SOLUBILITY AND DISSOLUTION IMPROVEMENT OF ROFECOXIB USING SOLID DISPESION TECHNIQUE

MOHAMED RAHAMATH ULLA, GANGADHARAPPA H V*, NEELKANT RATHOD**

Al Arab Medical Sciences University, Dept. of Pharmaceutics, Faculty of pharmacy, Benghazi 5341, Libya
**JSS College of Pharmacy, Dept. of Pharmaceutics, Faculty of Pharmacy, Mysore, India*
***Govt. College of Pharmacy, Dept. of Pharmaceutics, Faculty of Pharmacy, Bangalore, India*

ABSTRACT

Rofecoxib (RXB) is a potent and selective cyclo-oxygenase-2 (COX-2) inhibitor, highly effective in the treatment of various pains, inflammatory condition, post-operative pain, rheumatoid arthritis, other musculo-skeletal and joint disorders. Although they are completely absorbed upon oral administration, the peak plasma concentration is reached 2-3 hours after oral ingestion. The reason for delay being slow rate of absorption due to poor aqueous solubility. An attempt has been made to enhance solubility and dissolution of rofecoxib by solid dispersion(SD) technique using various hydrophilic excipients like PEG 4000, PEG 6000, PVP at different ratios by melting method and solvent evaporation method. The prepared SD of RXB were characterized to various physico-chemical properties and *in vitro* drug dissolution studies in 0.1N HCl with 0.25% SLS (pH 1.1) media for a period of 90 min using USP XXIII electro lab 8 basket tab dissolution test apparatus using paddle. The result of study indicated that there was no drug-polymer interaction found. The drug dissolution was found to enhance percent in PEG 4000, PEG 6000 and PVP, after 90mins of dissolution study 79.02%, 88.02%, 98.57% respectively. On comparison of various polymers used at varied concentrations PVP at 75:25 ratio by fusion method was found to be best suitable for the enhancement of dissolution and solubility of RXB.

Keywords: Rofecoxib, solid dispersion, PEG-4000, PEG-6000, PVP.

INTRODUCTION

RXB is Non steroidal anti-inflammatory drug; it is a potent and selective cyclo-oxygenase-2(Cox-2) inhibitor and also inhibit prostaglandins synthesis. It is mainly used for osteoarthritis, rheumatoid arthritis and joint disorder. RXB is practically insoluble in water and peak plasma level reaches between 2-3 hrs after oral administration (Thomas *et al*., 1999).

The rate and extent of dissolution of the drug from any solid dosage form determines the rate and extent of absorption of the drug (Rabasco *et al*., 1991; Ahmed *et al*., 1993). In case of poorly water soluble drug dissolution is rate limiting step in the process of drug absorption, potential bioavailability problem an relevant with extremely hydrophobic drug due to erratic and incomplete absorption from GIT (Kerc *et al*., 1993; Popli *et al*., 1994). The solid dispersion approach has been widely and successfully applied to improve the solubility, dissolution rate and consequently the bio availability of poorly water soluble drugs (Tanabe *et al*., 1994; Kearney *et al*., 1994; Khidr *et al*., 1994). A number of drugs have been shown to improve their dissolution character, when converted to SD. To data some reports on the formulation of these systems have appeared (Lu *et al*., 1995; Veiga *et al*., 1994; Patil *et al*., 2001). Because of poorly aqueous solubility of RXB may posses dissolution related absorption problem, hence an attempt was made to improve the dissolution of RXB through the formulation containing SD of RXB

Corresponding author: e-mail: rahmathmsu@yahoo.com

MATERIALS AND METHODS

RXB was obtained as gift sample from Eros Pharma, Bangalore, India. PEG 4000, PEG 6000, PVP and all other chemicals used as analytical reagent/pharmaceutical grade.

Phase-1 Preparation of solid dispersion

i) *Solvent evaporation method*

The solid dispersion has been prepared previously by many researchers. The drug RXB and polymers PEG 4000, PEG 6000 and PVP at different proportions (95:05, 85:15, 75:25) were dissolved in sufficient volume of chloroform then solvent was completely evaporated at 40-45^{o}C with continuous stirring to obtain drug granules and passed through the 120 mesh sieve (Lheritier *et al*., 1995, Sheen *et al.,* 1995).

ii) *Melting method*

The solid dispersion phase also been prepared previously by melting or fusion method. Accurate weighed amount of carrier with their concentration mentioned above was melted in a porcelain dish at 80-85^{o}C and to their calculated amount of RXB was added through mixing for 1-2 min followed by instant cooling obtained dry granules, which were passed through 120 mesh sieve.

