ISSN: 2230-7346

Shahista Mohi Ud Din et al. / JGTPS/ *5(3)-(2014) 1912–1922*

(Research Article)

Journal of Global Trends in Pharmaceutical Sciences

Journal home page: www.jgtps.com

FORMULATION DEVELOPMENT AND EVALUATION OF SOLID DISPERSION OF METHYLDOPA FOR SOLUBILITY ENHANCEMENT

Shahista Mohi Ud Din[1*], Govind Mohan[2], Tarkeshwar Prasad Shukla[1], Mehraj Ud Din[1], Shailesh Sharma[1], Irfan Hassan[2].

[1]Department of pharmaceutics, NIMS Institute of Pharmacy, Jaipur, Rajasthan India.

[2]Department of pharmacology, NIMS Institute of Pharmacy, Jaipur, Rajasthan India

ABSTRACT

The poor solubility of drug substances in water and their low dissolution rate in aqueous G.I.T fluid often leads to insufficient bioavailability. The present investigation is an attempt to improve the solubility and dissolution rate of methyldopa (a poorly soluble drug) by solid dispersion technique. Binary solid dispersions were made using PEG-4000 or PEG-6000 as carriers with varying drug: carrier ratios 1:1 and 1:3 by the fusion method. Binary solid dispersions were also prepared by the solvent evaporation method using PEG-4000 or PEG-6000 as carriers with varying drug: carrier ratios 1:0.5 and 1:2. Also ternary solid dispersions were made by both the fusion and the solvent evaporation method using the PEG-4000 or PEG-6000 and the poloxamer 407 in the ratios of 1:5:1, 1:5:2, 1:1:1 and 1:2:2. Twelve formulations were prepared and evaluated for drug content, in vitro release studies and compared with the marketed formulation of methyldopa. All formulae showed marked significant improvement in the solubility and dissolution rate of the drug. The interaction studies showed no interaction between the drug and any of the used carriers. Formulation FT6 (1:5:2) in phosphate buffer pH 6.8 showed the best in vitro release rate of 86.21% in 60 minutes. Also this formulation showed the highest drug content of 98.64%. It was concluded that combination of PEG-6000 and poloxamer 407 can be well utilized to improve the solubility of poorly soluble drugs.

Keywords: Methyldopa, Solid dispersion, Polyethylene glycol, poloxamer 407, *In-vitro* dissolution.

INTRODUCTION

The poor solubility and low dissolution rate of poorly water soluble drugs in the aqueous gastro-intestinal fluids often cause insufficient bioavailability. This may be achieved by incorporating the drug in a hydrophilic carrier material obtaining products called solid dispersions. Depending on the properties of both, drug and carrier, and depending on their ratio, a solid solution or a solid suspension of the drug in the carrier material may be formed. The mechanisms involved in solubility and dissolution rate enhancement include transformation of stable modifications into less stable ones or even into the amorphous state, reduction of particle size possibly to the molecular level as well as enhancement of wettability and solubility of the drug by the carrier material. According to the Biopharmaceutics Classification System, the bioavailability may be enhanced by increasing the solubility and dissolution rate of the drug in the gastrointestinal fluid.[1,2]

Address for correspondence

Shahista Mohi Ud Din*

Department of pharmaceutics, NIMS Institute of Pharmacy, Jaipur, Rajasthan India

E-mail:- shaistamohiuddin@gmail.com

Phone no. 09782328583, 09906682530

Process of solubilization

The process of solubilization involves the breaking of inter-ionic or intermolecular bonds in the solute, the separation of the molecules of the solvent to provide space in the solvent for the solute, interaction between the solvent and the solute molecule or ion.[3]Fig. 1.

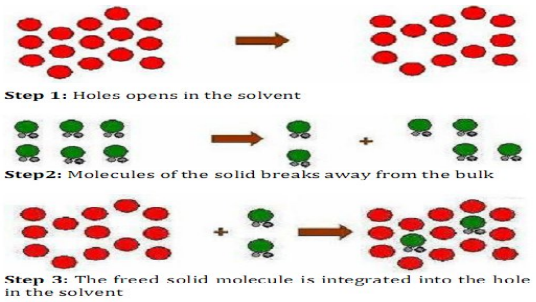

Fig. 1: Process of Solubilization

Solid dispersion

The term "solid dispersions" refers to the dispersion of one or more active ingredients in an inert carrier in a solid state, frequently prepared by the melting (fusion) method, solvent method or fusion solvent-method. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles. [4]

Numerous solid dispersion systems have been demonstrated in the pharmaceutical literature along with various hydrophilic carriers, such as polyethylene glycols, polyvinylpyrrolidone, hydroxypropyl methylcellulose, gums, sugar, mannitol and urea. [5]

Water insoluble drugs comprise nearly one-third of drugs in development and one-half of these fail in trials because of underprivileged pharmacokinetics (Savic *et al*., 2006). Mostly Poorly water soluble drugs belong to BCS class II and Class IV group of compounds (Amidon *et al*., 1995). In the process of absorption of drug from oral route, dissolution is the rate limiting step for lipophilic drugs. Therefore improving of dissolution is of great importance in order to ensure maximum therapeutic effect of these drugs.

It has been estimated that 40% of new chemical entities currently being discovered are poorly water soluble.[6,7] Among the various approaches to improve solubility, the solid dispersion (SD) technique has often proved to be the most successful in improving the dissolution and bioavailability of poorly soluble drugs because it is simple, economic, and advantageous.[8]

The carrier can be either crystalline or amorphous in nature. Most commonly used carriers for the preparation of SDs are different grade of polyethylene glycols (PEGs) and polyvinylpyrrolidone (PVPs), Glacier 44/14, Labra sol, sugars, and urea.[9-11]The first drug whose rate and extent of absorption was significantly enhanced using the solid dispersion technique was sulfathiazole by Sekiguchi and Obi.[12]This technique has been used by many researchers/scientists for a wide variety of poorly aqueous soluble drugs to enhance the solubility of the drugs and hence bioavailability.[8] Literature reviews on solid dispersion of past four decades suggests that there is an increasing interest in using this approach.[13]Despite an active research interest, the number of marketed products arising from this approach is really disappointing. Only few commercial products were marketed during the last four decades.[12,14,15]

Methyldopa {chemically 2-amino-3-(3,4-dihydroxyphenyl)-2-methyl-propanoic acid} is a antihypertensive drug which is used for treatment of moderate to severe hypertension usually in combination with diuretic or a beta-blocking agent. Methyldopa has molecular weight of 238.215 g/mol, oral bioavailability approximately 50%, protein binding is 70-76% and elimination half-life is 0.8-1 hr.

