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PREFORMULATION SCREENING OF REPAGLINIDE FOR TRANSDERMAL ANTI-DIABETIC THERAPY

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ABSTRACT

The aim of the present work is to study the preformulation parameters for Transdermal drug delivery system. The objective of Preformulation study is to generic information useful to the formulater in developing stable and bioavailable dosage form. The use of Preformulation parameter maximizes the chances in formulation an acceptable, safe, efficacious and stable product and at the same time provide the basis for optimization of the drug product quality. Administration of conventional tablets of repaglinide has been reported to exhibit fluctuations in plasma drug levels, resulting either in manifestation of side effects or reduction in drug concentration at the receptor sites also, the maintenance of a constant plasma concentration of a anti-diabetic drug is important in ensuring the desired therapeutic response, again since the half life of repaglinide is 01 hour hence multiple doses of the drug are needed to maintain a constant plasma concentration for a good therapeutic response, and improve patient compliance, hence the objective of the study was made to develop controlled release Transdermal Drug Delivery System of repaglinide using polymer like Eudragit RS 100, Eudragit RL 100 and HPMC, which will controlled the release of drug, increasing the bioavailability of the drug and thus decreasing the dosing frequency of the drug. The Preformulation studies were carried out in terms of test for identification (physical appearance, melting point, and uv spectrophotometer), solubility profile, determination of partition coefficient and quantitative estimation of drug. All the observation and results showed that the repaglinide could serve as suitable candidate for Transdermal drug delivery system that may improve the bioavailability.

Keywords: Transdermal, Repaglinide, Preformulation, Half Life, bioavailability

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INTRODUCTION

The advantages of transdermal drug delivery system (TDDS) include the control of drug release, prolongation of steady-state plasma concentration with much less peak and-trough variation, improving the safety and patient convenience. Intensive research has showed that transdermal route is a potential mode of delivery of lipophillic drugs in the systemic circulation. Matrix based transdermal formulations have been developed for a number of drugs such as Nitroglycerine and Ephedrine. [1-2] Diabetes mellitus is a major and growing health problem worldwide and an important cause of prolonged illness and early death. It is a chronic metabolic disorder characterized by a high blood glucose concentration (hyperglycemia) caused by insulin deficiency, and it is often combined with insulin resistance. Repaglinide, a carbamoylmethyl benzoic acid derivative, is the first of a new class of oral antidiabetic agents designed to normalise postprandial glucose excursions in patients with Type 2 Diabetes Mellitus. Like the Sulphonylureas, Repaglinide acts by stimulating release of insulin from the β-cells of the pancreas. Repaglinide is rapidly and completely absorbed, with maximum plasma concentrations (Cmax) occurring aproximatly within an hour after oral administration. It possesses low oral bioavailability (56%) due to hepatic first pass metabolism after oral administration and has a short

biological half life of 1h which makes frequent dosing 0.5 to 4 mg in 3 to 4 times in a day necessary to maintain the drug within the therapeutic blood levels for long periods. It has melting point of 130-131 ^{o}C, short half life (1 hr), Mol. wt. 452.584 and lipophilicity log P value 3.97. Hence, Repaglinide is an ideal drug candidate for transdermal drug delivery. The purpose of the present work was to undertake the preformulation study of Repagliide for transdermal delivery. [3-10]

The objective of Preformulation study is to generic information useful to the formulater in developing stable and bioavailable dosage form. The use of Preformulation parameters maximizes the chances in formulation for an acceptable, safe, efficacious and stable product and at the same time provides the basis for optimization of the drug product quality. The Preformulation studies were carried out in terms of test for identification (physical appearance, melting point, and uv spectrophotometer), solubility profile, determination of partition coefficient and quantitative estimation of drug.

MATERIALS & METHODS

Materials

Repaglinide was obtained as a gift sample from Alkem Laboratories, Mumbai. Eudragit RS 100, Eudragit RL100 & HPMC from Evonik Degussa India pvt. Ltd., Mumbai. Double Distilled water was used throughout the study & all other chemicals and solvents were analytical reagent grade and purchased from commercial suppliers.