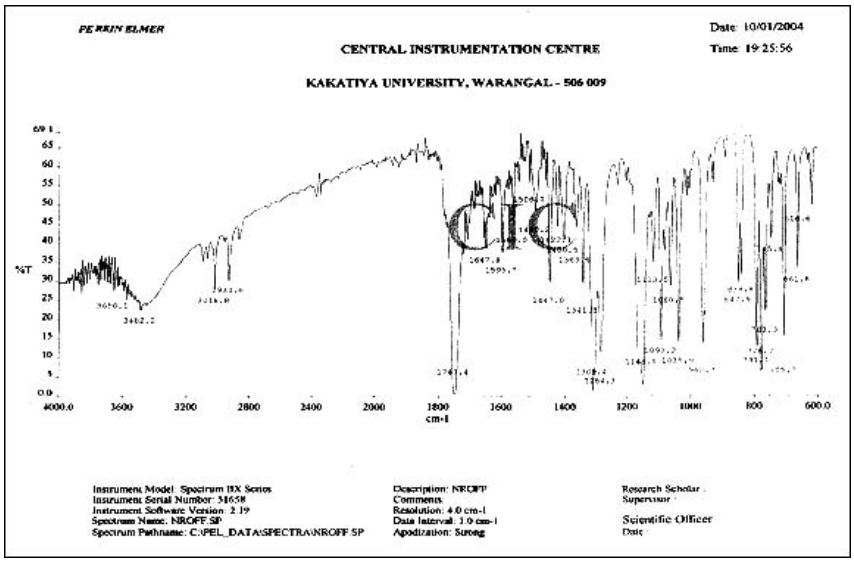

Fig. 1: FTIR spectra of pure rofecoxib.

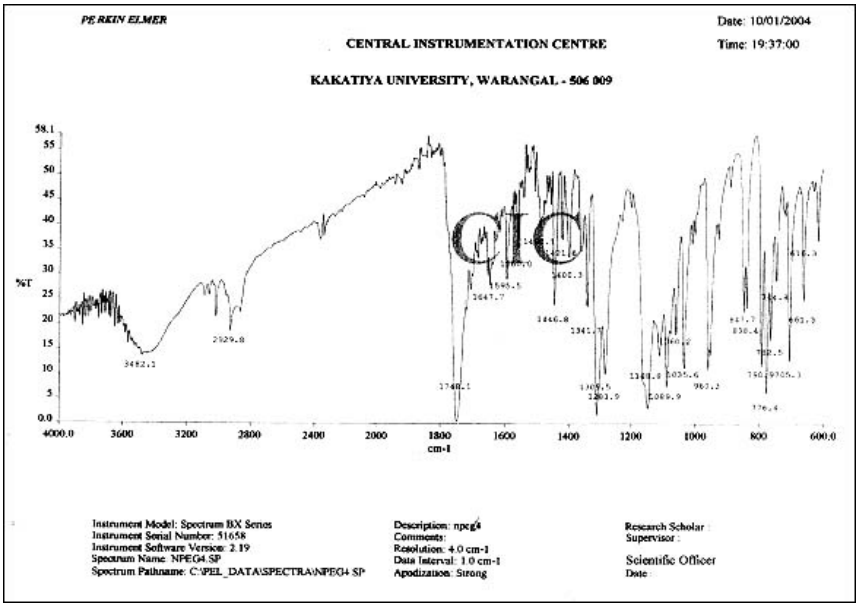

Fig. 2: FTIR spectra of rofecoxib-PEG 4000 solid dispersion.