The present work was conducted to improve the solubility of methyldopa using solid dispersion technique with PEGs and the poloxamer 407.

MATERIALS AND METHODS

Methyldopa was obtained from yarrow chemicals, Mumbai, India. PEGs were commercially obtained from Reidal chemical Pvt. Ltd. New Delhi. Poloxamer 407 was commercially obtained from Alcon Laboratories Pvt. Ltd, Bangalore, India. Ethanol was obtained from Changshu yangyuan chemical India. All ingredients used in the formulation were of analytical grade.

METHODS

I. Determination of λ max

The absorption was found to be 282 nm.

II. Calibration curve of methyldopa

Calibration curve of methyldopa in phosphate buffer pH (6.8) and in 0.1 N HCL were obtained at 282 nm with UV-VISIBLE spectrophotometer. Using concentration and absorbance data, a calibration curve was obtained.

III. Infra-red Spectrum [16]

The pure drug, Methyldopa and its mixture with the surfactant poloxamer 407 and carrier PEG 6000 in different ratios was mixed separately with IR grade KBr and pellets were prepared by applying a pressure of 10 tons in a hydraulic press. The pellets were scanned over a wavelength range of 400 cm^{-1} to 4000 cm^{-1} using an FTIR 8400S model instrument

Preparation of solid dispersion

Solid dispersion of methyldopa was prepared by fusion method and solvent evaporation method. The composition is shown in table No: 1.

Table 1: Composition of Solid Dispersion

Formulation code	Carrier	Drug: carrier	Method
FB_1	PEG 4000	1:1	Fusion method
FB_2	PEG 4000	1: 3	Fusion method
FB_3	PEG 6000	1:1	Fusion method
FB_4	PEG 6000	1: 3	Fusion method
FT_5	PEG 4000, Poloxamer 407	1:5:1	Fusion method
FT_6	PEG 6000, Poloxamer 407	1:5:2	Fusion method
FB_7	PEG 4000	1:0.5	Solvent evaporation method
FB_8	PEG 4000	1:2	Solvent evaporation method
FB_9	PEG 6000	1:0.5	Solvent evaporation method
FB_{10}	PEG 6000	1:2	Solvent evaporation method
FT_{11}	PEG 4000, Poloxamer 407	1:1:1	Solvent evaporation method
FT_{12}	PEG 6000, Poloxamer 407	1:2:2	Solvent evaporation method

In fusion method the binary solid dispersions were made using PEG-4000 or PEG-6000 as carriers with varying drug: carrier ratios 1:1 and 1:3 by the fusion method. Binary solid dispersions were also prepared by the solvent evaporation method using PEG-4000 or PEG-6000 as carriers with varying drug: carrier ratios 1:0.5 and 1:2. Also ternary solid dispersions were made by both the fusion and the solvent evaporation method using

the PEG-4000 or PEG-6000 and the poloxamer 407 in the ratios of 1:5:1, 1:5:2, 1:1:1 and 1:2:2. In the fusion method the drug is suspended in the melted carrier till homogeneous mixture was obtained then cooled to the room temperature to obtain solid mass. The solidified mass was then crushed and passes through sieve no.40 to get uniform sized particles. The obtained solid dispersion was stored in desiccators till further analysis.[17,18]

In the solvent evaporation method the drug and water soluble carrier is dissolved in a common solvent and the resulting clear solution is rapidly heated for evaporating the solvent and to get a glassy solid mass. Briefly, carrier was dissolved in 20% ethanol under stirring, until a clear solution was obtained, methyldopa was then added and stirring was continued for 45 min. The organic solvent was removed by evaporation on a water bath at 60 °C. The resultant solid dispersions were stored in a desiccator until constant mass was obtained, pulverized and passed through sieve No. 40. [19]

EVALUATION OF SOLID DISPERSIONS

Drug content

Drug content was determined by dissolving an amount of 100 mg of drug SDs in 100 mL phosphate buffer pH 6.8. The solution was filtered, suitably diluted and the absorbance was measured spectrophotometrically at 282 nm.[20]Percentage of drug content was calculated by following formula:

% Drug content= observed value/actual value × 100

Also the drug content was determined by dissolving an amount of 100 mg of drug SDs in 100 ml 0.1 N HCL. The solution was filtered, suitably diluted and the absorbance was measured spectrophotometrically at 282 nm.Percentage of drug content was calculated by following formula:

% Drug content= observed value/actual value × 100

In vitro drug release studies

The quantity of solid dispersion equivalent to 300 mg of methyldopa was filled in hard gelatin capsule by hand filling method. The dissolution study of capsules was conducted using dissolution testing USP apparatus 1 (basket method) in 900 ml of phosphate buffer of pH 6.8 at 37±0.5 ºC and at a speed of 100 rpm. Aliquot of 3ml was withdrawn at predetermined time interval and equivalent amount of fresh medium was replaced to maintain a constant volume after each sampling and analyzed spectrophotometrically at 282 nm using UV Visible spectrophotometer.

Another dissolution study of capsules was conducted using dissolution testing USP apparatus 1 (basket method) in 900 ml of 0.1 N HCL at 37±0.5^{o}C and at a speed of 100 rpm. Aliquot of 3 ml was withdrawn at predetermined time interval and equivalent amount of fresh medium was replaced to maintain a constant volume after each sampling and analyzed spectrophotometrically at 282 nm using UV Visible spectrophotometer.[21]

Comparison with marketed formulation

The percentage drug release of solid dispersions was compared with marketed formulation of Methyldopa (Alphadopa).

Selection of optimized formulation [22]

Optimized formulation will be selected on the basis of highest % drug content and highest % drug release at 60 minutes.

Stability study

Optimized solid dispersions were subjected to short term stability testing. Solid dispersions were placed in well closed containers and maintained at 40 + 2 ^{o}C and 75 + 5% RH for 2 month as per ICH guidelines. Changes in the appearance and drug content of the stored films were investigated after storage.[23]

RESULTS AND DISSCUSION

Percent of drug content

Solid dispersions of Methyldopa were prepared by different method using carriers like PEG-4000, PEG 6000 and poloxamer 407. In the present work, total 12 formulations were prepared in which 6 formulations were prepared by fusion method and others 6 formulations were prepared by solvent evaporation method. The percentage drug content of the above 12 formulations was carried out in two mediums i.e. in the phosphate buffer pH 6.8 and in 0.1 N HCL and percent drug content studies are shown in the table 04 and 05. The drug content of the prepared formulations was found to be in the range of 92.74- 98.64% in the phosphate buffer pH 6.8 and in the range of 90.58%-97.11% in 0.1 N HCL. In both the mediums the drug content was highest in FT_6. In the phosphate buffer pH 6.8 the drug content of FT_6 was 98.64% and in the 0.1N HCL it was 97.11%. The drug content of FT_6 in phosphate buffer pH 6.8 was greater than that of drug content of FT_6 in 0.1 N HCL. The % drug content of the prepared formulation in the phosphate buffer pH 6.8 and in 0.1 N HCL is shown in the fig. 07 and 08.

