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# Thermal, infrared characterization and in vitro evaluation of Repaglinide solid dispersion

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## ABSTRACT

*The objective of this research work was to improve the aqueous solubility and dissolution rate of repaglinide, a poorly water soluble anti-diabetic drug by solid dispersion technique. Hydroxyl propyl methyl cellulose and povidone K 30 were used as water soluble polymers for preparing solid dispersion of repaglinide. Solid dispersions were prepared by the solvent method. Methanol was used as solvent. In-vitro drug release was studied. A significant increase, almost 100% in the release of repaglinide within one hour was observed in case of the solid dispersion formulations. Solubility study was also found very effective. After incorporating water soluble polymers the solubility of repaglinide was increased to a significant amount. Solubility after sonication in sonicator was more than the solubility after shaking in thermal shaker for six hours. Infrared spectroscopy was used to characterize drug-polymer interactions in solid dispersions. There were no significant interactions between the drug and the carriers. Thermal analysis by differential scanning calorimeter was studied to detect the physicochemical transition by measuring the amount of heat absorbed or released as the sample is heated across its suspected transition range. The results showed that the incorporation of polymers transforms crystalline repaglinide into amorphous state, thus increasing its solubility and dissolution rate.*

**Key words:** Solid dispersion, Repaglinide, Solvent method, Hydroxyl propyl methyl cellulose, Povidone K 30.

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## INTRODUCTION

The rate and extent of drug absorption from gastrointestinal tract depends on the rate and extent of drug dissolution from any solid dosage form [1, 2].In case of poorly water soluble drug, dissolution rate is the rate limiting step in the process of drug absorption. Potential bioavailability problem occurs with extremely hydrophobic drug due to erratic and incomplete

absorption from GIT. [3]. If the aqueous solubility of a drug is less than 1mg/ml it causes serious absorption problem. Several techniques have been developed for increasing the solubility of poorly soluble drugs such as solid dispersion [4-8] ,inclusion complex [9.10], ultra rapid freezing process [11], melt sonocrystallization [12], solvent change method [13], melt granulation technique [14], supercritical solvent, supercritical and cryogenic technique, cosolvent approach. Numerous solid dispersion (SD) systems have been demonstrated in the pharmaceutical literature to improve the dissolution properties of poorly water soluble drugs. This technique was introduced in the early 1970s as a multicomponent system, such as nimesulide, ketoprofen, tenoxicam, nifedipine, nimodipine, ursodeoxycholic acid, and albendazole. Various hydrophilic carriers, such as polyethylene glycols (PEG), polyvinylpyrrolidone (PVP), hydroxypropyl methylcellulose (HPMC), gums, sugar, mannitol and urea have been investigated for improvement of dissolution characteristics and bioavailability of poorly water soluble drugs [15]. Chemically, Repaglinide is S (+)-2-ethoxy-4- [N- (1-(2-piperidinophenyl) - 3-methyl- 1-butyl)-aminocarbonyl methyl] benzoic acid, which belongs to a new class of hypoglycaemic benzoic acid derivatives, a fast and short-acting meglitinide analog. It is widely used for the treatment of diabetes. It has a very low bioavailability (50%) and poor absorption in the upper intestinal tract. Poor solubility in gastrointestinal fluids causes variations in its dissolution rate which leads to incomplete bioavailability [16]. Hence an attempt was made to improve the dissolution of repaglinide through the formulation containing SD of repaglinide. The physicochemical properties of repaglinide in solid dispersions were characterized by differential scanning calorimetry and infrared spectroscopy. The effects of hydrophilic carriers on the dissolution properties of repaglinide were investigated. An attempt was made in this study to enhance the aqueous solubility and dissolution rate of repaglinide by preparation of SDs using hydrophilic polymers like hydroxypropyl methyl cellulose (HPMC) 6 cps and povidone K 30.

## MATERIALS AND METHODS

Repaglinide was obtained as gift sample from Dr. Reddi, India. HPMC (6 cps), povidone K30 and all other chemicals were of analytical reagent grade and were used as received.

