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Original Article

Improving Dissolution of Meloxicam Using Solid Dispersions

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Abstract

Meloxicam is a poorly water soluble non steroidal anti-inflammatory drug and antipyretic agent. The aim of the present work was to investigate the effect of different types of carriers on in vitro dissolution of meloxicam. Meloxicam solid dispersions were prepared by physical mixing, co-grinding and solvent evaporation methods with polyethylene glycol (PEG) 6000. The effect of solubilization by sodium lauryl sulphate (SLS) was also studied. The dissolution was determined by USP XXVII Apparatus I, using phosphate buffer with a pH of 7.4 as the dissolution medium. The maximum in vitro dissolution of meloxicam, i.e. 97.45% in 60 min, was observed for solid dispersions containing meloxicam (150 mg), PEG 6000 (350 mg) and SLS (75 mg) prepared by solvent evaporation method containing a sum of 3 g of Lactose and MCC (4:1) as additives. The general trend indicated that there was an increase in dissolution rate for solid dispersions containing the solubilizer SLS. The best-fit model indicating the mechanism of dissolution from the formulation showing the highest release for was found to be Higuchi matrix release (r=0.9774, b=13.042, a=2.4798). Infra red spectroscopy (IR) indicated that meloxicam in solid dispersions showed physical entrapment. The increased in dissolution rate of meloxicam by solid dispersion technique may be due to increase wettability and hydrophilic nature of carrier.

Keywords: Meloxicam; Solid dispersion; Solubilizer; Dissolution.

Introduction

Solubility behavior of a drug is one of the key determinants of its oral bioavailability. 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).

Meloxicam is a non-steroidal anti-inflammatory and anti-pyretic agent. The major draw back of this drug is its low aqueous solubility that delays its absorption from the gastrointestinal tract. Prolonged use of the drug is associated with gastrointestinal side effects such as abdominal pain, diarrhea, flatulence, nausea and gastric and duodenal ulcers (2).

Dissolution of poorly soluble drugs can be increased by solid dispersion techniques (3, 4). Polyethylene glycol 6000 has been widely used as a carrier for solid dispersions of drugs such as griseofulvin (5), diazepam (6), bropirimine (7), tolbutamide (8), mequitazine (9), furosemide (10), norfloxacin (11), trimethoprim (12), carbamazepine (13), indomethacin (14),

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methaqualone (15), ibuprofen (16, 17), piroxicam (18), nimesulide (19), and naproxen (20). In literature, some information is available on the dissolution study of solid dispersions containing surfactants (21, 22). Some attempts have been made to modify the dissolution characteristics and therefore the absorption of meloxicam, such as its preparation of inclusion complexation with ß-cyclodextrin (23-25).

The aim of the present work was to compare the efficiency of several methods such as physical mixing, co-grinding method, and solvent evaporation method in improving dissolution of meloxicam.

Experimental

Materials

Meloxicam (Unichem Laboratories Ltd.), PEG 6000 (LOBA CHEMIE, Mumbai), SLS (sd. Fine Chemicals Ltd., Mumbai), microcrystalline cellulose (LOBA CHEMIE, Mumbai), lactose (sd. Fine Chemicals Ltd., Mumbai), N, N-dimethylformamide (sd. Fine Chemicals Ltd., Mumbai), sodium hydroxide (sd. Fine Chemicals Ltd., Mumbai), potassium dihydrogen orthophosphate (sd. Fine Chemicals Ltd., Mumbai), methanol (sd. Fine Chemicals Ltd., Mumbai), hard gelatin capsules (Yucca enterprises, Mumbai).

Methods

Preparation of meloxicam solid dispersions with PEG 6000

Solid dispersions of meloxicam in PEG 6000 were prepared using a 3^2 Factorial design with PEG 6000 and meloxicam amounts as independent variables while maintaining the amounts of lactose and microcrystalline cellulose (4:1) constant (Table 1). The methods used for preparation of these solid 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. Just before the dissolution studies, these granules were hand filled into zero-size hard gelatin capsules.

1. Co-grinding method

The calculated amounts of Meloxicam and carriers where 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 Petri dishes and dried at 60°C 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.

2. Solvent evaporation method

The required amounts of meloxicam and carriers were dissolved in N,N-dimethyl formamide and allowed to stand overnight. The solvent was removed at 60° 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.

