International Journal for Pharmaceutical Research Scholars (IJPRS)

V-3, I-4, 2014 ISSN No: 2277 - 7873

RESEARCH ARTICLE

Design and *In Vitro* Evaluation of Sustained Release Matrix Tablets of Repaglinide

Vishwanath Arakeri, P. Ashok Kumar*, Suresh V. Kulkarni

Department of Pharmaceutics, Sree Siddaganga College of Pharmacy BH Road, Tumkur, Karnataka, India.

Manuscript No: IJPRS/V3/I4/00430, Received On: 14/11/2014, Accepted On: 23/11/2014

ABSTRACT

The objective of the present work is to design sustained release matrix tablets of Repaglinide using *Prosophis juliflora* gum and HPMC K-100, Ethyl cellulose. Tablets were prepared by wet granulation method. Repaglinide is one of emerging short acting drug. Granules were prepared and evaluated for loose bulk density, tapped bulk density, compressibility index and angle of repose. The developed tablets were subjected to various tests for physical parameters such as thickness, hardness, friability, drug content and *in vitro* release studies. Release kinetics was evaluated by using United States Pharmacopeia USP type II dissolution apparatus. The *in vitro* dissolution study was carried out for 12 hrs. For first 2hrs in 0.1 N hydrochloric acid (pH 1.2) followed by using phosphate buffer pH 7.4 for the remaining 10 hrs. The results of dissolution studies indicated that formulations containing natural gum *Prosophis juliflora* gum showed better dissolution than synthetic gums (HPMC K-100, Ethyl cellulose). The dissolution study proved enhanced sustained release when dried *Prosophis juliflora* gum was used as a matrix forming material.

KEYWORDS

Sustained Release Matrix Tablet, Repaglinide, Prosophis Juliflora Gum, HPMC K-100, Ethyl Cellulose

INTRODUCTION

Oral drug delivery is the most preferred and convenient option as the oral route provides maximum active surface area among all drug delivery system for administration of various drugs. Normally conventional dosage form produces wide range of fluctuation in drug concentration in the bloodstream and tissues with consequent undesirable toxicity and poor efficiency. The maintenance of concentration of drug in plasma within therapeutic index is very critical for effective treatment. These factors as well as factors such as repetitive dosing and unpredictable absorption lead to the concept of oral Sustained release drug delivery systems.

***Address for Correspondence:**
Dr. P. Ashok Kumar
Associate Professor, Department of Pharmaceutics,
Sree Siddaganga College of Pharmacy, Tumkur -572 102
Karnataka. India.
E-Mail Id: ashokkumarscp@yahoo.com

Developing oral sustained release matrix tablets for drug with constant release rate has always been a challenge to the pharmaceutical technologist. Drug release through matrix system is determined by Water penetration, Polymer swelling, Drug dissolution, Drug diffusion, Matrix erosion have been utilized as formulation approaches.[1]

Sustained release systems include any drug delivery system that achieves slow release of drug over an extended period of time.

If the system is successful in maintaining constant drug levels in the blood or target tissue, it is considered as a controlled-release system. If it is unsuccessful at this but nevertheless extends the duration of action over that achieved by conventional delivery, it is considered as a prolonged release system. [2]

Matrix systems are widely used for the purpose of sustained release. The first sustained release tablets were made by Howard Press in New Jersy in the early 1950's. The first tablets released under his process patent were called 'Nitroglyn' and made under license by Key Corp. in Florida[3].

Diabetes mellitus (DM) metabolic disorder resulting from a defect in insulin secretion, insulin action, or both insulin deficiency in turn leads to chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism. As the disease progresses tissue or vascular damage ensues leading to severe diabetic complications such as retinopathy, neuropathy, nephropathy, cardiovascular complications and ulceration. Thus, diabetes covers a wide range of heterogeneous diseases[4].

Repaglinide is an oral blood glucose-lowering drug of the meglitinide class used in the management of type 2 diabetes mellitus. It is derivative of benzoic acid, It belongs to the meglitinide class of short-acting insulin secretagogues.

After oral administration, Repaglinide is rapidly and completely absorbed from the gastrointestinal tract. After single and multiple oral doses in healthy subjects or in patients, peak plasma drug levels (C_{max}) occur within 1 hour (T_{max}). Repaglinide is rapidly eliminated from the blood stream with a half-life of approximately 1 hour. The mean absolute bioavailability is 56%. When Repaglinide was given with food, the mean Tmax was not changed, but the mean Cmax and AUC (area under the time/plasma concentration curve) were decreased 20% and 12.4%, respectively.[5]

MATERIALS AND METHODS

Repaglinide were purchased from yarrow chemicals Mumbai, *Prosophis juliflora* gum was collected from plants growing near by the areas of Sree Siddaganga mutt Tumkur, and authenticated at the Botany Department of Sree Siddaganga College Of Arts, Science & Commerce B.H. Road Tumkur, Karanataka. HPMC K-100, Ethyl cellulose, Microcrystalline cellulose were purchased from Research- Lab Fine Chem Industries, Mumbai. Magnesium stearate, Talc, PVP K 30 were purchased from SD Fine chemicals Ltd, Mumbai.

Formulation of Sustained Release Matrix Tablets

Tablet formulations were prepared by wet granulation method. Non-aqueous granulation process was adopted to prepare Repaglinide SR matrix tablets Proportion of excipients with drug was as given in Table no 1. All ingredients were sifted through sieve no.60. The sifted ingredients were mixed thoroughly in a polybag for 15min. PVP K30 was dissolved in isopropyl alcohol and used for wet granulation of the final blend. To get the desired wet mass. This wet mass was passed through sieve # 16. The prepared granules were dried at 60^0C for 1 hour in hot air oven, dried granules were sized by passing it through sieve no.20 and lubricated with magnesium stearate and Talc for 1 minutes. Finally tablets were compressed at 200 mg weight on a 10 station mini rotary tableting machine (Shakti Pharmatech Pvt. Ltd, Ahmedabad) with 8 mm flat-shaped punches.

