Int. J. Chem. Sci.: 10(1), 2012, 377-390
ISSN 0972-768X
www.sadgurupublications.com

ENHANCEMENT OF SOLUBILITY OF REPAGLINIDE BY SOLID DISPERSION TECHNIQUE

R. KAVITHA and A. ABDUL HASAN SATHALI*

Department of Pharmaceutics, Madurai Medical College, MADURAI – 625020 (T.N.) INDIA

ABSTRACT

The present study involved preparation of solid dispersions of repaglinide to improve the aqueous solubility and dissolution rate in order to enhance bioavailability. Repaglinide is a BCS Class II drug, having low aqueous solubility and therefore, low bioavailability. In the present study, solid dispersions of repaglinide with different carriers [poly ethylene glycol 6000 (PEG 6000), poly vinyl pyrrolidone k30 (PVP K30), poloxamer 188 and crospovidone in different ratios (1 : 1, 1 : 2, 1 : 4, 1 : 6)] were prepared by melting and solvent evaporation methods. *In vitro* release studies revealed that the solid dispersions prepared by solvent evaporation method showed faster drug release when compared to the melting method. So, the dissolution profile of solid dispersion containing PVP K30 (1 : 4) was selected as the best formulation because of its faster drug release among all formulations. X-ray diffraction spectral studies showed a significant decrease in crystalline nature of drug in solid dispersions which resulted in increased dissolution rate of repaglinide. Differential scanning calorimetry (DSC) and Fourier transform infrared spectroscopy (FTIR) studies of solid dispersion revealed that no interactions exist between drug and polymer. Phase solubility studies of the best formulation indicated that the solubility was improved compared to the pure drug. Similarly tablets prepared from solid dispersed drug had better dissolution than tablets prepared from normal drug powder. In conclusion, solid dispersions of repaglinide in PVP K30 have shown to be a promising approach to improve the bioavailability of repaglinide.

Key words: Solid dispersion, Dissolution enhancement, Repaglinide.

INTRODUCTION

Repaglinide is a meglitinide phenylalanine analogue, which is prescribed as an oral antidiabetic drug for the treatment of type II (non-insulin dependent) diabetes mellitus. It acts primarily by decreasing insulin resistance. 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[1,2]. To overcome this disadvantage, the solid dispersion of repaglinide was prepared using different polymers. In the present work, solid dispersion of repaglinide was prepared

*Author for correspondence; E-mail : abdulhasan@hotmail.com

by melting method and solvent evaporation methods using polymers such as PEG 6000, PVP K30, poloxamer 188, crospovidone etc.

EXPERIMENTAL

Material and methods

Repaglinide was obtained as a gift sample from Dr. Reddy's Laboratories (P) Ltd., Hyderabad. Polyethylene glycol 6000 (S.d. Fine chemicals, Mumbai, India) and poloxamer 188 (Nice Chemicals, Mumbai, India), were procured locally. The polymers, polyvinyl pyrrolidone K_{30} and crospovidone (Madras Pharmaceuticals, Chennai) were obtained as gift samples. All the other reagents and solvents used were of analytical grade.

Preparation of repaglinide solid dispersion formulation[3-5]

Solid dispersions were prepared with the drug repaglinide and polymers (PEG 6000, PVP K_{30}, poloxamer 188, crospovidone) using 1 : 1, 1 : 2, 1 : 4 and 1 : 6 weight ratios by means of solvent evaporation and melting methods. Physical mixtures were prepared by mixing manually. The mixtures are passed through a sieve No. 120.

Melting method

PEG 6000 is melted in a water bath at 70°C. The drug repaglinide was added in the solid state and the mixture was stirred well until homogeneity is attained. The mixture was allowed to cool slowly at room temperature, and then pulverized using a glass mortar and pestle. The pulverized mass sifted through a sieve No. 120; then weighed and transferred to an amber coloured bottle. The same procedure is repeated for poloxamer 188, where the polymer is melted at temperature of 55°C.

Solvent evaporation method

Repaglinide and PEG 6000, PVP K30, poloxamer 188 and crospovidone were taken in different ratios separately. Then the mixtures were triturated and dissolved in methanol. The solutions are evaporated at 40°C and then the residual mass is scraped and shifted through sieve No. 120 and kept in a dessiccator for drying. The composition is given in the Table 1.

Drug content

Solid dispersions equivalent to 2 mg of repaglinide were taken and dissolved in minimum quantity of methanol and volume was made up to 50 mL. From this solution, aliquot was taken and again diluted with methanol up to 50 mL. The solution was assayed for drug content using UV-spectrophotometer method by measuring the absorbance at 283 nm.