Preparation of meloxicam solid dispersions with PEG 6000 and SLS

Solid dispersions of meloxicam in PEG 6000 were prepared using a 32 Factorial design with PEG 6000 and SLS as independent variables while maintaining the amount of meloxicam (150 mg) and the ratio of lactose and microcrystalline cellulose (4:1) constant (Table 2). The methods used for the preparation of these solid dispersions were physical mixing, co-grinding, and solvent evaporation methods as described above for preparation of meloxicam solid dispersions with PEG 6000.

Determination of meloxicam content

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 spectrophotometerically at

362 nm using Shimadzu 1700 UV-Visible spectrophotometer.

In vitro dissolution

The dissolution study was carried out using USP XXVII Apparatus I (Electrolab TDT-06T). The dissolution medium was 900 ml of phosphate buffer with a pH of 7.4 kept at 37 ± 1° C. The drug, physical mixtures or solid dispersions were filled in empty hard gelatin capsules and then kept in the baskets of dissolution apparatus rotating at 50 rpm. Samples of 5 ml were withdrawn at specified time intervals and analyzed spectrophotometerically at 362 nm 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.

Statistical comparisons

The dissolution profiles were compared using two parameters D_{30} (percentage of meloxicam dissolved at 30 min) and D_{60} (percentage of meloxicam dissolved at 60 min). The comparisons were made between the methods and carriers by analysis of variance (ANOVA). The dissolution release kinetics and the results of best-fit model among the preparations were also compared.

Wettability study

Drug powder, powder mixture or granules (300 mg) were placed in a sintered glass funnel with 33 mm internal diameter. The funnel was plunged into a beaker containing water such that the surface of water in the beaker was at the same level as the powder or granules in the funnel. Methylene blue powder (10 mg) was layered uniformly on the surface of the powder or granules in the funnel. The time required for wetting of methylene blue powder was measured. The mean of three observations was used for drawing the conclusions (26).

Infrared spectroscopy

The Infrared spectra (IR) of meloxicam and some selected preparations were obtained using FTIR (Perkin Elmer 1600 Series). The IR spectroscopy was carried out by KBR pellet method.

Results and Discussion

Content of meloxicam

The content of meloxicam in each preparation was assayed by UV spectroscopy. The assay values were between 96% and 99% of the theoretical values.

In vitro dissolution

The in vitro dissolution characteristics of different types of preparations were compared with the pure drug. The solid dispersions of meloxicam with PEG 6000 showed improved dissolution when compared with physical mixtures and pure drug (Figure 1). The trend observed for percent dissolution of meloxicam from solid dispersions containing PEG 6000 and prepared by physical mixing and solvent evaporation methods, was an increase in dissdution rate by an in crease in PEG 6000 percentage. The dissolution rate also showed a significant increase as the amount of meloxicam was increased (Figure 1). The highest dissolution rate was found for the experimental run number of 27, having a D_{30} of 73.10% and D_{60} of 84.62% (Table 1).

Solid dispersions containing PEG 6000 and SLS showed a significant increase in dissolution rate with an increase in PEG 6000 and the solubilizer sodium lauryl sulphate (Figure 2). The maximum rate of dissolution of meloxicam was observed for the experimental run number 54, having a D_{30} of 82.69% and D_{60} of 97.45% (Table 2).

Solid dispersions prepared by solvent evaporation method showed a higher dissolution of meloxicam than those prepared by physical mixing technique, while solid dispersions prepared by cogrinding technique showed a rather variable dissolution and no significant relationship between the drug to additive ratio and dissoulution rate was observed. This may be attributed to the fact that solid dispersions prepared by solvent evaporation and physical mixing result in a more uniform dispersion of drug in the hydrophilic carrier (PEG 6000) matrix as compared to those prepared by the cogrinding method. Addition of sodium lauryl sulphate improved the aqueous solubility and dissolution of meloxicam.

The mechanisms of dissolution of meloxicam

Table 1. Factors and Level in the Design[a]

Independent Variables	Levels		
	Low (-1)	Medium (0)	High (+1)
PEG 6000 (X_1), mg	250	300	350
Meloxicam (X_2), mg	100	125	150

Amount of the other additives, lactose and microcrystalline cellulose 3g (4:1) was maintained constant in all the preparations.