Extraction of *Prosophis Juliflora* Gum

The *Prosophis juliflora* gum was collected and soaked in water for 5–6 hrs, boiled for 30 minutes and left to stand for 1 h to allow complete extraction of the gum into the water. The gum was filtered using a multi-layer muslin cloth bag to remove the dirt and foreign matter from the solution. Acetone (three times the volume of filtrate) was added to precipitate the gum. The gum was separated, dried in an oven at 35°C, collected, ground, passed through a # 80 sieve and stored in desiccator at 30°C & 45% relative humidity till use [6].

Evaluation of Granules[7,8,9]

Angle of Repose

The angle of repose of granules was determined by the funnel method. The granules were allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

Table 1: Composition of matrix tablet of Repaglinide

Ingredients	Formulation code (in mg)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Repaglinide	10	10	10	10	10	10	10	10	10
Prosophis juliflora Gum	20	40	60	-	-	-	-	-	-
HPMC K-100	-	-	-	20	40	60	-	-	-
Ethyl cellulose	-	-	-	-	-	-	20	40	60
PVP K 30	20	20	20	20	20	20	20	20	20
Microcrystalline cellulose	144	124	104	144	124	104	144	124	104
Magnesium stearate	4	4	4	4	4	4	4	4	4
Talc	2	2	2	2	2	2	2	2	2

$$\tan \theta = h/r$$

Where, h and r are the height and radius of the powder cone.

Bulk Density

Both loose bulk density and tapped bulk density were determined and calculated by using the following formulas.

LBD = weight of the powder / volume of the packing

TBD = weight of the powder / tapped volume of the packing

Compressibility Index

The compressibility index of the granules was determined by Carr's compressibility index.

Carr's index (%) = [TBD-LBD] X 100 / TBD

Where, TPD is Tapped bulk density

LBD is Loose bulk density

The physical properties of granules were shown in Table 3.

Evaluation of Tablets [7,8,9]

Post Compression Parameters

A. Thickness and Diameter

Control of physical dimension of the tablet such as thickness and diameter is essential for consumer acceptance and tablet uniformity. The thickness and diameter of the tablet was measured using Vernier calipers. It is measured in mm.

B. Hardness

The Monsanto hardness tester was used to determine the tablet hardness. The tablet was held between a fixed and moving jaw. Scale was adjusted to zero; load was gradually increased until the tablet fractured. The value of the load at that point gives a measure of hardness of the tablet. Hardness was expressed in Kg/cm^2.

C. Friability (F)

Tablet strength was tested by Roche friabilator. Pre weighed tablets were allowed for 100 revolutions (4min), taken out and were dedusted. The percentage weight loss was calculated by rewriting the tablets.

$$F = \frac{(W_{initial}) - (W_{final})}{(W_{initial})} \times 100$$

D. Weight Variation

Randomly selected twenty tablets were weighed individually and together in a single pan balance. The average weight was noted and standard deviation calculated. The tablet passes the test if not more than two tablets fall outside the percentage limit and none of the tablet

differs by more than double the percentage limit.

All prepared matrix tablets were evaluated for its uniformity of weight, hardness, friability and thickness according to official methods shown in Table 4.

E. Uniformity of Drug Content

Weigh and powder 20 tablets. Weigh accurately a Quantity of the powder equivalent to 100 mg of Repaglinide, transfer to a 250 ml volumetric flask. Add about 150 ml of 0.1N HCL, shake well and sonicate it for 25-30 min. Make up the volume up to 250 ml with 0.1N HCL. Filter the solution, take 10 ml of filtrate in 100 ml volumetric flask and make up the volume with 0.1N HCL. Measure the absorbance, of the resulting solution at the maxima at about 242 nm spectrophotometrically. Measure the concentration of drug in tablet powder using following equation:

Cu/Cs = Au/As * dilution factor

Cu = Concentration of unknown sample,

Cs = Concentration of Standard sample

Au = Absorbance of unknown sample

As = Absorbance of standard sample[10].

F. In-Vitro Dissolution Study

Dissolution tests were performed in a USP Dissolution Test Apparatus II (Paddle method) at 37 ± 0.5°C. The Paddles were rotated at a speed of 50 rpm. The prepared tablets of (Repaglinide) tablets were placed in the dissolution vessel containing 0.1 N HCl solutions (pH 1.2) for 2 hrs. These were then transferred to phosphate buffer (pH 7.4) and continue dissolution. 5 ml of solution were withdrawn at different time intervals, filtered through 0.45 µm filter paper and the content of Repaglinide was determined spectrophotometrically at a wavelength of 242nm for first 2 hr and then after take in 278nm. At each (hour) time of Withdrawal, 5 ml of fresh corresponding medium was replaced into the dissolution flask. On the basis of release studies the formulation which gave desired once a day release of Repaglinide was chosen as the optimized formulation. The dissolution profiles of different formulations are shown in figure 10, 11. The drug release from the formulations were sustained in the following manner F1 > F2> F5.

In all the formulations, it has been observed that by increase the concentration of polymers in the formulations there by respectively retard the drug release form the matrices.

Drug Release Kinetics

To determine the mechanism of drug release from this formulation, the drug release data of *in-vitro* dissolution study was analyzed with various kinetic equations. Various kinetic equations. The data were treated according to:

1. Zero order kinetic model – Cumulative % drug released versus time.
2. First order kinetic model – Log cumulative percent drug remaining versus time.
3. Higuchi's model – Cumulative percent drug released versus square root of time.
4. Korsmeyer equation / Peppa's model – Log cumulative percent drug released versus log time.