Phase 11: Physico chemical characters

i) *Drug content analysis*

An accurately weighed quantity of solid dispersion equivalent to 40 mg of RXB was taken into a 100 ml volumetric flask, dissolved in a small quantity of methanol and make up to the mark with methanol. Then the solution was suitably diluted and assayed for drug content by measuring the absorbance at 240 nm (Chowdary *et al*., 1995; Pawar *et al*., 1995).

ii) Infra Red studies

IR spectra of RXB and solid dispersions were obtained by KBr pellet method using Perkin Elmer FTIR series model 1615 spectrometer in order to rule out drug carrier interaction occurring during the formulation process (Nakagami H *et al.,* 1991).

iii) *Saturation solubility*

Known excess (approximately 10 mg) of RXB was added to 10 ml of 0.1 N HCl with 0.25% SLS (pH 1.1). Samples were rotated at 20 rpm in a water bath (37^{o}C) for 72 h. The samples were then filtered, suitably diluted and analyzed by UV spectrophotometer at 240 nm (Suzuki *et al*., 1996; Palmieri *et al*., 1996).

iv) *TLC studies*

A thin layer chromatography (TLC) was used to study the chemical stability of RXB in solid dispersions. The

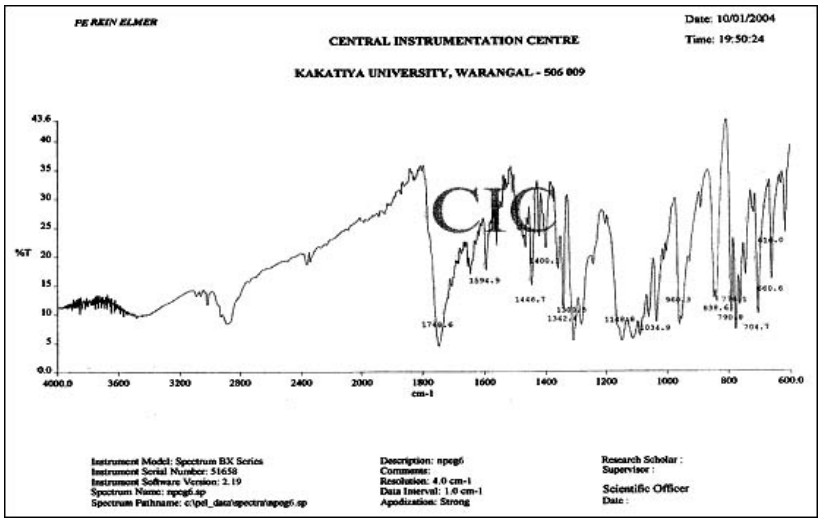

Fig. 3: FTIR spectra of rofecoxib-PEG 6000 solid dispersion.

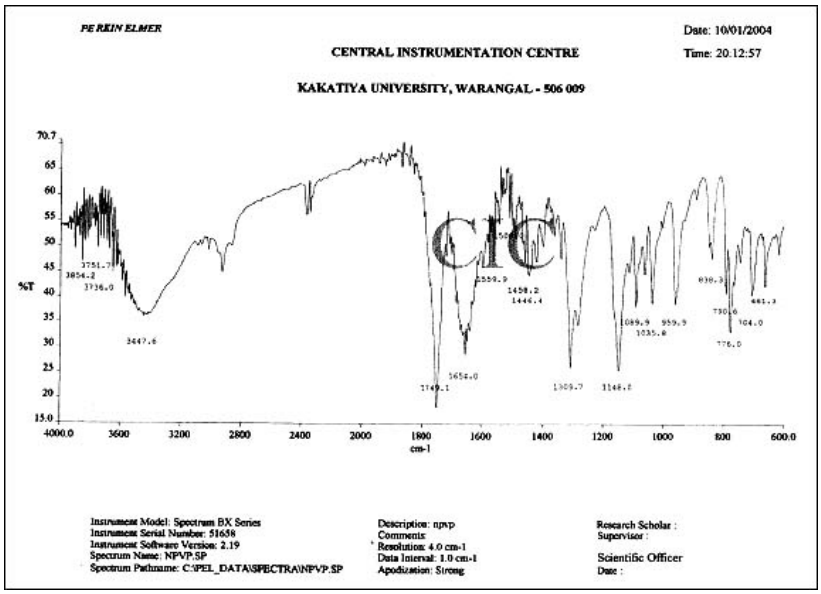

Fig. 4: FTIR spectra of rofecoxib-PVP solid dispersion.

solvent system consisting of accetonitrile and water (7:3) was used. Each SD was subjected to TLC using pure RXB drug as reference. Sample RXB was detected by exposing the TLC plate to iodine vapors (Kai *et al.*, 1999).

