International Journal of Applied Pharmaceutics
Vol 2 Issue 1, 2010

Research Article

ENHANCEMENT OF DISSOLUTION AND ANTI-INFLAMMATORY EFFECT OF MELOXICAM USING SOLID DISPERSIONS

MOHAMMED JAFAR[1*], DEHGHAN MHG[2] , ADIL SHAREEF[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. E mail: jafar_31957@yahoo.com

ABSTRACT

Meloxicam, a non-steroidal anti-inflammatory drug is widely used in the treatment of rheumatoid arthritis, ankylosing spondulytis 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 solid dispersions of meloxicam were prepared using hydrophilic carriers polyvinyl pyrrolidone (PVP) and poly ethylene glycol (PEG6000) to increase its aqueous solubility, solid dispersions of meloxicam were prepared using 3^2 factorial design with PVP and PEG6000 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 solid 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 Formulation containing meloxicam (150 mg), PVP (250mg), PEG6000 (125mg) and lactose: MCC 3gm (4:1) prepared by solvent evaporation method. The efficacy was evaluated by anti-inflammatory activity on albino rats using carrageenan induced rat paw edema model. Solid dispersions of meloxicam showed increase in anti-inflammatory activity as compared to pure meloxicam. Dispersions studied remained stable during stability studies. The increase in dissolution rate and anti-inflammatory effect of meloxicam by solid dispersion technique may be due to increase wettability and hydrophilic nature of carriers.

Keywords: Meloxicam, Solid dispersion, Dissolution, In-vivo study.

INTRODUCTION

In recent years, the number of poorly soluble drug candidates has increased tremendously. The formulation of poorly soluble drugs for oral delivery presents a challenge to the formulation scientists[1]. Oral bioavailability of a drug depends on its solubility and/or dissolution rate, and dissolution may be the rate determining step for the onset of therapeutic activity, several techniques have been developed over the years to enhance the dissolution of the drug, such as inclusion complexation, salt formation, and solvent deposition. Among other techniques solid dispersion (SD), which was introduced in the early 1970s, is an effective method for increasing the dissolution rate of poorly soluble drugs, hence, improving their bioavailability. Chiou and Riegelman defined the term SD as 'a dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (fusion), solvent, or melting-solvent method. When SD is exposed to aqueous media, the carrier dissolves and the drug releases as fine colloidal particles. The resulting enhanced surface area produces higher dissolution rate and bioavailability of poorly water soluble drugs. In addition, in SD, a portion of drug dissolves immediately to saturate the gastrointestinal tract fluid, and excess drug precipitates as fine colloidal particles or oily globules of submicron size[2]

The addition of more than one hydrophilic substance in solid dispersions, enhances the solubility and dissolution of drugs, such as piroxicam[3] and itraconazole[4].Multi component dispersion systems have higher dissolution rates than single or two component dispersion systems[5]. Polyethylene glycol and polyvinyl pyrrolidone have been widely used as carriers for solid dispersions of drugs such as griseofulvin[6] diazepam[7], bropirimine[8] and tolbutamide[9]. Furosemide[10], oxaprozin[11], nimodipine[12] and albendazole[13]. Meloxicam is a nonsteroidal anti inflammatory drug belonging to the class of oxicams and is widely used in the treatment of rheumatoid arthritis, ankylosing spondulytis and osteoarthritis. Prolonged use of the drug is associated with gastrointestinal side effects such as abdominal pain, diarrhea, flatulence, nausea and gastric and duodenal ulcers[14]. It has very poor aqueous solubility and therefore an attempt has been made to prepare a solid dispersion system with polyvinyl pyrrolidone and polyethylene glycol with an aim of improving its extent and rate of dissolution, there by enhancing its anti-inflammatory effect.

Materials and Methods

Materials

Meloxicam (Sun Pharmaceutical pvt Ltd, Mumbai), Polyvinyl pyrrolidone, polyethylene glycol 6000. (SD Fine chemicals Ltd Mumbai), Other reagents and chemicals used were of analytical grade.

Methods

Preparation of meloxicam solid dispersions with PVP and PEG6000

Solid dispersions of meloxicam were prepared using a 3^2 factorial design with PVP and PEG6000 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

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.

