

# Extended Release System of Hypoglycemic Agent Containing Solid Dispersions: Strategies and Mechanisms

Amit Kumar, Ramendeep Grawal, Peeyush Sharma, Dinesh Puri, Anil Bhandari

**Abstract**—The main perspective of the present study aims at overcoming solubility problems by using the technique of solid dispersion. Repaglinide is a BCS Class II drug, having low aqueous solubility and therefore, low bioavailability. Solid dispersions of repaglinide with different carriers Polyvinyl Pyrrolidone (PVP) and Ethyl Cellulose (EC) in different ratios were prepared by suspending method and Dissolving methods. *In vitro* release studies revealed that the F7 formulation showed extended drug release. So, the dissolution profile of solid dispersion containing EC and PVP K30 (1: 3) was selected as the best formulation because of its extended drug release among all formulations. In conclusion, solid dispersions of Repaglinide in PVP have shown to be a promising approach to improve the bioavailability of Repaglinide.

**Keywords**—Ethyl Cellulose, Glibenclamide, Polyvinyl Pyrrolidone, Repaglinide, Solid Dispersion.

## I. INTRODUCTION

CONSIDERABLE attention has been focused in recent years on the development of extended drug delivery systems, due to significant advances in developing and commercializing oral extended release products. The basic rationale of extended drug delivery system is to optimize the Biopharmaceutics, pharmacokinetic and pharmacodynamic properties of a drug in such a way that its utility is maximized through reduction in side effects and cure or control of conditions, in the shortest possible time by using smallest quantity of drug administered by most suitable route. [13], [15] The concept of extended release dosage form system can be utilized to provide a long lasting and more reliable release of drug in GIT to ultimately develop a once/two daily formulation. [2], [4] Thus, they prolong the dosing intervals, but also increase patient compliance beyond the level of existing conventional dosage forms. An ideal extended drug delivery system delivers the drug at a predetermined rate, locally or systemically for a specified period of times. Extended drug delivery system not always releases the drug by zero order kinetics, it may release by first order or any other kinetic model [1], [18]. The solubility behavior of drug is one of most challenging aspect in formulation development. [19], [29] Thus a greater understanding of dissolution & absorption behavior of drug with low aqueous solubility is required to successfully formulate them into more soluble and hence

bioavailability product. [5], [32] Therefore different approaches are being explored to enhance the solubility of poorly water soluble drugs. [7] Solid dispersion technique has come into existence to eliminate all these problems and it appear to be a better approach to improve drug solubility than these techniques, because they are easier to produce and more applicable. [5], [31] Solid dispersion is one of the major techniques adopted for the formulation of such poorly water soluble drugs. [23] It has attracted considerable interest as an efficient means of improving the dissolution rate and hence the bioavailability of a range of poorly water-soluble drugs. [9], [10], [12]

Repaglinide is a new class of oral hypoglycemic, designed to normalize the meal time glucose excursions and is indicated only in type II diabetes mellitus. [6] Repaglinide is a meglitinide phenylalanine analogue, acts as primarily by decreasing insulin resistance. [3], [27], [28], [30] Repaglinide is poorly water soluble drug and it belongs to Class II in Biopharmaceutics Classification System. Due to the poor solubility of drug, the dissolution is reduced and hence, it suffers oral bioavailability problems. [24] To overcome this disadvantage, the solid dispersion of Repaglinide was prepared using different polymers. [11]

## II. MATERIALS AND METHODS

### A. Materials

Repaglinide was a gift sample from Torrent research centre, Ahmedabad. Polyvinyl Pyrrolidone (PVP) and Ethyl Cellulose (EC) were supplied from Lobachemie Pvt. Ltd., Mumbai. All other reagents used were of analytical grade.

### B. Methods

#### 1. Preparation of PM and SDs

Physical mixture and solid dispersions of RPG in PVP and EC [22] containing different weight ratio was prepared by following methods: (Table I)

#### 2. Physical Mixture

Physical mixtures were prepared by mixing the powered drug and polymers in a mortar. Repaglinide and two different polymers in different drug to polymer ratios were accurately weighed mixed for 15 minutes than sifted through sieve no. #60 and kept in desiccators under vacuum until use.