Phase III: Dissolution rate studies

All the formulation prepared subjected for *in vitro* dissolution studies in the media of 0.1 N HCL with 0.25% SLS (pH 1.1) for a period of 90 min using USP XXIII electrolab 8 basket tab dissolution test apparatus using paddle stirrer, 900 ml of dissolution media taken, prepared SD equivalent 25 mg was weighed and tied in the muslin cloth and thereby to paddle stirrer maintained at 37±0.5^{o}C at speed of 50 rpm; 5 milliliter of samples were withdrawn at regular time intervals of 10, 20, 30, 40, 50, 60, 70, 80 and 90 min. The volume of dissolution fluid was adjusted to 900ml by replacing each 5ml aliquot withdrawn with 5 ml dissolution media. The concentration of RXB in each sample was determined by UV spectrophotometer at 240 nm and data was analyzed by standard curve equation (Torrado *et al.*, 1996; Ho H *et al*., 1996).

Phase 1V- Stability study

The stability of SDRXB was monitored up to 45 days at ambient temperature and relative humidity (30^{o}C/60% RH). Periodically samples were withdrawn and characterized by dissolution rate measurements (Sanghavi NM *et al*., 1981; Dhanaraju *et al.*, 2001).

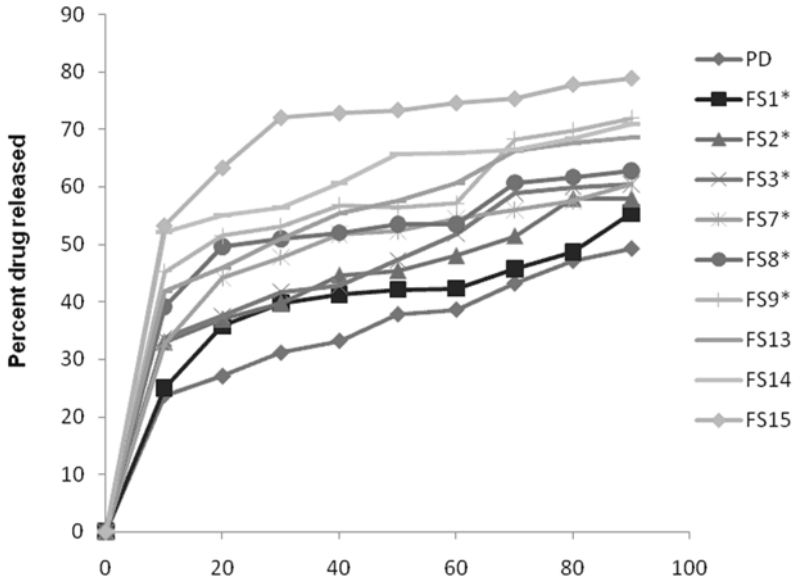

Fig. 5: Dissolution of Rofecoxib in pure form and from various Rofecoxib-PEG 4000, PEG 6000, and PVP solid dispersions prepared by solvent method (Dissolution fluid: 0.1N HCl with 0.25% SLS).

