International Journal of Pharmacy and Pharmaceutical Sciences
Vol 2, Issue 1, 2010

MELOXICAM-PVP-SLS TERNARY DISPERSION SYSTEMS:

IN-VITRO AND IN-VIVO EVALUATION

AEJAZ A [*1], JAFAR M[1], DEHGHAN. MHG[2], ADIL SHAREEF S[1]

[1]Department of Pharmaceutics,Luqman college of pharmacy, Gulbarga -585102, Karnataka, India, [2]Y.B. Chawan college of pharmacy, Rauza Bagh, Aurangabad, Maharashtra, India.

ABSTRACT

Meloxicam, a non-steroidal anti-inflammatory agent is widely used as a first line drug in symptomatic relief of rheumatoid arthritis and osteoarthritis. One of the major problems with this drug is its low solubility in biological fluids, which results into poor bioavailability after oral administration. Therefore ternary dispersions of meloxicam were prepared using hydrophilic carrier polyvinyl pyrrolidone (PVP) and solubilizer sodium lauryl sulphate (SLS) to increase its aqueous solubility ternary dispersions of meloxicam in PVP were prepared using 3^2 factorial design with PVP and SLS as independent variables while maintaining the amount of meloxicam (150mg) and the ratio of lactose and micro crystalline cellulose (4:1) constant. The methods used for the preparation of these dispersions were physical mixing, co-grinding and solvent evaporation technique. The prepared dispersions were evaluated in terms of drug content, wettability, In-vitro drug release study and screened dispersions were evaluated for In-vivo anti-inflammatory activity. The drug content of the prepared dispersions was found to be in the range of 98% - 100% indicating the application of the present methods for the preparation of tee nary dispersions with high content uniformity. Absence of significant drug-carrier interaction was confirmed by IR data. In-vitro release profiles of all dispersions were comparatively evaluated and also studied against pure meloxicam. Faster dissolution was exhibited by ternary dispersion (S_3) containing meloxicam (150 mg), PVP (250mg), SLS (75mg) and lactose : MCC 3gm (4:1) prepared by solvent evaporation method. The best – fit model indicating the mechanism of drug release from the formulation showing the highest release was found to be first order release (r=0.9916, b=1.9977, a=0.0160). The efficacy was evaluated by anti-inflammatory activity on albino rats using carrageenan induced rat paw edema model. Formulation S_3 showed 87% edema inhibition at 1 hr. Formulations studied remained stable during stability studies. The increase in dissolution rate of meloxicam by ternary dispersion technique may be due to increase wettability and hydrophilic nature of carrier.

Keywords: Meloxicam; ternary dispersion; in-vitro release; in-vivo study; surfactant

INTRODUCTION

Surfactants lower the interfacial tension between a drug and the dissolution medium, and thereby promote wetting of the drug. The addition of surfactants in solid dispersions leads to the formation of a ternary system, which enhances the solubility and dissolution of drugs, such as piroxicam[1] and itraconazole[2]. Ternary dispersion systems have higher dissolution rates than binary dispersion systems. The effect of surfactant type on the properties of a sparingly soluble drug in solid dispersion was determined for anionic, cationic and non-ionic surfactants[3] Dehghan MH and Jafar M[4] were able to improve the dissolution of meloxicam by incorporating small amounts of sodium lauryl sulphate (SLS) to its solid dispersions prepared with PEG 6000. polyvinyl pyrrolidone has been widely used as a carrier for solid dispersions of drugs such as furosemide[5], oxaprozin[6], nimodipine[7] and albendazole[8]. Meloxicam is a nonsteroidal anti inflammatory drug belonging to the class of oxicams[9]. It has very poor aqueous solubility and therefore an attempt has been made to prepare a ternary system of the drug with polyvinyl pymolidone and sodium louryl sulphate with an aim of

improving its extent and rate of dissolution.

MATERIALS AND METHODS

Materials

Meloxicam (Unichem laboratories Ltd, Mumbai), Polyvinyl pyrrolidone, sodium lauryl sulphate.(SD Fine chemicals Ltd Mumbai), Other reagents and chemicals used were of analytical grade.