Amit Kumar is associated with the Department of Pharmaceutics, Faculty of Pharmaceutical Sciences, Jodhpur National University, Jodhpur-334001, India (Mobile: 00919252059985; e-mail: amit\_jana81@rediffmail.com).

### 3. Dissolving Method

Solid dispersion consisting of RPG, EC and PVP was prepared as follows. RPG was dissolved in ethanol of 100ml followed by dissolving EC in this solution. Then, PVP was suspended in the solution. Then methylene chloride of 100ml was added to dissolve PVP before the evaporation of the solvent. The solvents was evaporated at 40°C in a water bath and then dried completely in vacuum desiccators for two days. The solid sample was ground gently with a mortar pestle and passed through a 44 mesh sieve. [17]

### 4. Suspending Method

Solid dispersion consisting of RPG, EC and PVP was prepared as follows. RPG was dissolved in ethanol of 100 ml followed by dissolving EC in this solution. Then, PVP was suspended in the solution. Then solvents was evaporated at 40°C in a water bath and then dried completely in vacuum desiccators for two days. The solid sample was ground gently with a mortar pestle and passed through a 44 mesh sieve. [17]

TABLE I  
COMPOSITION OF FORMULATIONS EACH COMPOSITION PREPARED BY PHYSICAL METHOD, SUSPENDING METHOD AND DISSOLVING METHOD

Formulation	Drug (mg)	EC (mg)	PVP (mg)
F1	100	150	300
F2	100	100	200
F3	100	50	100
F4	100	150	100
F5	100	50	300
F6	100	150	200
F7	100	100	300
F8	100	100	100
F9	100	50	200

### C. Quantitative Solubility Study

Solubility studies were performed in triplicate by adding excess amounts of repaglinide to water and buffer solutions having pH 1.2 and pH 6.8. These solutions containing flasks were kept on a rotary shaker for 24h. After 24h, solutions were filtered using Whitman filter paper and analyzed using UV spectrophotometer at 243 and 283nm, which was the absorption maxima determined earlier and drug concentrations were calculated. [27]

### D. pH Partition Study

pH partition study was performed in order to check the aqueous solubility and organic phase solubility of drug, at different pH. In order to perform this study, Chloroform and water were mixed in the ratio of 50:50, and were shaken for 30 minutes in a separating funnel. Aqueous phase was discarded. Now 10ml of organic solution was mixed with 10ml of 1.2 pH buffer solution and 10mg of drug was added in it and shaken for 5 minutes. Now organic phase was discarded and absorbance of aqueous phase was observed at 240nm. Same procedure was repeated for 4.5 pH buffer, 6.8 pH buffer, 7.4 pH buffer, 8.6 pH buffer and water. [20]

### E. Solubility Studies of Solid Dispersion Formulation

Excess of solid dispersions and physical Mixture was added to 25ml distilled water taken in stoppered conical flask, vortexed for 2 minutes and shaken (in the mechanical shaker) for 24 hours. Resultant samples containing undissolved solid dispersions suspended in the test medium were centrifuged at 10,000 rpm for 5 minutes and the clear supernatant obtained was filtered (Whatman No. 40) and suitably diluted with distilled water to analyze spectrophotometrically at 283nm for the drug content estimation. Same procedure was repeated for 1.2 and 6.8 buffers. [14, 16]

### F. Drug Content

Solid dispersions equivalent to 4mg of repaglinide were taken and dissolved in minimum quantity of methanol and volume was made up to 50ml with 1.2 pH buffer. [8] The sample was filtered through Whatman filter paper. The solution was assayed for drug content using UV-spectrophotometer method by measuring the absorbance at 243nm. Same procedure was repeated for 6.8 pH buffer and absorbance was taken at 281nm.