Stability Study

The optimized formulation was subjected to stability at $25^0C\pm 2^0C$ / 60% ± 5% RH, $30^0C \pm 2^0C$ / 65% ±5% RH and $40^0C \pm 2^0C$ / 75% ± 5% RH for period of 90 days. After each month tablet sample was analyzed for physical characteristics and drug release profile.[11]

RESULTS AND DISCUSSION

Table 2: Preliminary confirmatory tests for dried gum

Sr. No	Chemical Test	Observation *P. Joliflora* gum
1	**Test for Carbohydrate** Molish's Test	+
2	**Test for Mucilage** Ruthenium Test	+

3	**Test for Polysaccharide** Iodine Test	+
4	**Test for Tannins** Ferric Chloride Test	+
5	**Test for Alkaloids** Wagner's Test	+

FTIR Spectroscopy

The FT-IR Spectrum of pure Repaglinide and its physical mixture with polymers and different excipients are shown in Figure: 1-9.

The FT-IR Spectrum of pure Repaglinide (Figure 1) showed Amine stretching at 3303.78cm^{-1}, 2933.83 cm^{-1} (CH aromatic stretching), CH aliphatic stretching at 2850.86 cm^{-1}, carboxylic OH at 2801.6 cm^{-1}, C=O stretching at 1684.52 cm^{-1}, C=O stretch of amide/esters at 1631.91cm^{-1},C=C Stretching at 1489.6 cm^{-1}, C-N Stretching at 1210.51cm^{-1}, Ether linkage (R-O-R) at 1147.6 cm^{-1}, C-N (Amines) stretch at 1089.49 cm^{-1}.

The FT-IR Spectrum of optimized formula F-3 (Figure 3) showed Amine stretching at 3304.89cm^{-1}, 2933.28 cm^{-1} (CH aromatic stretching), CH aliphatic stretching at 2851.52 cm^{-1}, carboxylic OH at 2804.934cm^{-1}, C=O stretching at 1685.42 cm^{-1}, C=O stretch of amide/esters at 1631.39cm^{-1}, C=C Stretching at 1489.81 cm^{-1}, C-N Stretching at 1211.353cm^{-1}, Ether linkage (R-O-R) at 1147.83 cm^{-1}, C-N (Amines) stretch at 1089.69 cm^{-1}.

Table 3: Evaluation of Pre-Compression Parameters

Formulations	Bulk Density* (g/ml)	Tapped bulk* density (g/ml)	Carr's index (%)	Angle of repose*
F1	0.286±0.004	0.310±0.016	7.74±1.40	27.20±1.18
F2	0.251 ± 0.005	0.277 ± 0.010	9.38±1.32	26.12±1.42
F3	0.282 ±0.004	0.322 ± 0.017	12.42±1.43	28.37±1.44
F4	0.259 ± 0.003	0.289 ± 0.014	10.38±1.40	26.16±1.66
F5	0.264±0.004	0.286±0.014	7.69±1.33	27.79±1.42
F6	0.288±0.006	0.316±0.012	8.86±1.28	26.80±1.33
F7	0.298 ± 0.003	0.331 ± 0.014	9.96±1.41	27.12±1.81
F8	0.292±0.004	0.324±0.012	9.87±1.38	28.91±1.90
F9	0.298 ±0.004	0.328 ± 0.011	9.14±1.39	27.33±1.72

*The values represent mean ± SD, n=3.

Table 4: Evaluation of Repaglinide SR tablets

Formulations	Thickness* (mm)	Hardness* (kg/cm^2)	Friability* (%)	Drug content (%)
F1	1.93±0.05	6.1±0.15	0.35±0.31	98.63
F2	1.92±0.06	6.2±0.20	0.30±0.12	99.17
F3	1.90±0.02	6.1±0.08	0.30±0.31	99.12
F4	1.94±0.10	6.1±0.09	0.29±0.12	99.62
F5	1.92±0.13	6.0±0.01	0.22±04	99.22
F6	1.92±0.15	6.3±0.12	0.26±0.10	99.41
F7	1.94±0.06	5.9±0.16	0.27±0.26	99.04
F8	1.91±0.15	6.1±0.19	0.30±0.13	99.44
F9	1.94±0.04	6±0.09	0.32±0.11	99.16

*The values represent mean ± SD, n=3

Table 5: Correlation coefficients of different mathematical models for formulations F- 1 to F-9

Formulation Code	Zero Order R^2	First Order R^2	Higuchi R^2	Peppas- model	
				R^2	Slope n
F1	0.995	0.935	0.965	0.983	0.823
F2	0.994	0.947	0.962	0.981	0.807
F3	0.991	0.983	0.980	0.992	0.841
F4	0.986	0.663	0.932	0.960	0.785
F5	0.992	0.745	0.948	0.962	0.903
F6	0.989	0.726	0.950	0.963	0.944
F7	0.991	0.939	0.952	0.968	0.750
F8	0.993	0.978	0.959	0.966	0.727
F9	0.990	0.964	0.942	0.963	0.759