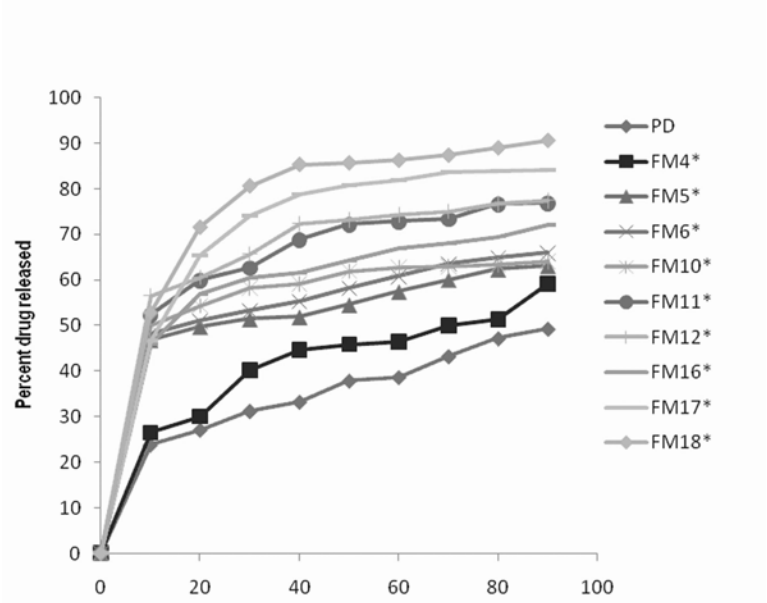

Fig. 6: Dissolution of Rofecoxib in pure form and from various Rofecoxib-PEG 4000, PEG 6000, and PVP solid dispersions prepared by Melting method (Dissolution fluid: 0.1N HCl with 0.25% SLS).

RESULTS AND DISCUSSIONS

All Solid dispersions (18 formulations) were found to be fine and free flowing the dispersions prepared by melting method were found to be relatively more hard when compared to those prepared by common solvent method, low standard deviation values in percent drug content ensured uniformity of drug content in each batch, all the dispersions contained 100±5% of the drug. IR spectra (figs. 1-4) of pure RXB and its SDs were found to be identical, thus indicates no interaction between RXB and carriers in the prepared solid dispersions. In TLC studies RXB dispersed in various carriers showed the same R_f value as pure compound and no additional spots were detected. TLC and IR spectra thus indicated no interaction between RXB and carriers in the solid dispersion prepared. The saturation solubility of RXB in distilled water was found to be 9µg/ml. The saturation solubility in

Table 1: Dissolution of Rofecoxib in pure form and from various Rofecoxib-PEG 4000, PEG-6000, PVP solid dispersions prepared by solvent evaporation method (Dissolution fluid: 0.1N HCl with 0.25% SLS)

Method	Time	Pure drug	PEG 4000			PEG 6000			PVP		
			95:05	85:15	75:25	95:05	85:15	75:25	95:05	85:15	75:25
			FS1*	FS2*	FS3*	FS7*	FS8*	FS9*	FS13	FS14	FS15
Solvent Method	10	23.74	24.99	33.05	33.65	32.88	39.22	45.11	41.94	52.22	53.25
	20	27.07	35.80	37.02	37.51	44.17	49.65	51.40	45.94	55.14	63.31
	30	31.18	39.65	39.74	41.71	47.77	51.02	53.11	50.88	56.42	72.06
	40	33.22	41.28	44.71	42.82	51.79	52.05	56.77	55.48	60.77	72.83
	50	37.85	42.14	45.48	47.19	52.39	53.54	56.42	57.62	65.85	73.37
	60	38.65	42.31	48.08	51.79	54.47	53.51	57.02	60.71	66.02	74.61
	70	43.21	45.65	51.51	58.82	56.08	60.80	68.14	66.20	66.54	75.34
	80	47.15	48.62	57.99	59.94	57.54	61.71	69.62	67.62	68.51	77.82
	90	49.25	55.42	58.02	60.45	60.54	62.85	71.82	68.61	70.99	78.91

Table 2: Dissolution of Rofecoxib in pure form and from various Rofecoxib-PEG-4000, PEG-6000, PVP solid dispersions prepared by melting method (Dissolution fluid: 0.1N HCl with 0.25% SLS)

Method	Time	Pure drug	PEG 4000			PEG 6000			PVP		
			95:05	85:15	75:25	95:05	85:15	75:25	95:05	85:15	75:25
			FM4*	FM5*	FM6*	FM10*	FM11*	FM12*	FM16*	FM17*	FM18*
Melting Method	10	23.74	26.51	46.80	48.19	50.08	52.31	56.42	46.00	46.65	52.77
	20	27.07	30.02	49.71	50.99	54.37	59.94	60.54	56.91	65.34	71.54
	30	31.18	40.19	51.42	53.17	58.31	62.68	65.68	60.34	74.17	80.60
	40	33.22	44.57	51.85	55.28	59.17	68.85	72.28	61.54	78.94	85.31
	50	37.85	45.85	54.51	58.25	61.91	72.19	73.14	64.25	80.91	85.65
	60	38.65	46.45	57.42	60.77	62.77	72.80	74.17	66.85	82.00	86.22
	70	43.21	49.97	60.03	63.54	63.00	73.39	75.02	68.05	83.65	87.34
	80	47.15	51.34	62.34	64.82	63.33	76.65	76.74	69.44	84.02	88.94
	90	49.25	59.17	63.08	65.97	64.10	76.91	77.39	72.02	84.20	90.57

optimized SD was determined 13mg/ml. There was 1300 fold enhancement in solubility of RXB in SD as compared to aqueous solubility of RXB.

