Research Unit, Department of Pharmaceutics, Faculty of Pharmaceutical Sciences University of Nigeria Nsukka, Enugu State, Nigeria.
[2]Department of Pharmaceutical Technology and Industrial Pharmacy, Faculty of Pharmaceutical Sciences University of Nigeria Nsukka, Enugu State, Nigeria.
[3]Department Pharmaceutics and Pharmaceutical Technology, University of Uyo, Akwa-Ibom, Nigeria.

Received: 10 July 2017
Accepted: 09 August 2017
Published: 31 October 2017

Abstract

Metformin is a hydrophilic hypoglycemic agent with permeability and short half-life problems which leads to its low bioavailability. Solid dispersion is one of the unique approaches, to improve bioavailability profiles of drugs. The aim of this study was to prepare and evaluate solid dispersions (SDs) of metformin with polyethylene glycol 4000 (PEG 4000) and Gelucire®50/13 in order to increase its permeability and bioavailability. Solid dispersions of Metformin containing various ratios of PEG 4000: Gelucire®50/13 (1:1, 1:2, 2:1, 1:4, 4:1 as Batch A, Batch B, Batch C, Batch D and Batch E) was prepared using solvent evaporation and fusion techniques. The physical mixtures which served as controls were also prepared. The SDs was evaluated using encapsulation efficiency, percentage yield. The formulations were also characterized with FTIR and DSC. The in vitro drug release studies were also evaluated. The results obtained showed that solid dispersion formulations at pH, 1.2 and 7.4 demonstrated higher release rates than the pure drug. The SDs showed high drug release rates and encapsulation efficiency (% EE) although Batch C containing PEG 4000 and Gelucire 50/13 in the ratio of 2:1 appeared as the batch with most % EE, drug release with broad melting peak. The release rate of metformin increased with increasing amount of PEG 4000. Batch C, SDs containing PEG 4000 and Gelucire 50/13 in the ratio of 2:1 were found to be the most optimized batch with enhanced encapsulation efficiency, most drug release and therefore, improved permeability and bioavailability of metformin.

Keywords: Solid dispersion, Metformin, Gelucire, bioavailability and characterization.

Introduction

Metformin is an oral antihyperglycemic agent from biguanide class. It is used for the management of patients with noninsulin-dependent diabetes mellitus (NIDDM), particularly those with refractory obesity [1]. It belongs to class III of biopharmaceutical classification system with low permeability property. It is highly water-soluble, whose low bioavailability and short and variable biological half-life (1.5–4.5 h) needs frequent administrations to maintain effective plasma concentrations [2]. It has a relatively low bioavailability (50 – 60%) [3,4]. Solid dispersion (SDs) is one of the approaches to increase permeability of drug substance. SDs enables reduction of particle sizes up to molecular level which will enhance permeability of the poorly permeable drugs. Therefore, particle size reduction, leading to increased surface area, is a very promising approach to enhance permeability rate and, thus, the bioavailability of poorly permeable compounds. When the solid dispersion formulation is exposed to aqueous media, the drug-carrier dissolves and the drug releases as fine colloidal dispersions and the particles having being in a very reduce or molecular level during the formulation will be able to permeate the membrane without much difficulty. The present study was based on the objective of improving the permeability of poorly permeable anti-hyperglycemic drug, metformin using solvent evaporation and fusion methods of solid dispersion techniques with combined ratio of two lipophilic polymers.

The use of polymeric carriers in enhancing the solubility and bioavailability of drugs has increased tremendously. The two polymers, PEG and Gelucire have been used in the formulations of solid dispersions [5, 6].

PEG is often used as vehicle because of its low toxicity, low melting point, rapid solidification rate, high aqueous solubility, availability in various molecular weights, economic cost, and physiological tolerance. A particular advantage of PEGs for the formation of SDs is that they have good solubility in many organic solvents. The melting point of PEG is low in all cases, which is advantageous for manufacturing SDs. Additional attractive features of PEGs include their ability to solubilize some compounds and improve compound wettability. These and other properties make PEG a suitable vehicle in the formulation of dosage forms s [7, 5-6, 8-10].

Gelucire on the other hand, is a member of vehicle deduced from the mixture of mono- di- and triglycerides with PEG esters of fatty acids. They have numerous uses in pharmaceutical preparations such as in formulation of immediate and controlled release drugs [11-13].

DOI:10.5138/09750215.2162

These polymers were selected as carriers in this research work for the formulation of solid dispersion of a hydrophilic drug, Metformin, for two distinct reasons: to equip and improve the poor permeability nature of the drug in order to cross the cell membrane without difficulty and to improve the short half life of the drug by the sustained activity of the carriers.

Material and Methods

Materials

Metformin (Indoco Remedies Goa, India), PEG 4000 (Sisco Research laboratories Pvt Ltd), Gelucire®50/13 (Gattefosse, St. Priest, France), HCl (Merck, Germany). All other reagents and solvents used were of analytical grade.

Methods

Preparation of metformin solid dispersions by solvent evaporation method

Metformin solid dispersions were prepared with PEG 4000 and Gelucire® 50/13 in various ratios (1:1, 1:2, 2:1, 1: 4, and 4:1 as Batch A, Batch B, Batch C, Batch D and Batch E respectively) using solvent evaporation and fusion methods. The amount of metformin was constant in all the five (5) batches in all the methods. The appropriate weight of the drug and the polymers was weighed out as shown in Table 1. Gelucire® 50/13 was dissolved in methylene chloride while PEG 4000 was dissolved in methanol (as little quantity as can dissolve the polymer were used). Then, both of them were mixed together before the drug was introduced and stirred vigorously for up to 5 min as the solvent evaporates. It was then kept to dry at room temperature for one week.

Preparation of metformin solid dispersions by Melting (fusion) method

Solid dispersions were prepared by melting the accurately weighed amounts of PEG 4000 and Gelucire® 50/13 (Table. 1) in a water bath and the drug was dispersed in the molten solution. The mixtures were stirred repeatedly, after 10 min. they were cooled by placing the container in an ice bath. Solid mass obtained was passed through the No. 80 sieve and stored in air tight container until used.

Physical mixtures

The physical mixtures were prepared by using the formula in Table 1. Then mixed in a mortar by trituration. The resultant mixture was passed through No. 80 sieve and stored until used.

Table 1: Table for the formulation of glibenclamide solid dispersions

Ratio	PEG 4000 (mg)	Gelucire (mg)	Metformin (mg)
Batch A	200	200	100
Batch B	200	400	100
Batch C	400	200	100
Batch D	200	800	100
Batch E	800	200	100

Preparation of Beer-Lambert's plot for metformin

A 10 mg quantity of pure metformin was weighed out into a measuring cylinder. A 10 ml of methanol was used to dissolve the drug. The solution filtered and the volume was made up to 100 ml with phosphate buffer. It was filtered and the filtrate was diluted serially to obtain (2 - 12 mg %) concentrations of metformin. The absorbance readings of these solutions were taken using UV-spectrophotometer (Jenway, 6405, UK) at 232 nm. A graph of absorbance against concentration was plotted and the slope measured.

Determination of Percentage Yield

The percentage yield is useful to determine the efficiency of a preparation technique. The percentage yield was calculated by using the equation [14]:

$$Percentage\ yield = \frac{Obtained\ weight}{Theoritical\ amount\ of\ the\ drug} \times 100 \quad ...1$$

Determination of encapsulation efficiency

An amount containing 100 mg metformin prepared by different methods and the different ratios was weighed out. It was dissolved in 10 ml of methanol, filtered and was made up to 100 ml using phosphate buffer. Then, a 2-10 fold dilution was prepared with phosphate buffer. This was assayed using spectrophotometer

(Jenway, 6405, UK) at 232 nm. Their encapsulation efficiency was calculated using the formula below:

$$Encapsulation\ Efficiency\ (\%) = \frac{Actual\ drug\ content}{Theoritical\ drug\ content} \times 100$$ 2

In vitro dissolution analysis of metformin solid dispersions

The *in vitro* dissolution analysis was carried out on all the batches of metformin solid dispersions and metformin pure drug. This was carried out using USP XXII type I dissolution test apparatus with dialysis membrane placed in a dissolution medium. A 900 ml of the dissolution medium (SIF) at pH, 7.4 was maintained at 37±1^{o}C by means of a thermostat set at 100 rpm. The dialysis membrane was immersed in the SIF for 20 min, with the aid of an insulin needle; it was opened and was then tied at one end with a thread. Then, an amount containing 100 mg of metformin was weighed out and transferred into the dialysis membrane. The other end of the dialysis membrane was then tied and immersed in the dissolution medium. A 5 ml aliquot withdrawn from the dissolution medium was made and replaced with 5 ml of fresh SIF at different time intervals (30, 60, 90, 120 … 360 min). They were analyzed for their drug content using spectrophotometer (Jenway, 6405, UK) at 232 nm. This was performed for all the batches and the procedure repeated using simulated gastric fluid (SGF) at pH 1.2 for about 6 h.

Characterization of the solid dispersion formulation Differential scanning calorimetric analysis

Melting transitions and changes in heat capacity of the lipid matrices were determined using a calorimeter (Netzsch DSC 204 F1, Germany). About 1 mg of each excipient and solid dispersion were weighed into an aluminum pan, hermetically sealed and the thermal behavior determined in the range of 10-80 C at a heating rate of 5 C/min. The temperature was held at 80 C for 10 min and thereafter, cooled at the rate of 5 to 10 C/min. Baselines were determined using an empty pan, and all the thermograms were baseline corrected.