### G. In vitro Dissolution Studies

*In vitro* release profile of the solid dispersion was evaluated using rotating basket dissolution apparatus. 900ml of acid buffer (pH1.2), and phosphate buffer (pH7.4) maintained at 37±0.5°C were used as dissolution media respectively, and the basket was rotated at a constant speed of 75 rpm. Accurately weighed amount of solid dispersion equivalent to 4mg of drug were placed in the baskets. Aliquots of samples were withdrawn at the interval of 1 hour for pH 1.2 for 2 hrs and for 6.8 pH for 10hrs. The samples withdrawn were filtered, diluted suitably and analyzed at 243nm and 281nm spectrophotometrically for drug release. [21], [25], [26]

## III. RESULTS AND DISCUSSION

### A. Solubility of Drug

The solubility of repaglinide in pH 1.2, 6.8 and in water was determined, by calculating its concentration in mg/ml. The study shows that solubility of repaglinide decreased as pH increases. The maximum solubility was observed at pH 1.2. (Table II)

TABLE II  
SOLUBILITY OF DRUG IN WATER, 1.2 AND 6.8 PH

S. No.	Medium	Result (mg/ml)
1	1.2 pH	0.140±0.002
2	6.8 pH	0.051±0.001
3	Water	0.026±0.0005

### B. pH Partition Study

The pH partition behavior of drug was studied at different pH. (Fig. 1) Solubility at different pH in aqueous phase and organic phase is represented through bar graph. From the above study it can be concluded that there was no significant difference present between pH 6.8 & 7.4 and maximum drug solubility was found in pH 1.2. (Table III)

TABLE III  
pH PARTITION STUDY OF REPAGLINIDE AT VARIOUS pH

Sr. No	Medium	Aqueous Phase (mg/ml)	Organic Phase (mg/ml)
1	water	0.004±0.02	9.996±0.0006
2	1.2	0.003±0.0001	9.997±0.0006
3	4.5	0.008±0.0006	9.992±0.0006
4	6.8	0.007±0.0005	9.992±0.0006
5	7.4	0.005±0.0005	9.995±0.0006
6	8.6	0.004±0.0006	9.996±0.0006

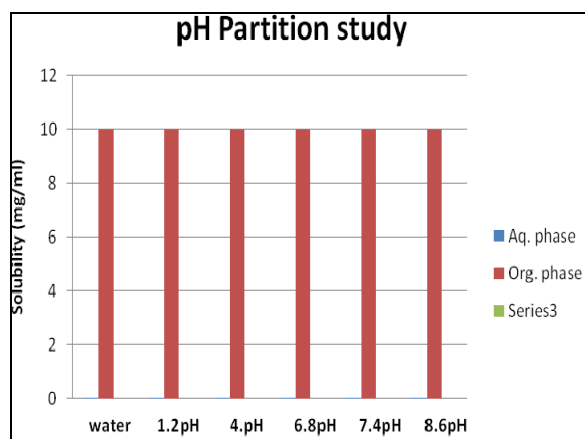


Fig. 1 pH partition study of drug at different pH

### C. Drug Content

Drug content of all the solid dispersion prepared by dissolving method and suspending method was determined in triplicate and were found to be between 96%-99.68%, which concludes that drug is uniformly distributed in the solid dispersions. (Table IV)

TABLE IV  
DRUG CONTENT OF FORMULATION F1-F9 OF DISSOLVING AND SUSPENDING METHOD

Formulation code	Dissolving Method (%)	Suspending Method (%)	Physical Mixture (%)
F1	99.08 ± 0.436	99.02 ± 0.192	98.06 ± 0.967
F2	97.65 ± 0.507	98.74 ± 0.831	96.21 ± 0.198
F3	99.14 ± 0.145	98.85 ± 0.320	99.15 ± 0.243
F4	97.72 ± 0.438	97.09 ± 0.105	96.03 ± 0.113
F5	99.27 ± 0.180	98.39 ± 0.938	97.19 ± 0.796
F6	96.8 ± 0.519	99.16 ± 0.533	98.01 ± 0.398
F7	99.68 ± 0.283	99.10 ± 0.344	99.01 ± 0.295
F8	97.85 ± 0.516	98.73 ± 0.856	96.73 ± 0.561
F9	98.84 ± 0.60	97.73 ± 0.640	98.13 ± 0.734