In vitro drug release data revealed that all SD showed significant dissolution of RXB as compared to the pure drug ($p<0.05$). In each case the dissolution found to be first order kinetics, increase in the carrier proportion led to an increase in the dissolution rate. The dissolution rate of solid dispersion prepared by melting (fusion) method was significant than the dissolution rate of solid dispersion prepared by solvent method as shown in table 1and 2 ($p<0.05$).

The solid dispersions using PEG 4000 (75:25), PEG 6000 (75:25) and PVP (75:25) were found to be superior in improving the dissolution among all other ratios studied and found to be 65.97%, 77.39% and 90.57% respectively. PVP gave the maximum enhancement dissolution of RXB as compare to the carriers, as shown in figs. 5 and 6. The order of increase in dissolution by various carriers was PVP > PEG 6000 > PEG 4000. Optimized solid dispersion formulation FM 18 was subjected to stability studies and there was no significance change in the drug content 45 days at 27±1°C. FM 18 was found to be physico-chemically stable and shown best release.

CONCLUSION

Rofecoxib is practically insoluble in water and aqueous fluids. As such the oral absorption of RXB is dissolution rate limited. Among the various approaches to improve the dissolution of poorly soluble drugs, the preparation of solid dispersions has often proven to be very successful; these hydrophilic carriers were used in the preparation of solid dispersions and evaluated for their efficiency in increasing the dissolution rate of RXB. Solid dispersions of RXB in PEG-4000, PEG-6000 and PVP were prepared by melting method and common solvent method. The solid dispersions were prepared at two different ratios of drug and carriers namely 95:5%, 85:15% and 75:25%. The infra-red spectra and TLC of the above solid dispersions shows that the drug is compatible with the

carriers. The dissolution rate of RXB in solid dispersions prepared by the melt method shows the faster dissolution than the dispersions prepared by the solvent method. Out of the 18 prepared SD systems, the formulations FM18 prepared from PVP (75:25%) respectively by melting method were found to give optimum dissolution characteristics.

ACKNOWLEDGEMENT

Authors are thankful to Prof. KK Sirse, Principal, KRES College of Pharmacy, Bidar, for the encouragement and facilities provided for the research work. Authors also thanks to Prof. Navneet Kalyane for their constant support and help during the research work.

REFERENCES

Ahmed SM, Abdel Rahman AA, Saleh SI and Ahmed MO (1993). Comparative Dissolution Characteristics of Bropirimine-beta-cyclodextrin inclusion complex and its solid dispersions with PEG-6000. *Int. J. Pharm.,* **96**: 5-11.

Chowdary KP, Murthy KV and Prasad CD (1995). Solid Dispersions of Nimodipine: Physicochemical and Dissolution Rate Studies. *Indian Drugs,* **32**: 537-542.

Dhanaraju MD, Enose, Arno A, Sundarseelan, Muthu P Prasanna and Kamala Krishna R (2001). A Study of Solid Dispersions of Griseofulvin with Polyethylene Glycol 6000: Polysorbate 80 Mixture. *Indian Drugs*, **38** (12): 633-637.

Ho HO, Su HL, Tsai T and Sheu MT (1996). The Preparation and Characterization of Solid Dispersions on Pelletes using of Fluidized-bed system *Int. J. Pharm.,* **139** (1-2): 223-229.

Kai T, Akiyama Y, Nomura S and Sato M (1999). Oral Absorption Improvement of Poorly Soluble Drug Using Solid Dispersions Technique. *Chemi. Pharm Bull.*, **44** (3): 568-571.