FTIR Spectroscopy

The solid state interactions between the drug and carriers in solid dispersions was studied by Infrared spectroscopy. The finely powdered pure drug or drug carrier dispersion system was intimately mixed with potassium bromide and compressed into transparent pellet. I.R. spectra were obtained on a FTIR spectrometer (FTIR-640, Varian. Australia) at 4000 to 400cm^{-1} [15,16].

Results and Discussion

Results of the Beer-Lambert's plot

The Beer-Lambert's plot which is the plot of absorbance against concentrations is shown in Figure 1. The plot gave a linear graph at R^2 = 0.997.

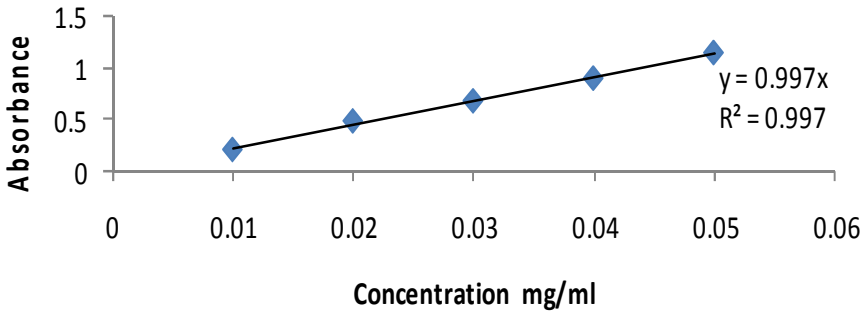

Figure 1: Beer-Lambert's plot for pure metformin

Percentage yield of metformin

The percentage practical yield was found to be high across the different batches with different methods. It ranged between 91.3 to 99.2 % as shown in Table. 2. The maximum percentage practical yield was found to be 99.2 % for Batch C. Among the methods Physical mix (PM) had the highest yield followed by Solvent evaporation (S.E) method and finally the fusion (FM) method.

Table 2: Percentage yield of metformin

Batches	S.E (%)	FM (%)	PM (%)
Batch A	95.2	93.7	98.3
Batch B	93.5	90.1	94.7
Batch C	98.8	95.3	99.2
Batch D	95.7	91.3	96.5
Batch E	95.5	93.3	97.7

The encapsulation efficiency

The encapsulation efficiency (% EE) represented in Table. 3 showed that the encapsulation efficiency increased with increased amount of polymers but was more at Batch C. Therefore, Batch C has the highest encapsulation efficiency.

Table 3: Table for the encapsulation efficiency

Batches	SE. (M±SD %)	FM (M±SD %)	PM (M±SD %)
Batch A	42 ±0.27	42 ±0.95	42 ±0.50
Batch B	50 ±0.15	51 ±0.76	51 ±0.15
Batch C	81±0.10	72 ±0.89	74 ±0.66
Batch D	62±0.74	72 ±0.07	67 ±0.11
Batch E	53 ±0.66	54 ±0.76	51 ±0.15

Results of the *in vitro* dissolution studies

The results of *in vitro* dissolution properties of metformin solid dispersion formulations and pure metformin sample were shown in Figures 2-7. Comparing the release profiles of the pure samples of metformin and the solid dispersions, it was shown that metformin solid dispersion formulations gave higher release than the pure sample. This might be due to increased permeability of metformin as a result of high porosity created by solid dispersion formulations. Also Batch C with higher encapsulation efficiency gave the highest release in the dissolution studies in both SGF and SIF. The fusion melting method gave the highest release followed by solvent evaporation method and then, the physical mix.

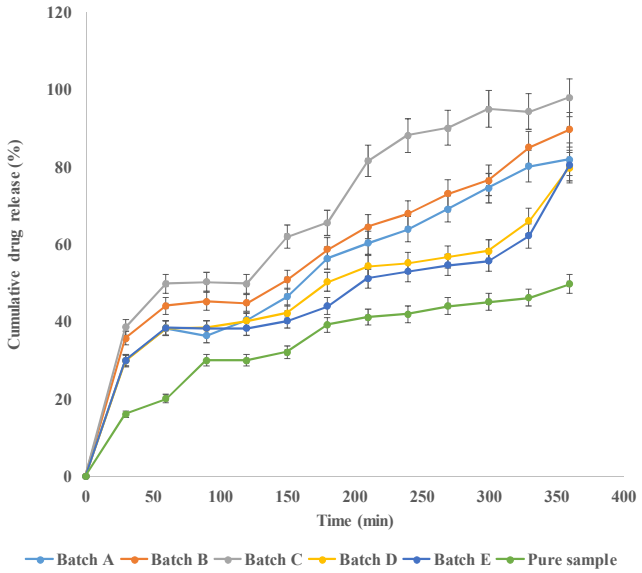

Figure 2: Dissolution of metformin from the solid dispersions prepared by solvent evaporation method in SIF.

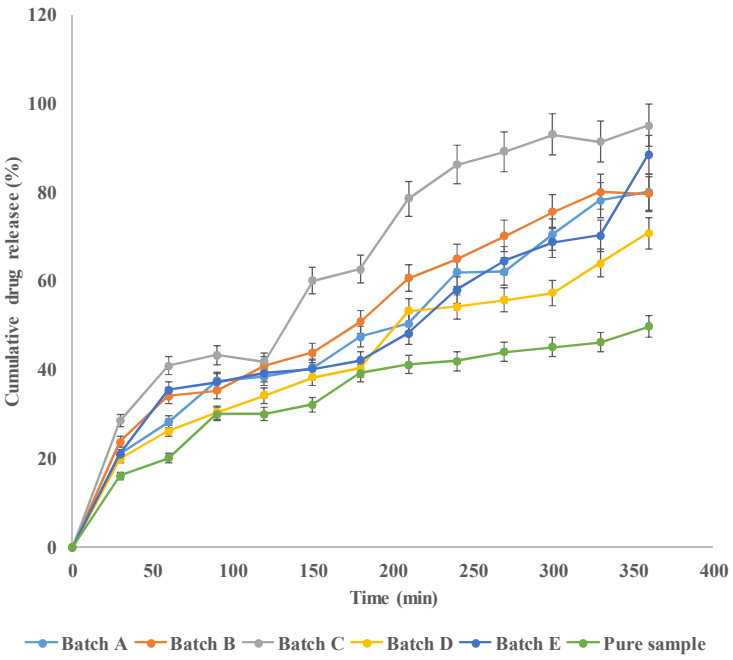

Figure 3: Dissolution of metformin from the physical mixtures in SIF.

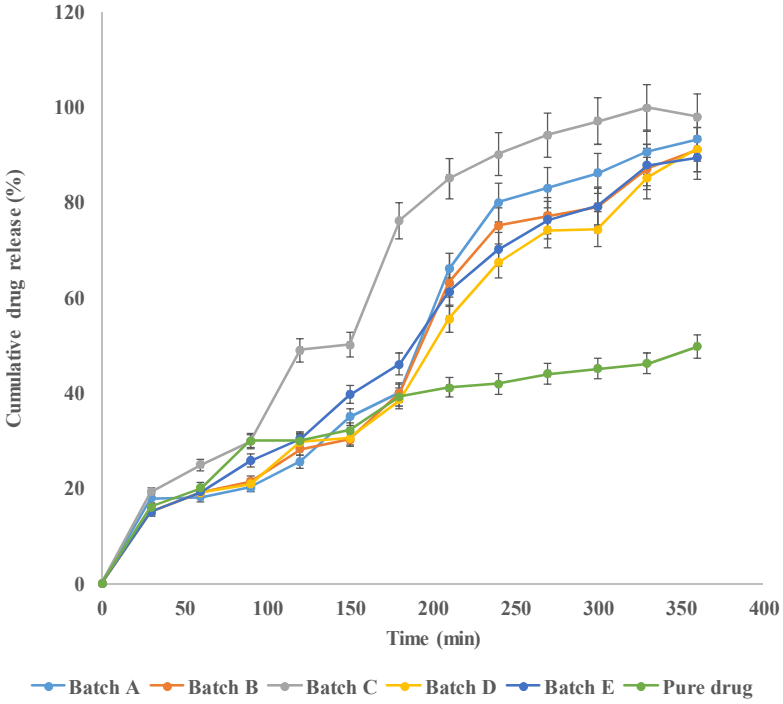

Figure 4: Dissolution of metformin from the SDs prepared by fusion method in SIF.

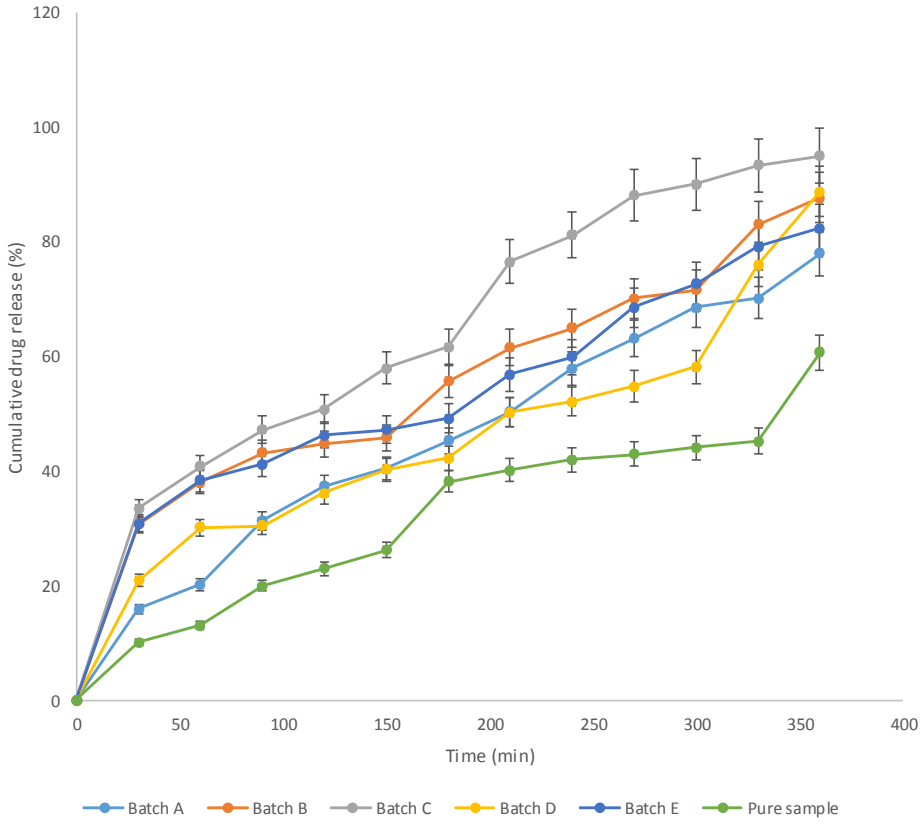

Figure 5: Dissolution of metformin from the SDs preparation by physical mixture in SGF.