Methods

Preparation of meloxicam ternary dispersions with PVP and SLS

Ternary dispersions of meloxicam in PVP were prepared using a 3^2 factorial design with PVP and SLS as independent variables, while maintaining the amount of meloxicam (150mg) and the ratio of lactose and microcrystalline cellulose 3gm (4:1) constant (Table 1) The methods used for preparation of these dispersions were physical mixing, co-grinding and solvent evaporation methods.

1. Physical mixture

The physical mixtures were prepared by weighing the calculated amounts of meloxicam and carriers and then mixing them in a glass mortar by triturating. The resultant physical mixtures were passed through 44-mesh sieve and stored in desiccator until used for further studies.

2. Co-grinding method

The calculated amounts of meloxicam and carriers were weighed and mixed together with one ml of water. The damp mass obtained was passed through a 44-mesh sieve; the resultant granules were dispesed in petridishes and dried at 60^0c under Vacuum, until a constant weight was obtained. The granules obtained were stored in a desiccator until used for further studies. These granules wre hand filled into zero-size hard gelatin capsules just before the dissolution studies[10].

3. Solvent evaporation method

The required amounts of meloxicam and carriers were dissolved in few ml of N, N^1-dimethyl formamide and allowed to stand overnight. The solvent was removed at 60^0 c under vaccum until the solid dispersion was dry. The dried mass was pulverized, passed through 44-mesh sieve and stored in a desiccator until used for further studies. This mass was hand filled into zero-size hard gelatin capsules just before the dissolution studies[10].

Drug content estimation

An accurately weighed amount of each preparation was dissolved in small volume of methanol and further diluted in phosphate buffer with PH of 7.4. The content of meloxicam was determined spectrophotometrically at 362nm using Shimadzu 1700 Uv-visible spectro photometer.

Wettability Study

Drug powder, powder mixture or granules (300mg) was placed in a sintered glass funnel (3mm internal diameter). The funnel was plunged into beaker containing water such that the surface of water in the beaker remains at the same level as the powder or granules in the funnel. Methylene blue powder (10mg) was layered uniformly on the surface of the powder or granules

in the funnel. The time required for wetting methylene blue powder was measured. The average of three observations was used for drawing the conclusions[10].

In-vitro dissolution

The dissolution study was carried out using USP XXVII Apparatus I (Electrolab TDT-06T). The dissolution medium was 900ml of phosphate buffer with a PH of 7.4 kept at 37 ± 1^0c. The drug, ternery dispersions were filled in empty hard gelatin capsules and then kept in the baskets of dissolution apparatus rotating at 50 rpm. Samples of 5ml were withdrawn at specified time intervals and analyzed Spectrophotometrically at 362mm using Shimadzu 1700 UV-visible spectrophotometer, the samples withdrawn were replaced by fresh buffer solution. Each preparation was tested in triplicate and the mean values were calculated.

In-Vivo study

Wistar albino rats (150-200g) of either sex roughly the same age (8-10 weeks) were housed under constant temperature (22±2^0c), humidity (55%) and light / dark conditions (12/12 h), They are provided with standard food and free access to drinking water *ad libitum.*

Anti-inflammatory activity

The animals were divided randomly into 5 groups of 6 animals each. pure meloxicam and 3 different ternary dispersions were administered orally at a dose of 4mg / kg of meloxicam to the first four groups respectively. The fifth group received 1% w/v carboxy methyl cellulose sodium suspension serving as vehicle control, after 1 hr the edema was induced by subplantor injection of 0.1ml of 1% w/v freshly prepared suspension of carrageenan into the right hind paw of each rat after 1 hr of the drug treatment and the paw volume was measured at 0,1,2,3,4, and 5 hr after the injection of carrageenan using a plethysmometer[11].

Infrared spectroscopy

The infrared (IR) spectra of meloxicam and some selected preparations were obtained using FTIR (perkin Elmer 1600 series). The IR spectroscopy was carried out by Kbr pellet method.