Table 1: Formulation of repaglinide solid dispersions

S. No.	Name of the formulation	Ratio of the drug and carrier	Name of the carrier used
1	MM 1	1 : 1	PEG 6000
2	MM 2	1 : 2	PEG 6000
3	MM 3	1 : 4	PEG 6000
4	MM 4	1 : 6	PEG 6000
5	MM 5	1 : 1	Poloxamer 188
6	MM 6	1 : 2	Poloxamer 188
7	MM 7	1 : 4	Poloxamer 188
8	MM 8	1 : 6	Poloxamer 188
9	SEM 1	1 : 1	PEG 6000
10	SEM 2	1 : 2	PEG 6000
11	SEM 3	1 : 4	PEG 6000
12	SEM 4	1 : 6	PEG 6000
13	SEM 5	1 : 1	PVP K_{30}
14	SEM 6	1 : 2	PVP K_{30}
15	SEM 7	1 : 4	PVP K_{30}
16	SEM 8	1 : 6	PVP K_{30}
17	SEM 9	1 : 1	Poloxamer 188
18	SEM 10	1 : 2	Poloxamer 188
19	SEM 11	1 : 4	Poloxamer 188
20	SEM 12	1 : 6	Poloxamer 188
21	SEM 13	1 : 1	Crospovidone
22	SEM 14	1 : 2	Crospovidone
23	SEM 15	1 : 4	Crospovidone
24	SEM 16	1 : 6	Crospovidone

In vitro release studies[6-8]

In vitro release studies of repaglinide solid dispersions and their physical mixtures were performed by using USP type I basket dissolution apparatus in 900 mL of citro

phosphate buffer pH 5 maintained at 37°C ± 1°C and 75 rpm. Samples (10 mL) were withdrawn at regular intervals of 5 minutes for 1 hr and the same volume of fresh dissolution medium was replaced after every withdrawal. The withdrawn samples were analyzed by UV visible spectrophotometer at λ_{max} 283 nm.

The above procedure was repeated for repaglinide powder sample.

FT-IR studies[9-11]

The possibility of drug-excipient interactions were further investigated by FT-IR (Shimadzu FT-IR Spectrometer). The FT-IR spectrum of pure drug and combination of drug with excipients were recorded in the range of 450-4000 cm^{-1} and the resolution is 4 cm^{-1}. Samples were prepared in KBr pellets.

DSC studies[4,10]

DSC was performed using Perkin-Elmer STA 6000 Thermal Analyzer. The instrument was calibrated with indium standard.

Powder X-ray diffraction (PXRD) studies[5]

X- ray diffraction measurements of the solid dispersions were performed on a Rigaku X-ray generator (Japan) with a copper anode (cu Kά radiation, λ = 1.540598 nm, 40 kV), over the 2θ range of 10-70^{o}C to find out the crystalline nature of pure drug and solid dispersed formulations.

Solubility studies[12,13]

Excess (usually more than 1 mg/mL concentration) of solid dispersion and physical mixture, pure drug was added to 25 mL 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 283 nm for the drug content estimation.

Stability studies[9]

The stability studies of repaglinide solid dispersions (containing 1 : 4 ratio of drug and polymer) was carried out at ambient temperature and relative humidity (40°C ± 2°C/60% RH) for 45 days to find out any physicochemical changes in the dispersions as per the ICH guidelines. Periodically samples were withdrawn to estimate the drug content.

Preparation of tablets[5]

Of all the prepared solid dispersions, the solid dispersion (SEM 7) selected on the basis of release studies and x-ray diffraction studies, was further compressed into tablets. These tablets had a theoretical repaglinide content of 1 mg. Lactose was added as a diluent. The solid dispersions were blend with talc and magnesium stearate (1% of the total weight of the mixture) and compressed into tablet with a total weight of 200 mg. As a reference, tablets from a plain drug (i.e. without any polymer) are made to compare the dissolution behaviour of both the formulations. The composition of the tablet is shown in Table 5.

RESULTS AND DISCUSSION

Drug content

The drug content of the prepared solid dispersion was found to be in the range of (94.45 - 98.97%) indicating the applications of the present method for the preparation of solid dispersion with high content uniformity Table 2.