### D. Solubility Studies of Solid Dispersion Formulation

Solubility of all the solid dispersion formulations and physical mixture was determined in triplicate in water, 1.2 pH HCl buffer and in 6.8 pH phosphate buffer. Solubility of all the formulations were decreased as the pH increases. Solubility is increased as the concentration of PVP gets increased in the formulations. Solubility of F-7 formulation prepared by suspending and dissolving method was maximum as compared to other formulations and that of physical mixture was less as compared to solid dispersions. (Figs. 2-4)

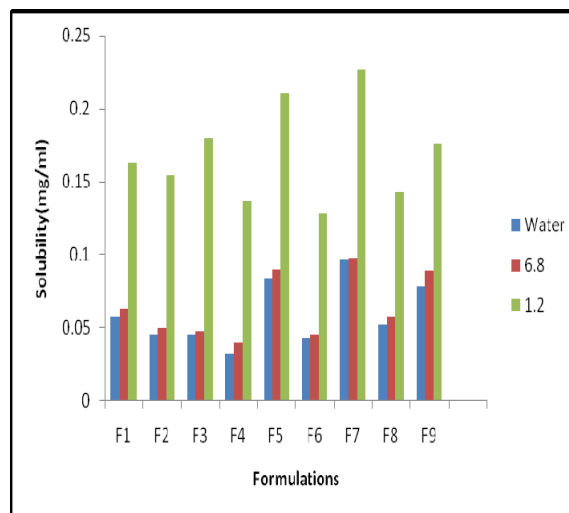


Fig. 2 Solubility of formulations by Dissolving Method

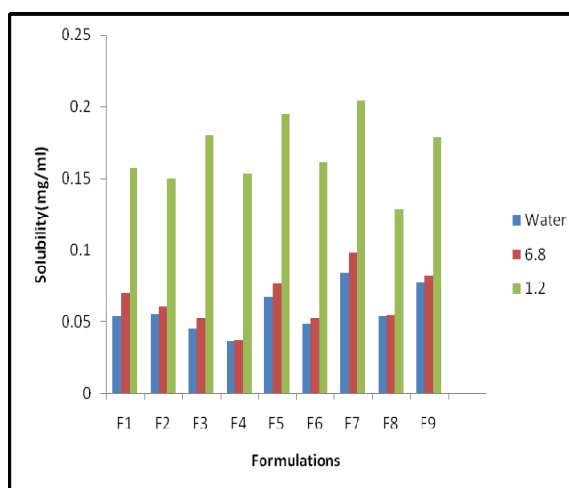


Fig. 3 Solubility of formulations by Suspending Method

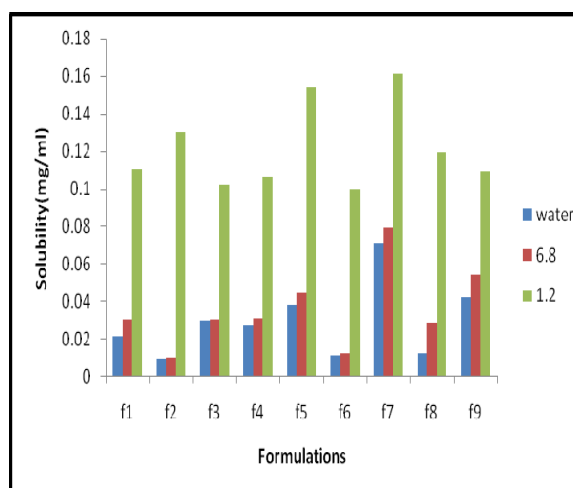


Fig. 4 Solubility of formulations by Physical Mixture

### E. In vitro Dissolution Studies

In vitro dissolution studies were performed for all the solid dispersions in 0.1 N HCl for first 2 hours and for next 10