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 dispersed 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 were hand filled into zero-size hard gelatin capsules just before the dissolution studies[15].

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 vacuum 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[15].

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[5].

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, solid 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

Wister 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 8 groups of 6 animals each. Pure meloxicam and 6 different solid dispersions were administered orally at a dose of 4mg / kg of meloxicam to the first four groups respectively. The 8th 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[16].

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 solid dispersions was carried out by storing 1 gm of solid 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[17].

RESULTS AND DISCUSSION

Content uniformity of Meloxicam

The content of meloxicam in each preparation was assayed 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 solid dispersions with high content uniformity.

Wettability Study

The average wettability of pure meloxicam was found to be 36 seconds, after preparation of dispersions of meloxicam in general it was found that dispersions prepared by solvent evaporation method were more wettable than those prepared by physical mixing, where as co-grinding method yielded least wettable dispersions.

The minimum mean wetting time (16 sec) was observed for the dispersion containing high levels of polyethylene glycol and low levels of polyvinyl pyrrolidone prepared by solvent evaporation method (dispersion C3).

The maximum mean wetting time (26 Sec's) was observed for the dispersion (Formulation B_7) prepared by co grinding method.

The delay in wetting of pure meloxicam may be due to less surface area available for drug particles to wet with the surrounding liquid medium, but when solid dispersion of meloxicam is exposed to aqueous media, the carrier dissolves and the drug releases as fine colloidal particles. The resulting enhanced surface area produces high wetting power(less wetting time) thereby higher dissolution rate and bioavailability of meloxicam.

In-Vitro dissolution

The In-Vitro dissolution characteristics of different types of preparations were compared with the pure drug. The solid dispersions of meloxicam prepared by different methods showed improved dissolution when compared with pure meloxicam (Figure: 1). solid dispersions of meloxicam containing PVP and PEG6000 prepared by physical mixing and solvent evaporation methods showed a significant increase in dissolution rate with an increase in the amount of PEG6000. Formulation C_3 showed maximum release i.e. 83.62% in 60 mins (Figure 1C) and also formulation A_4, A_5, B_2, B_3, showed maximum release in 1 hr (Figure 1 A &1 B) among the other preparations of solid 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 solid dispersions prepared by solvent evaporation and physical mixing result in a more uniform dispersion of the drug in the hydrophilic carrier matrix as compared to those prepared by the co-grinding method.

Table 1: Factors and levels in the design

Independent Variables	Levels		
	Low (-1)	Medium (0)	High (+1)
PVP (X_1) mg	250	300	350
PEG6000 (X_2) mg	125	150	175

Amount of meloxicam (150 mg) and mixture of lactose and microcrystalline cellulose 3g (4:1) was maintained constant in all the preparations.

Formulation Code	X_1	X_2	% Drug content	Wetability (sec)
A_1	-1	-1	100	22
A_2	-1	0	98	20
A_3	-1	+1	98	21
A_4	0	-1	99	20
A_5	0	0	99	19
A_6	0	+1	98	21
A_7	+1	-1	98	21
A_8	+1	0	99	22
A_9	+1	+1	98	20
B_1	-1	-1	99	23
B_2	-1	0	98	22
B_3	-1	+1	99	22
B_4	0	-1	98	22
B_5	0	0	98	23
B_6	0	+1	99	22
B_7	+1	-1	98	26
B_8	+1	0	98	25
B_9	+1	+1	100	23
C_1	-1	-1	99	19
C_2	-1	0	98	18
C_3	-1	-1	98	16
C_4	0	0	99	20
C_5	0	+1	98	19
C_6	0	-1	98	18
C_7	+1	0	99	22
C_8	+1	+1	98	20
C_9	+1	-1	98	19

*Formulation codes A_1- A_9, B_1- B_9 and C_1- C_9 correspond to solid dispersions prepared by physical mixture, co-grinding and solvent evaporation methods respectively.