Methods

Pre-Formulation Studies

Organoleptic Properties of drug [13,14]

Color: A small quantity of the drug was taken on butter paper and viewed in well- illuminated place.
Odor: Very less quantity of the drug was smelled to get the odor.
Taste: Very less quantity of the drug was put on tongue to get the taste.

Solubility [6,11,15,16]

The spontaneous interaction of two more substances to form a homogenous molecular dispersion is known as solubility.

The sample was qualitatively tested for its solubility in various aqueous and non-aqueous solvents at room temperature.

Method

- Weight 100 mg finally powdered substance in a stoppered tube (16 mm in internal diameter and 160 mm long) added 0.1 ml of solvent if the substance was completely dissolve, it was very soluble.
- If not completely dissolved added 0.9 ml of solvent if substance was completely dissolved it was freely soluble.
- If not completely dissolved added 2 ml of solvent if substance was completely dissolve it was soluble.
- If not completely dissolved added 7 ml of solvent if substance was completely dissolve it was sparingly soluble.
- If not completely dissolve added 10 ml of solvent if substance was completely dissolved it was slightly soluble.

If not completely dissolved weight 1 mg of finely substance in stoppered tube, add 10 ml of the solvent it was very slightly soluble

Table No.1: Descriptive terms of Solubility and their Qualitative designations

S.No.	Descriptive terms	Approximate volume of solvent in milliliters per gram of solute.
1	very soluble	less than 1
2	freely soluble	from 1 to 10
3	Soluble	from 10 to 30
4	sparingly soluble	from 30 to 100
5	slightly soluble	from 100 to 1000
6	very slightly soluble	from 1000 to 10,000
7	practically insoluble	more than 10,000

Partition coefficient [6,11,15,16]

The partition studies were conducted by shake flask method. n-octanol was saturated with phosphate buffer, pH 7.4 for 24 hours before the experiment. Accurately weighed amount about, 10 mg of repaglinide was added to each 20 mL of n-octanol and phosphate buffer, pH 7.4 mixture (1:1 ratio). n-octanol layer was less dense than PBS pH 7.4, so the n-octanol layer was on the top of the phosphate buffer, pH 7.4. The solution was kept for 24 hours shaking at room temperature on rotary shaker. Two phases were separated through separating funnel and filtered through whatman filter paper. The concentration of the drug in the aqueous phase was analyzed against reagent blank on a double beam UV/ visible spectrophotometer at 288 nm; concentration of the drug in n-octanol was calculated from the difference between the initial amount and amount in aqueous phase. The partition coefficient ($P_{o/w}$) of Repaglinide was calculated from the ratio between the concentration of MT in organic (C_{oil}) and aqueous phase (C_{aq}.) using following equation.

$$P_{o/w} = (C_{oil}/C_{aq}.) \text{ equilibrium}$$

Usually expressed in a logarithmic scale, log P refers to partitioning of unionized species. Lipophilicity (log P) is represented by logarithm of partition coefficient in octanol/PBS 7.4.

Melting Point [6,11,17,18]

Melting point of the drug was determined by capillary method using Melting point apparatus. Here, the capillary tube was filled by pressing the open end gently into sample by tapping the bottom of the capillary on a hard surface so that the drug pack down into the bottom of the tube. When the drug packed into the bottom of the tube, the tube was placed into the slot behind the eye-piece on the Melt-temperature. Make sure the unit is plugged in and set to zero, and then turn it on. The temperature were noted when the drug start to melt and the drug till complete melt.