In vitro drug release studies

The in vitro dissolution study of different formulation is shown in figures 09, 10, 11 and 12. In-vitro drug release was carried in two mediums that is in phosphate buffer pH 6.8 and in 0.1N HCL. The in vitro drug release of formulations FB_1-FT_{12} carried in phosphate buffer pH 6.8 is shown in the table 06 and 07 and also another in vitro drug release for formulations FB_1-FT_{12} was carried in 0.1N HCL which is shown in the table 08 and 09 .The highest in vitro release was observed with FT_6 in both the mediums that is in the phosphate buffer pH 6.8 and in the 0.1N HCL in which ratio of drug: carrier: surfactant is 1:5:2 and its release rate was found to be 86.21% in the phosphate buffer pH 6.8 and 85.80% in 0.1N HCL. The in vitro release rate of FT_6 in phosphate buffer pH 6.8 was greater than the in vitro release of FT_6 in 0.1N HCL. Thus it was selected as best formulation.

Comparison with marketed formulation

The solid dispersion formulation FT_6 showed drug release 86.21% in 60 minutes whereas the marketed product was found to release only 65.80% of the drug in 60 minutes in the phosphate buffer pH 6.8. Also the formulation FT_6 has shown the drug release about 85.80% whereas the marketed product was found to release only 62.21% of the drug in 60 minutes in

0.1NHCL.The in-vitro release pattern of solid dispersion formulations FT_6 in the phosphate buffer pH 6.8 and in the 0.1 N HCL compared with the marketed formulations is shown in the figures 13 and 14.

Stability study

Optimized solid dispersion was subjected to short term stability testing. Solid dispersions were placed in closed containers and maintained at 40 + 2° C and 75+ 5% RH for 2 month as per ICH guidelines. The drug content was found almost constant for up to two months. The in vitro dissolution time of the solid dispersions after the stability study was also not found to be affected.

DISCUSSION

Drug content was determined by dissolving an amount of 100 mg of drug SDs in 100 mL phosphate buffer pH 6.8. The solution was filtered, suitably diluted and the absorbance was measured spectrophotometric ally at 282 nm. Drug content was also carried in 0.1N HCL. The solution was filtered, suitably diluted and the absorbance was measured spectrophotometrically at 282 nm. The highest percent drug content has been observed with the formulations FT_6 in the phosphate buffer pH 6.8 i.e. 98.64%.

In vitro dissolution studies were carried out in the two dissolution medium. One is the phosphate buffer pH 6.8 and the other is 0.1N HCL, in both the mediums dissolution were carried for the formulations FB_1-FT_{12}. The in vitro drug release from formulation FB_1-FT_{12} carried in phosphate buffer pH 6.8 and 0.1N HCL has shown in fig. 09, 10, 11 and 12. The best in vitro release was shown by the formulation FT_6 i.e. 86.21% in phosphate buffer dissolution medium. It has been observed that the FT_6 in 0.1 N HCL shows the less in vitro release than FT_6 in phosphate buffer pH 6.8 because of acid degradation.

Drug compatibility was performed by the IR spectroscopy method. The drug methyldopa, PEG 6000 and poloxamer 407 in the ratios (1:1:1), (1:2:2) and (1:3:3) did not yield any kind of deviation in the finger print region i.e. 2000 – 600 c.m-1. However the little changes in the functional group area between 4000 – 2000 c.m-1. Peak is shifted very marginally which is negligible in fact possibly due to the availability of poloxamer 407 to form H- bounding with the O-H of methyldopa. Thus we can conclude that the PEG 6000 and poloxamer 407 do not intercept the methyldopa and thus is fully compatible with API i.e. methyldopa.

Twelve formulations were prepared and the detailed composition is presented in table 01. Out of these twelve formulations six formulations were prepared by the fusion method and other six formulations were prepared by the solvent method. These prepared solid dispersions were then subjected to the % drug content, in vitro released studies and also the prepared solid dispersion is compared with the marketed formulation of methyldopa. It has been observed that the in vitro release rate of the marketed formulation was lesser than of the prepared solid dispersion of methyldopa. The prepared solid dispersion i.e. FT_6 showed in vitro drug release about 86.21% respectively in 60min. whereas the marketed formulation was found to release only 65. 80% of the 60 min. (shown in fig. 13) this dissolution was carried in phosphate buffer pH 6.8. The other dissolution was carried in 0.1N HCL in which FT_6 has shown in vitro release 85.80% in 60 min. and the marketed formulation has shown the in vitro release rate 62.21% in 60 min. (shown in fig.14). In both the cases the marketed formulation shows the lesser in vitro drug release i.e. when compared to the formulation FT_6 in which the dissolution was carried in phosphate buffer pH 6.8 and in the 0.1 N HCL.

Stability study for the optimized formulation was carried out for 2 months. It has been observed that the formulation FT_6 has shown no change in drug content and in vitro release.

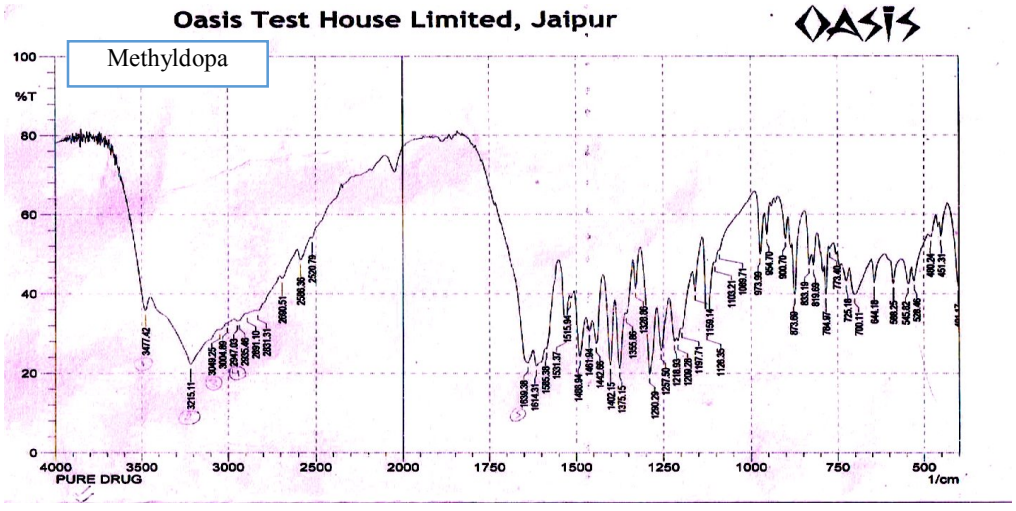

Fig. 1: IR Spectrum of Methyldopa (pure drug)