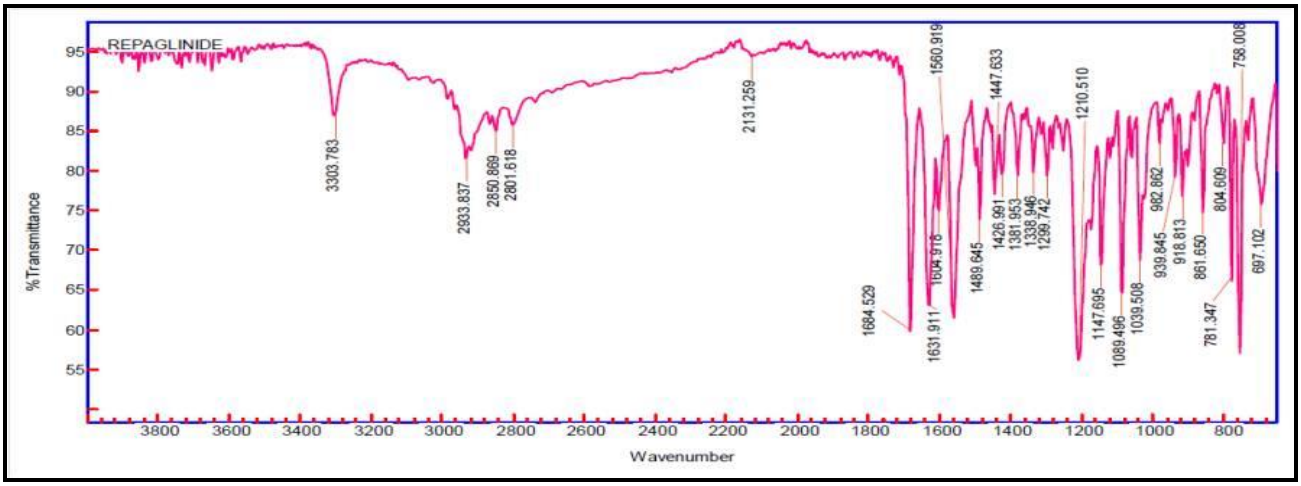

Figure 1: FT-IR of Repaglinide

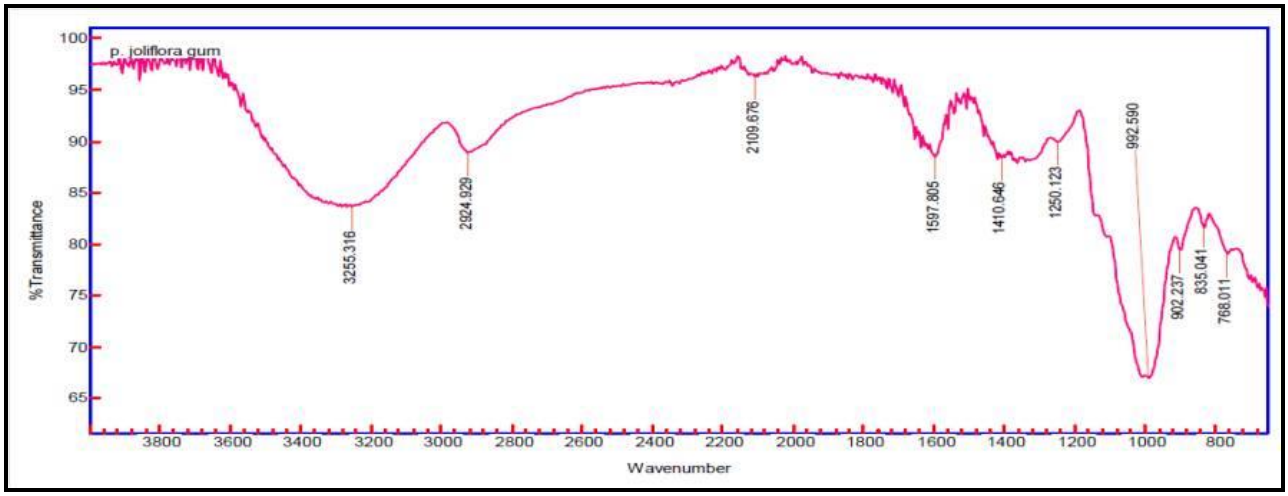

Figure 2: FT-IR of *Prosophis joliflora* gum

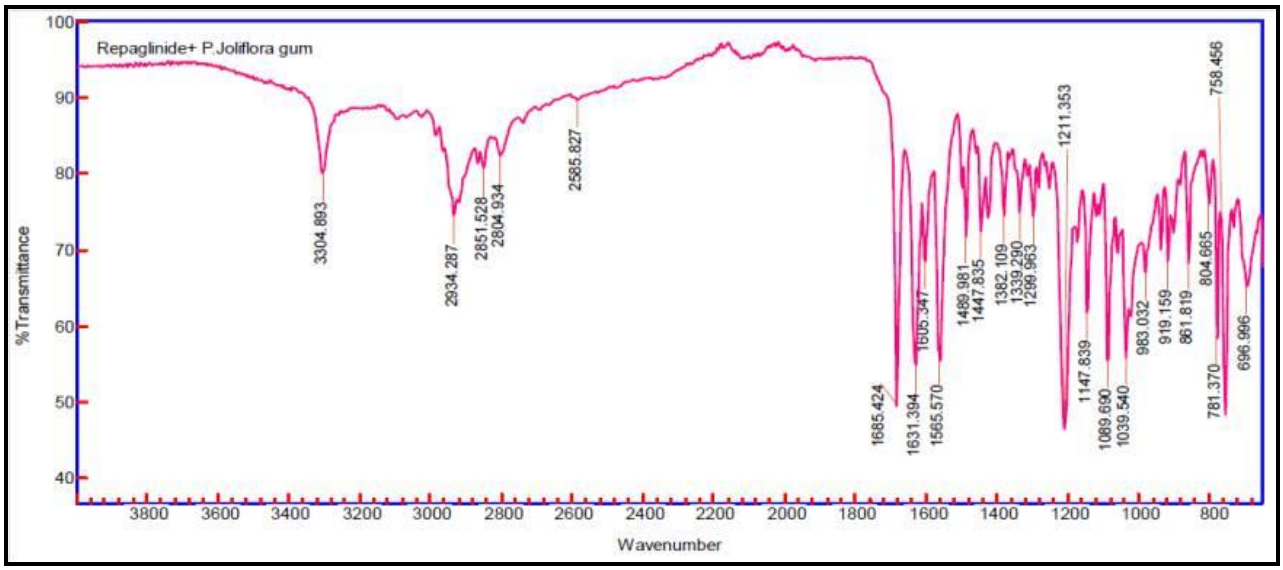

Figure 3: FT-IR of Repaglinide + *Prosophis joliflora* gum

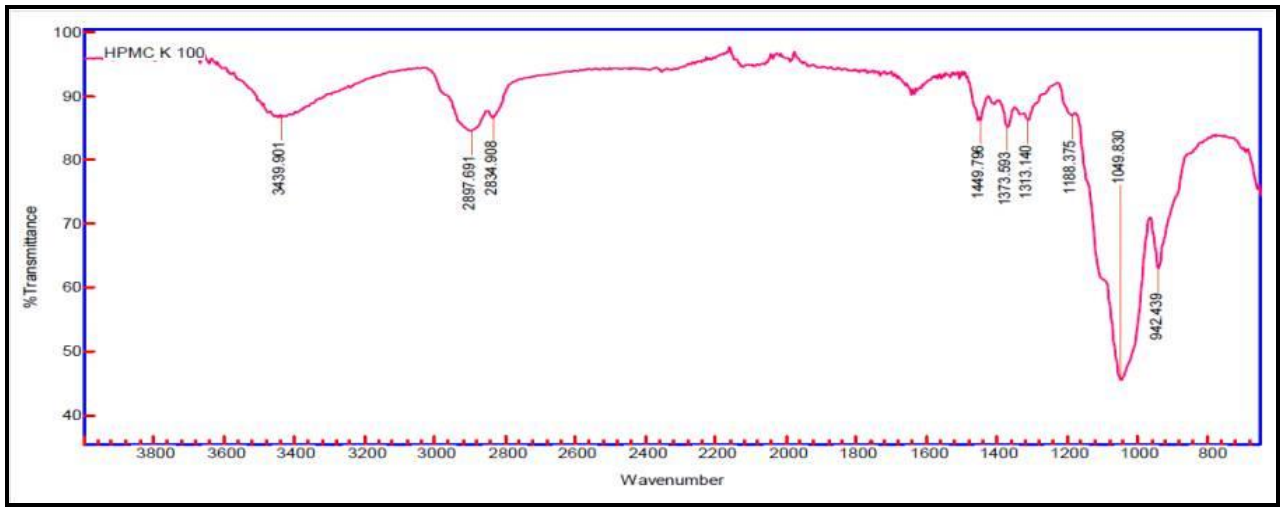