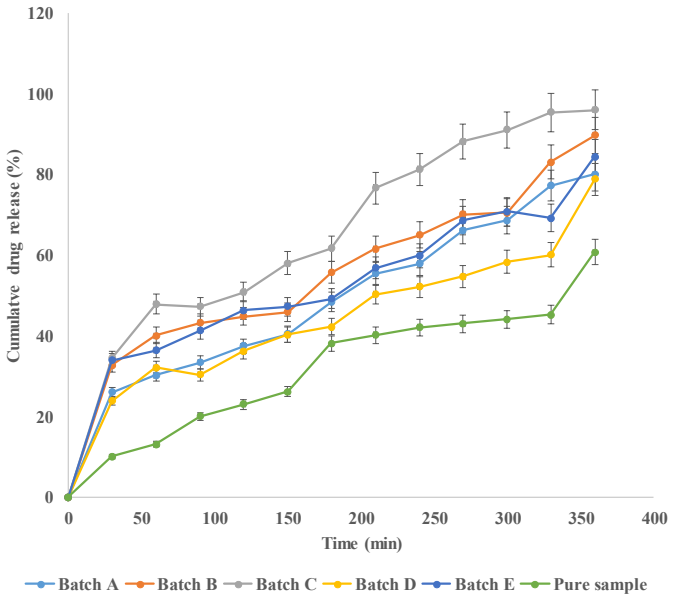

Figure 6: Dissolution of metformin from the SDs preparation by solvent evaporation in SGF.

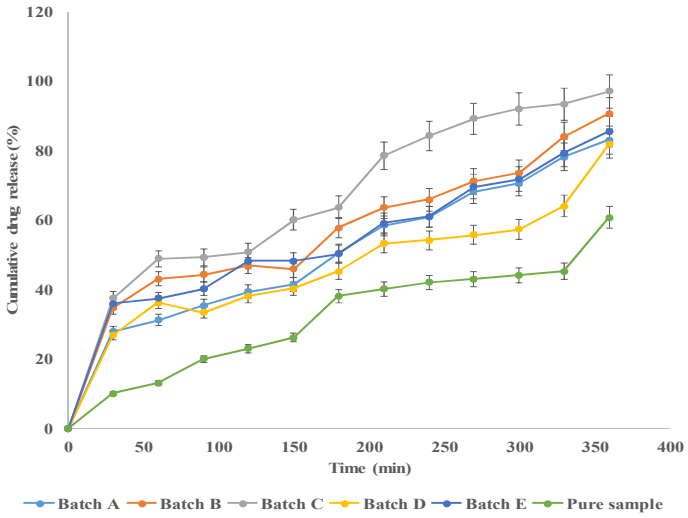

Figure 7: Dissolution of metformin from the SDs preparation by fusion method in SGF.

Thermal properties

The thermograms of the pure metformin exhibited a sharp endothermic melting peak at 232.0 ºC as shown in figure 9. While figure 9-11 is showing the DSC thermograms of pure PEG 4000 and gelucire 13/50 showed an endothermic peak at 63.7 and 39.9 ºC respectively. The DSC of SD Batch A, Batch B, Batch C, Batch D and Batch E showed an endothermic peak at 64.3, 64.3, 68.4, 63.0 and 68.6 ºC respectively (figure 12-15). The sharp peaks of the drug and the excipients showed crystallinity existence. In the solid dispersion formulations, there were two different thermograms which was due that the hydrophilic nature of the drug. Batch C and E had more broad peak than other batches. The broad peak is an indication that the formulations existed in an amorphous state and will molecularly entrap more of the drug and which will more create pores for drug localization and this will enhance drug release and loading efficiency and capacity of drugs. Figure 16 showed the combination of all the batches.