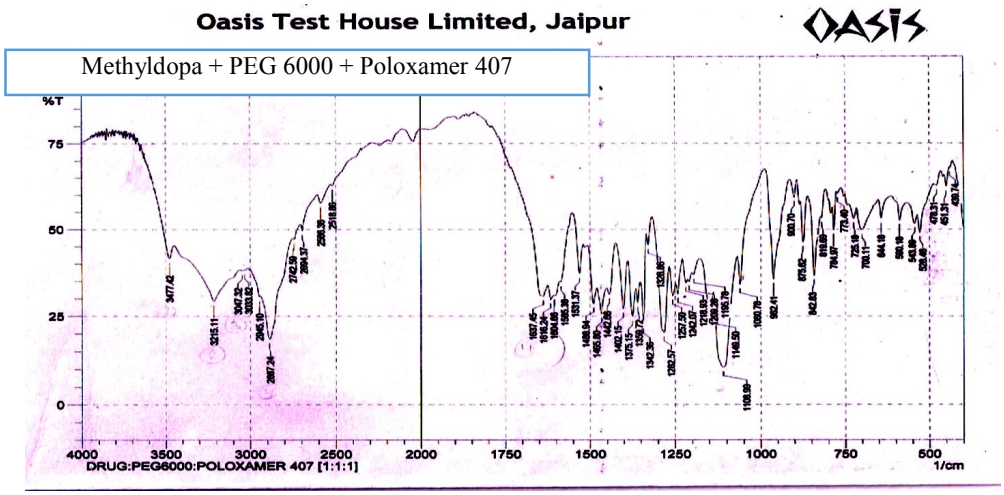

Fig. 2: IR spectrum of Methyldopa: PEG 6000: Poloxamer 407(1:1:1)

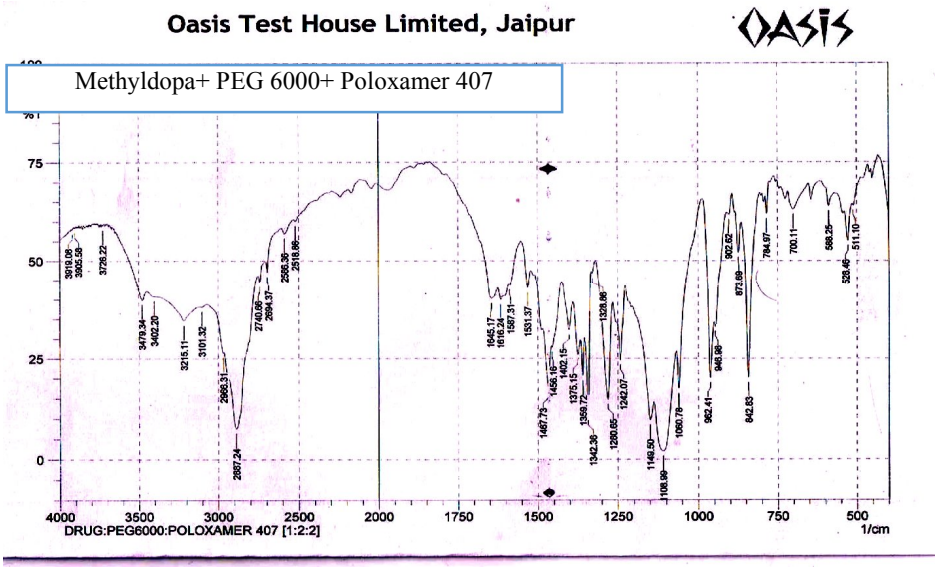

Fig. 3: IR spectrum of Methyldopa: PEG 6000: Poloxamer 407(1:2:2)

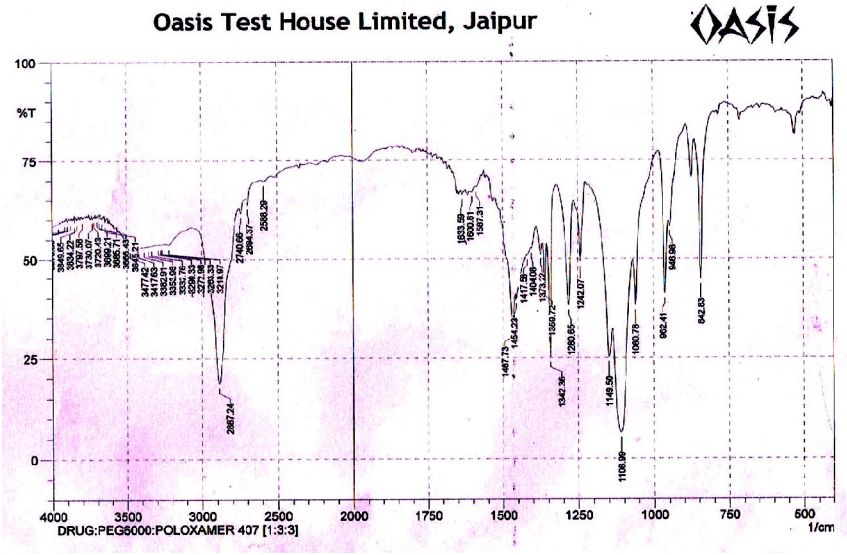

Fig. 4: IR spectrum of Methyldopa: PEG 6000: Poloxamer 407(1:3:3)

Table 2: Different absorbance value of drug in different concentration in pH 6.8 phosphate buffer

Sr. no.	Concentration (µg/ml)	Absorbance
1.	2	0.131
2.	4	0.246
3.	6	0.362
4.	8	0.486
5.	10	0.627