Table 2: Evaluation of solid dispersion of repaglinide

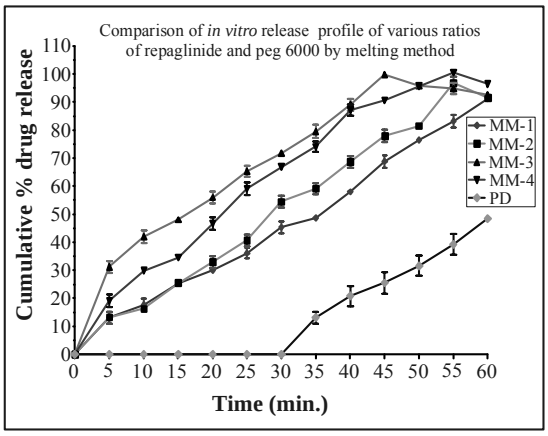
S. No.	Formulations	% Practical yield	% Drug content
1	MM 1	96.21	98.97
2	MM 2	95.10	96.90
3	MM 3	93.40	95.90
4	MM 4	92.20	94.94
5	MM 5	90.15	97.97
6	MM 6	90.25	96.96
7	MM 7	89.90	95.97
8	MM 8	91.80	.96.96
9	SEM 1	92.25	95.92
10	SEM 2	90.50	96.91
11	SEM 3	92.10	95.92
12	SEM 4	90.54	94.95
13	SEM 5	91.15	96.94
14	SEM 6	92.20	95.99

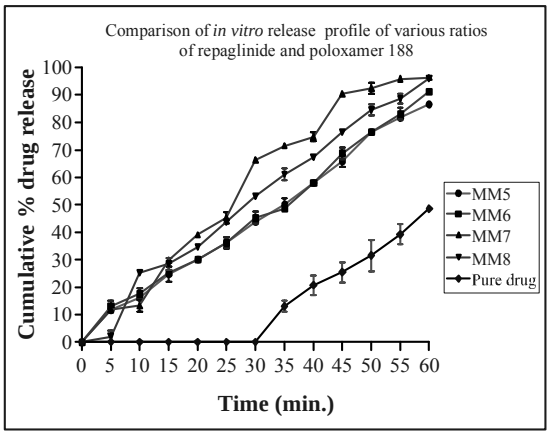
Cont…

S. No.	Formulations	% Practical yield	% Drug content
15	SEM 7	91.25	96.98
16	SEM 8	93.20	97.92
17	SEM 9	95.10	97.97
18	SEM 10	91.00	97.94
19	SEM 11	90.50	96.93
20	SEM 12	92.20	95.95
21	SEM 13	90.60	94.94
22	SEM 14	91.20	96.95
23	SEM 15	92.20	97.99
24	SEM 16	90.60	95.91

In vitro release studies

From the release studies, it has been observed that, the dissolution rate is more when compared to pure drug. Further, it has been found that the formulations MM3, MM7, SEM3, SEM7, SEM11, SEM15 and SEM19 showed faster drug release when compared to other formulations (all prepared with 1 : 4 ratio). The results indicated that increasing the polymer concentration will increase the dissolution of the drug. Of the selected formulations those prepared with PVP K 30 showed desired release profile when compared to other polymers (PEG 6000, Poloxamer 188 and Cros povidone). Among the formulations SEM7 (PVPK30 1 : 4) was selected as a best formulation because it showed more release than other polymers Fig. 1 and 2.