### 2.1 Preparation of solid dispersions

The preparation of dispersions of repaglinide with water soluble carriers HPMC (6 cps) and povidone K30 was based on the solvent evaporation method. The first step in this method is the preparation of a solution containing both matrix material and drug. The second step involves the removal of solvent resulting in formation of a solid dispersion. Drug and polymer were dissolved in methanol to get a clear solution. The resulting solution was stirred at ambient temperature for 30 minutes. The preparations were kept in a desiccator for the least 48 hours and then grounded in a glass mortar for size reduction. Finally they were passed through 150 micron sieve and stored in a desiccator over fused calcium chloride.

### 2.2 Characterization of solid dispersion [17-18]

#### 2.2.1 Solubility experiments

Maximum solubility of repaglinide was observed under two different conditions.

**2.2.1.1 Maximum solubility of repaglinine after shaking**

The amount of solid dispersion powder containing 2.5 mg equivalent of repaglinide was weighed accurately from each batch and dissolved in phosphate buffer. Each batch was placed in thermal shaker. After three hours additional amount of solid dispersion powder containing 2.5 mg equivalent of repaglinide were added to each batch. The experiment was carried out for six hours. The samples were analyzed spectrophotometrically. From the absorbance value, the amount of repaglinide dissolved was determined.

**2.2.1.2 Maximum solubility of repaglinine after sonicating**

The amount of solid dispersion powder containing 2.5 mg equivalent of repaglinide was weighed accurately from each batch and dissolved in phosphate buffer. The batches were placed in the sonicator and sonicated for three minutes. The samples were analyzed using spectrophotometry method and from the absorbance value, the amount of repaglinide dissolved was determined.

**2.2.2 Differential Scanning Calorometry (DSC)**

DSC experiments were carried out using a DSC-7 (Perkin-Elmer, Norwalk, CT, USA) equipped with a liquid nitrogen subambient accessory (Perkin-Elmer, Norwalk, CT, USA). The samples were analyzed using aluminium open pans and scanned at 10˚c/min from 25˚c to 200˚c.

**2.2.3 Infrared Spectroscopy**

Fourier transform infrared (FTIR) spectroscopy has been used frequently to characterize drug-polymer interactions in solid dispersions. Using FTIR, a spectrum of solid dispersion and that of its corresponding physical mixture is compared. Infrared spectra were recorded on a Perkin-Elmer 298 infrared spectrometer, from samples prepared in potassium bromide (KBr) discs. The scanning range was 2000 to 400 $cm^{-1}$ at a scan period of 14 minute.

**2.2.4 Drug content**

Solid dispersions containing 2 mg equivalent repaglinide were taken and dissolved in minimum quantity of methanol. The final volume was made up to 50ml with phosphate buffer. From this solution, 5 ml was taken and again diluted with buffer up to 50 ml. The solution was assayed for drug content using spectrophotometry method by measuring the absorbance at 291 nm.

**2.2.5 In Vitro dissolution**

In-vitro dissolution study was performed in a paddle type Dissolution Apparatus (USP Type III Dissolution Apparatus, VEEGO, INDIA). A fixed amount of solid dispersion containing 2.5mg of repaglinide from each batch was calculated for dissolution purpose. 900 ml of phosphate buffer (pH 5) was used as dissolution medium in each dissolution basket. Temperature was 37˚ c and paddle speed was 100 rpm. Dissolution was carried out for 1 hour and 10 ml sample was withdrawn at predetermined intervals of 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60 minutes. Each and every time 10 ml dissolution sample was compensated by another fresh 10 ml phosphate buffer. The samples were then analyzed spectrophotometrically in a UV-VIS spectrophotometer (UV- mini-1240, SHIMADZU CORP., Kyoto, Japan). The dissolution study for each batch was performed in duplicate.

## RESULTS AND DISCUSSION

### 3.1 Solubility study

The solubility of repaglinide was greatly increased when water soluble polymers were incorporated in solid dispersions. This is because they provided a good surrounding for physical interaction with water. Povidone K30 was more efficient in increasing the solubility of repaglinide compared to HPMC 6 cps. [Table: 1]

### 3.2 In-vitro release study of repaglinide from solid dispersion

The dissolution rate of pure repaglinide was low compared to that of the formulations that incorporated water soluble polymers. Figure [1] shows that almost 80 percent repaglinide was released within 45 minutes, in case of the formulations that contained water soluble polymers. However in case of pure repaglinide, 46 percent drug was released within 45 minutes. About 100 percent drug was released within 60 minutes, in case of the formulations that contained water soluble polymers. However in case of pure repaglinide, approximately 53 percent drug was released within 60 minutes.