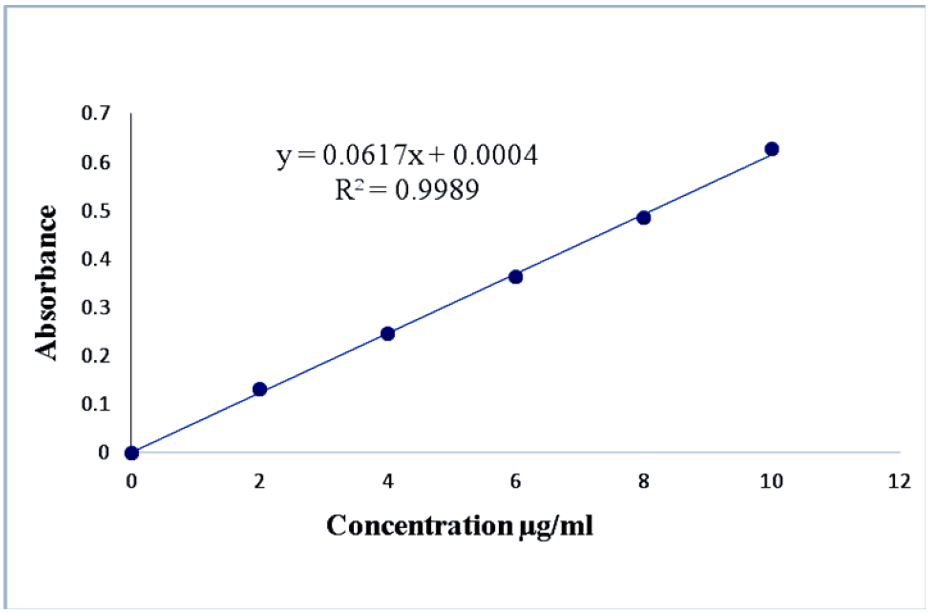

Fig. 5: Calibration curve of Methyldopa in phosphate buffer pH 6.8

Table 3: Different absorbance value of drug in different concentration in 0.1 N HCL

Sr. no.	Concentration (µg/ml)	Absorbance
1.	5	0.121
2.	10	0.227
3.	15	0.330
4.	20	0.44
5.	25	0.563

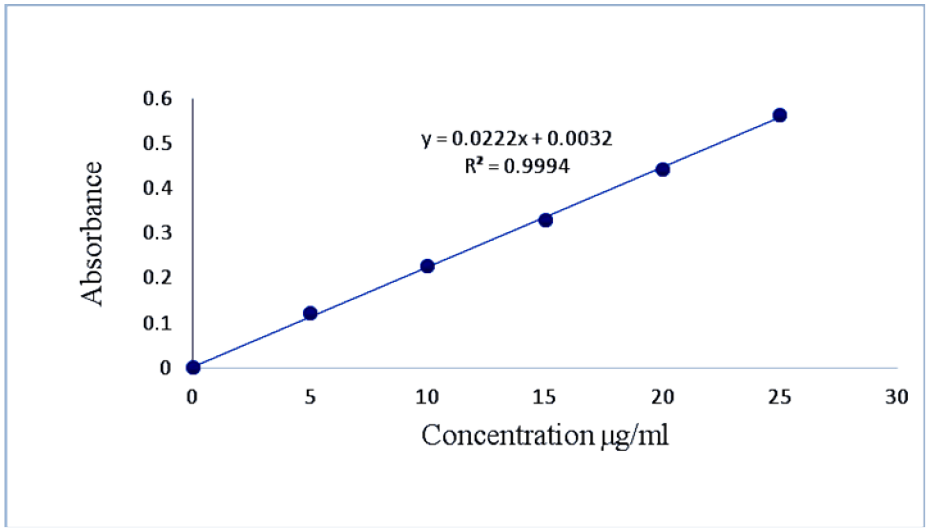

Fig. 6: Calibration curve of Methyldopa in 0.I N HCL

Table 4: Percentage of drug content uniformity of different formulations of solid dispersion prepared by different methods in phosphate buffer pH 6.8

Formulation code	Carrier	Drug :carrier	Drug Content (%)	Method
FB_1	PEG 4000	1:1	93.87	Fusion method
FB_2	PEG 4000	1: 3	94.65	
FB_3	PEG 6000	1:1	95.87	
FB_4	PEG 6000	1: 3	96.65	
FT_5	PEG 4000, Poloxamer 407	1:5:1	97.54	
FT_6	PEG 6000, Poloxamer 407	1:5:2	98.64	
FB_7	PEG 4000	1:0.5	92.74	Solvent evaporation Method
FB_8	PEG 4000	1:2	93.52	
FB_9	PEG 6000	1:0.5	94.74	
FB_{10}	PEG 6000	1:2	95.52	
FT_{11}	PEG 4000, Poloxamer 407	1:1:1	96.11	
FT_{12}	PEG 6000, Poloxamer 407	1:2:2	97.61	

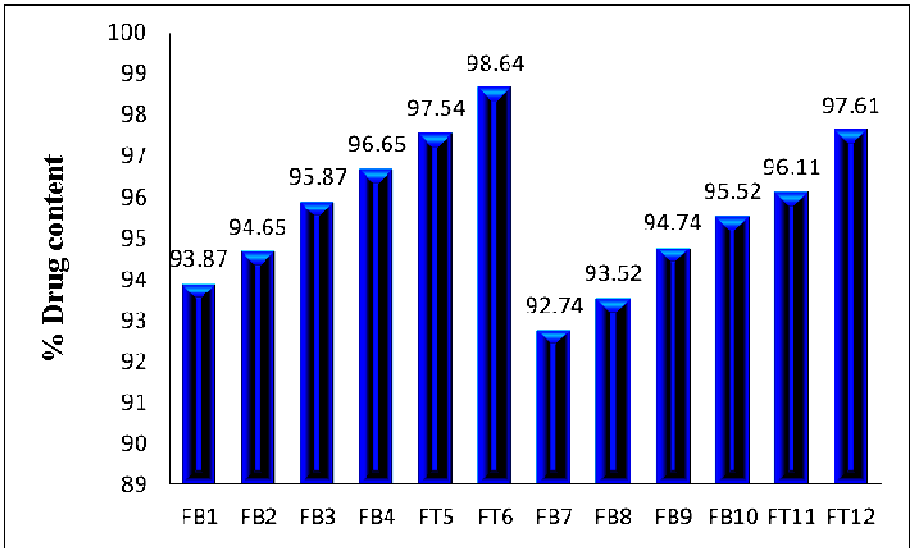

Fig. 7: Percentage of drug content uniformity of different formulations of solid dispersion prepared by different methods in phosphate buffer pH 6.8

Table 5: Percentage of drug content uniformity of different formulations of solid dispersion prepared by different methods in 0.1 N HCL