Kearney AS, Gabriel DL, Mehta SC and Radebaugh GW (1994). Effect of Polyvinylpyrrolidone on the Crystallinity and Dissolution Rate of Solid Dispersions of the Antiinflammatory CI-987. *Int. J. Pharm.,* **104** (2): 169-174.

Kerc J, Mohar M, Srcic S, Kofler B and Smid Korbar J (1993). Dissolution Study of Felodipine Solid Dispersions. *Acta Pharm*., **43** (2): 113-120.

Khidr SH (1994). Effect of Block Copolymers on the Dissolution of some Water-insoluble drugs. Part-1, Nifedipine-pluronic F-127 solid dispersions system. *Bull. Pharm. Sci.,* **17**(1):81-86.

Lheritier J, Chauvet A, Abramovici B and Masse J (1995). Improvement of the Dissolution Kinetics of SR 33557 by means of solid dispersions containing PEG-600. *Int. J. Pharm.,* **123** (2): 273-279

Lu JW, Wang MZ, Ding P and Pan ZS (1995). Preparation and Dissolution of Nimodipine PEG Solid dispersions. *Chinese Pharm. J.,* **30**: 23-25.

Nakagami H (1991). Solid Dispersions of Indomethacin and Griseofulvin in Non-porous fumed silicon dioxide, prepared by melting. *Chem. Pharm. Bull*., **39**(9): 2417-2421.

Palmieri GE, Antonini I and Martelli S (1996). Characterization and Dissolution Studies of PEG-4000/ fenofibrate solid disperseions. *STP Pharma Sci.,* **6**(3): 188-184.

Patil CC, Dr.Rao KP, Raghavendra Kulkarni, Habbu PV Dr.Marihal SC, Kulkarni RG, Kotnal RB, Hunasagi BS(, 2001). Improvement in Dissolution Efficiency of Poorly Soluble Naproxen. *East. Pharm.* **16**: 107-110.

Pawar SP, Gudsoorkar VR and Shete JS (1995). Solid Dispersions of Trimethoprim. *Eastern Pharm.,* **38**: 147-149.

Popli H, Murthy RS and Miglani BD (1994). Solid Dispersions as a Drug Delivery System for Sulfamethoxazole and Nitrofurantoin. *Ind. J. Hosp. Pharm*., **31**: 97-100.

Rabasco AM, Ginesh JM, Fernandez. Arevalo M and Holgado MA (1991). Dissolution Rate of Diazepam from Polyethylene glycol 6000 solid dispersions. *Int. J. Pharm.,* **67**(2): 201-206.

Sanghavi NM, Kotwaney HN and Shah VJ (1981). Solid State Dispersion System of Methaqualone and its Effect on the Dissolution Rate. *Ind Drugs,* **19**(3): 1-3.

Sheen PC, Khetarpal VK, Cariola CM and Rowlings CE (1995). Formulation Studies of a poorly water-soluble drug in solid dispersions to improve bioavailability, *Int. J. Pharm.,* **118**: 221-227.

Suzuki H, Miyamoto N, Masada T, Hayakawa E and Ito K (1996), Solid Dispersions of Benidipine Hydrochloride Part 1. Preparations using different solvent systems and dissolution properties. *Chemi Pharm. Bull.,* **44**: 364-371.

Tanabe K, Itoh S, Iwasaki T, Nakano Y and Yamazaki M (1994). Rectal Absorption Enhancement of Oxaprozin using Solid Dispersions with Polyvinylpyrrolidone. *Jpn. J. Hosp. Pharm.,* **20**(6): 509-514.

Thomas J. Schnitzer, Ken Truit, Roy Fleischmann, Paul Dalgin, Joel Block, Qi Zeng, James Bolognese, Beth Seidenberg, and Elliot W. Ehrich (1999). The Safety Profile, Tolerability, and Effective Dose Range of Rofecoxib in the Treatment of Rheumatoid Arthritis. *Clin. Theraps* **2**(10): 1688-1702.

Torrado S, Torrado JJ and Cadorniga R (1996). Preparation Dissolution and Characterization of Albendazole Solid Dispersions. *Int. J. Pharm.,* **140**(2): 247-250.

Veiga MD, Diaz P, Gines JM and Rabasco AM (1994). Preparation and Evaluation of Mequitazine/PEG-6000 binary systems. *Pharmazie.,* **49**: 906-909.