Experimental runs and measured responses

Run No.	X_1	X_2	D_{30}	D_{60}	Wettability (sec)
1	-1	-1	54.59	67.71	20
2	-1	0	56.92	68.52	20
3	-1	+1	57.94	71.44	21
4	0	-1	61.56	72.33	21
5	0	0	61.79	72.57	20
6	0	+1	62.93	73.72	19
7	+1	-1	56.50	71.31	21
8	+1	0	54.82	70.16	21
9	+1	+1	64.50	75.96	20
10	-1	-1	27.19	43.60	23
11	-1	0	29.19	47.58	22
12	-1	+1	32.1	53.14	23
13	0	-1	23.31	37.47	21
14	0	0	26.85	41.93	24
15	0	+1	31.10	47.86	23
16	+1	-1	16.26	39.62	23
17	+1	0	33.78	53.36	21
18	+1	+1	37.33	59.95	20
19	-1	-1	57.95	70.46	20
20	-1	0	56.96	70.72	20
21	-1	+1	66.54	79.39	20
22	0	-1	65.43	78.82	18
23	0	0	67.30	79.61	20
24	0	+1	72.54	82.82	21
25	+1	-1	47.10	68.97	20
26	+1	0	67.71	81.35	19
27	+1	+1	73.10	84.62	17

[a]Experimental Runs 1-9, 10-18, 19-27 corresponds to physical mixtures, cogrinding and solvent evaporation methods respectively.

from various preparations of solid dispersions were studied. The data were treated to study the best linear fit for the following equations (27)

a) Zero order $\%R = Kt.$

b) First order $\text{Log \% unreleased} = Kt/ 2.303$

c) Matrix (Higuchi matrix) $\% R = Kt^{0.5}$

d) Peppas-Korsmeyer equation $\frac{\text{Amount of drug released at time t}}{\text{Amount of drug released at time '}\infty\text{'}} = Kt^n$

e) Hixson-Crowell equation $(\% \text{ unreleased})^{1/3} = Kt$

Where 'n' is the diffusion coefficient, which is indicative of transport mechanism.

The mechanism of dissolution for the solid dispersion prepared with PEG 6000 having the highest rate of dissolution (the experimental run

Table 2. Factors and Level in the Design

Independent Variables	Levels		
	Low (-1)	Medium (0)	High (+1)
PEG 6000 (X_1), mg	250	300	350
SLS (X_2), mg	100	125	150

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

Experimental runs and measured responses

Run No.	X_1	X_2	D_{30}	D_{60}	Wettability (sec)
28	-1	-1	73.78	86.56	18
29	-1	0	76.87	89.26	17
30	-1	+1	76.88	90.25	16
31	0	-1	67.72	82.17	17
32	0	0	71.88	85.40	16
33	0	+1	76.20	90.58	16
34	+1	-1	57.19	68.20	20
35	+1	0	61.83	80.51	19
36	+1	+1	69.86	83.79	17
37	-1	-1	47.72	64.83	20
38	-1	0	29.75	47.33	22
39	-1	+1	38.35	61.30	20
40	0	-1	48.88	62.01	20
41	0	0	39.86	56.51	21
42	0	+1	39.52	54.61	20
43	+1	-1	28.32	42.00	24
44	+1	0	38.80	51.30	20
45	+1	+1	40.38	51.17	20
46	-1	-1	85.96	92.16	15
47	-1	0	87.19	95.86	15
48	-1	+1	84.96	93.48	15
49	0	-1	86.80	97.16	14
50	0	0	83.90	91.95	15
51	0	+1	84.89	89.85	15
52	+1	-1	70.56	85.30	16
53	+1	0	83.13	89.83	15
54	+1	+1	82.69	97.45	14

number 27) was matrix (r = 0.97130, b=11.01, a = 6.57). The dissolution mechanism of PEG 6000 and SLS-containing formulation with the highest dissolution rate (experimental run number 54) was also found to be matrix (r = 0.9774, b = 13.042 a = 2.4798). The r, a, b are the correlation coefficients, slopes and constants respectively for the best-fit kinetic model.

Wettability study

The minimum mean wetting time (17sec) for PEG 6000 meloxicam solid dispersions was observed for the preparation containing high levels of PEG 6000 and meloxicam,i.e. 350 mg and 150 mg respectively prepared by solvent evaporation method (the experimental run number 27).