Formulation code	Carrier	Drug :carrier	Drug Content (%)	Method
FB_1	PEG 4000	1:1	91.37	Fusion method
FB_2	PEG 4000	1: 3	92.15	
FB_3	PEG 6000	1:1	93.46	
FB_4	PEG 6000	1: 3	95.82	
FT_5	PEG 4000, Poloxamer 407	1:5:1	96.17	
FT_6	PEG 6000, Poloxamer 407	1:5:2	97.11	
FB_7	PEG 4000	1:0.5	90.58	Solvent evaporation Method
FB_8	PEG 4000	1:2	92.79	
FB_9	PEG 6000	1:0.5	93.11	
FB_{10}	PEG 6000	1:2	94.03	
FT_{11}	PEG 4000, Poloxamer 407	1:1:1	95.42	
FT_{12}	PEG 6000, Poloxamer 407	1:2:2	96.61	

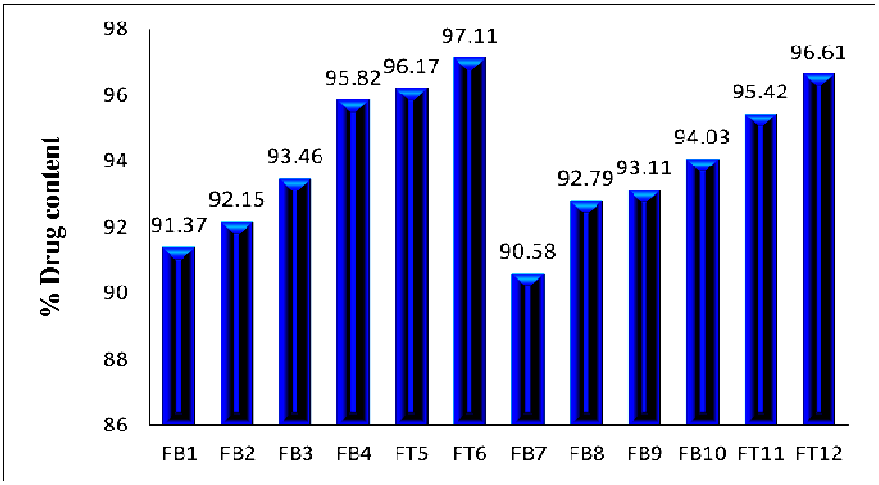

Fig. 8: Percentage of drug content uniformity of different formulations of solid dispersion prepared by different methods in 0.1 N HCL

Table 6: Dissolution profile of formulations FB_1-FT_6 and marketed preparation in phosphate buffer pH (6.8)

Time(Min)	Cumulative % Drug Release						
	FB_1	FB_2	FB_3	FB_4	FT_5	FT_6	Marketed product B. No. EM3035 (250 mg)
5	20.68	21.38	22.75	23.44	25.51	26.20	18.97
15	40.65	43.45	46.90	48.96	51.03	53.10	38.98
30	60.69	63.44	64.83	66.90	68.23	70.34	56.96
45	67.59	71.03	76.55	79.31	82.06	84.13	60.68
60	70.34	75.86	80.69	82.75	84.80	86.21	65.80

Table 7: Dissolution profile of formulations FB_7-FT_{12} and marketed preparation in phosphate buffer pH (6.8)

Time(Min)	Cumulative % Drug Release						
	FB_7	FB_8	FB_9	FB_{10}	FT_{11}	FT_{12}	Marketed product B. No. EM3035 (250 mg)
5	19.04	20.95	21.85	22.30	24.66	27.57	17.94
15	38.09	41.90	45.71	47.61	49.52	51.43	35.09
30	55.24	59.04	62.86	64.76	66.66	68.57	45.27
45	66.60	70.47	74.28	78.09	81.90	83.81	52.02
60	69.75	72.80	80.04	81.50	83.71	85.71	57.09

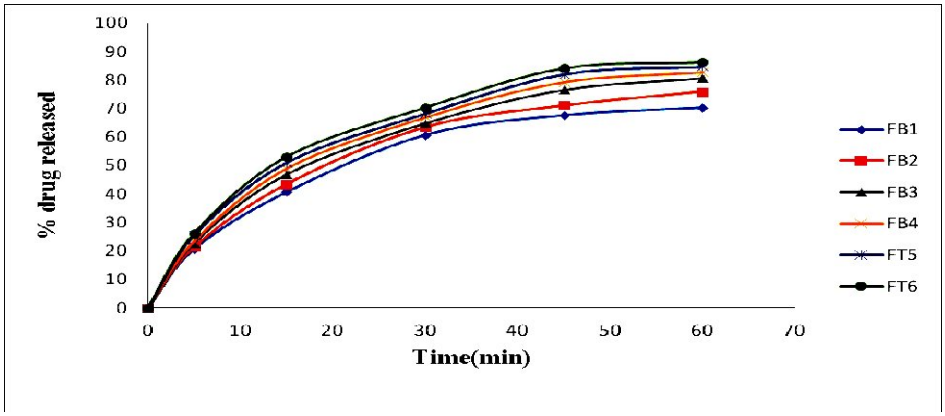

Fig. 9: In-vitro drug release of formulations from FB_1-FT_6 in phosphate buffer pH 6.8

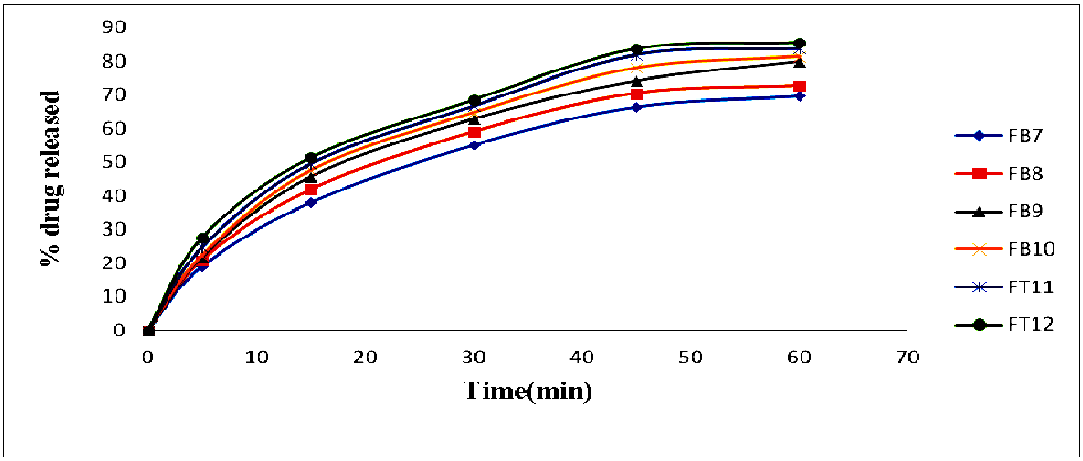

Fig. 10: *In-vitro* drug release of formulations from FB_7-FT_{12} in phosphate buffer pH 6.8

Table 8: Dissolution profile of formulations FB_1-FT_6 and marketed preparation in 0.1 N HCL