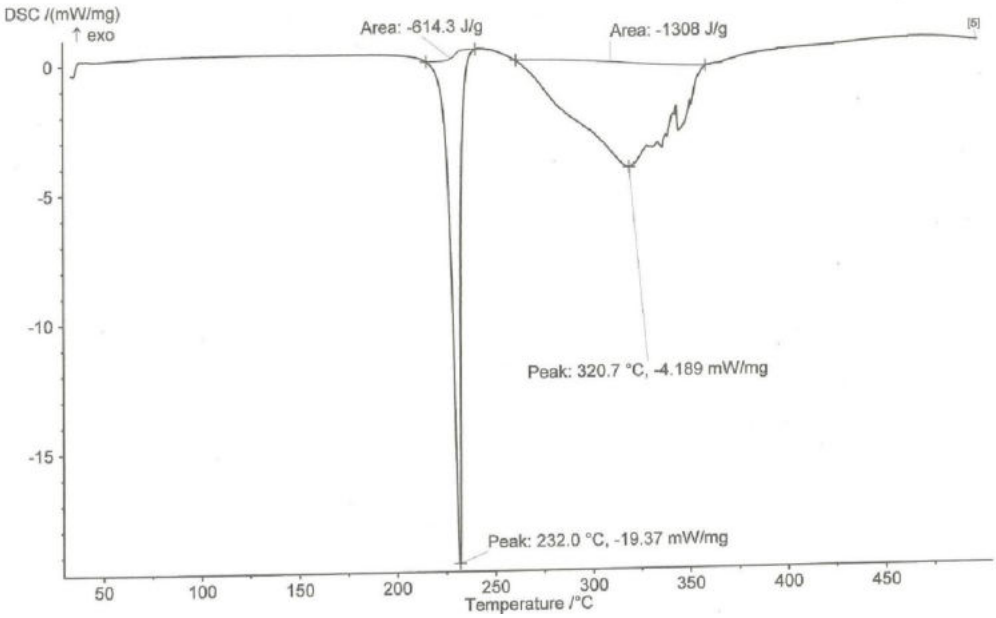

Figure 8: DSC thermogram of pure metformine

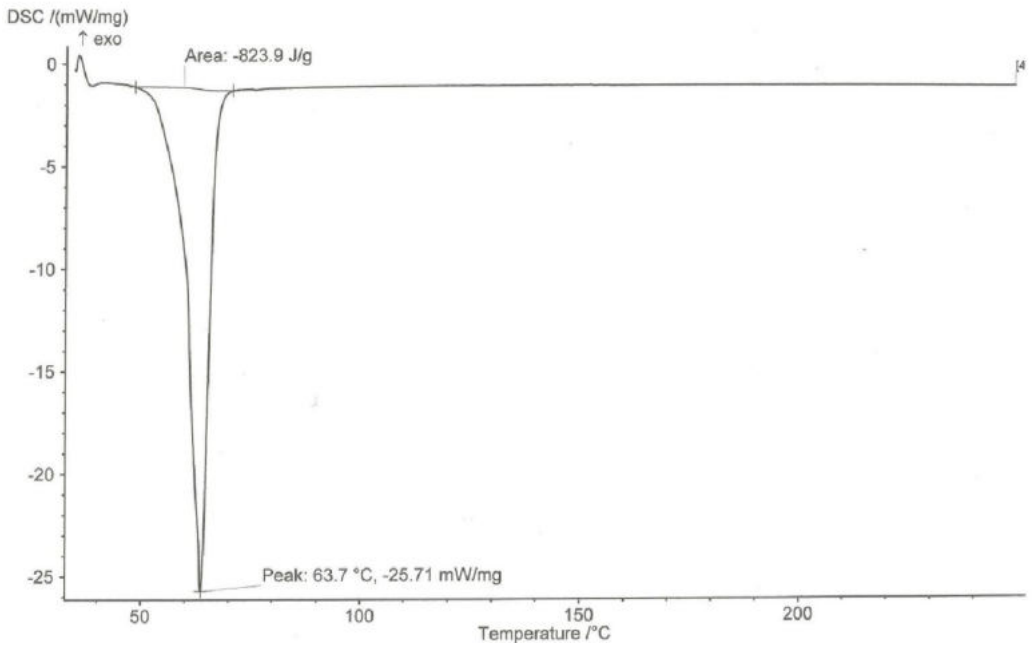

Figure 9: DSC thermogram of PEG 4000

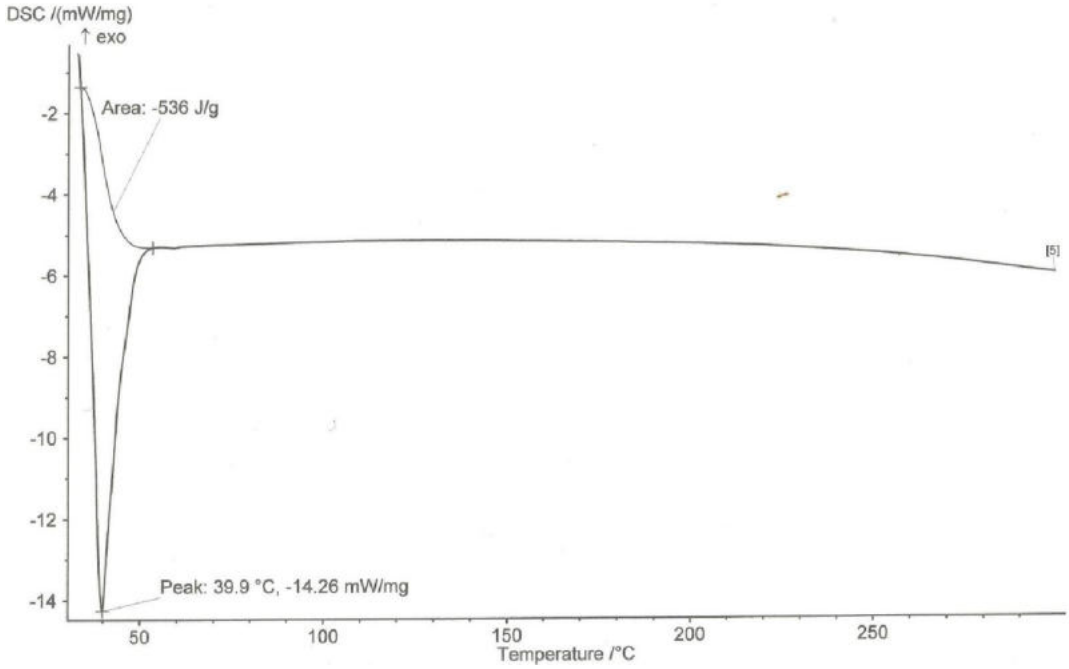

Figure 10: DSC thermogram of Gelucire 13/50

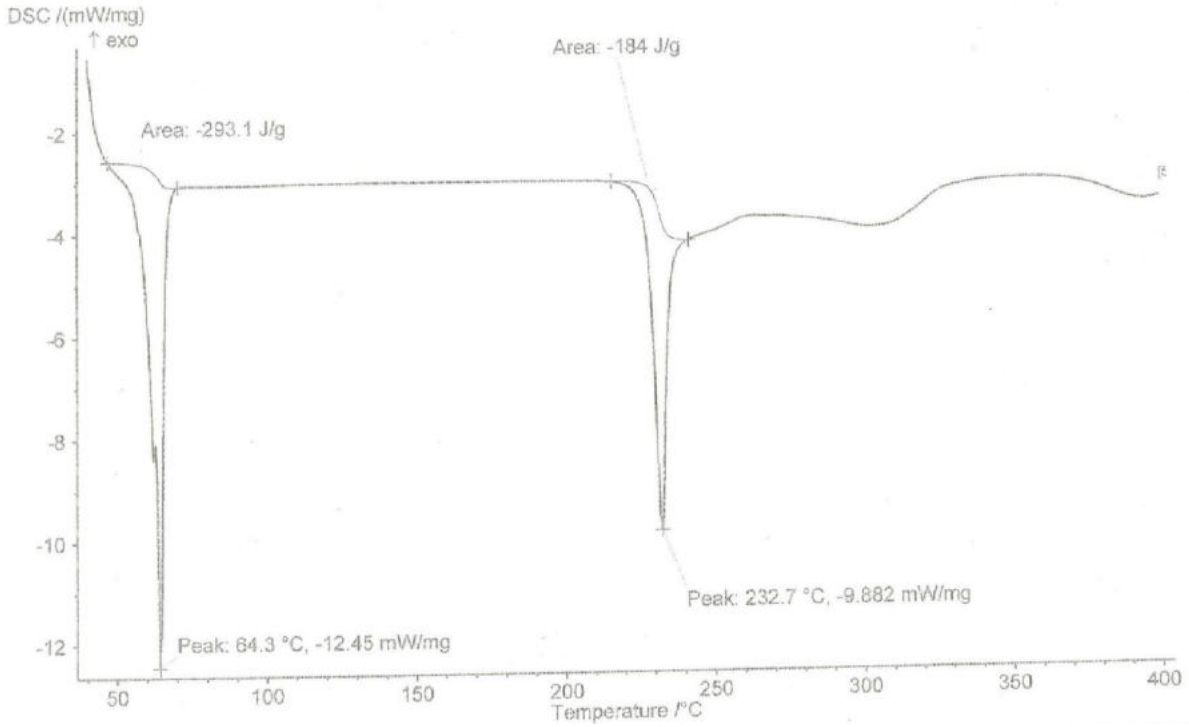

Figure 11: DSC thermogram of Batch A (1:1) Solid dispersion formulation

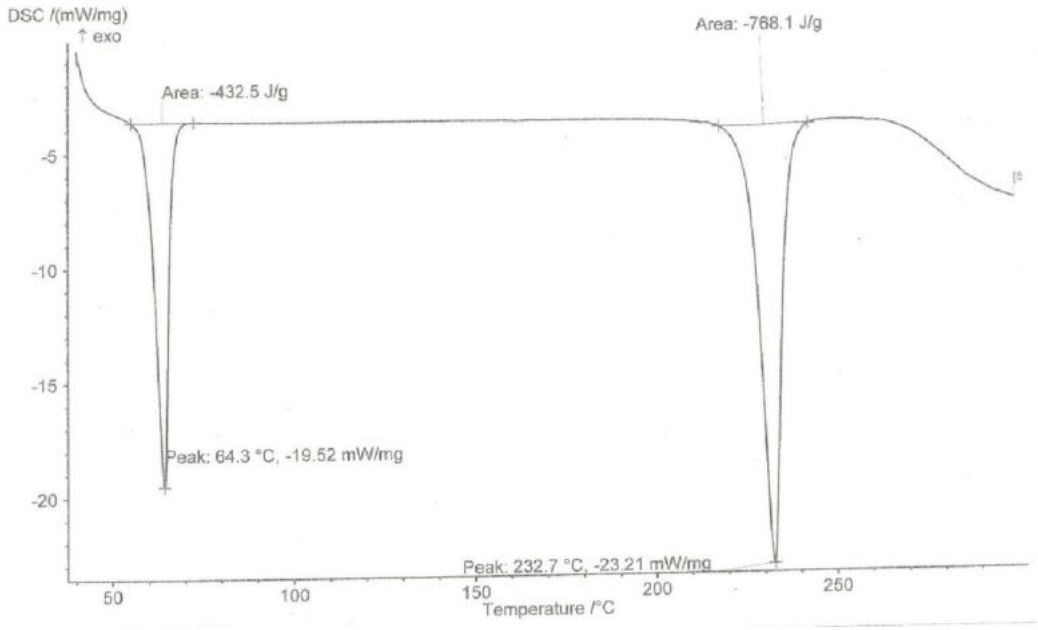

Figure 12: DSC thermogram of Batch B (1:2) Solid dispersion formulation

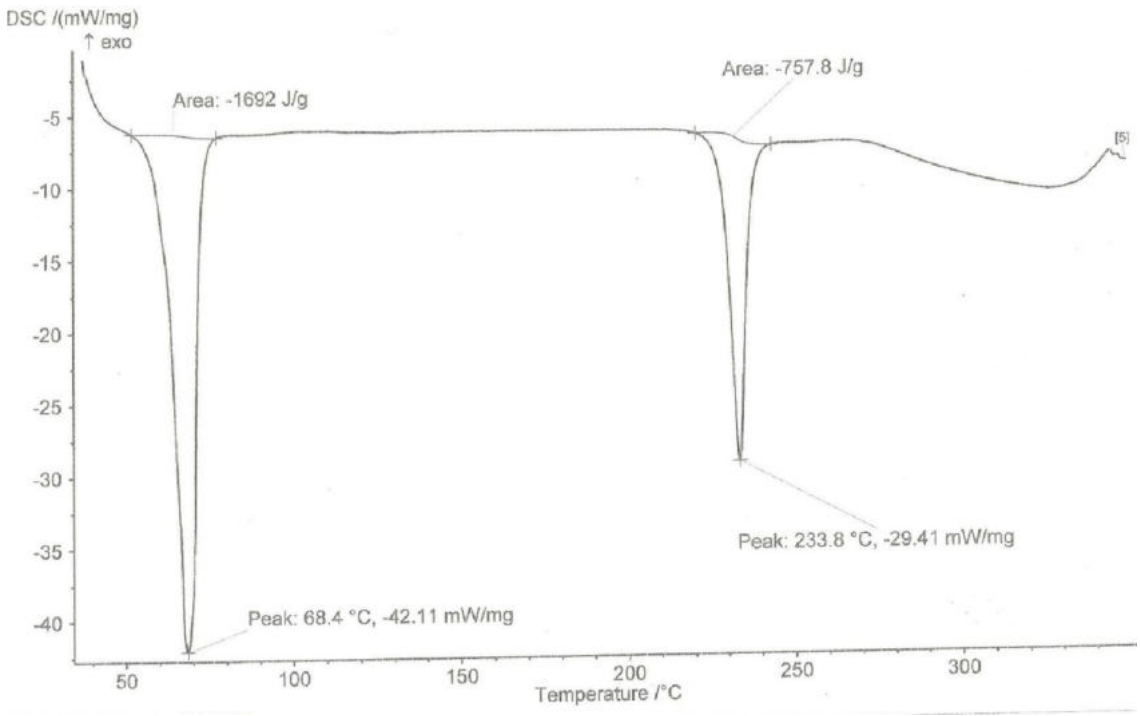

Figure 13: DSC thermogram of Batch C (2:1) Solid dispersion formulation

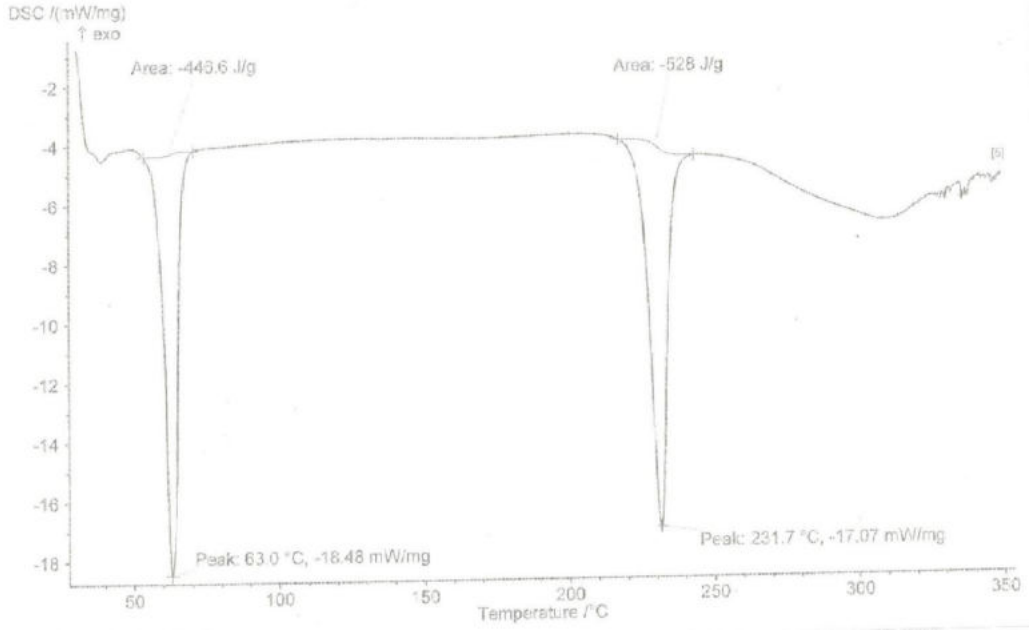

Figure 14: DSC thermogram of Batch D (1:4) Solid dispersion formulation

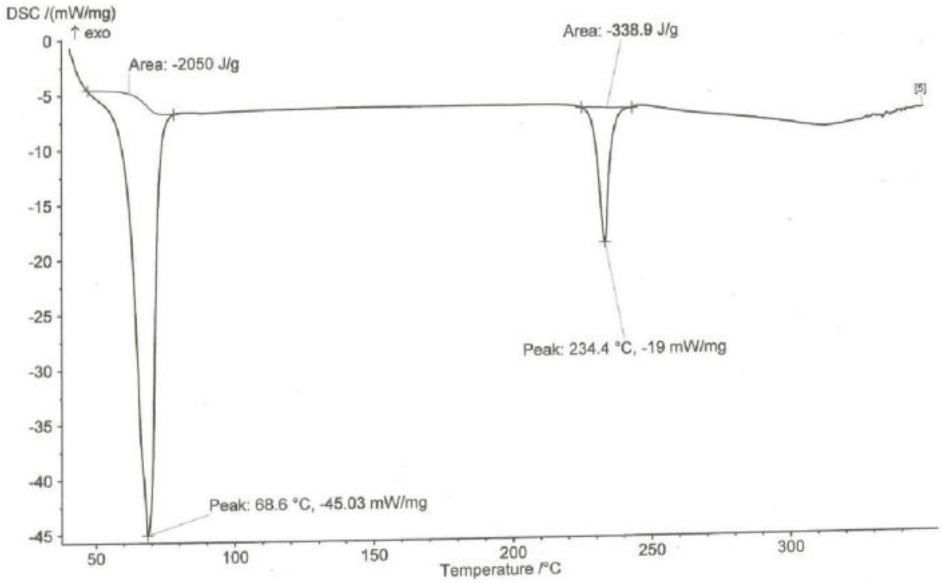

Figure 15: DSC thermogram of Batch E (4:1) Solid dispersion formulation

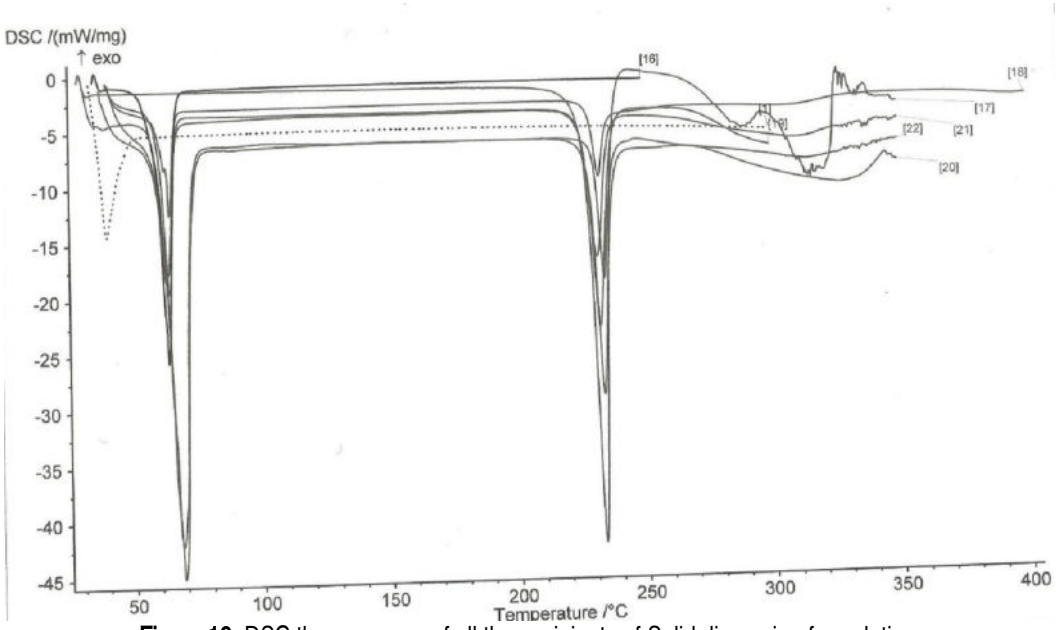

Figure 16: DSC thermograms of all the excipients of Solid dispersion formulation

Interpretation of FTIR spectrum

When an Infrared (IR) radiation falls on a molecule, it either gets absorbed, reflected or transmitted. Absorption leads to the FTIR spectrum, while reflection leads to scattering which is utilized in Raman Spectroscopy (Clarke *et al.* 1999). Infrared (IR) absorption of the functional groups may vary over a wide range. It has been found that many functional groups give characteristics IR absorption at specific narrow frequency range [17-19]. The pure metformin spectra showed sharp peaks between 1628.62, 3357.15, and 1067.05 cm^{-1} signifies the presence of C=N, N-H and C-N functional groups respectively in the FTIR spectrum result of the pure metformin sample. When compared with the FTIR of the optimum batch C, there was no significant change between the spectra of the pure drug and the polymers with the formulation. Batch A and B solid dispersion by solvent evaporation method had disappearance

of sharp peaks unlike in other spectra ratios. This might be an indication of an interaction which might be stipulated to be a hydrogen bonding between hydrogen atom at N-H and a pair of oxygen atom in PEG. Previous reports identified similar type of interaction [20-21]. It may also be due to small concentration of ratios of the carriers or the method used. Hydrogen bonding has a significant influence on the peak shape and intensities, generally causing peak broadening and shifts in absorption to lower frequencies. The results are shown in Figure 8-20.