Loss on drying (% LOD) [6,11,15,16]

1gm of the pure drug sample was transferred to the glass stoppered shallow weighing bottle. Before keeping the drug sample, the weighing bottle has been dried for 60 minutes under the same conditions to be employed in the determination. It was then cooled in a desiccator. The empty bottle was weighed (W1). The sample was kept in the bottle, replaced the cover, and accurately weighed the bottle and the contents (W2). By gentle, sidewise shaking, distributed the sample as evenly as practicable to a depth of about 5 mm. placed the loaded bottle in the drying chamber (drying oven) at 60°C for 4 hours. The bottle was weighed every hour until a constant weight was obtained (W3). The loss on drying is calculated by the formula

% LOD = (W2-W3/W2-W1)×100

Analytical Method used in The Determination of Repaglinide[6,11,12]

The UV spectrophotometry method was developed for the analysis of drug using double beam Shimadzu spectrophotometer. Repaglinide was dissolved in 30% v/v Methanolic isotonic phosphate buffer (MIPB) pH 7.4. and determination of λmax and standard graph of Repaglinide was determined.

Procedure:

Determination of λmax

Repaglinide was dissolved in MIBS pH 7.4 and further diluted with the same and scanned for maximum absorbance in UV double beam spectrophotometer [Shimandzu- 1700] in the range from 190 to 380 nm, using MIBS pH 7.4 as blank.

Standard graph of Repaglinide

Accurately weighed 10 mg of drug was dissolved in 10 ml of MIBS (7.4 pH) to get 1000µg/ml. Then prepare suitable dilution of sample with concentration range of 5-25µg/ml. The spectrum of this solution was run in 190 to 380 nm range in U.V spectrophotometer.

Drug Polymer Compatibility study [6,11,13-18]

FTIR Analysis

FTIR spectra of pure drug Repaglinide, polymers (Eudragit RS 100, Eudragit RL 100 & HPMC) and mixture of drug and polymers were carried out by FT-IR spectrophotometer. The IR spectra were recorded using IR Spectrophotometer by KBr pellet method.

RESULT AND DISCUSSION

Pre-Formulation Studies

Organoleptic Properties of drug

Drug repaglinide was found to be white crystalline powder, odorless and Tasteless. The drug was found to comply with the literature specifications. The table below shows the organoleptic properties of the drug.

Table 2: Organoleptic Properties of drug

S.No.	Test	Specification	Practical Observation
1.	Color	White crystalline powder	White crystalline Powder
2.	Odour	Odourless	Odourless
3.	Taste	Tasteless	Tasteless

Melting Point

The melting point of repaglinide has been observed to melt close to literature specification range.

Table 3: Melting Point of drug

Test	Specification (Range)	Practical Observation (Range)
Melting Point	130-135 °C	131-135°C

Solubility

The drug Repaglinide was found to be freely soluble in acetone and Phosphate buffer pH 9.0. The dug was found to be soluble in Ethanol, Methanol, Dichloromethane and chloroform, Phosphate buffer pH 7.4, slightly soluble in distilled water, insoluble in Phosphate buffer pH 1.0. The drug was found to comply with the literature specifications.

Table 4: **Solubility of drug in different solvents**

S.N.	SOLVENT	SOLUBILITY	RESULT
1	Acetone	Freely soluble	++++
2	Dichloromethane	Soluble	+++
3	Ethanol (95%)	Soluble	+++
4	Methanol	Soluble	+++
5	$CHCL_3$	Soluble	+++
6	Distilled Water	Slightly soluble	++
7	Phosphate buffer pH 1.0	Insoluble	- - -
8	Phosphate buffer pH 7.4	Soluble	+++
9	Phosphate buffer pH 9.0	Freely soluble	+++++

Very soluble	Less than 1	+++++
Freely soluble	1-10 Parts	++++
Soluble	10-30 Parts	+++
Sparingly soluble	30-100 Parts	++
Slightly soluble	100-1000 Parts	+
Practically insoluble	greater than 1000	- - -

Partition coefficient

The partition coefficient of the drug was conducted by shake-flask method and was found to be 3.81± 0.015. The drug was found to comply with the literature specifications. It showed that drug lipophilic in nature.

Table 5: **Partition Coefficient of the drug**

Solvent System	Partition Coefficient Mean±SD
n-octanol: phosphate buffer, pH 7.4	3.81 ± 0.015

SD: Standard Deviation; n=3

Loss on drying (%): The Percentage loss on drying for repaglinide was found to be 0.31% w/w±0.021. The % LOD was found to be under the limit as per the literature.