hours in 6.8 pH phosphate buffer. Test was performed in triplicate for each formulation. *In vitro* drug release of formulations prepared by dissolving method revealed that formulation 1 and 7 gave the complete release approx 100% in 12 hours. But in F-7 drug was best controlled as compared to F-1. Hence, F-7 can be selected as the best formulation. In Formulations 3, 4 8 and 9 drug solubility was not increased, but was controlled more than it was required. This might be due to less quantity of PVP and high quantity of ethyl cellulose. *In vitro* drug release of formulations prepared by suspending method revealed that formulations were not controlled because 100% release was given in between 7–10 hours only. This might be due to the less interaction of drug and ethyl cellulose, in suspending method. As compared to other formulations in F-7 drug was best controlled, and gave release up to hour. Hence it was selected as the best formulation. (Figs. 5-7)

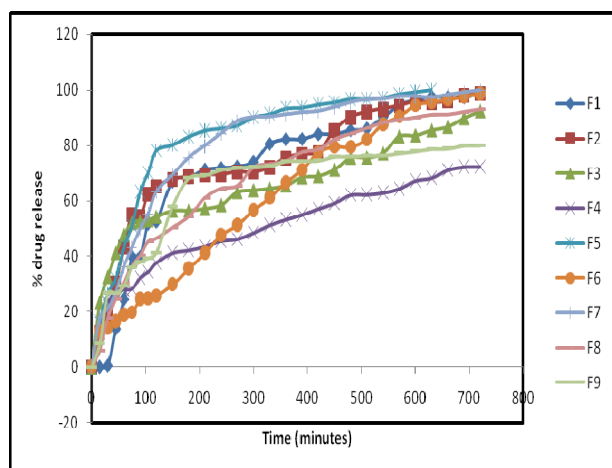


Fig. 5 % drug release of F1-F9 formulations prepared by Dissolving Method

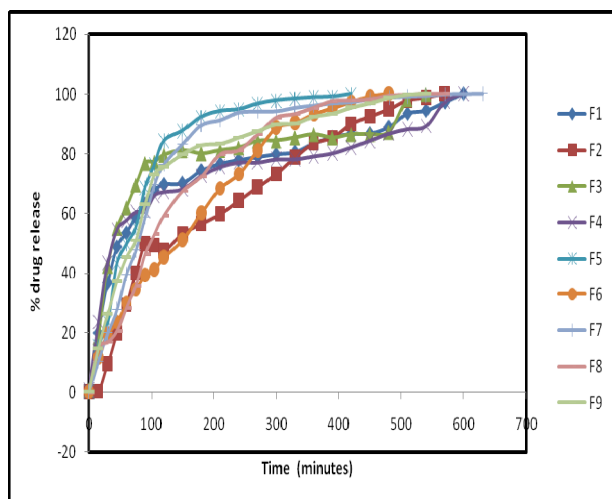


Fig. 6 % drug release of F1-F9 formulations prepared by Suspending Method

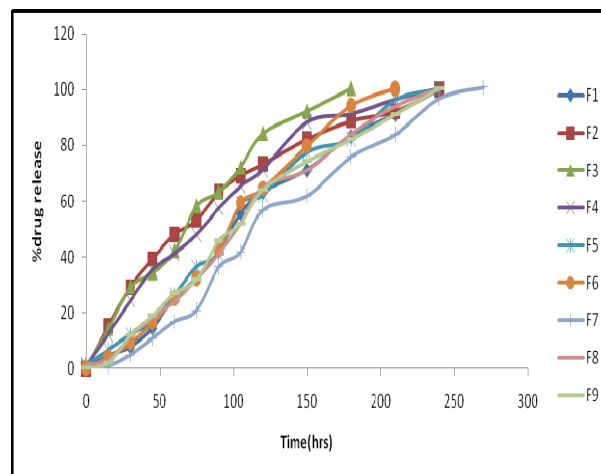


Fig. 7 % drug release of F1-F9 formulations of Physical Mixture

#### IV. CONCLUSION

The results revealed that the preparation conditions governed the internal structure and dissolution mechanism by solid dispersions. EC as a hydrophobic carrier polymer was capable of extended the drug release rate at all weight ratio employed, but was insufficient alone to give complete drug release. When hydrophilic PVP was combined along with EC in 1:3 ratios, the drug release profiles were modified towards more gradual and complete release of GLB from combined polymer matrix. The studies provided better forecasting and understanding of particulate systems to be incorporated to develop delivery systems.