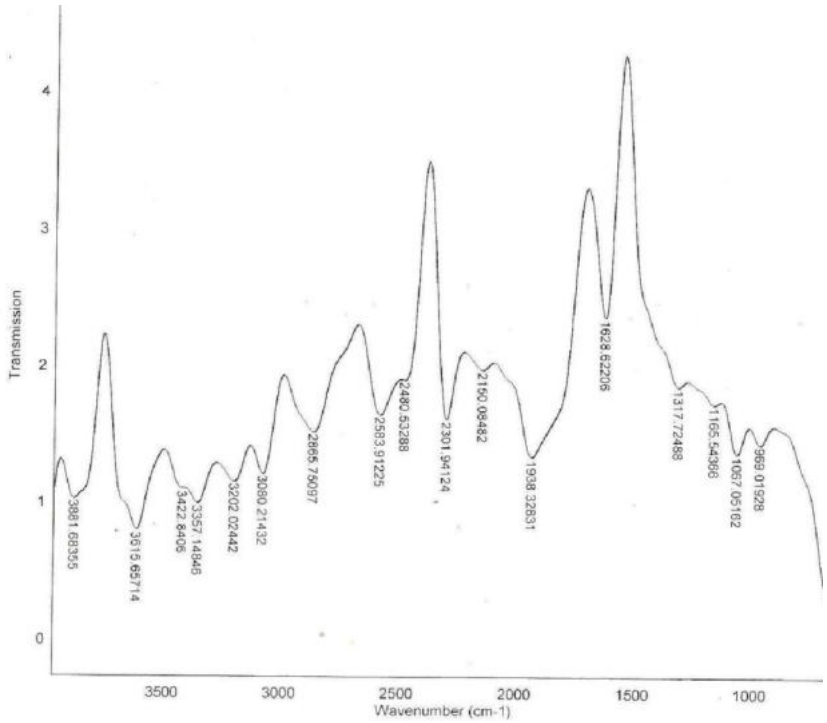

Figure 8: FTIR spectrum of pure metformin

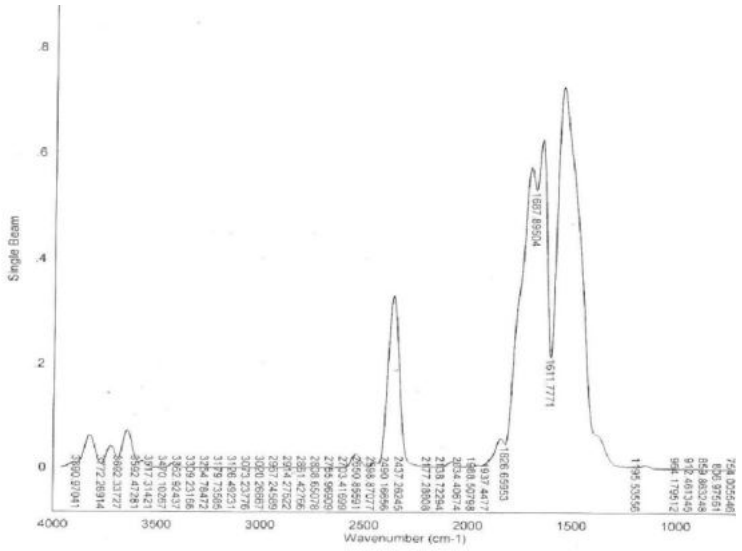

Figure 9: FTIR spectrum of pure PEG 4000

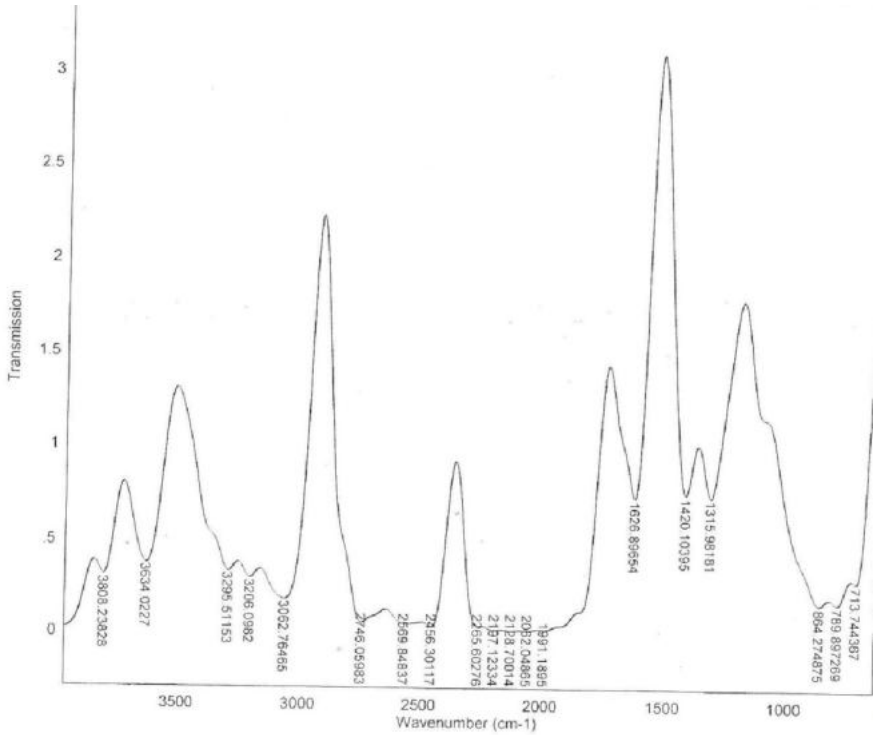

Figure 10: FTIR spectrum of pure Gelucire®50/13

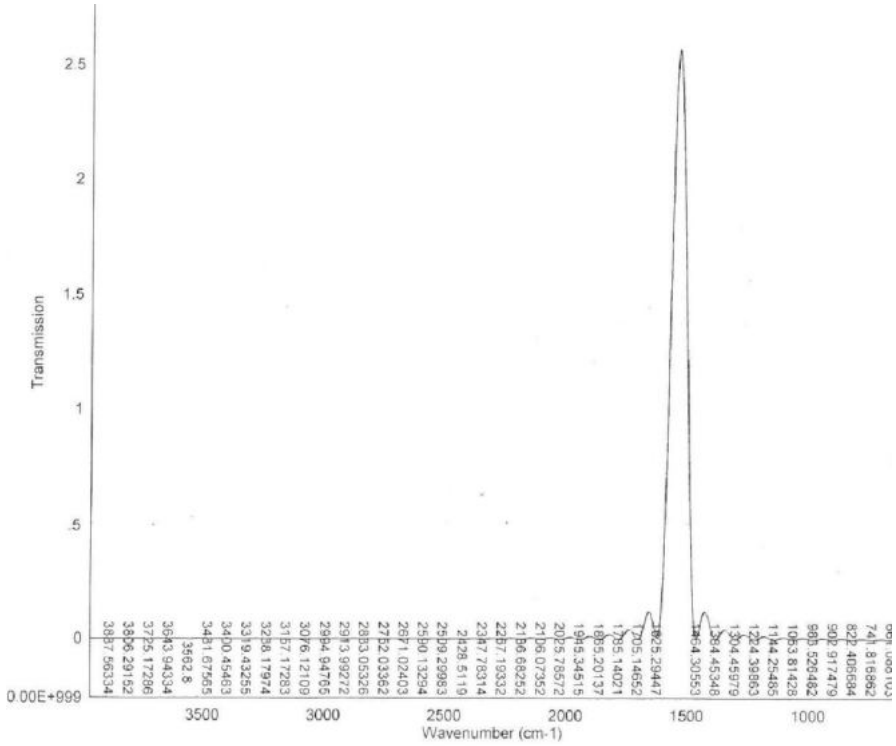

Figure 11: FTIR spectrum of metformin solid dispersion by solvent evaporation (1:1).

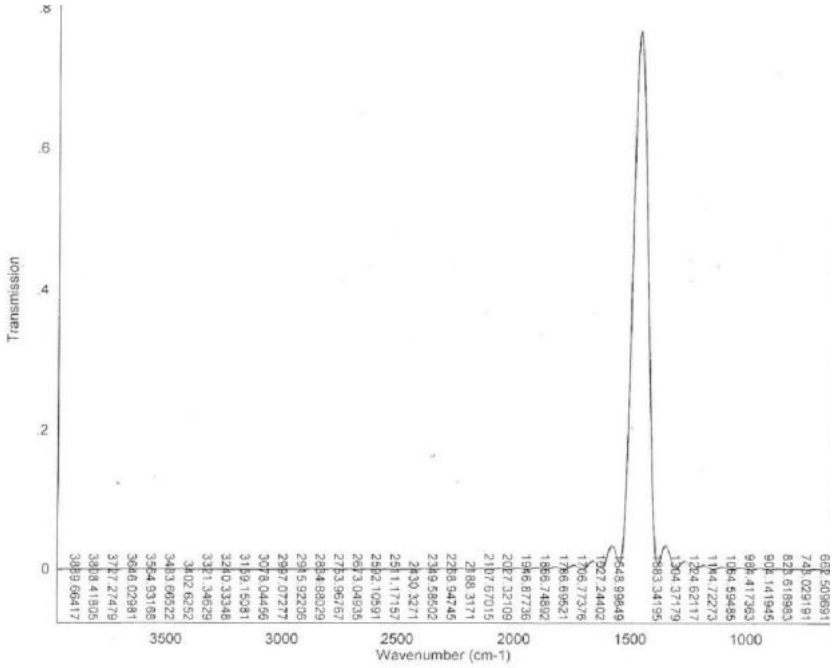

Figure 12: FTIR spectrum of metformin solid dispersion by solvent evaporation (1:2).

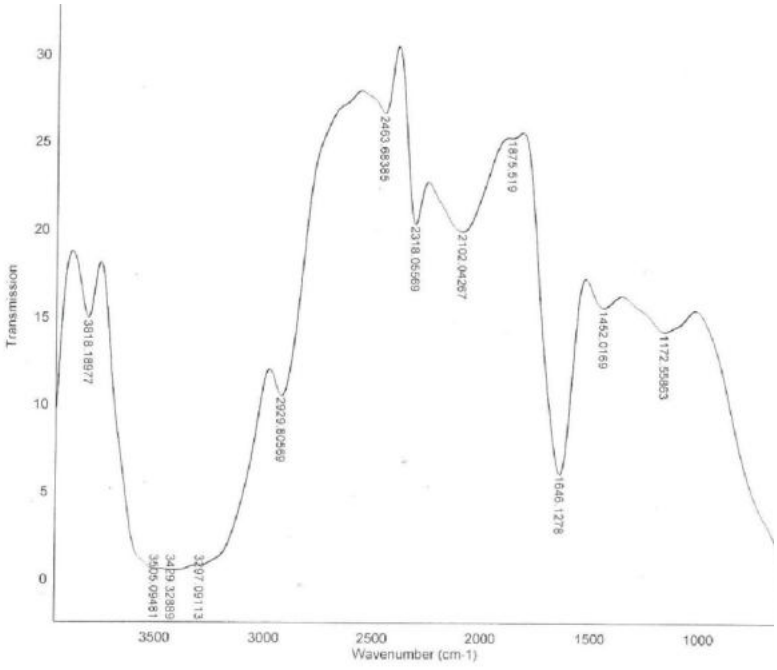

Figure 13: FTIR spectrum of metformin solid dispersion by solvent evaporation (2:1).