Figure 4: FT-IR of HPMC K 100

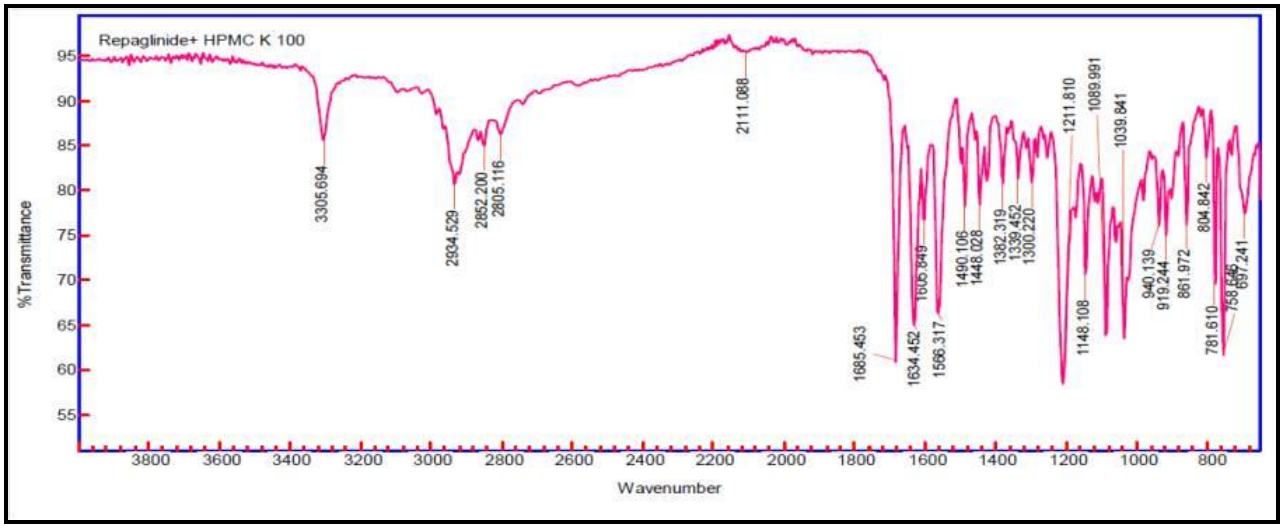

Figure 5: FT-IR of Repaglinide+ HPMC K 100

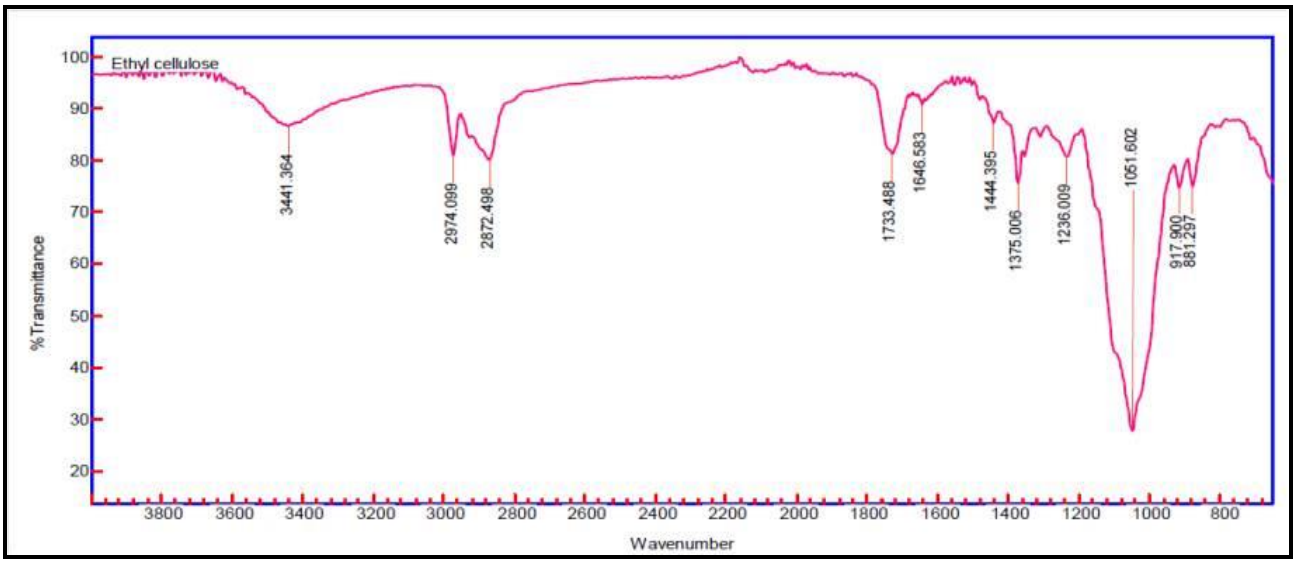

Figure 6: FT-IR of Ethyl cellulose

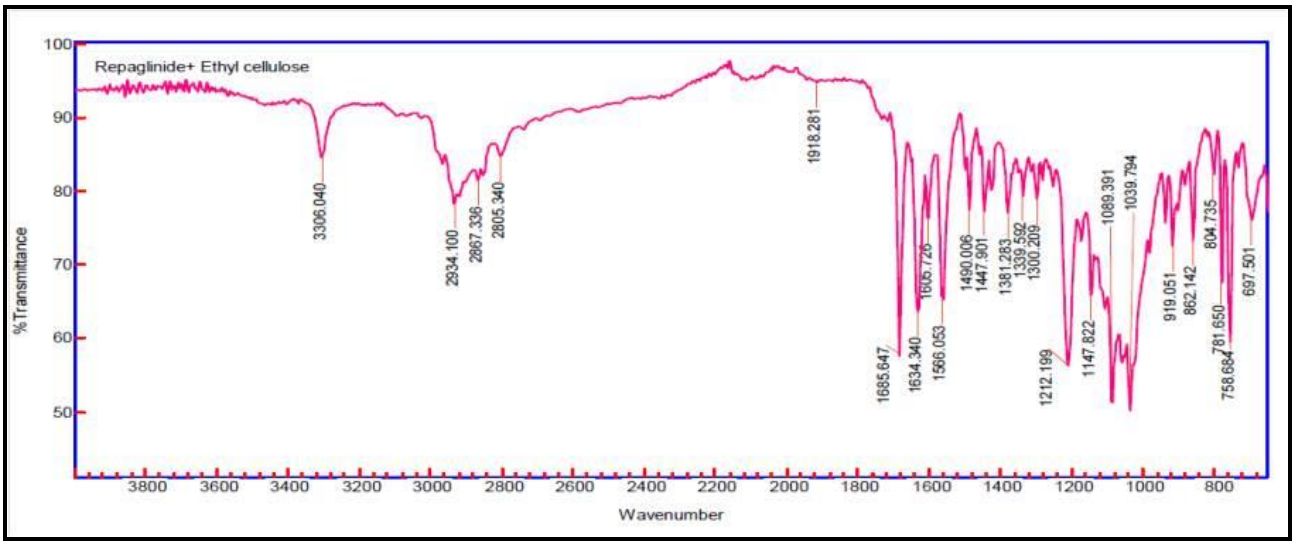

Figure 7: FT-IR of Repaglinide + Ethyl cellulose