Table 2: Evaluation of storage stability of the formulations

Formulation code	Physical appearance			% Drug content			% Dissolution (60 min)		
	Initial	25°c 60% RH 3M	40°c 75% RH 3M	Initial	25°c 60% RH 3M	40°c 75% RH 3M	Initial	25°c 60% RH 3M	40°c 75% RH 3M
A_4	Pale Yellow Powder	Pale Yellow Powder	Pale Yellow Powder	99	98	99	65.32	65	65.46
A_5	Pale Yellow Powder	Pale Yellow Powder	Pale Yellow Powder	99	99	99	71.21	70.23	71.12
B_2	Pale Yellow Granules	Pale Yellow Granules	Pale Yellow Granules	98	98	96	54.18	51.03	52.51
B_3	Pale Yellow Granules	Pale Yellow Granules	Pale Yellow Granules	99	97	98	48.31	46.78	47.32
C_3	Pale Yellow Powder	Pale Yellow Powder	Pale Yellow Powder	98	98	97	83.62	80.11	83.12
C_2	Pale Yellow Powder	Pale Yellow Powder	Pale Yellow Powder	98	97	98	81.65	80.10	80.86

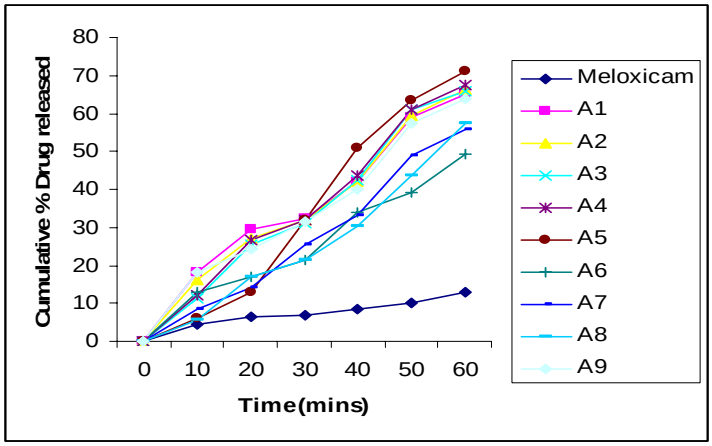


Fig. 1A: Cumulative % drug release Vs time profile of meloxicam and its solid dispersion systems (Formulation codes A_1- A_9) prepared by physical mixture method

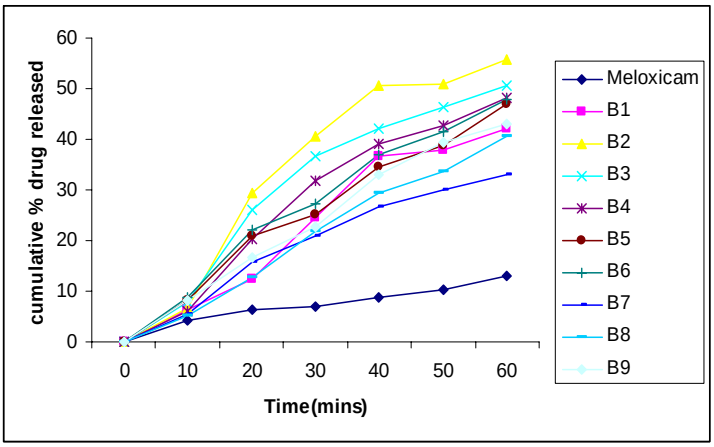
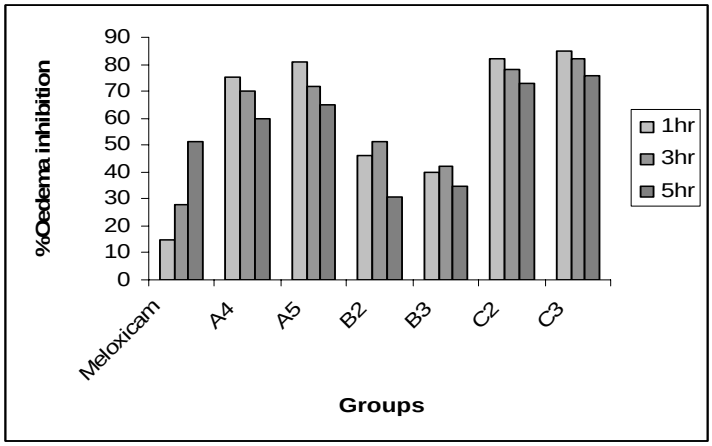