Table 6: Loss on drying (%) of the drug

Loss on drying (%) Specification as per literature	**Loss on drying (%) Mean±SD**
The loss should not be more than 0.5%	0.31±0.021

SD: Standard Deviation; n=3

Analytical Method used in the Determination of Repaglinide

Determination of λmax

The λ_{max} of the drug was found to be 288 nm.

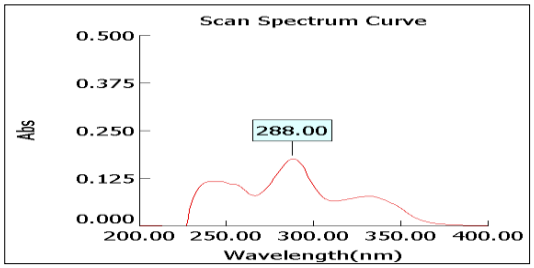


Figure 1: λ_{max} of the Drug

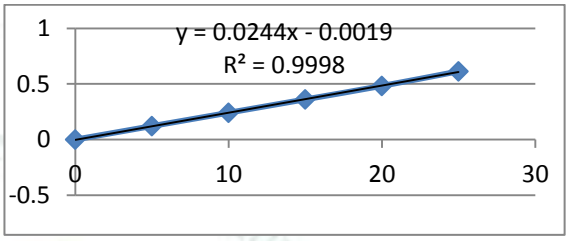
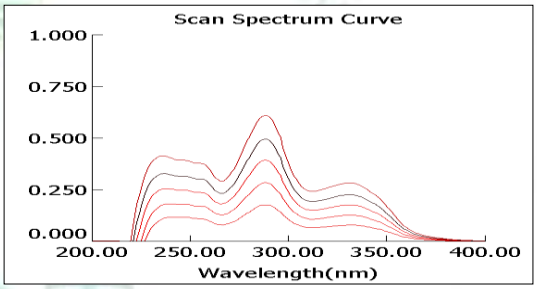


Figure 2: Standard graph of Repaglinide



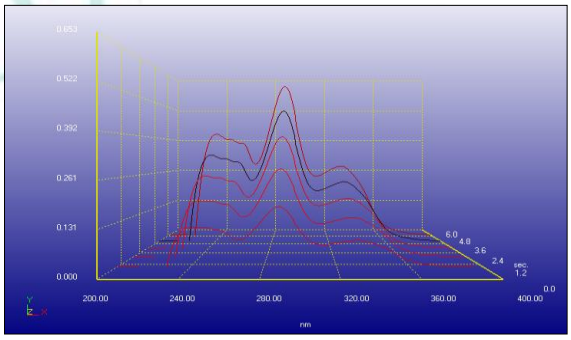


Figure 3: 3D Standard graph of Repaglinide

Drug Polymer Compatibility study

As described in the methodology section the Fourier Transform infrared spectroscopy studies were carried out for pure drug and along with polymers. The results are summarized as follows. IR spectra of drug repaglinide and polymers Eudragit RL 100, Eudragit RS 100 and HPMC alone and their combinations are shown in Figures.

Table 7: Major peak observed in the FTIR spectrum

Bands	Wave number(cm^{-1})
OH (Str.)	3411.04
CH Aromatic (Str.)	2960.42
CH Aliphatic (Str.)	2915.38
C=O (Str.)	1667.03
C-O-C (Str.)	1260.78
C - N (Str.)	1314.97

The appearance or disappearance of peaks and/or the shift of their positions are often indications of interactions such as hydrogen bonding. Repaglinide presented characteristic peak at 3411.04 cm^{-1} due to OH stretching, 2990 cm^{-1} was due to CH aromatic stretching vibration and in 2915.98 due to CH aliphatic stretching vibration. C-O-C (Str.) shows the peak at 1260.78 cm^{-1}, peak at 1414.97 cm^{-1} was due to C - N scissor stretching vibration. When the data obtained from FTIR spectra is compared with the standard spectra it was observed that there are similar peaks for functional groups in repaglinide, this shows the purity of repaglinide.