### 3.3 Differential scanning calorimetry

The DSC thermogram of pure repaglinide shows an endothermic peak at 138.99°c. The DSC thermograms of repaglinide solid dispersion with water soluble polymers show that the peaks of repaglinide has been lowered from that of the peak of pure repaglinide i.e. 138.99°c [ Table 1, Figure 2-4]. This indicates that the presence of polymers has decreased the crystallinity of repaglinide and stabilizes the amorphous structure of repaglinide which has greater solubility [19]. The decrease in the height of the peak of repaglinide indicates the system moving towards solid dispersion with the addition of the polymer.

### 3.4 Infrared Spectroscopy

Pure repaglinide spectra showed sharp characteristic peaks within 800 to 1400 $cm^{-1}$ range. The infrared spectrum of the binary systems shows characteristic peaks within the same range [Figure 5-8]. This indicates no modification or interaction between the drug and carrier [20].

**Table 1:Formulation codes of solid dispersion with water soluble carriers; comparison of solubility, drug content and DSC thermogram data.**

| Formulation code | Carrier | Drug to Carrier Ratio | Solubility(micgm/ml) after shaking | Solubility(micgm/ml) after sonicating | % Drug content | DSC thermogram peaks |
|---|---|---|---|---|---|---|
| SD1 | HPMC 6cps | 1:1 | 23.08 | 144.77 | 98.75 | 136.23 °c |
| SD3 | Povidone K30 | 1:1 | 45.06 | 179.30 | 97.15 | 132.51 °c |
| Pure repaglinide | | | 6.19 | 44.02 | | 138.99 °c |