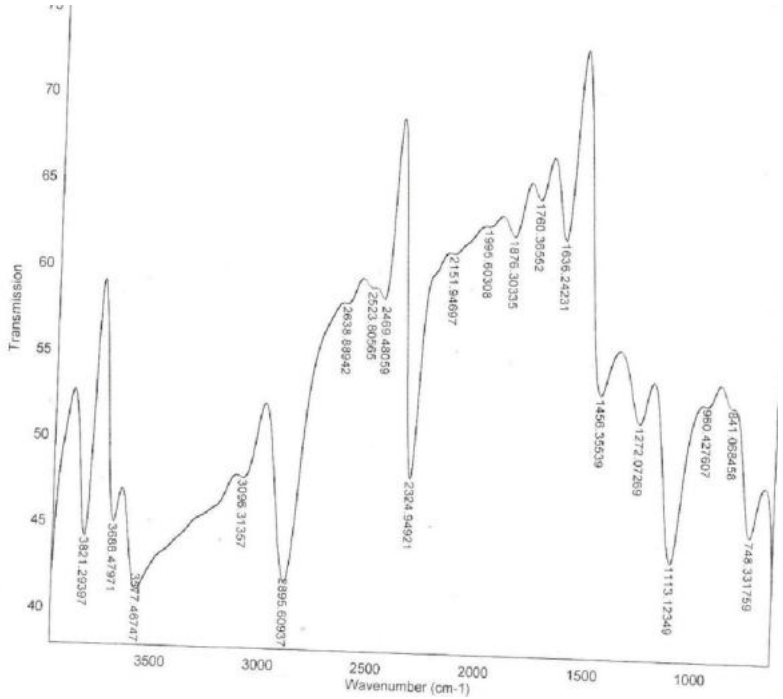

Figure 14: FTIR spectrum of metformin solid dispersion by solvent evaporation (1:4).

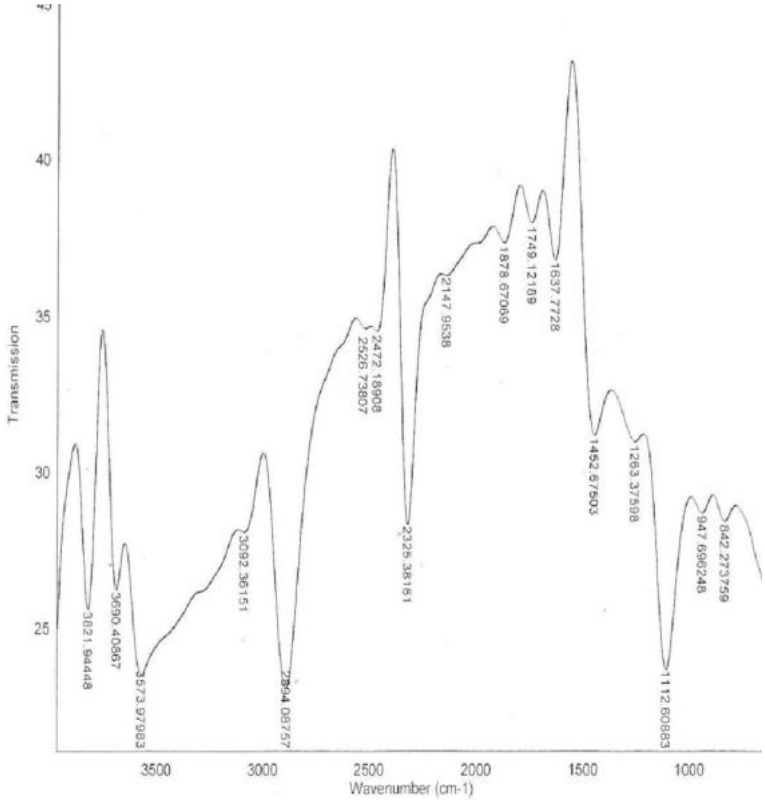

Figure 15: FTIR spectrum of metformin solid dispersion by solvent evaporation (4:1).

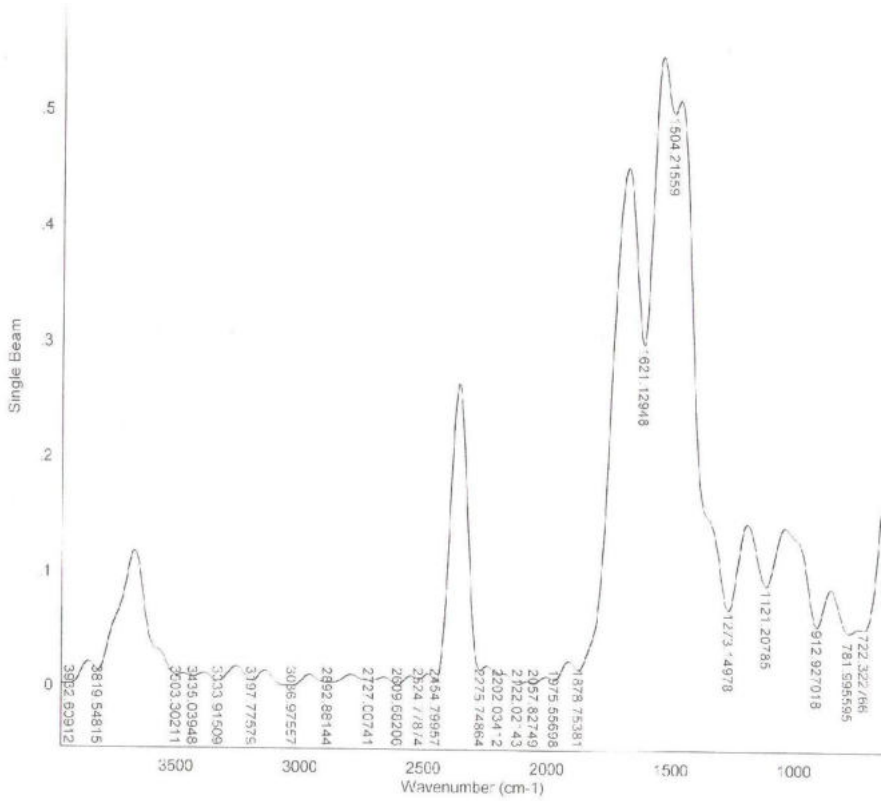

Figure 16: FTIR spectrum of metformin solid dispersion by physical mixture (1:1).

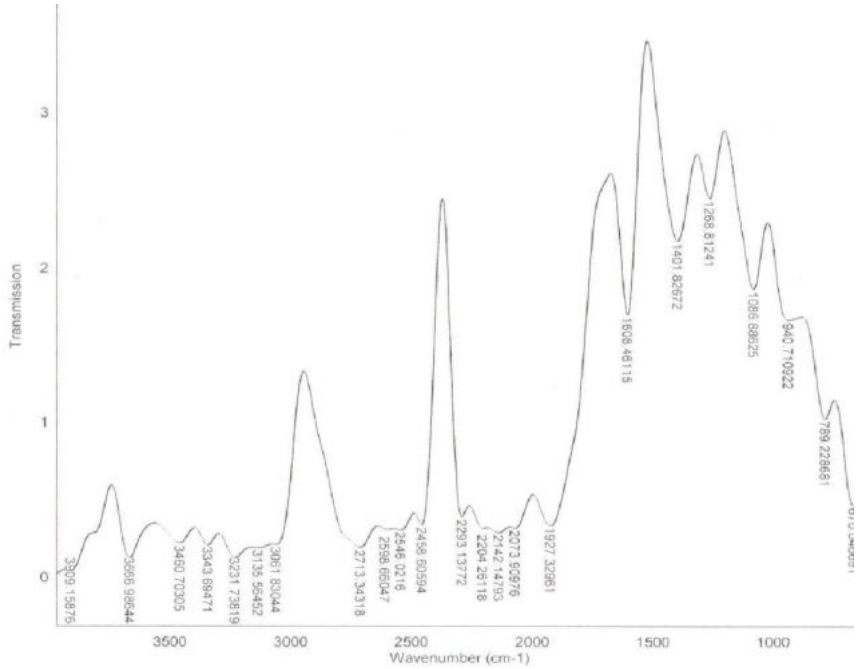

Figure 17: FTIR spectrum of metformin solid dispersion by physical mixture (1:2).

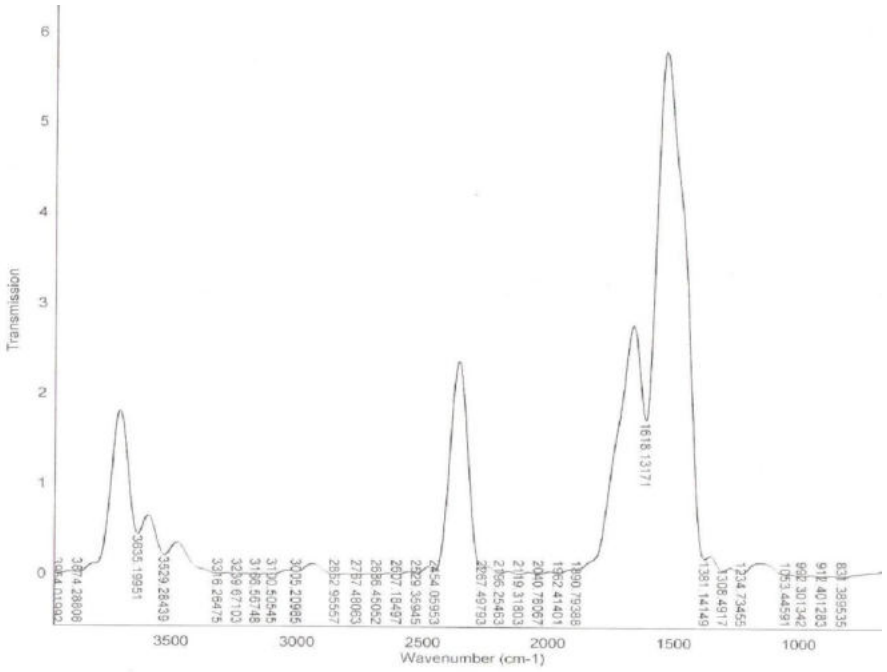

Figure 18: FTIR spectrum of metformin solid dispersion by physical mixture (2:1).