Fig. 1B: Cumulative % drug release Vs time profile of meloxicam and its solid dispersion Systems (Formulation codes B_1- B_9) prepared by Co-grinding method

Fig. 1C: Cumulative % drug release Vs time profile of meloxicam and its solid dispersion Systems (Formulation codes C_1- C_9) prepared by Solvent evaporation method



*Formulation codes A_4 & A_5, B_2 & B_3 and C_2 & C_3 in the above figure correspond to solid dispersions prepared by physical mixture, co-grinding and solvent evaporation methods respectively.

Fig. 2: Comparison of % edema inhibition of pure meloxicam and A_4, A_5, B_2, B_3, C_2 and C_3 formulations

The release mechanism of meloxicam from various preparations of solid dispersions was studied. The data was treated to study the best linear fit for the following equations[18].

1. Zero order ---------- % R=Kt
2. First order ---------- log % unreleased = Kt/2.303
3. Matrix (Higuchi matrix) ---------- % R=$Kt^{0.5}$
4. Peppas – Korsmeyer equation ----------

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

Hixson – Crowell equation ---------- (% unreleased)$^{1/3}$=Kt where 'n' is the diffusion coefficient which is indicative of transport mechanism. The mechanism of release for the formulations was of mixed type i.e. some dispersions showed first order release, some other showed matrix type of release, etc.

In-Vivo Study

Formulation A_4, A_5, B_2, B_3, C_2 and C_3 prepared by solvent evaporation, physical mixing 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 A_4, A_5, B_2, B_3, C_2 and C_3. All six 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 C_3 showed maximum anti-inflammatory effect i.e., 86% at 1 hr, which is consistent with reported results[19].

The In-vivo result of formulation C3 showed that an increase of the anti-inflammatory activity was accompanied by decrease in the wetting time and increase in the amount of melexicam dissolved.

Infrared spectroscopy

Fourier transform infrared spectroscopy was performed on meloxicam, the prominent peaks were obtained at 3291, 1620, 1552, 1340, and 1180/cm because of stretching vibration bands of NH, C=O, C-C, and two S=O, respectively. The group frequencies of drug confirmed to the respective structure. In case of Solid dispersion of meloxicam, polyethylene glycol and poly vinyl pyrrolidone (Figure3D) both drug and polymers peaks were present. The spectra revealed no difference in the positions of the absorption bands, especially with respect to OH, =O, NH, hence providing the evidence for the absence of hydrogen bonding interaction in solid state between polymers and meloxicam. These observations clearly support the formation of Meloxicam-PVP-PEG6000 multicomponent 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 colored 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.

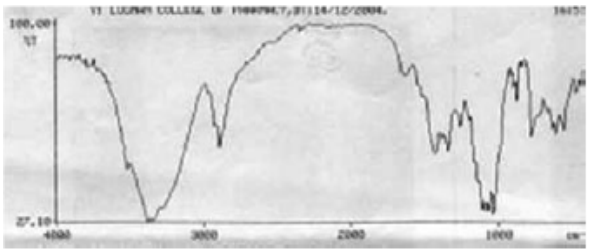
CONCLUSION

Solid dispersions of meloxicam prepared by solvent evaporation method showed highest in-vitro dissolution enhancement and also in-vivo anti-inflammatory activity as compared to pure meloxicam and dispersions prepared by physical mixture and co-grinding method. The In-vivo results of formulations C2 & C3 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 solid dispersion systems with PVP and PEG6000.