Stability Study

Stability study for selected preparations was carried out by storing 1 gm of ternary dispersions in an amber colored screw capped bottle at different temperatures and relative humidity for a period of 3 months. The dispersions were visually examined for any physical change and drug content was estimated at the end of 3 months[12].

RESULTS AND DISCUSSION

Content uniformity of Meloxicam

The content of meloxicam in each preparation was assyed by UV-spectroscopy. The meloxicam content of the prepared dispersions was found to be in the range of 98% - 100% (Table:1) indicating the application of the preparation methods for the preparation of ternary dispersions with high content uniformity.

Table 1: Factors and levels in the design

Independent Variables	Levels Low (-1)	Medium (0)	High (+1)
PVP (X_1) mg	250	300	350
SLS (X_2) mg	25	50	75

Formulation Code	X_1	X_2	% Drug content	Wet ability (sec)
P_1	-1	-1	99	22
P_2	-1	0	98	21
P_3	-1	+1	98	21
P_4	0	-1	99	20
P_5	0	0	100	19
P_6	0	+1	98	23
P_7	+1	-1	98	21
P_8	+1	0	99	20
P_9	+1	+1	98	20
C_1	-1	-1	99	23
C_2	-1	0	98	22
C_3	-1	+1	99	22
C_4	0	-1	98	23
C_5	0	0	98	23
C_6	0	+1	99	22
C_7	+1	-1	100	24
C_8	+1	0	98	24
C_9	+1	+1	98	23
S_1	-1	-1	99	19
S_2	-1	0	98	18
S_3	-1	-1	98	17
S_4	0	0	99	20
S_5	0	+1	98	19
S_6	0	-1	98	18
S_7	+1	0	99	22
S_8	+1	+1	100	20
S_9	+1	-1	98	19

*Formulation codes P_1- P_9, C_1- C_9 and S_1- S_9 correspond, to physical mixtures, co-grinding and solvent evaporation methods respectively. Amount of meloxicam (150 mg) and mixture of lactose and microcrystalline cellulose 3g (4:1) was maintained constant in all the preparations.

The minimum mean wetting time (17 sec) was observed for the dispersion containing high levels of sodium lauryl sulphate and low levels of polyvinyl pyrrlidone prepared by solvent evaporation method (formulation S_3)

The maximum mean wetting time (24 Sec's) was observed for the dispersions (Formulation C_7 and C_8) prepared by co grinding method.

In-Vitro dissolution

The In-Vitro dissolution characteristics of different types of preparations were compared with the pure drug. The ternary dispersions of meloxicam prepared by different methods showed improved dissolution when compared with pure drug (Figure:1). Ternary dispersions of meloxicam containing PVP and SLS prepared by physical mixing and solvent evaporation

methods showed a significant increase in dissolution rate with an increase in the amount of SLS. Formulation S_3 showed maximum release

Table 2 : Evaluation of storage stability of the formulation.

Formulation code	Physical appearance			% Drug content			% Dissolution (60 min)		
	Initial	25⁰c 60% RH 3M	40⁰c 75% RH 3M	Initial	25⁰c 60% RH 3M	40⁰c 75% RH 3M	Initial	25⁰c 60% RH 3M	40⁰c 75% RH 3M
P_5	Pale Yellow Powder	Pale Yellow Powder	Pale Yellow Powder	100	99	99	76.01	78.23	76.12
C_2	Pale Yellow Granules	Pale Yellow Granules	Pale Yellow Granules	98	98	96	59.99	57.03	56.51
S_3	Pale Yellow Powder	Pale Yellow Powder	Pale Yellow Powder	98	98	97	88.42	88.10	86.32

i,e. 88.42% in 60 mins (Figure 1C) and also formulation P_5 and C_2 showed maximum release in 1 hr (Figure 1 A &1 B) among the other preparations of ternary dispersions prepared by physical mixing & co grinding method respectively. In general the dispersion prepared by solvent evaporation method showed faster release of meloxicam followed by dispersion obtained by physical mixture technique. Co-grinding method comparatively did not give good results. This may be due to the fact that ternary dispersions prepared by solvent evaporation and physical mixing result in a more uniform dispersion of the drug in the hydrophilic carrier (PVP) matrix as compared to those prepared by the co-grinding method. Addition of sodium lauryl sulphate improved the aqueous solubility and dissolution of meloxicam.