#### ACKNOWLEDGEMENTS

The authors would like to acknowledge the staff and management of the Faculty of Pharmaceutical Sciences, Jodhpur National University for providing all the facilities to carry out the present research work.

#### REFERENCES

- [1] Ahuja N, Kishore K, Garg A, Purohit S, Solid Dispersions-Preparation Methods, Pharmaceutical Applications and Evaluation Techniques: A Review, Novel Science International Journal of Pharmaceutical Science, 2012, pp. 103-114.
- [2] Arora G et al., Preparation and Evaluation of Solid Dispersions of Modified Gum Karaya and Aceclofenac: Controlled Release Application, Pelagia Research Library, 2011, pp. 142-151.
- [3] Bhanja SB et al., Preparation and Evaluation of Solid Dispersions of Poorly Soluble Drug Repaglinide, Asian Journal of Biochemical and Pharmaceutical Research, 2011, Vol. 1, pp. 201-221.
- [4] Chen X, Wen H, Park K, Challenges and New Technologies of Oral Controlled Release, Published by John Wiley & Sons, 2010, pp. 257-277.
- [5] Dixit AK, Singh RP, Singh S, Solid Dispersion- A Strategy for Improving the Solubility of Poorly Soluble Drugs, International Journal of Research in Pharmaceutical and Biomedical Sciences, 2012, June, pp. 960-966.
- [6] Gupta A, Nagar M, Sharma P, Formulation and Evaluation of Repaglinide Microspheres, International Journal of Pharmacy and Life Sciences, 2012, pp. 1437-1440.
- [7] Jatwani S, Rana AC, Singh G, Aggarwal G, An Overview on Solubility Enhancement Techniques for Poorly Soluble Drugs and Solid Dispersion as an Eminent Strategic Approach, International Journal of Pharmaceutical Sciences and Research, 2012, March, pp. 942-956.