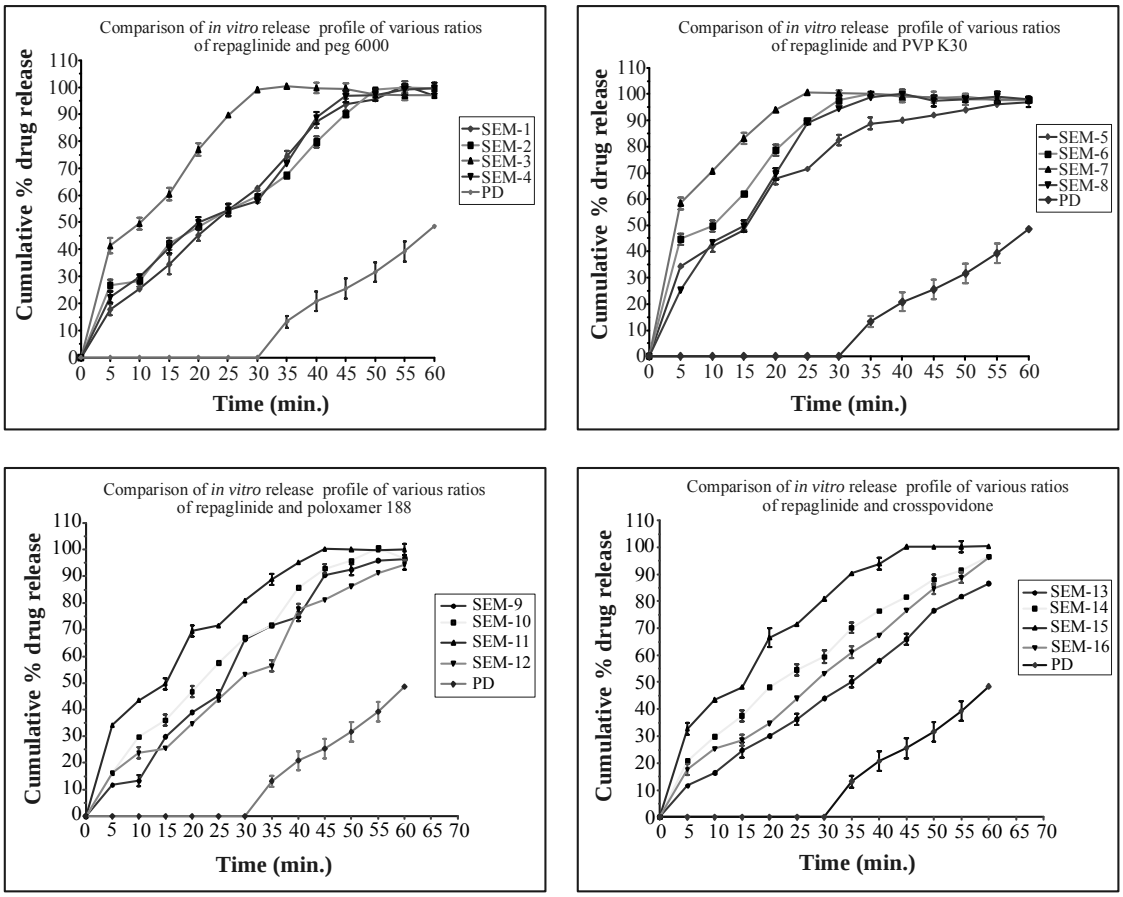


Fig. 1: *In vitro* release profile of all formulations

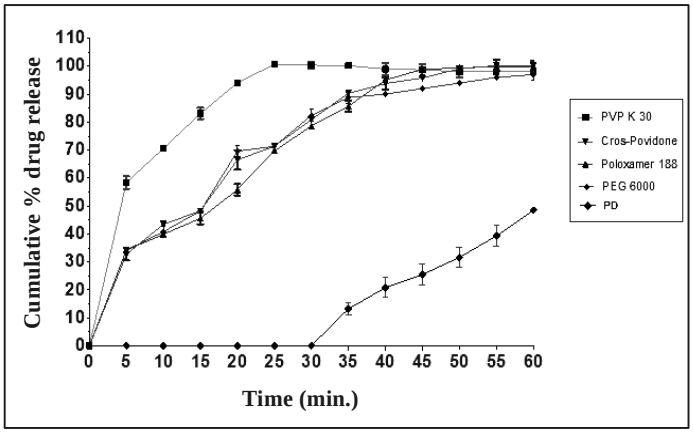
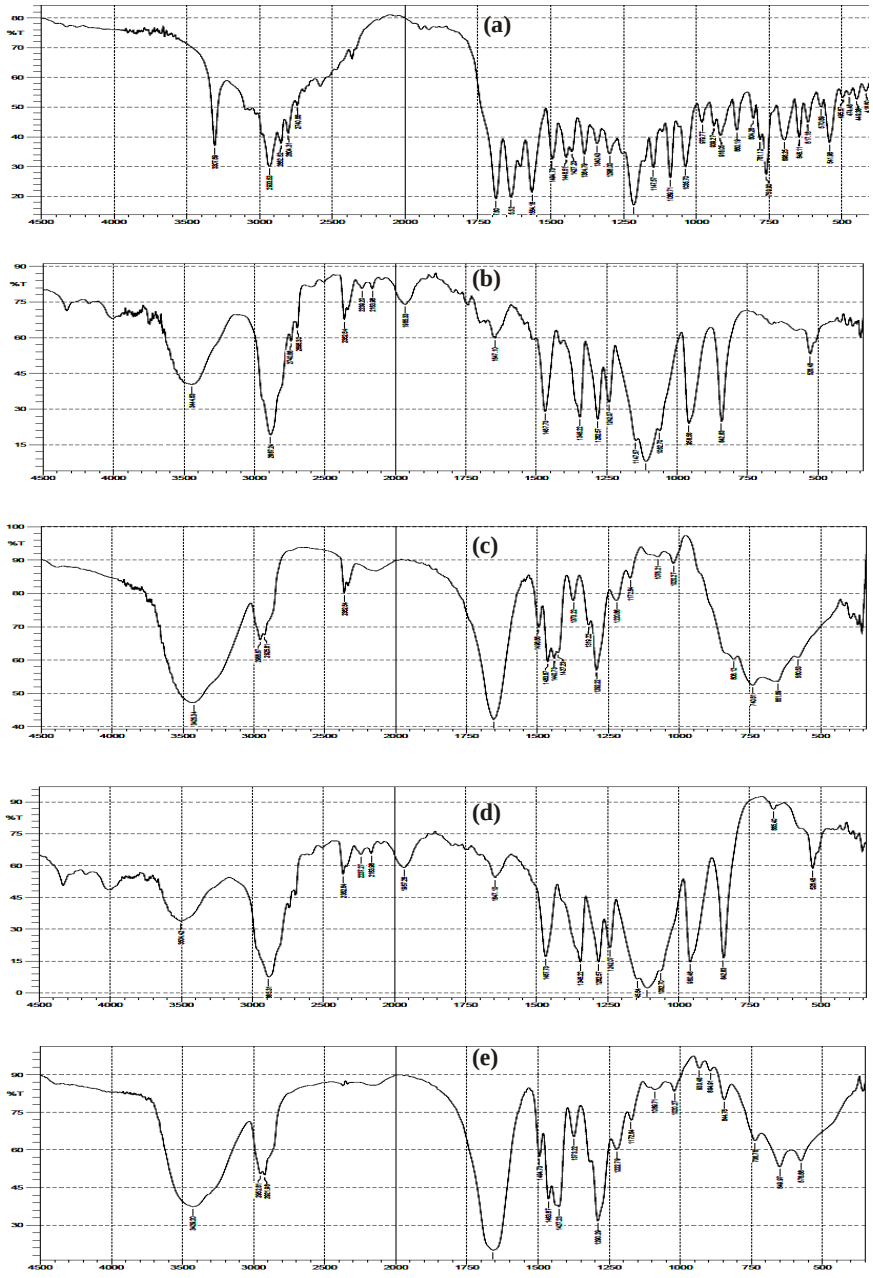


Fig. 2: Comparison of *in vitro* release of best formulations

FT-IR studies

The results of IR studies revealed that there is no interaction exists between carrier and drug in the formulations. The results of IR studies are shown in Fig. 3.