The release mechanism of meloxicam from various preparations of ternary dispersions was studied. The data was treated to study the best linear fit for the following equations[13].

Zero order

$$\% R = Kt$$

First order

$$\log \% \text{ unreleased} = Kt/2.303$$

Matrix (Higuchi matrix)

$$\% R = Kt^{0.5}$$

Peppas – Kors meyer equation

$$\frac{\text{Amount of drug released at time 't'}}{\text{Amount of drug release at '}\infty\text{'}} = Kt^n$$

Hixon – crowell equation ----- $(\%\ \text{unreleased})^{1/3} = Kt$ where 'n' is the diffusion coefficient which is indicative of transport mechanism.

The mechanism of release for the formulations S_3, P_5, and C_2, was first order (r = 0.9916, b = 1.99770, a=0.01600), peppas (r = 0.98600, b=0.99650, a=1.66590), and First order (r = 0.97720, b=1.99130, a = 0.00710) respectively. The r,a and b are correclation coefficient, slope and constant respectively for the best fit kinetic model.

In-Vivo Study

Formulation S_3, P_5, and C_2, prepared by solvent evaporation, physical mixing

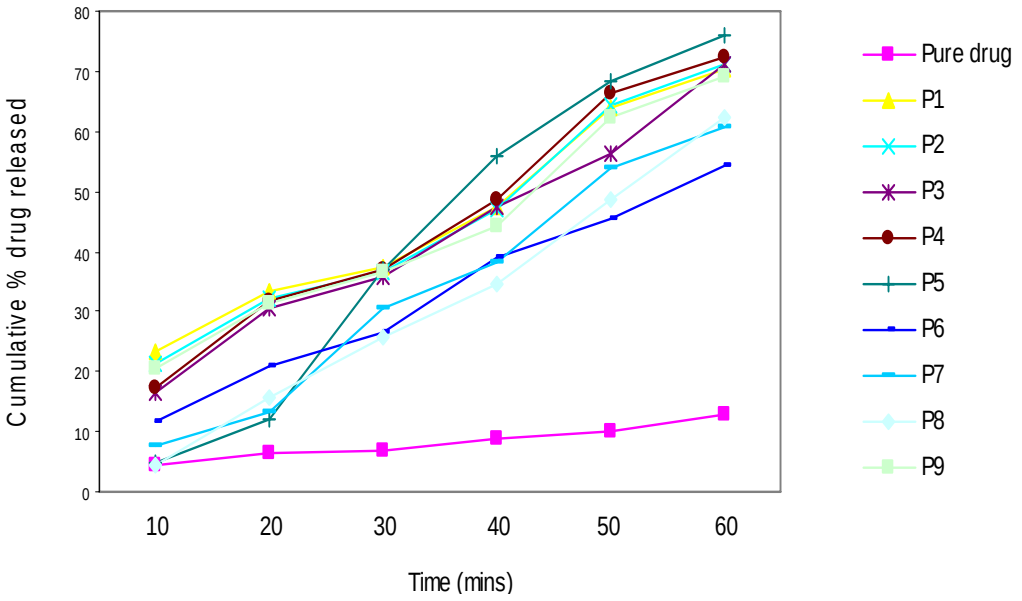

Fig. 1A : Cumulative % drug release Vs time profile of meloxicam-PVP-SLS ternary dispersion systems prepared by physical mixture method