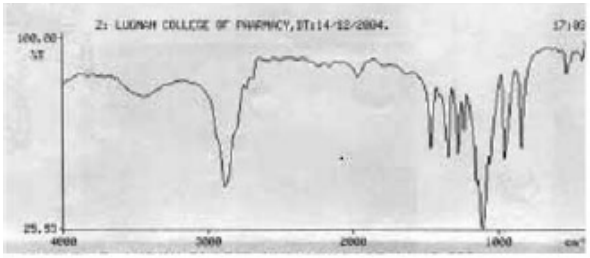
ACKNOWLEDGEMENT

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

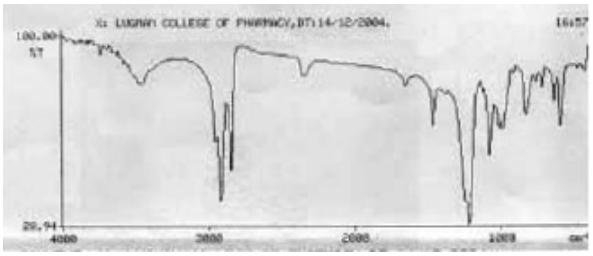
A



B



C



D

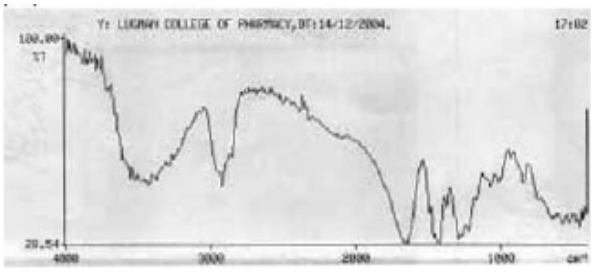


Fig. 3: IR Spectrum of A) Meloxicam B) Polyethylene glycol C) Polyvinyl pyrrolidone and D) Meloxicam- PVP- PEG6000 Solid dispersion. (Formulation C3) prepared by solvent evaporation method

REFERENCES

1. Emara LH, Badr RM and Abd EA. Improving the dissolution and bioavailability of nifedipine using solid dispersions and solubilizers. *Drug Dev. Ind. Pharm.* (2002) 28: 795-807
2. Chiou.W.L. and Riegelman.S. Pharmaceutical applications of solid dispersion systems.Jr.Pharm.Sc.1971, 60(9), 1283.
3. 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.
4. Chowdary KPR, Srinivasarao SK. Effect of surfactants on the solubility and dissolution rate of Intraconazole. The Eastern pharmacist 2001 ; 44 : 121-123.
5. Dehghan MH and Jafar M. Improving Dissolution of Meloxicam using solid dispersions. Iranian J. Phar. Research 2006; 4: 231-238.
6. Sjokviste. et al., The effects of some ionic and non-ionic surfactants on properties of sparingly soluble drug solid dispersions. Int.J.Pharm. 1992; 79; 123-134.
7. Rabasco.A.M, et al., Dissolution rate of diazepam from polyethylene glycol 6000 solid dispersions. . Int.J.Pharm. 1991; 67; 201-206.
8. Ahmed S.M., et al., Comparative dissolution characteristics of bropirimine betacyclodextrin inclusion complex and its solid dispersions with PEG6000. Int.J.Pharm. 1993; 96; 5-11.
9. Kedzierewicz.F. et al., Bioavalability study of tolbutamide beta cyclodextrin inclusion compounds, solid dispersions and bulk powder.Intr. Jr. Pharm 1993: 94; 69-74.
10. Akbuga J. Effect of Additives on dissolution characteristics of furosemide – polyvinyl pyrrolidone solid – dispersion systems. Pharm Ind. 1991; 53 (9): 857-860.
11. 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.
12. Chowdary KP, Murthy KV, Prasad CD. Solid dispersion of Nimodipine; physicochemical and Dissolution rate studies. Indian Drugs 1995 Nov; 32: 537 – 542.
13. Torrado S, Torrado JJ, cadorniga R. preparation, dissolution and characterization of Albendazole Solid Dispersions. Int J pharmaceutics 1996; 140 (2): 247- 250.
14. Ellsworth AJ, Witt DM, Dugdale DC ,Oliver LM, Mosbay's 2004 Medical Drug Reference. Elsevier science, Missouri, 2003: 610-612.
15. 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.
16. 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.
17. Ajit S. Narang, Anand K. Srivastava. Evaluation of solid dispersions of clofazimine. Drug dev and Ind pharm 2002; 28 (8): 1001 – 101.
18. Costa P, Sousa Lobo JM. Modeling and comparison of dissolution profiles.Eur J Pharm Sci 2001; 13: 123-133.
19. 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.