FT-IR spectra of standard drug exhibited C-O-C (Str.) peak at 1260.78 cm^{-1} & peak at 1414.97 cm^{-1} was due to C - N scissor stretching vibration. The mixture of drug and excipients which was kept in accelerated condition of 40^0C/ 75% RH for 30 days and subjected to FT-IR analysis. The characteristic peak of C-O-C (Str.) & C - N does not deviated from its position that predicts that there is no interaction between drug and excipients.

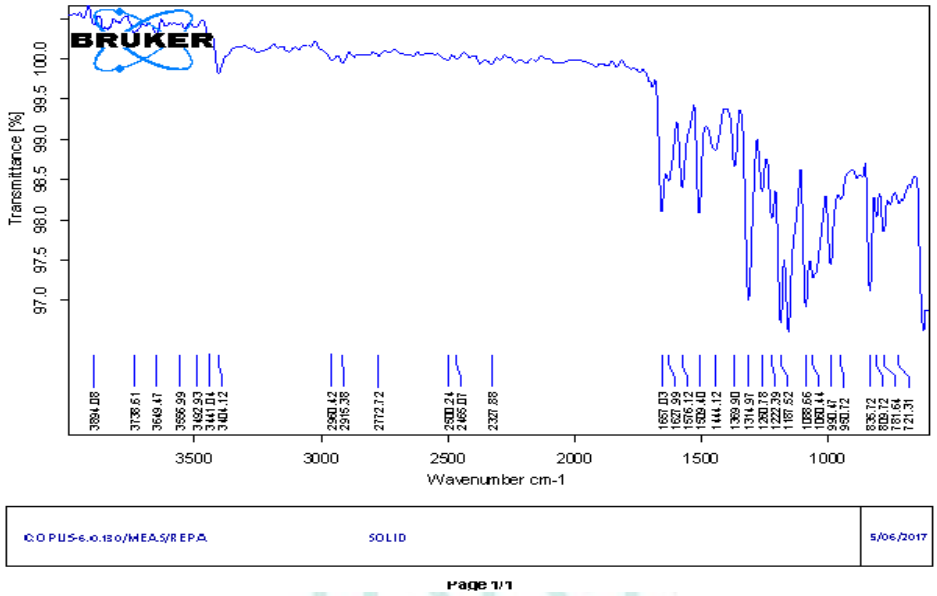


Figure 4: FTIR of Repaglinide

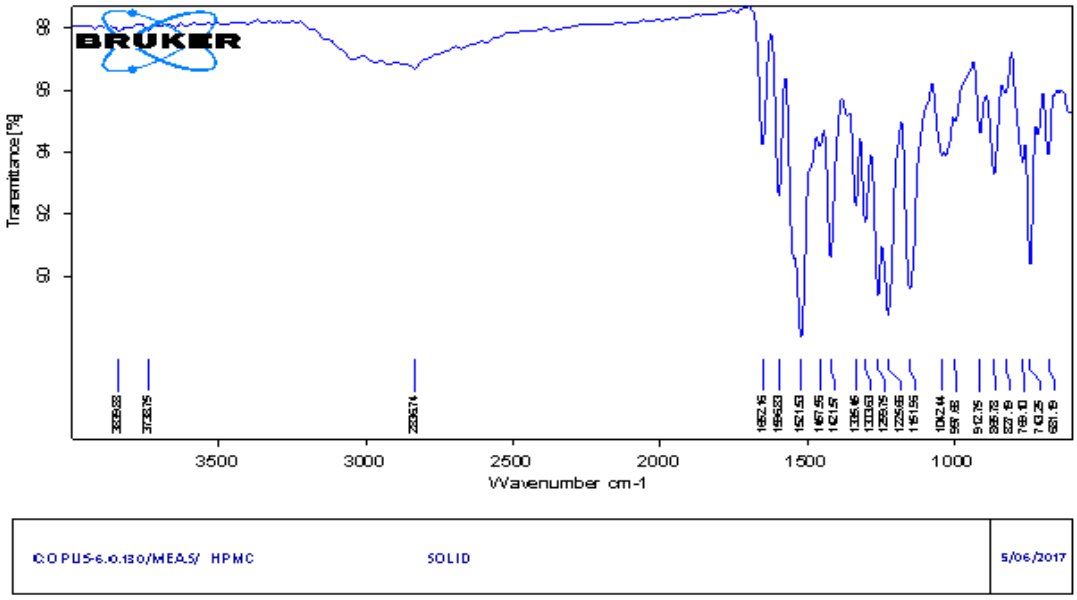