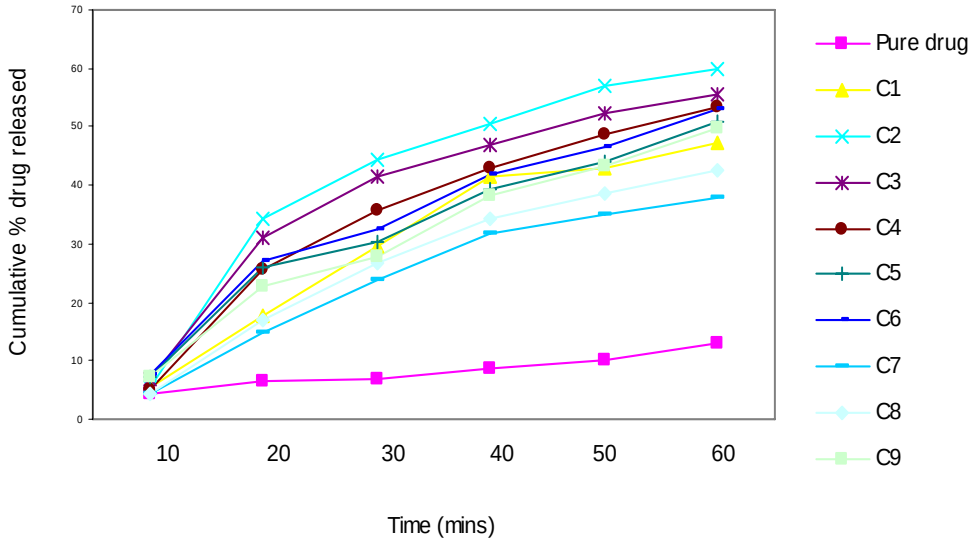

Fig. 1B : Cumulative % drug release Vs time profile of meloxicam-PVP-SLS ternary dispersion systems prepared by Co-grinding method.

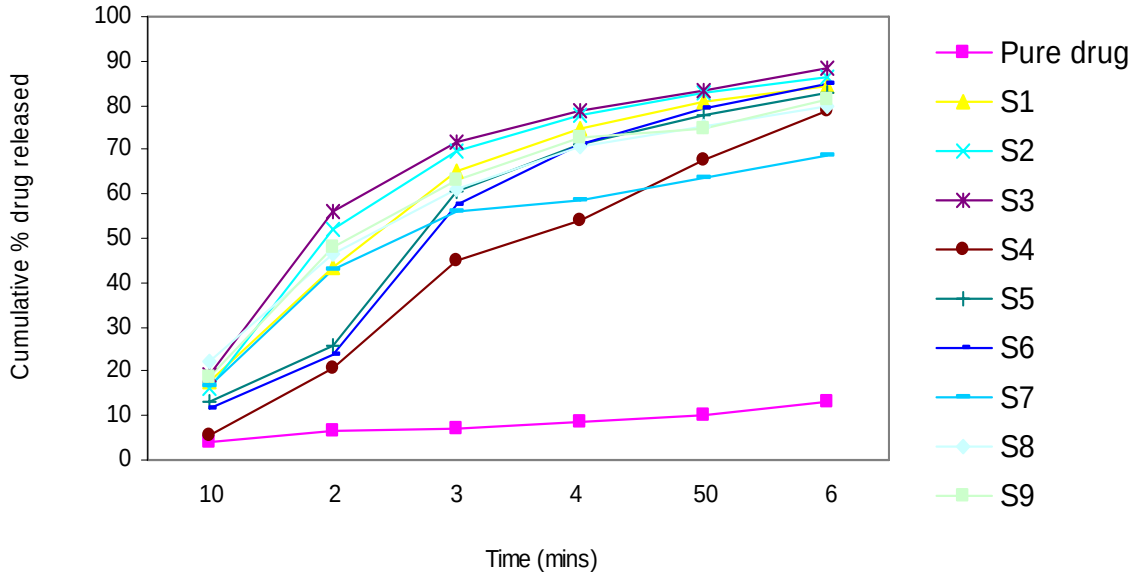

Fig. 1C : Cumulative % drug release Vs time profile of meloxicam-PVP-SLS ternary dispersion systems prepared by Solvent evaporation method.