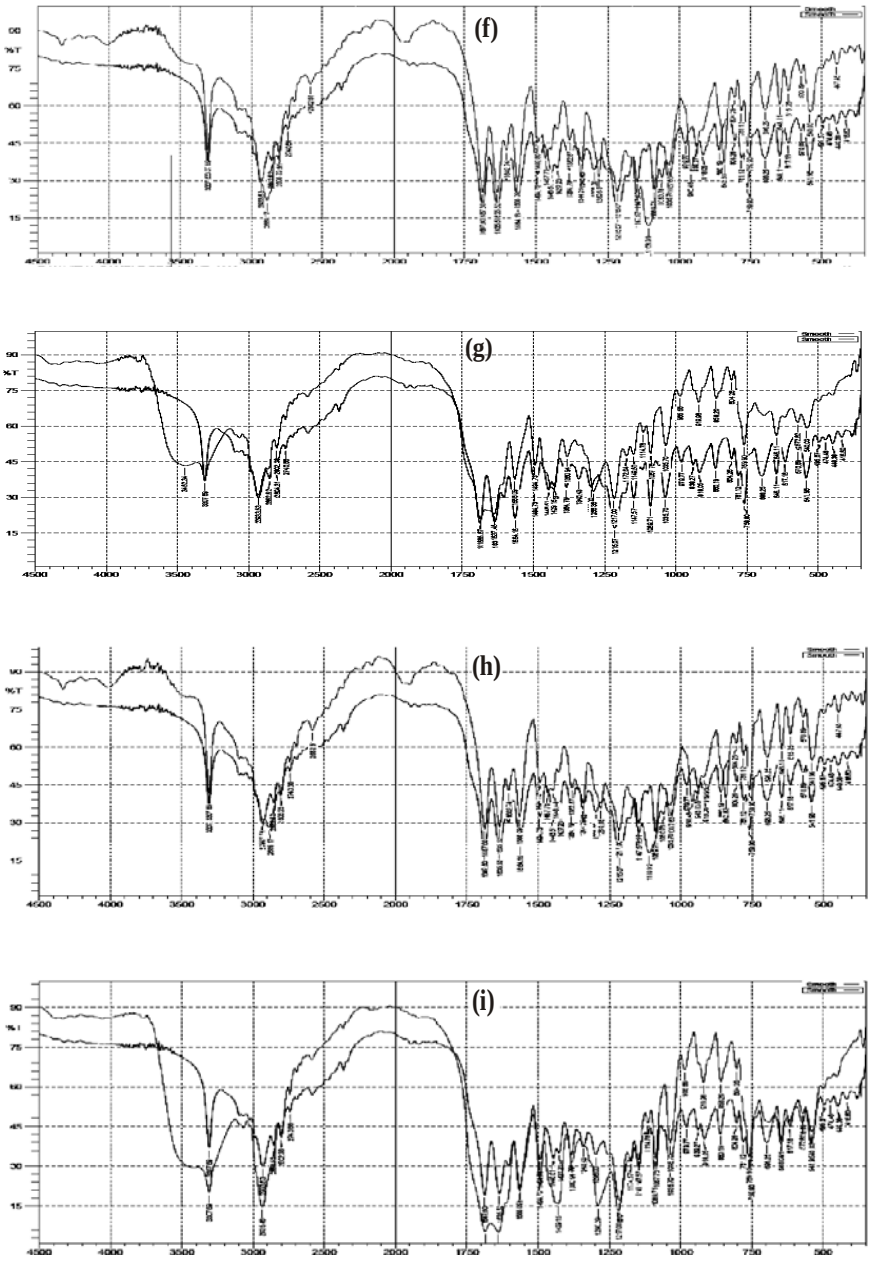


Fig. 3: FT-IR studies (a) Pure drug- repaglinide, (b) PEG 6000, (c) PVP K30, (d) Poloxamer 188, (e) Crospovidone, (f) Drug + PEG 6000, (g) Drug + PVP K30, (h) Drug + Poloxamer 188, (i) Drug + Crospovidone

Differential scanning calorimetry

Thermal behavior of pure drug and corresponding drug carrier system are depicted in Fig. 4. The DSC curve of repaglinide profiles sharp endothermic peak (131.8^{o}C) corresponding to its melting point, indicating its crystalline nature. However, the characteristic endothermic peak, corresponding to drug was broadened and shifted toward lower temperature, with reduced intensity in solid dispersions. This could be attributed to higher polymer concentration and uniform distribution of drug in the crust of polymer, resulting in complete miscibility of drug in polymer. Moreover, the data also indicate there seems to be no interaction between the drug and polymer.

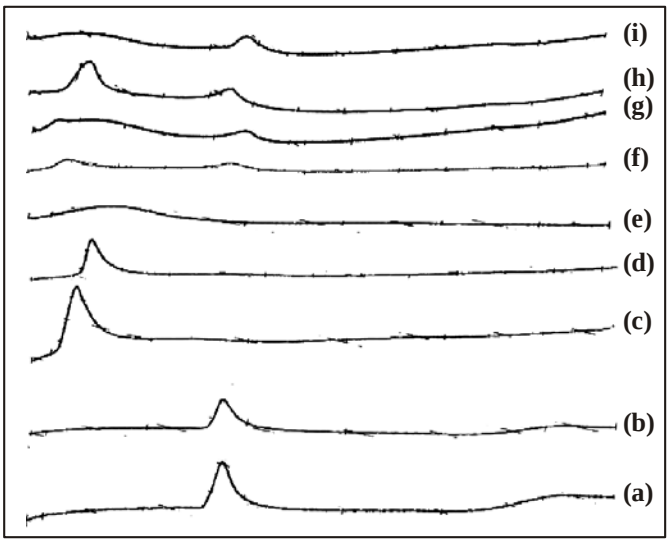


Fig. 4: DSC studies (a) Pure drug-repaglinide, (b) PEG 6000, (c) PVP K30, (d) Poloxamer 188, (e) Crospovidone, (f) Drug + PEG 6000, (g) Drug + PVP K30, (h) Drug + Poloxamer 188, (i) Drug + Crospovidone

Powder X-ray diffraction (PXRD) studies

The X- ray diffraction pattern of Repaglinide exhibited sharp, highly intense and less diffused peaks indicating the crystalline nature of drug, as shown in Fig. 5 but in the formulations no characteristic diffraction peaks were seen for the drug. It revealed that the crystallinity of the drug was highly reduced indicating the drug was converted to its amorphous form. Among all, the formulation SEM 7 (PVP K30 1 : 4) is amorphous in nature further considered for the preparation of tablet formulation.