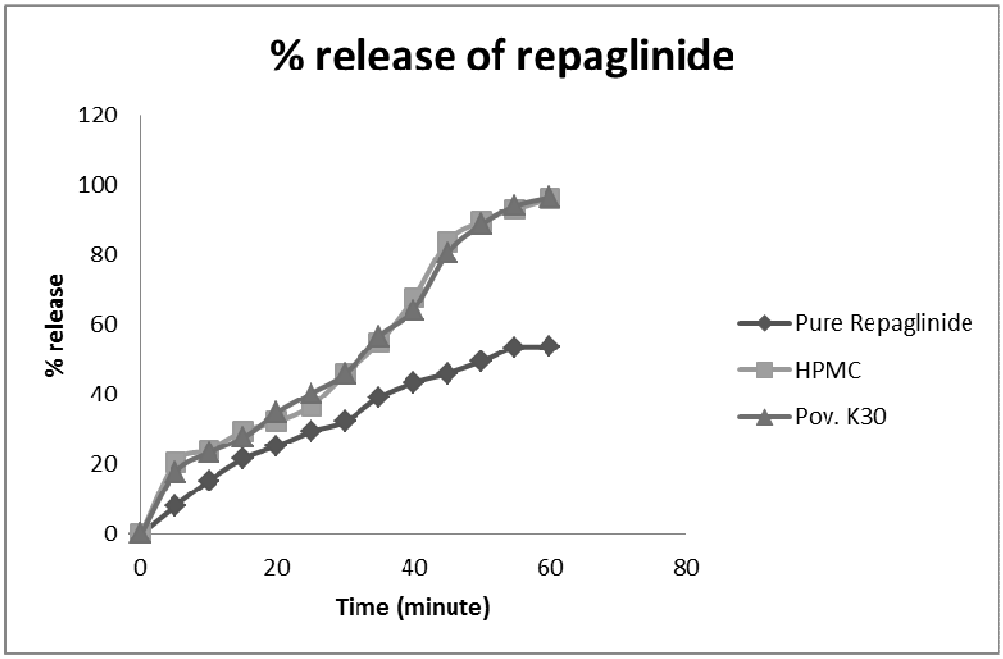


**Figure 1 : The dissolution rates of repaglinide from solid dispersion incorporating HPMC and Povidone K 30**

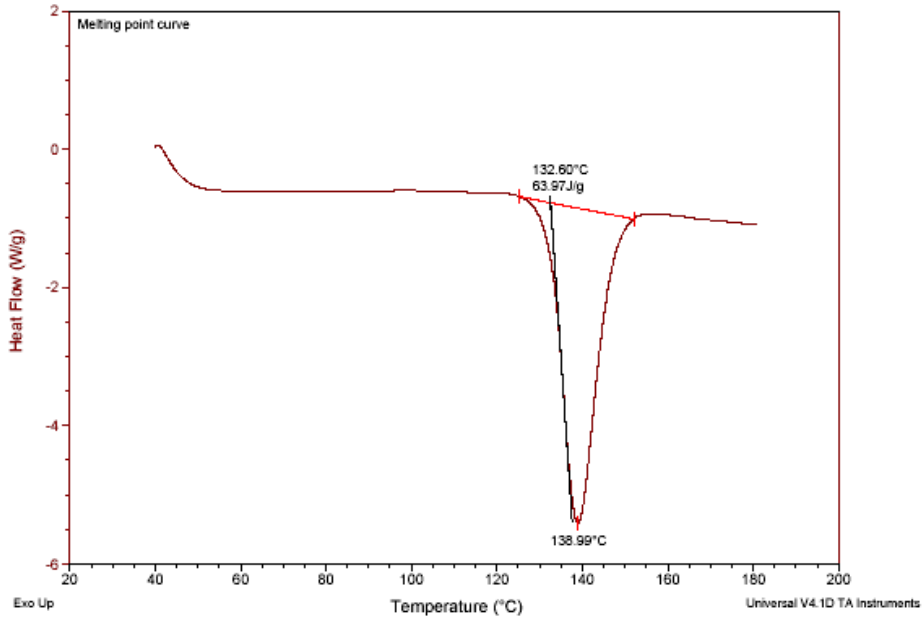


**Figure 2: DSC thermogram of pure Repaglinide**

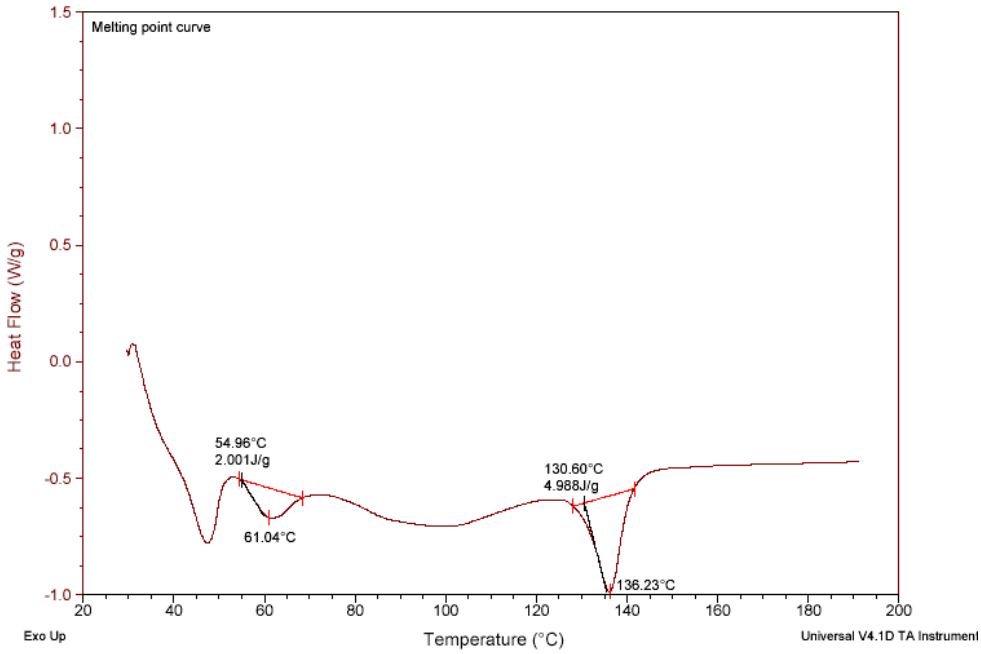


**Figure 3: DSC thermograms of repaglinide solid dispersion with HPMC (1: 1)**

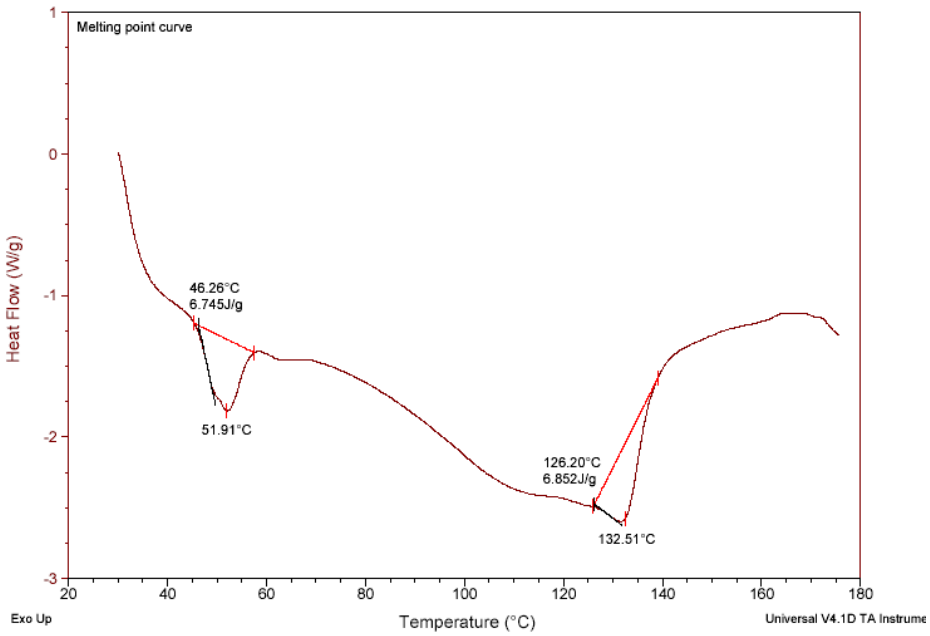


**Figure 4: DSC thermograms of repaglinide solid dispersion with Pov. K30 (1: 1)**

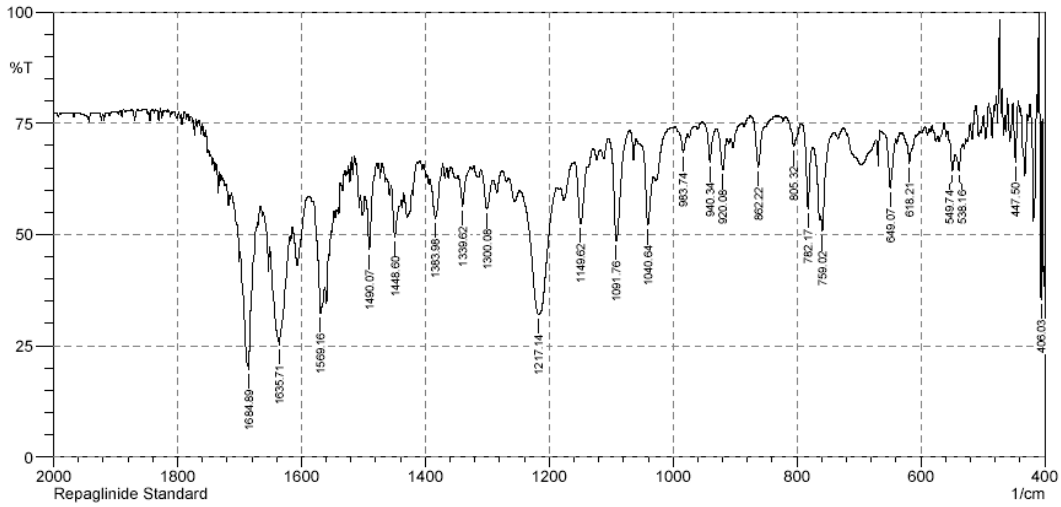