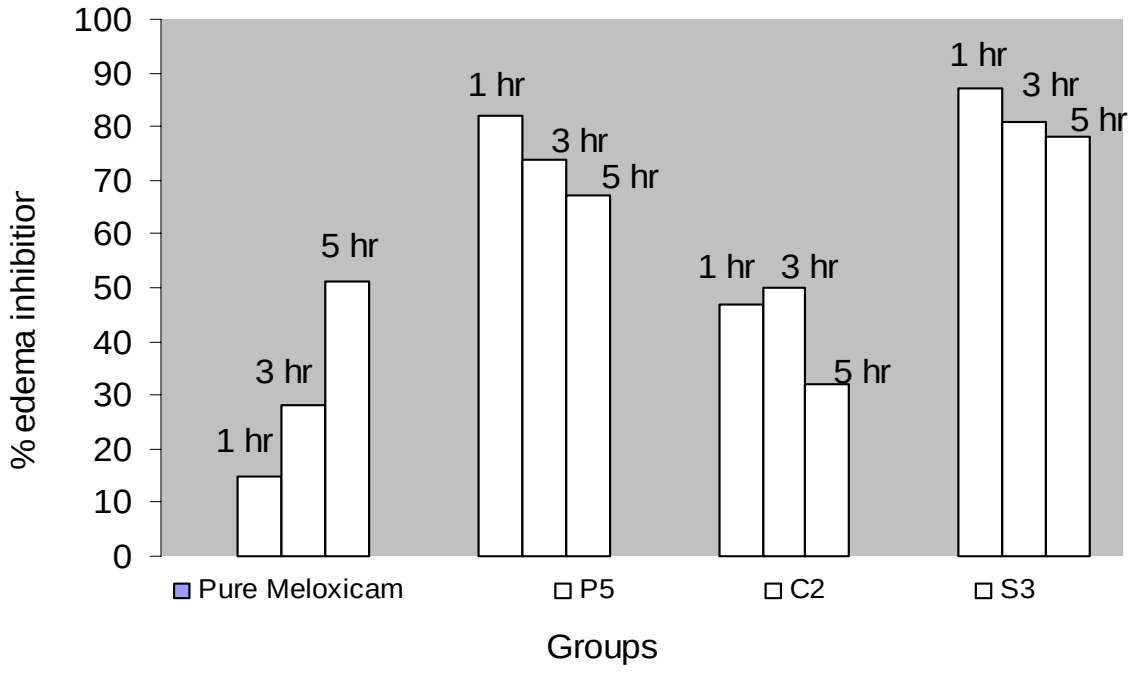

Fig. 2: Comparison of % edema inhibition of pure meloxicam and P_5, C_2 and S_3 formulations

and co-grinding method respectively were selected based on their highest drug release profile among the other formulations of the same methods, and were subjected to In-Vivo anti–inflammatory activity. Figure 2 illustrates the anti inflammatory effect of pure meloxicam, Formulation P_5, C_2, and S_3. All three formulations showed significant increase in anti-inflammatory effect, in the carrageenan induced paw edema compared to pure meloxicam at 1,3 and 5 hr after carrageenan injection. The formulation S_3, showed maximum anti-inflammatory effect i.e, 87% at 1 hr, which is consistent with reported results[14].

Infrared Spectroscopy

FT-IR Spectra of meloxicam showed a distinct peak at 3291 cm^{-1}, 1620 cm^{-1} (NH) and 1580 cm^{-1} (CO). The corresponding IR spectra of formulation S_3 showed broader peaks at 3342 cm^{-1}, 1661 cm^{-1} (NH) and 1584 cm^{-1} (CO). Thus it indicates that there is a physical interaction between meloxicam and the carrier molecules; the shift in the bands may be due to over lapping of the hydroxyl bands. These observations clearly supports the formation of Meloxicam-PVP-SLS ternary dispersion systems, which will enhance the aqueous solubility and dissolution of meloxicam.