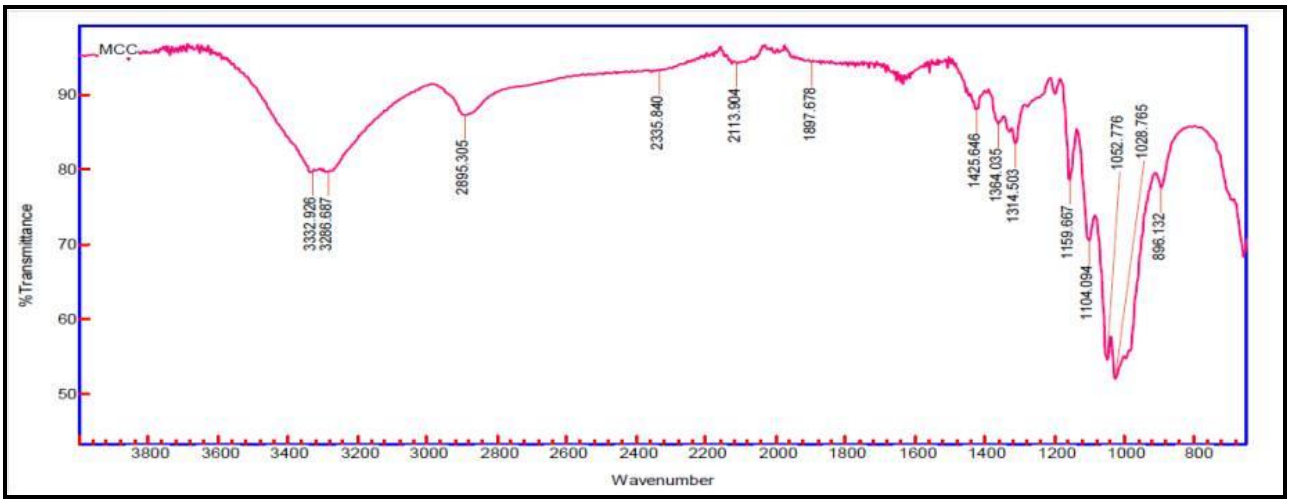

Figure 8: FT-IR of MCC

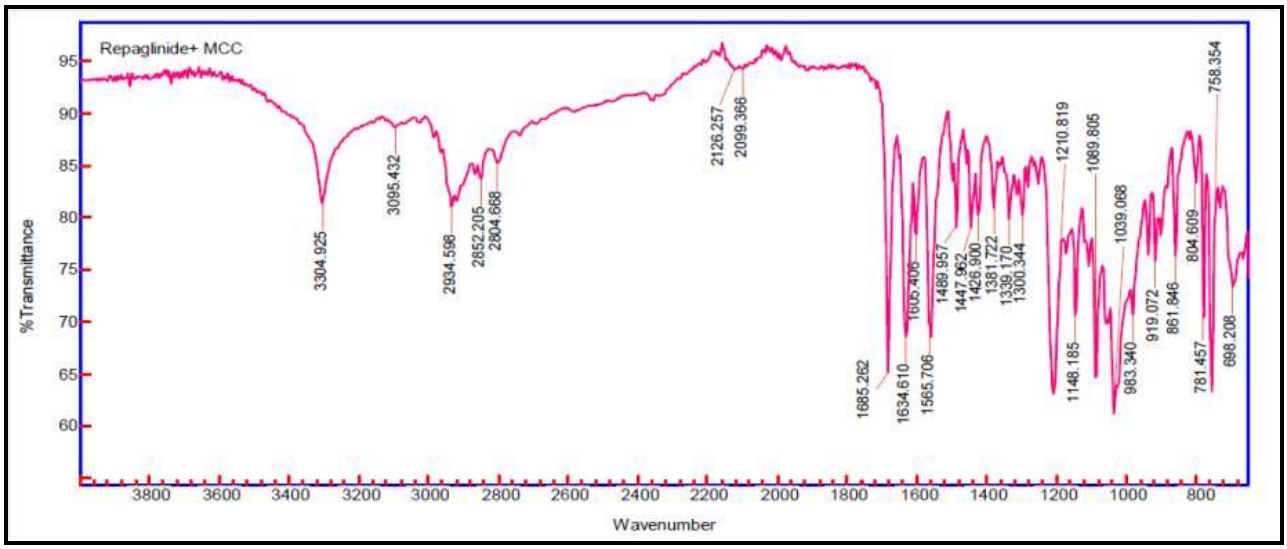

Figure 9: FT-IR of Repaglinide + MCC

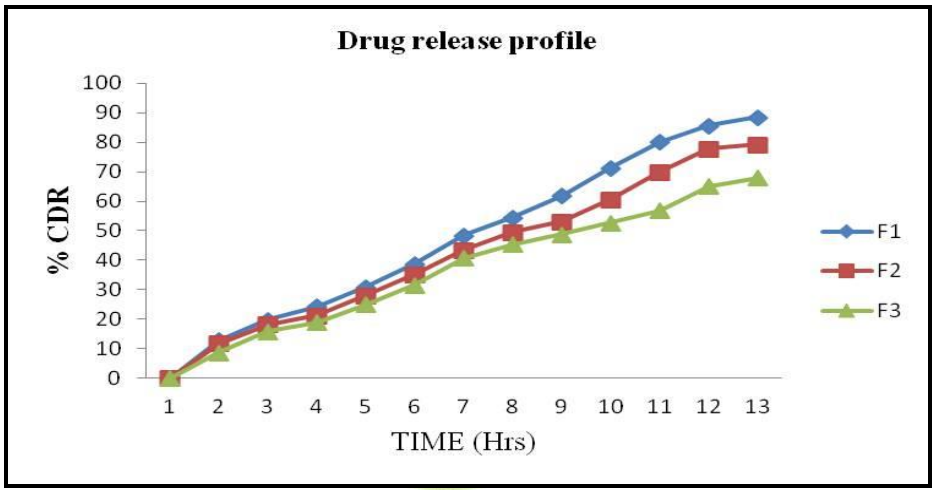

Figure 10: *In Vitro* Dissolution Profile of F-1 to F-3 Formulations

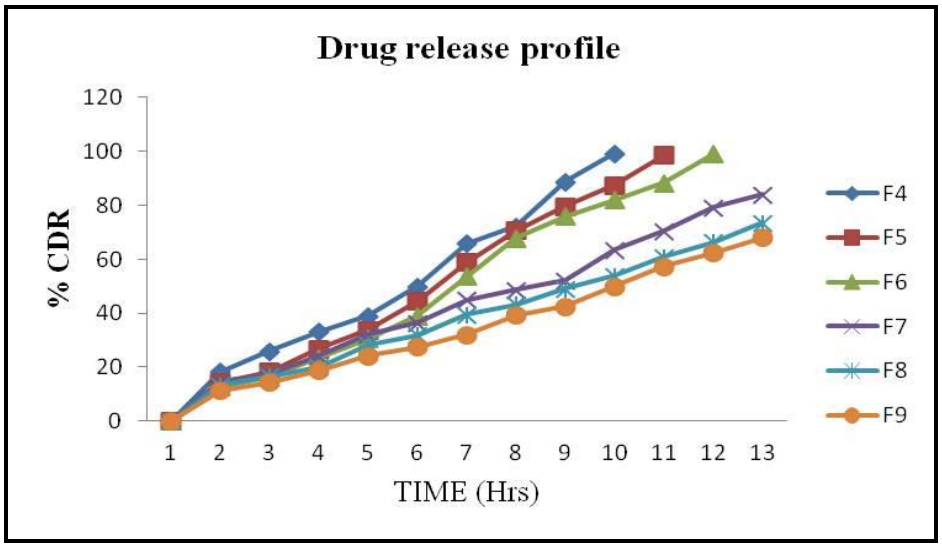

Figure 11: *In Vitro* Dissolution Profile of F-4 to F-9 Formulations

All the tablet formulations showed acceptable quality control properties like hardness, friability, thickness, weight variation, drug content uniformity etc. Complied with in the specifications for tested parameters.