**Figure 5: Infrared spectra of pure repaglinide**

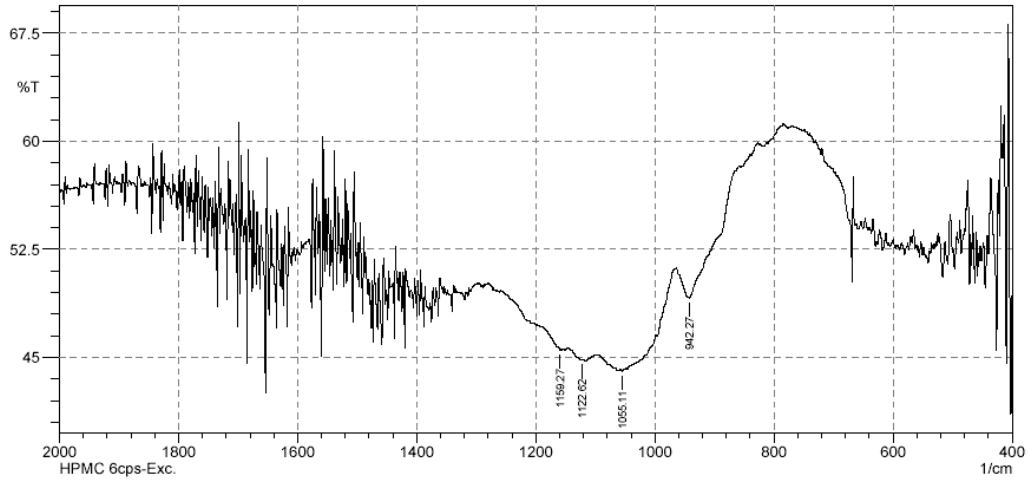


**Figure 6: Infrared spectra of HPMC**

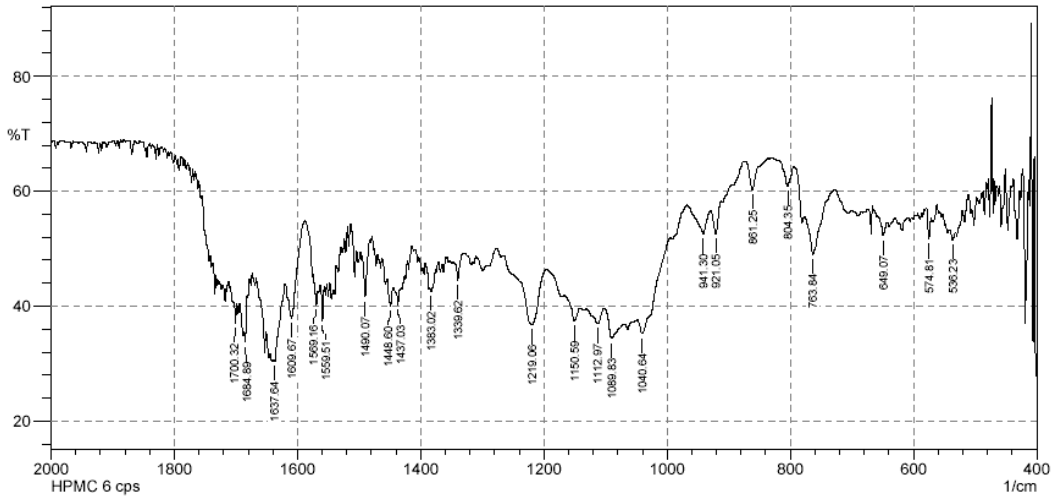


**Figure 7: Infrared spectra of repaglinide + HPMC**

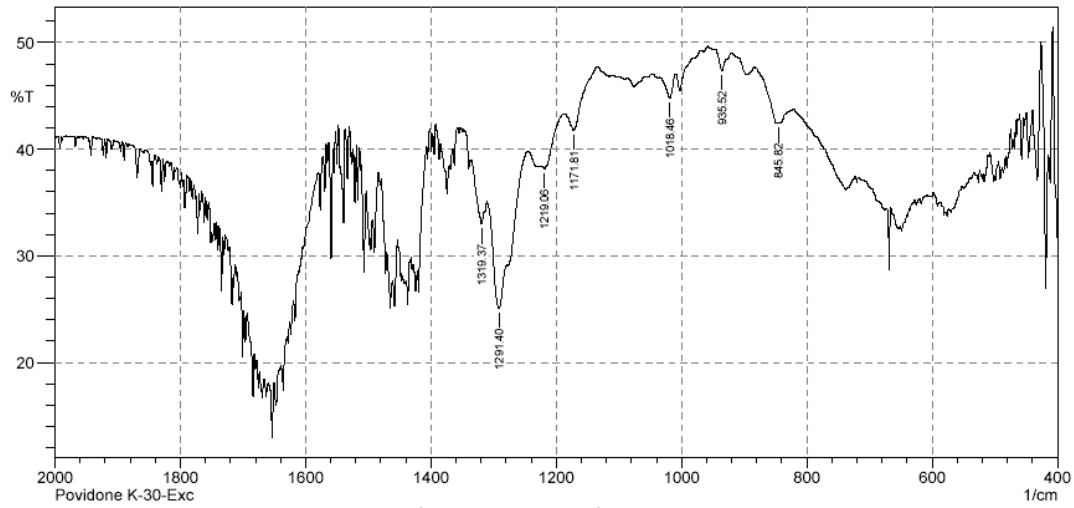


**Figure 8: Infrared spectra of Povidone K 30**

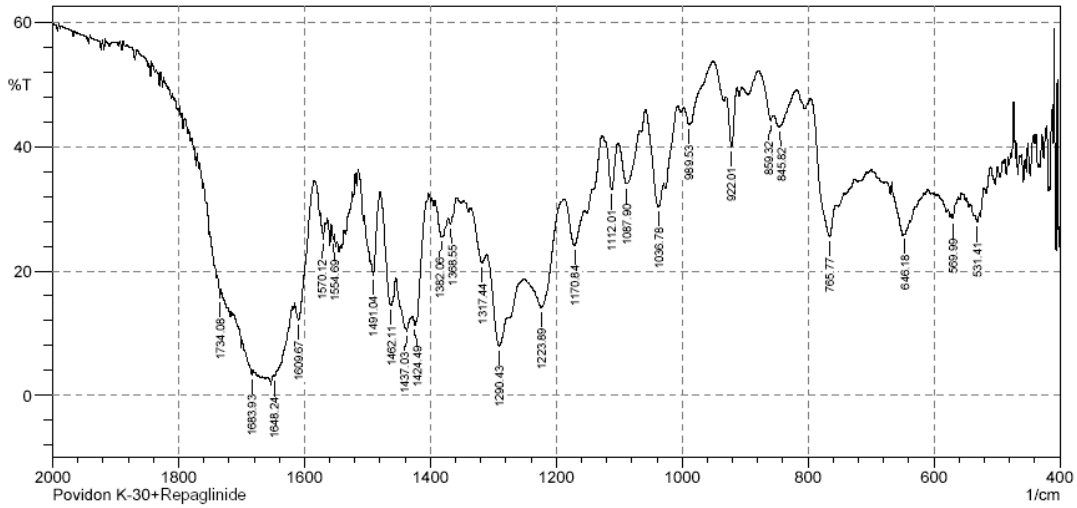


**Figure 9: Infrared spectra of repaglinide + Povidone K 30**

## CONCLUSION

This study was started to establish the possibility of preparing repaglinide solid dispersions with improved aqueous solubility and dissolution rate.Solid dispersions were prepared by the solvent method. Different water soluble polymers were used as carriers. A significant increase in the release of the drug was observed in each batch with different polymers. The solubility of repaglinide increased significantly in the solid dispersions with different carriers.The infrared spectroscopy study showed that there were no significant interactions between repaglinide and the carriers in solid dispersion. The differential scanning thermograms of repaglinide revealed that the carriers added in the solid dispersions with repaglinide transforms crystalline structure of repaglinide into amorphous structure. Solid dispersion preparation by the method demonstrated in this study thus may be an ideal means of drug delivery system for poorly water soluble drugs.

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