Time (Min)	Cumulative % Drug Release						
	FB_1	FB_2	FB_3	FB_4	FT_5	FT_6	Marketed product B. No. EM3035 (250 mg)
5	19.44	20.83	21.57	22.53	24.50	25.26	17.79
15	38.17	40.11	43.40	45.78	49.03	51.70	36.82
30	59.79	61.59	62.38	64.12	67.23	69.43	52.11
45	64.92	69.95	73.54	78.38	80.60	82.19	59.96
60	68.43	72.68	79.68	81.75	83.87	85.80	62.21

Table 9: Dissolution profile of formulations FB_7-FT_{12} and marketed preparation in 0.1 N HCL

Time(Min)	Cumulative % Drug Release						
	FB_7	FB_8	FB_9	FB_{10}	FT_{11}	FT_{12}	Marketed product B. No. EM3035 (250 mg)
5	17.40	18.20	19.89	20.66	22.30	23.57	16.92
15	34.51	40.12	43.77	47.25	49.43	50.52	32.94
30	51.42	57.04	60.62	60.62	65.75	67.66	43.72
45	60.72	68.47	72.28	72.28	80.02	81.90	50.11
60	65.81	70.80	79.50	80.71	83.17	84.15	55.47

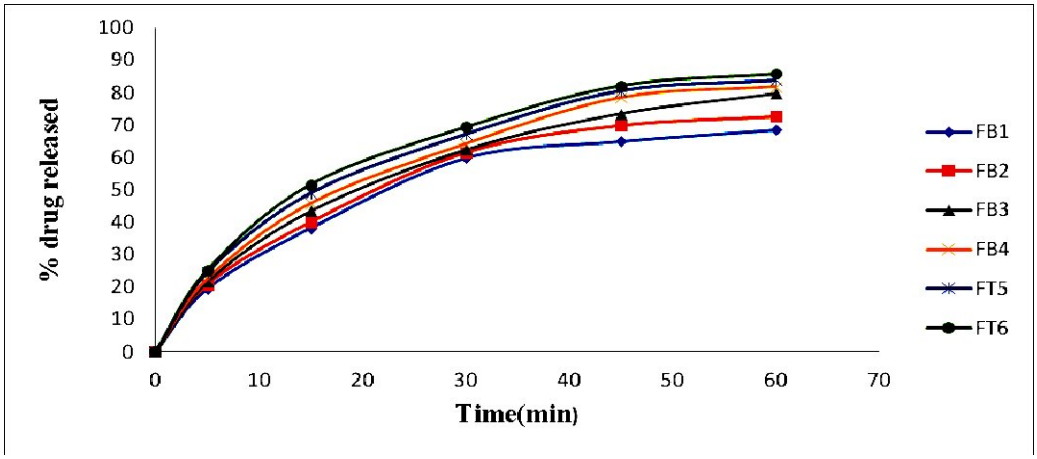

Fig. 11*: In-vitro* drug release of formulations from FB_1-FT_6 in 0.1 N HCL

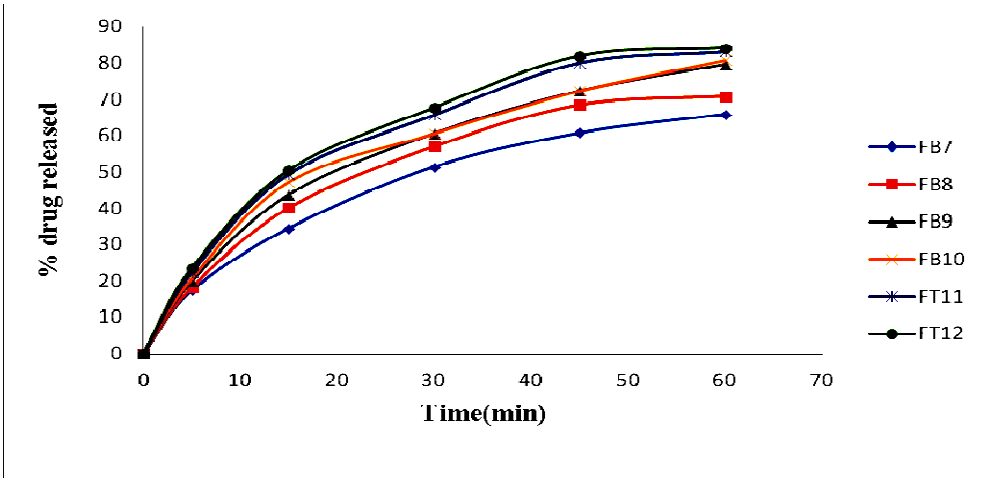

Fig. 12: *In-vitro* drug release of formulations from FB_7-FT_{12} in 0.1 N HCL

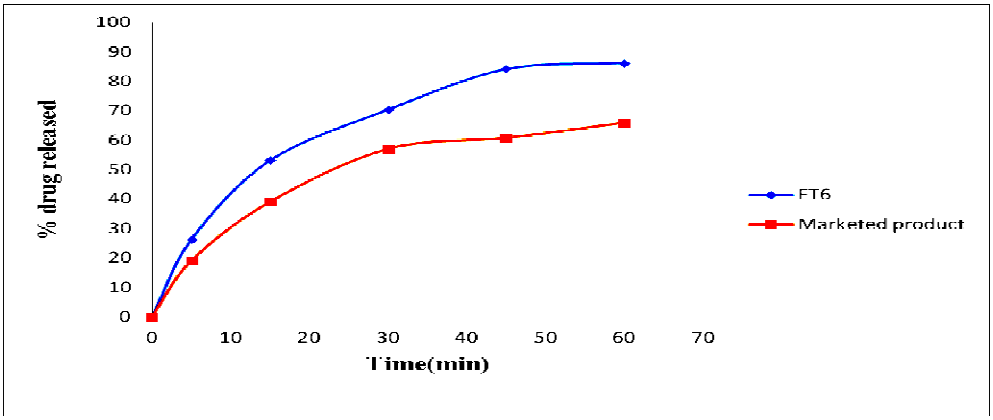

Fig. 13: Comparison of In-vitro drug release pattern of FT_6 with marketed formulation of methyldopa in phosphate buffer pH 6.8