Figure 5: FTIR of HPMC

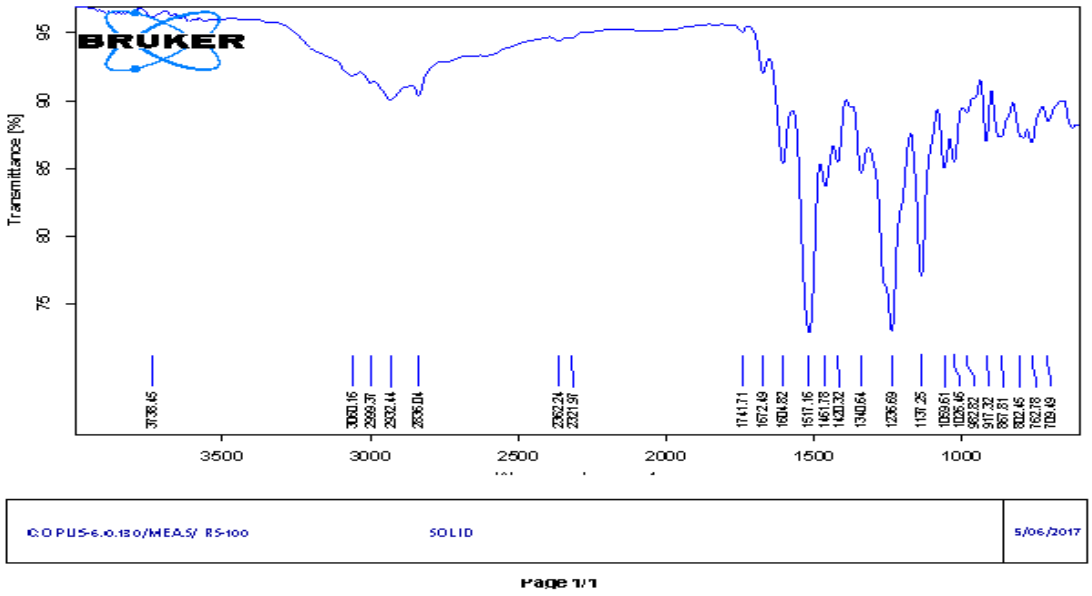


Figure 6: FTIR of EUDRAGIT RS100

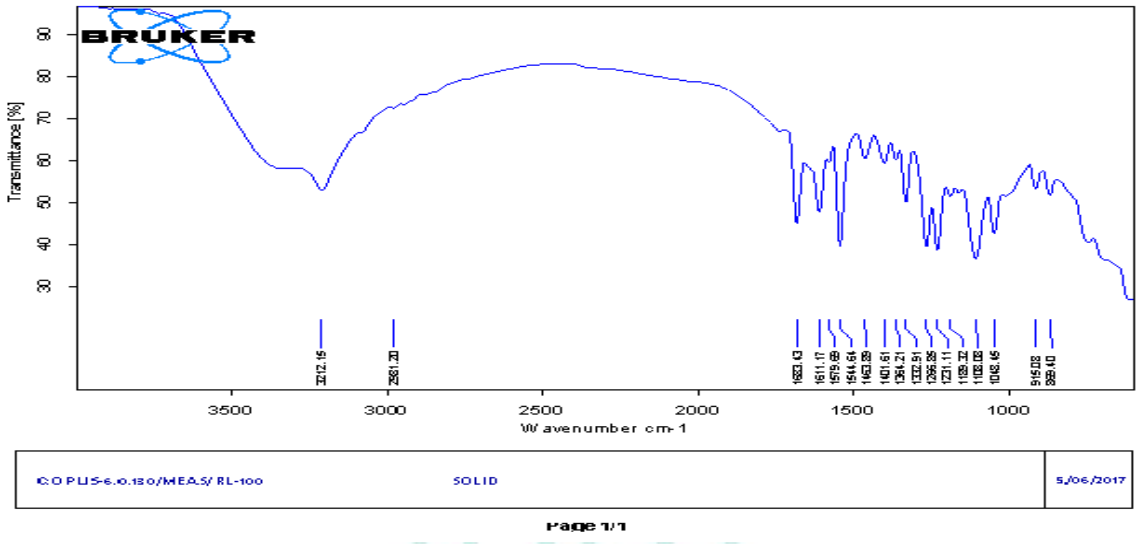


Figure 7: FTIR of EUDRAGIT RL100

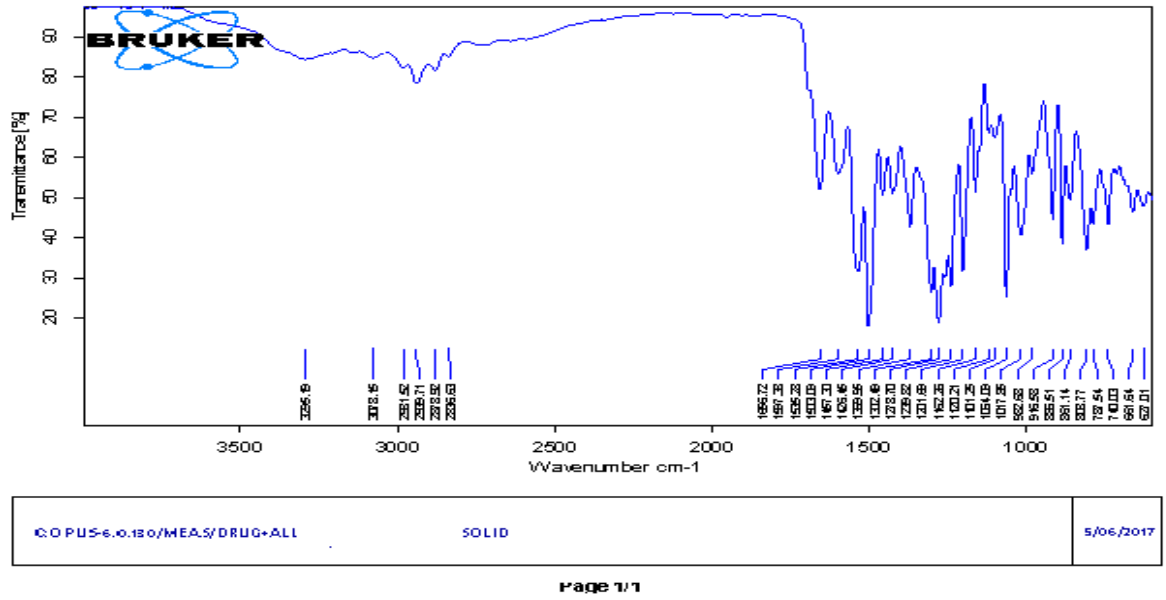


Figure 8: FTIR of Drug-Polymer Mixture

CONCLUSION

Transdermal drug delivery system promises many advantages over oral and/or inravenous administration,such as better control of blood levels,a reduced incidenc of systemic toxicity and absence of hepatic first pass metabolism.An ideal drug to be formulated as transdermal drug delivery should posses several physico-chemical prerequisites,such as short half life,small molecular size,low dose etc. The present investigation was aimed to evaluate the possibility of using different parameters for the development of transdermal delivery of repaglinide, an anti-diabetic drug. Preformulation studies were done using various parameters such as the description and appearance, melting point and solubility, FT-IR, analytical UV method were performed for characterization & it was found that all results were satisfactory.

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