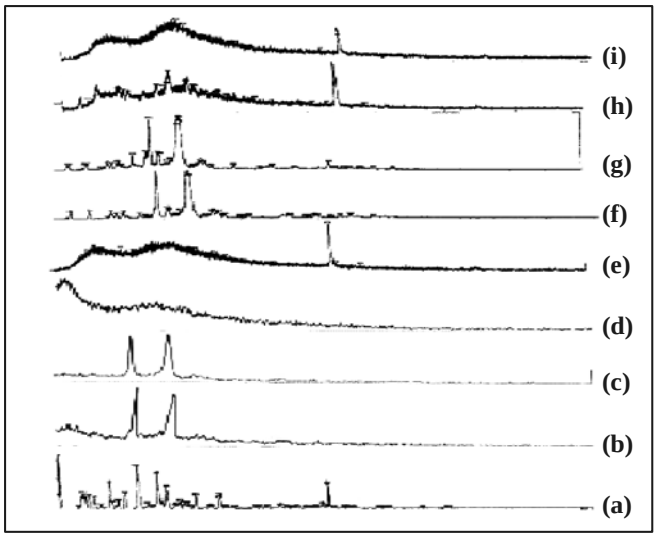


Fig. 5: X-RAY diffraction studies (a) Pure Drug- Repaglinide, (b) PEG 6000, (c) Poloxamer 188, (d) PVP K30, (e) Crospovidone, (f) Drug + PEG 6000, (g) Drug + Poloxamer 188, (h) Drug + PVP K30, (i) Drug + Crospovidone

Drug solubility

The equilibrium solubility was determined after 24 hours. The solubility of repaglinide in water is known to be 2.94 µg/mL at ambient temperature. The physical mixture, formulation was found to have more solubility when compared to pure drug. This may be due to the presence of polymer both in physical mixture and solid dispersion was helping to improve the solubility of drug and the results are shown in Table 3.

Table 3: Solubility study

Form of drug	Solubility (µg/mL) ± SD*
Pure drug	2.94 ± 0.11
Physical Mixture	4.86 ± 0.12
Solid dispersion	8.74 ± 0.15

Stability studies

The results of stability studies showed that there was no significant change in the drug content as shown in Table 4.

Table 4: Stability studies-drug content estimation

Formulation code	Percentage drug content				
	0 day	7th day	15th day	30th day	45th day
MM3	98.54	97.65	97.47	97.94	97.23
MM7	98.47	98.67	98.71	98.12	97.69
SEM3	98.57	99.47	98.15	98.97	96.12
SEM7	97.25	96.98	98.72	96.10	97.15
SEM11	98.45	98.12	97.69	97.98	96.30
SEM15	96.15	97.18	97.76	98.92	96.65

Comparison of tablet formulations

The tablets were prepared as per the formula given in Table 5 and the tablets were easy to prepare. The preformulation and postformulation parameters are within the accepted limits as shown in the Table 6. All the tablets had uniformity in drug content. They also had enough friability (0.2%) and hardness to withstand any mechanical stresses.

The dissolution studies on the solid dispersed tablet and plain tablet were performed in citro-phosphate buffer pH 5 using USP-2 (Paddle type).

In vitro release profile of solid dispersion tablets showed a more rapid dissolution (100.0 % release in 35 minutes) of repaglinide than that of plain tablet (37 % release in 60 minutes) as shown in Fig 6. Hence solid dispersion technique may be useful to increase the dissolution rate of drug when compared to pure drug.

Table 5: Repaglinide tablet formulation

S. No.	Ingredients required	Quantity (mg/tablet)
1	Solid dispersion (equivalent to 1 mg of drug)	5 mg
2	Lactose	191 mg
3	Talc	2 mg
4	Magnesium stearate	2 mg

Table 6: Evaluation of physical parameters of repaglinide tablet formulations

Formulation	Weight uniformity (mg) ± SD*	Hardness (kg/cm^2) ± SD*	Friability (%) ± SD*	Disintegration time (sec) ± SD*	Drug content (%) ± SD*
SEM 7	195 ± 0.002	5.0 ± 0.003	0.20 ± 0.002	75 ± 0.001	96.2 ± 0.003
n = 3					