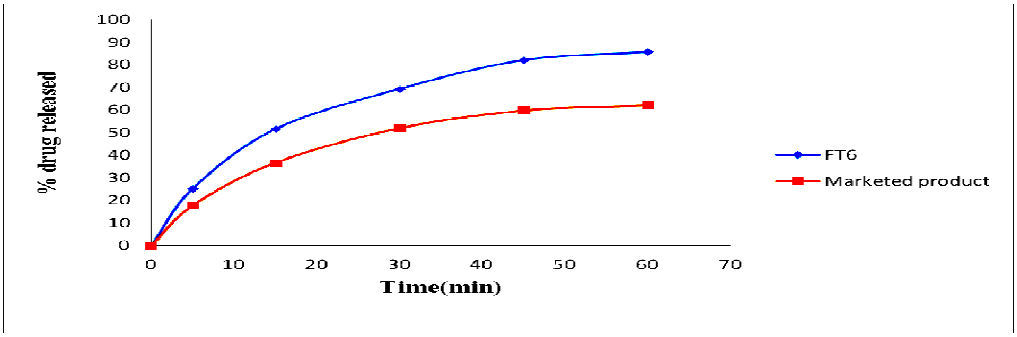

Fig. 14: Comparison of In-vitro drug release pattern of FT_6 with marketed formulation of methyldopa in 0.1 N HCL

Table 10: stability study of formulation FT_6

Time(weeks)	Percentage drug content	In-vitro drug release % at 60 min.
0	98.64	86.21
2	98.43	86.17
4	98.33	86.11
6	98.24	86.09
8	98.09	86.05

CONCLUSION

The present investigation revealed that the combination of PEG-6000 and poloxamer 407 is a proper choice as a carrier to enhance the solubility of methyldopa from SDs. Among the ratios used, a ternary SD with a 1:5:2 (drug: PEG-6000: Poloxamer 407) ratio

was found to be optimal because of its superior performance in enhancing the solubility of methyldopa. The physicochemical characterization of solid dispersion shows that there is no chemical interaction between drug and polymers. Therefore, it can be concluded that the aqueous solubility of poorly soluble drugs can be significantly improved by utilizing the solid dispersion technique.

ACKNOWLEDGEMENTS

The authors would like to thank the NIMS institute of pharmacy, NIMS University, Jaipur, Rajasthan for providing the necessary facilities for carrying out this investigation.

REFRENCES

1. Dau K, Sharma VK. Solid dispersion technology. Pharmacist. 2009; 10:1-2.
2. Robert CJ, Armas HN, Janssen S. Characterization of ternary solid dispersion of intraconazole PEG 6000. J Pharm sci. 2008; 97: 2110-2120.
3. Chiou WL, Rielman S. Pharmaceutical application of solid dispersion system. J Pharm.sci. 1971; 78: 10-12.
4. Chiou WL, Riegelman S, Pharmaceutical applications of solid dispersion systems, J. Pharm. Sci. 1971;60: 1281-1302.
5. Dingra D, Bhandari A, Sharma RB, Ranjana G and Sachin G, Enhancement of dissolution rate of slightly soluble drug Clomophen Citrate by solid dispersion. *Int. J. Chem Tech Res.* 2010; 2: 1691-1697.
6. R. A. Prentis, Y. Lis, and S. R. Walker, "Pharmaceutical innovation by seven UK-owned pharmaceutical companies (1964-1985)," Br. J. Clin. Pharmacol. 1988; 25: 387-396.
7. C. A. Lipinski, "Avoiding Investment in doomed drugs, is poor solubility an industry wide problem?" Curr. Drug Dis. 2001; 4: 17-19.
8. T. J. Shah, A. F. Amin, J. R. Parikh, and R. H. Parikh, "Process optimization and characterization of poloxamer solid dispersions of a poorly water-soluble drug," AAPS Pharm Sci Tech. 2007; 8:18-24.
9. G. V. D. Mooter, P. Augustijns, N. Blaton, and R. Kinget,"Physicochemical characterization of solid dispersions of temazepam with polyethylene glycol 6000 and PVP K30," Int. J. Pharm. 1988; 164: 67-80.
10. D. Law, S. L. Krill, E. A. Schmitt, J. J. Fort, Y. Qiu, W. Wang, and W. R. Porter, "Physicochemical considerations in the preparation of amorphous ritonavir-poly (ethylene glycol) 8000 solid dispersions," J. Pharm. Sci. 2001; 90: 1015-1025.
11. M. J. Habib, Pharmaceutical Solid Dispersion Technology, Washington: CRC. 2000, 35-78.
12. Sekiguchi K. Studies on absorption of eutectic mixture. Pharma bull. 1961; 9: 866-872.
13. C. Leunner, and J. Dressman, "Improving drug solubility for oral delivery using solid dispersions," Eur. J. Pharm. Biopharm. 2000; 50: 47-60.
14. D. Q. M. Craig, "The mechanisms of drug release from solid dispersions in water soluble polymers," Int. J. Pharm. 2002; 231(2): 131-144.
15. S. Sethia, "Solid dispersions-revival with greater possibilities and applications in oral drug delivery," Crit. Rev. Ther. Drug Carrier Syst. 2003; 20 (2-3): 215-247.
16. Na GC, Stevens HJ Jr, Yuan BO, Rajagopalan N. Physical stability of ethyl diatrizoatenano crystalline suspension in steam sterilization. Pharm Res. 1999; 16(4):569–574.
17. Zajc N, Obreza A, Bele M, Srcic S. Physical properties and dissolution behaviour of nifedipine/mannitol solid dispersions prepared by hot melt method. Int J Pharm. 2005; 291: 51-58
18. Punitha S, VedhaHari BN, Karthikeyan D. Enhancement of celecoxib solubility by solid disperson using mannitol. Int J Pharm Pharm Sci. 2010; 2(4): 109-111.
19. Yonemochi E., Ueno Y., Ohmae T., Oguchi T., Nakajima S.,Yamamoto K., Evaluation of amorphous ursodeoxycholic acid by thermal methods, Pharm.Res. 1997; 14:798–803.
20. Moore JW, Flanner H. Mathematical comparison of dissolution profiles. Pharm Technol. 1996; 20: 64-74.
21. HecqJ,Deleers M, Fanara D, Vranckx H and Amighi K. Preparation and characterization of noncrystals for solubility amd dissolution rate enhancement of nifedipine. Int J pharma. 2005; 299:167-177.
22. Muller R, Keck C. Challenges and solutions for the delivery of biotech drugs – A review of drug nanocrystal technology and lipid nanoparticles, Journal of Biotechnology. 2004; 113(1-3):151-170.
23. David JM. International stability testing, Bufflo grove; Interpharm Press Inc. 1999.

How to cite this article:
Shahista Mohi Ud Din,* Mehraj Ud Din, Dr. Govind Mohan, Tarkeshwar Prasad, Shukla Irfan Hassan.: formulation development and evaluation of solid dispersion of methyldopa for solubility enhancement, 5(3): 1912-1922. (2014)