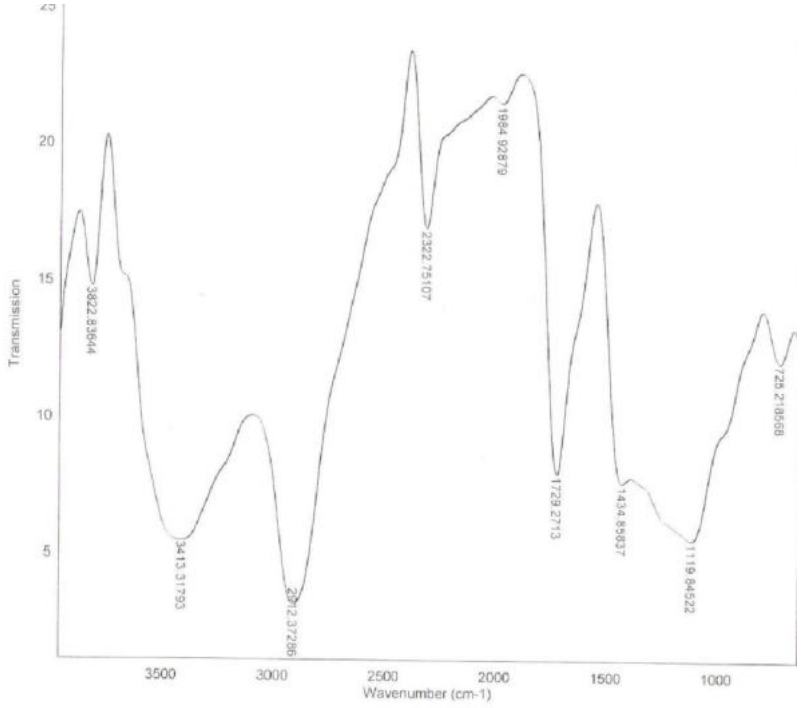

Figure 19: FTIR spectrum of metformin solid dispersion by physical mixture (1:4).

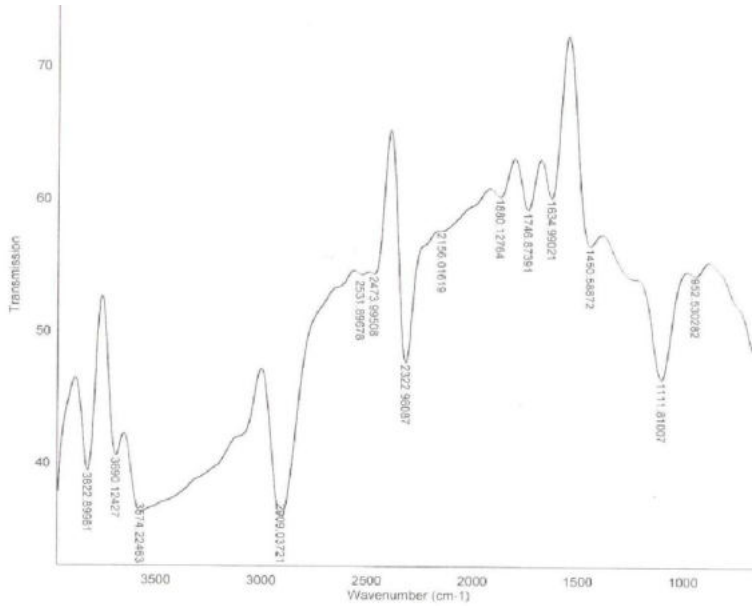

Figure 20: FTIR spectrum of metformin solid dispersion by physical mixture (4:1).

Conclusion

The solid dispersion technique is a promising alternative for the formulation of low permeable drugs such as metformin. The encapsulation efficiency (% EE) of Batch C had the highest encapsulation efficiency. It was observed that the batch containing more PEG 4000 had higher release (Batch C), and after which no significant effect was observed when PEG 4000 ratio was further increased. This higher percentage release rate of the most optimized Batch C will eventually result in an enhanced oral bioavailability.

It was also observed that the release of metformin in SIF was more than in SGF medium.

The FTIR results indicated that absence of any significant change in the IR spectral pattern of drug-polymer except with solvent evaporation method.

References

[1]. Choudhury PK and Kar M. Controlled release metformin hydrochloride microspheres of ethyl cellulose prepared by different methods and study on the polymer affected parameters, Journal of Microencapsulation. 2009; 26(1): 46–53.

[2]. Farago PV, Raffin RP, Pohlmann AR, Guterres SS, Zawadzki SF. Physicochemical characterization of a hydrophilic model drug-loaded PHBV Micro particles obtained by the double emulsion/solvent evaporation technique. J Braz Chem. Soc. 2008; 19:1298–1305.

[3]. Corti G, Capasso G, Maestrelli F, Cirri M, Mura P. Physical-chemical characterization of binary systems of metformin hydrochloride with triacetyl-β-cyclodextrin. J Pharm Biomed Anal. 2007; 45:480–6.

[4]. Jag dale SC, Patil SA, Kuchekar BS and Chabukswar AR. Preparation and Characterization of Metformin Hydrochloride — Compritol 888 ATO Solid Dispersion. J Young Pharm. 2011; 3(3): 197–204.

[5]. Improving drug solubility for oral delivery using solid dispersions. Eur. J. Pharm. Biopharm. 2000; 50:47–60.

[6]. El-Badry M, Fetih G and Fathy M. Improvement of solubility and dissolution rate of Indomethacin by solid dispersions in Gelucire 50/13 and PEG 4000. 2009.

[7]. Craig DQM. The mechanisms of drug release from solid dispersions in water-soluble polymers. Int. J. Pharm. 2002; 231: 131–144.

[8]. Lin CW, Cham TM. Effect of particle size on the available surface area of nifedipine from nifedipine–

polyethylene glycol 6000 solid dispersions. Int. J. Pharm. 1996; 127:261–272.

[9]. Liu C, Desai KG. Characteristics of rofecoxib-polyethylene glycol 4000 solid dispersions and tablets based on solid dispersions. Pharm. Dev. Technol. 2005; 10: 467–477.

[10]. Ahuja N, Katare OP, Singh B. Studies on dissolution enhancement and mathematical modelling of drug release of a poorly water-soluble drug using water soluble carriers. Eur. J. Pharm. Biopharm. 2007; 65: 26–38.

[11]. Aı¨naoui A, Ouriemchi EM, Bidah D, El-Amrani MK, Vergnaud JM. Process of drug release with oral dosage forms with lipidic gelucire matrix. J. Polym. Eng. 1997; 17: 245–257.

[12]. Cavallari C, Rodriguez L, Albertini B, Passe-rini N, Rosetti F, Fini A. Thermal and fractal analysis of diclofenac/Gelucire 50/13 microparticles obtained by ultra-sound-assisted atomization. J. Pharm. Sci. 2005; 94: 1124–1134.

[13]. Dennis AB, Farr SJ, Kellaway IW, Taylor G, Davidson R. In vivo evaluation of rapid release and sustained release gelucire capsule formulation. Int. J. Pharm. 1990; 65: 85–100.

[14]. Chauhan B, Shimpi S, Paradkar A. Preparation and characterization of etoricoxib solid dispersions using lipid carriers by spray drying technique. AAPS Pharm Sci Tech. 2005; 6:405–12.

[15]. Willard HH, Merrit LL (Jr.), Dean JA. Instrumental Methods of Analysis, 7th Edition, CBS Publishers and Distributors, New Delhi. 1986; 287-320.

[16]. Indian Pharmacopoeia. The Controller of Publications, Govt of India, Ministry of Health and Family Welfare, New Delhi.1996; 2: S-44.

[17]. Clarke RH, Londhe S, Premasiri WR, Womble ME. Low-Resolution Raman Spectroscopy: Instrumentation and Application in Chemical Analysis. J Raman Spectrosc 1999; 30: 827-32.

[18]. Silverstein RM, Webster FX. Spectrometric Identification of Organic Compounds.6th ed, New York: Jhon Wiley and Sons; 2002.Dani VR. Organic Spectroscopy. 1st ed, New Delhi: Tata McGraw-Hill Publishing Company Limited; 1995.

[19]. Precautions for Making KBr Pellets; Available from http:/ / www.chemistry.nmsu.edu /Instrumentation /KBr_New.html, accessed on 20.01.2010.

[20]. Harshal Mohan Balpande, Neha Sureshrao Raut, Milind Janrao Umekar, Nandkishor Ramdas Kotagale. Compatibility Study of Metformin with Pharmaceutical Excipients. International Journal of Chem Tech Research. 2015 ;(4): 1684-1693.

[21]. Khattab I, Nada A, Zaghloul AA. Physicochemical characterization of gliclazide–macrogel solid dispersion and tablets based on optimized dispersion, Drug. Dev. Ind. Pharm. 2010; 36(8):893–902.