- [8] Kavitha K, Puneet KP, Development and Evaluation of Rosiglitazone Maleate Floating Tablets, International Journal of Applied Pharmaceutics, Vol 2, 2010, pp. 6-10.
- [9] Kavitha R, Sathali AA, Enhancement of Solubility of Repaglinide by Solid Dispersion Technique, International Journal of Chemical Sciences, 2012, pp. 377-390.
- [10] Kumar DP., Arora V., Solid Dispersions: A Review, Journal of Pharmaceutical and Scientific Innovation, 2012, pp. 27-34.
- [11] Kumar DA, kumar PK, Ranjhita D, Muethy PN, Kumar PA, Method Development, Validation and Stability Study of Repaglinide in Bulk and Pharmaceutical Dosage form by UV Spectrometric Method, International Journal of Biological and Pharmaceutical Research, 2011, pp. 7-10.
- [12] Lachman L, Lieberman HA, Pharmaceutical Dosage form: Parenteral Medication, Printed by Replica Press Pvt. Ltd, India, vol. 1, 1992, pp. 115-144.
- [13] Modi SA, Gaikwad PD, Bhankar BH, Pwar SP, Sustained Release Drug Delivery System: A Review, International Journal of Pharma. Research & Development-Online, 2011, pp. 147-160.
- [14] Modi VS, Thorat YS, Dhavale SC, Formulation and Evaluation of Controlled Release Delivery of Trmadol Hydrochloride, International Journal of Chemtech Research, 2012, March, pp. 669-675.
- [15] Mohanachandran PN, Sidhumol PG, Kiran TS, Enhancement of Solubility and Dissolution Rate: An Overview, International journal of Comprehensive Pharmacy, Vol. 1, 2010, pp. 1-10.
- [16] Nair S, Walikhindi AK, Jamkandi VJ, Formulation and Evaluation of Repaglinide Microspheres, International Journal of Pharmacy and Life Sciences, 2010, pp. 191-196.
- [17] Ohara T et al, Dissolution Mechanism of Poorly Water-Soluble Drug from Extended Release Solid Dispersion System with EC and HPMC, International Journal of Pharmaceutics, 2005, pp. 95-102.
- [18] Hemnani M et.al, Matrix Tablet: A Tool of Controlled Drug Delivery, American Journal of Pharmtech Research, 2011, November, pp. 1-17.
- [19] Patel M, pandya N, Bhaskar VH, Preparation, Characterization and *in vitro* Evaluation of Repaglinide Binary Solid Dispersions with Hydrophilic Polymers, International Journal of Drug Development & Research, Vol. 3, 2011, pp. 111-121.
- [20] Patidar K, Kshirsagar MD, Saini V, Joshi PB, Soni M, Solid Dispersion Technology: A Boon for Poor Water Soluble Drugs, Indian Journal of Noval Drug Delivery, 2011, june, pp. 83-90.
- [21] Patel NR et. al, Formulation and Evaluation of Controlled Release Matrix Tablets of a Model Antibiotic Drug, American Journal of Pharmtech Research, 2012, March, pp. 1-14.
- [22] Rowe RC, Sheskey PJ, Quinn M, Handbook of Pharmaceutical Excipients, Pharmaceutical Presss, 6<sup>th</sup> edition, pp. 278, 611.
- [23] Rathore DS, Thakur RR, Narwal S, Solid Dispersion: A New Horizon in Novel Drug Delivery System, Journal of Pharmacy Research, 2012, February, pp. 1007-1014.
- [24] Shinde SS, Patil SS, Mevkari FI, Satpute AS, An Approach for Solubility Enhancement: Solid Dispersion, International of Advances in Pharmaceutical Sciences, 2012, pp. 299-308.
- [25] Sonali D et al., Silymarin-Solid Dispersions: Characterization and Influence of Preparation Methods on Dissolution, Acta Pharm. 60, 2010, pp. 427-443.
- [26] Shams T et al., Thermal Infrared Characterization and *in vitro* Evaluation of Repaglinide Solid Dispersion, Scholars Research Library-Der pharmacia lettre, 2011, pp. 142-150.
- [27] Singh S., Bhagel RS., Yadav L., A Review on Solid Dispersion, International Journal of Pharmacy and Life Sciences, Vol. 2, 2011, pp. 1078-1095.
- [28] Sweetman s.c; "Martindale- The Complete Drug Reference"; 36<sup>th</sup> Edition; Pharmaceutical Press- 2009; pp. 457,458.
- [29] Tiwari R et al., Solid Dispersions: An Overview to Modify Bioavailability of Poorly Water Soluble Drugs, International Journal of PharmTech Research, Vol. 1, 2009, pp. 1338-1349.
- [30] Tripathi KD, Essentials of Medical Pharmacology, 6<sup>th</sup> edition, Jaypee Brothers Medical Publishers Ltd, 2008, pp. 268,269.
- [31] Verma S, Rawat A, Kaul M, Saini S, Solid Dispersion: A Strategy for Solubility Enhancement, International Journal of Pharmacy and Technology, 2011, June, pp. 1062-1099
- [32] Vasconcelos T, Sarmento B, Costa P, Solid Dispersion as Strategy to Improve Oral Bioavailability of Poor Water Soluble Drugs, Vol. 12, 2007, pp. 1068-1075.