Stability study

Representative formulations were tested for stability with respect to physical appearance, assay and dissolution, at accelerated (40^0 c / 75% RH) and controlled room temperature (25^0 c / 60% RH) conditions for 3 months in amber coloured glass containers with 1 gm silica gel desiccant. The results are appended in Table 2. The results indicated the formulations were stable under the tested conditions of storage.

CONCLUSION

Ternary solid dispersions of meloxicam prepared by solvent evaporation method showed highest in-vitro dissolution enhancement and also in-vivo anti-inflammatory activity (Formulation S_3) as compared to pure meloxicam and dispersions prepared by physical mixture and co-grinding method. The In-vivo results of formulation S_3 revealed that an increase of the anti-inflammatory activity was accompanied by an increase in the amount of melexicam dissolved. Finally it can be concluded that improved drug dissolution and anti-inflammatory activity could be achieved by formulating meloxicam as ternary dispersion systems with PVP and SLS.

ACKNOWLEDGEMENT

Authors thanks to Unichem Laboratories Pvt. Ltd, Mumbai for providing gift sample of Meloxicam, and to the Principal of Luqman College of Pharmacy,Gulbarga for providing laboratory facilities.

REFERENCES

1. Patel DM, Shah RR and Jogani PD. Tablet formulation of piroxicam containing PVP K-30 and sodium lauryl sulphate. Indian J. Pharm Sc. 2004; 66 : 49-55.

2. Chowdary KPR ,Srinivasarao SK. Effect of surfactants on the solubility and dissolution rate of Intraconazole. The Eastern pharmacist 2001 ; 44 : 121-123.

3. Muhammad J. Habib. Pharmaceutical solid dispersion Technology. Technomic publishing co., INC, Lancaster U.S.A: 74-75.

4. Dehghan MH ,Jafar M. Improving Dissolution of Meloxicam using solid dispersions. Iranian J. Phar. Research 2006; 4 : 231-238.

5. Ak buga J. Effect of Additives on dissolution characteristics of furosemide – polyvinyl pyrrolidone solid – dispersion systems. pharm Ind. 1991; 53 (9) : 857-860.

6. Tanabe K, Itoh S, Iwasakit, Nakano Y, Yamazaki M. Rectal absorption enhancement of Oxaprozin using solid dispersions with polyvinyl pyrrolidone. Jpn J Hosp pharm 1994; 20 (6) :509-514.

7. Chowdary KP, Murthy KV, Prasad CD. Solid dispersion of Nimodipine; physicochemical and Dissolution rate studies. Indian Drugs 1995 Nov ; 32 : 537 – 542.

8. Torrado S, Torrado JJ, cadorniga R. preparation, dissolution and characterization of Albendazole Solid Dispersions. Int J pharmaceutics 1996 ; 140 (2) : 247- 250.

9. Ellsworth AJ, Witt DM, Dugdale DC ,Oliver LM, Mosbay's 2004 Medical Drug Reference. Elsevier science, Missouri,2003 : 610-612.

10. Gohel MC and Patel LD. processing of Nimesulide PEG 400 – PG – PVP solid dispersions : preparation characterization and in vitro dissolution. Drug dev and Ind pharm 2003 ; 29 (3) : 299-310.

11. Winter CA, Risley EA, Nuss GW. Carrageenan induced edema in hind paw of the rat as an assay for anti-inflammatory drugs. Proc Soc Exp Biol. Med 1962 ; 111 : 544 – 7.

12. Ajit S. Narang ,Anand K. Srivastava. Evaluation of solid Disperions of clofazimine. Drug dev and Ind pharm 2002 ;28 (8) : 1001 – 101.

13. Costa P ,Sousa Lobo JM. Modeling and comparison of dissolution profiles.Eur J Pharm Sci 2001 ;13 : 123-133.

14. Barzegar Jalali M, Maleki N, Garjani A, Khandar AA Haji – Hosseinlo M, Jabbari R, Dastmalachi S. Enhancement of dissolutions rate and anti inflammatory effects of piroxicam using solvent deposition technique. Drug dev and Ind Pharm 2002 ;28 : 681-6.