Matrix tablet of formulation F-1 to F-3, were containing Prosophis juliflora gum as polymer. Among these formulations, the release rate was decreased in the following order:

F-1> F-2>F-3. This result has shown that as the proportion of Prosophis juliflora gum increased, the overall time of release of the drug from the matrix tablet was also increased. For F-1 (88.5%) up to 12 hrs, F-2 (79.3%) up to 12 hrs, F-3 (68.01%) in 12 hrs respectively. Formulation F-3 having drug–polymer ratio of 1:6 (Drug : Prosophis juliflora gum) gave better drug release rate over a period of 12 hours. Thus, formulation F-3 was found to be the most promising formulation on the basis of acceptable tablet properties and in vitro drug release. Drug releases from matrix tablets were by drug dissolution, drug diffusion or a combination of both.

The addition of gel forming polymer like HPMC K 100M (Synthetic polymer) in formulation of F4- to F-6, showed better control in retarding the release rate. Drug release was decreased with increased polymer concentration, this might be due to quick hydration and gel forming abilities of HPMC K 100 can be used to prolong the drug release of the active ingredient. It shows 99.1% drug release in 11 hrs.

F7 to F9 when the polymer concentration of Ethyl cellulose increased the drug release rate was reduced from the above formulations. Ethyl cellulose shows less water permeability character. The drug release among these three formulations F-9 shows 68.14% of drug release up to 12 hrs and F-7, F-8 formulations shows 83% and 73.8% of drug release at the end of 12 hrs.

The n values obtained from Korsmeyer Peppas plots range from (0.727 to 0.944) indicate that mechanism of release of formulations F-1 to F-9 was Anomalous (non- Fickian) diffusion.

Stability studies were conducted for the optimized formulations as per ICH guidelines.

There was not much variation in matrix integrity of the tablets at all the temperature conditions. There were no significant changes in drug content, physical stability, hardness, friability and drug release for the selected formulation F-3 after 90 days.

CONCLUSION

Sustained release Matrix tablet of Repaglinide be able to prepare by using wet granulation method, using Prosophis juliflora gum, HPMC K 100 and ethyl cellulose polymers as retardant and by using microcrystalline cellulose as filler. From the above observations it was concluded that slow and sustained release of Repaglinide over a period of 12 hours was obtained from matrix tablets F-3. It was found that increase in the polymeric concentration in polymeric ratio decreases the drug release.

The results suggest that the developed sustained-release tablets of Repaglinide might achieve better than conventional dosage forms, leading to improve efficacy and patient compliance.

ACKNOWLEDGEMENT

The authors are thankful to the Management, Sree Siddaganga College of Pharmacy, Tumkur for providing necessary facilities to carry out this work.

REFERENCES

1. Ratnaparkhi, M. P., & Gupta Jyoti, P. (2013). Sustained Release Oral Drug Delivery System-An Overview. *Terminology*, *3*, 4.
2. Sarika, P., Ashutosh, B., Deepak, S. (2013). Sustained release matrix technology and recent advance in matrix drug delivery system: a review. *International Journal of Drug Research and Technology*, *3*(1), 12-20.
3. Kumar, V., Prajapati, S. K., Soni, G. C., Singh, M., & Kumar, N. (2012). Sustained release matrix type drug delivery system: a

review. *World Journal of Pharmacy and Pharmaceutical Sciences*, *1*(3), 934-960.

4. Olokoba, A. B., Obateru, O. A., & Olokoba, L. B. (2012). Type 2 diabetes mellitus: a review of current trends. *Oman Medical Journal*, *27*(4), 269-273.
5. http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020741s035lbl.pdf.
6. Ahed, H. A., Harika, B., & Leela, L. V. (2010). Formulation and In-vitro Evaluation of Once-Daily Sustained-Release Matrix Tablets of Glipizide.*Scholars Research Library*, *2*(1).
7. Patel, N. A., Makwana, S. T., Patel, Z. P., Solanki, S. M., Patel, M. B. (2012). Formulation & evaluation of once daily sustained release matrix tablet of pramipexole dihydrochloride. *International Journal for Pharmaceutical Scholars*, *1*(2), 370-6.
8. Deepak, P., Abhishek, J., Jatav Rakesh, K., & Hariharanand, S. (2011). Formulation and Evaluation of Pioglitazone Hydrochloride Matrix Tablet Containing Aloe Barbadensis Miller Mucilage Natural Antidiabetic Agent. *International Journal of Drug Discovery and Herbal Research*, *1*(3), 157-163.
9. Venkataramudu, T. S., Firoz, C. Y., Vikram, A., Divya Sree, K., & Murali Krishna, T. (2012). Design and characterisation sustained release matrix tablets of repaglinide using natural polymers. *International Journal of Pharmaceutics*, *2*(2), 73-83.
10. Barot, N., Darshan, M., Praful, D. B. (2014). Formulation development and evaluation of sustained release matrix tablets of repaglinide. *International Journal of Pharmaceutical Research and Bio-Science*, *3*(2), 370-96.
11. Kurian, J. K., Kumar, P. A., & Kulkarni, S. V. Influence of natural, synthetic polymers and fillers on sustained release matrix tablets of sildenafil citrate. *Der Pharmacia Lettre*, *6* (2), 106-17.