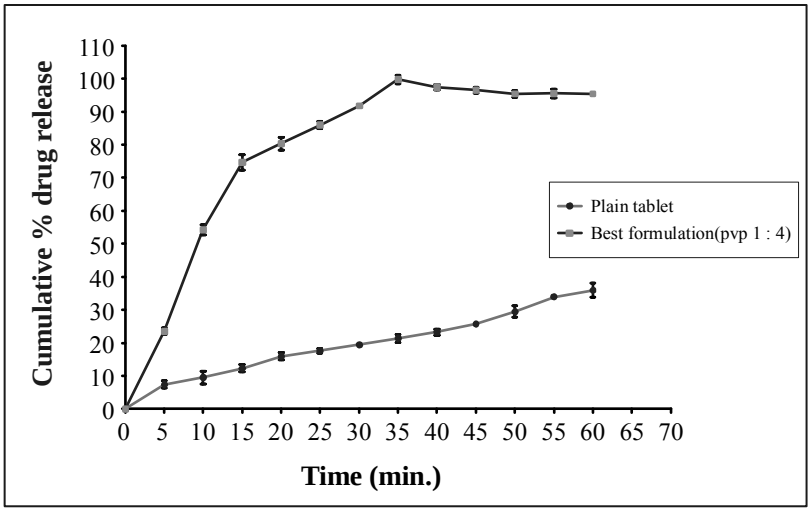


Fig. 6: Comparison of *in vitro* release profile of plain tablet and best formulation (PVP 1 : 4) compressed into tablet

CONCLUSION

It is concluded that the melting method and the solvent evaporation method are useful methods for the successful enhancement of solubility of poor water soluble drug repaglinide with faster dissolution rate. But from the evidence of PXRD studies, the crystallinity of the drug was much reduced in SEM7 compared to other six formulations. Further, it may be assumed that the bioavailability may be increase due to the conversion of crystalline matter into amorphous powder. Hence we can conclude that the solid dispersions of repaglinide by using the water soluble carrier PVP K30 in the ratio 1 : 4 prepared by solvent evaporation method provide best drug release (100.2% released in 30 minutes) among all the selected six formulations, and this technique can be used to enhance the bioavailabilty of poorly water soluble drugs like repaglinide.

ACKNOWLEDGEMENT

The authors are thankful to Dean, Principal, Department of Pharmaceutics, Madurai Medical College, Madurai for providing the facilities for carrying out the work.

REFERENCES

1. Abu T. M. Serajuddin, J. Pharm. Sci., **88**, No.10 (1999).
2. Sean C Sweetman, Martindale the Complete Drug Reference 36th Edition Pharmaceutical Press, 457-458 (2009).
3. S. Okonogi, T. Oguchi, E. Yonemochi, S. Puttipatkhachorn and K. Yamamoto, Int. J. Pharm., **156**, 175-180 (1997).
4. Vikrant Vyas, Pankajkum Sancheti, Poonam karekar and Manali Shah, Yogash Pore, Acta Pharm., **59**, 453-461 (2009).
5. Monica Rao, Y. Mandage and I. Khole, Indian J. Pharm. Edu. Res., **45**, 145-152 (2011).
6. USP 30-NF **25**, (2007) Page 3111.
7. Camelia Nicolescu, Corina Arama, Farmacia, **58**, 620-628 (2010).
8. Troy Purvis, Michal. E. Mattucci, Aaps Pharm. Sci. Tech**., 8**(3), E1- E9 (2007).
9. R. Kalaiselvan, G. P. Mohanta, P. K. Manna and R. Manavalan, Indian. J. Pharm. Sci., **68**, 599-607 (2006).
10. Aftab Modi and Pralhad Tayade, AAPS Pharm. Sci. Tech., **3**, E1-E6 (2006).
11. B. P. Patel, N. J. Patel and K. N. Patel, The Indian Pharmacist, 75-77 (2011).
12. Dong - Han Won, Min - Soo kim, Sibeum Lee and Jeong - Sook Park, Sung - Joo Hwang, Int. J. Pharm., **301**, 199-208 (2005).
13. Madhuri Newa, Krishna Hari Bhandari, Dong Xun Li and Tae - Hyub Kwon, Jung Ae Kim, Bong Kyu Yoo and Jong Soo Woo, Int. J. Pharm., **343**, 228-237 (2007).
14. Raymond C Rowe, Paul J Sheskey and Sian C Owen, Handbook of Pharmaceutical Excipients 5th Edition, Pharmaceutical Press, 545-550 (2006).

Revised : 26.09.2011 *Accepted : 29.09.2011*