The maximum wetting time (24 sec) was observed for the preparation containing 300 mg of PEG 6000 and 125 mg of meloxicam prepared by co-grinding method (the experimental run number 14) (Table 1). The minimum mean wetting time (14 sec) for solid dispersions

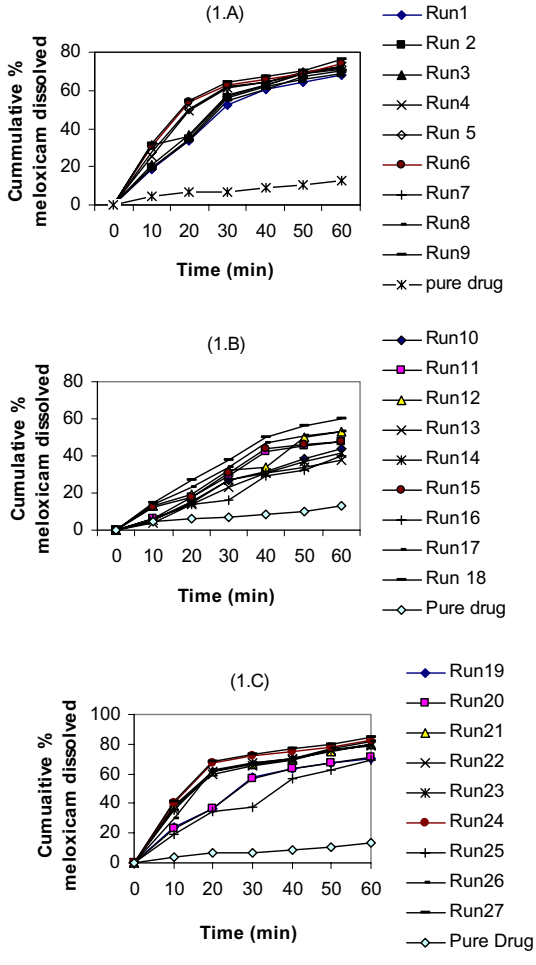

Figure 1. Effect of PEG 6000 and meloxicam content and method of preparation on the dissolution behavior. (A) Physical mixtures; (B) cogrinding method; (C) solvent evaporation method.

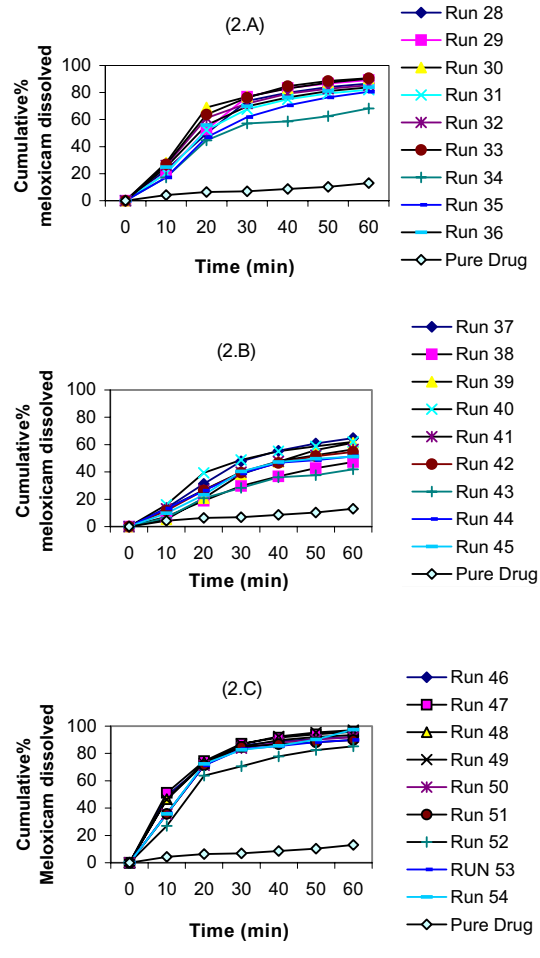

Figure 2. Meloxicam solid dispersions: Effect of PEG 6000 and SLS content and method of preparation on the dissolution behavior. (A) Physical mixtures; (B) cogrinding method; (C) solvent evaporation method.

containing PEG 6000 and SLS prepared was observed in samples by solvent evaporation method (the experimental run numbers 49 and 54), while maximum wetting time (24 sec) was observed for solid dispersions prepared by co-grinding method (the experimental run number 43) (Table2).

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 for PEG 6000 and SLS formulation (experiment run number 54) showed broader peaks at 3384 cm^{-1}, 1631 cm^{-1} (NH), and 1582 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 overlapping of the hydroxyl bands (Figure 3).

It can be concluded that maximum in vitro dissolution was observed for solid dispersion containing PEG 6000 (350 mg), SLS (75 mg), and meloxicam (150 mg) containing 3 g of lactose and MCC (4:1) as additives and prepared by solvent evaporation method. The general trend indicated that there was an increase in dissolution rate from solid dispersions containing the solubilizer SLS. Finally, it may be concluded that dissolution rate of meloxicam can be increased by solid dispersion technique, which is due to wettability and hydrophilic nature of carrier.

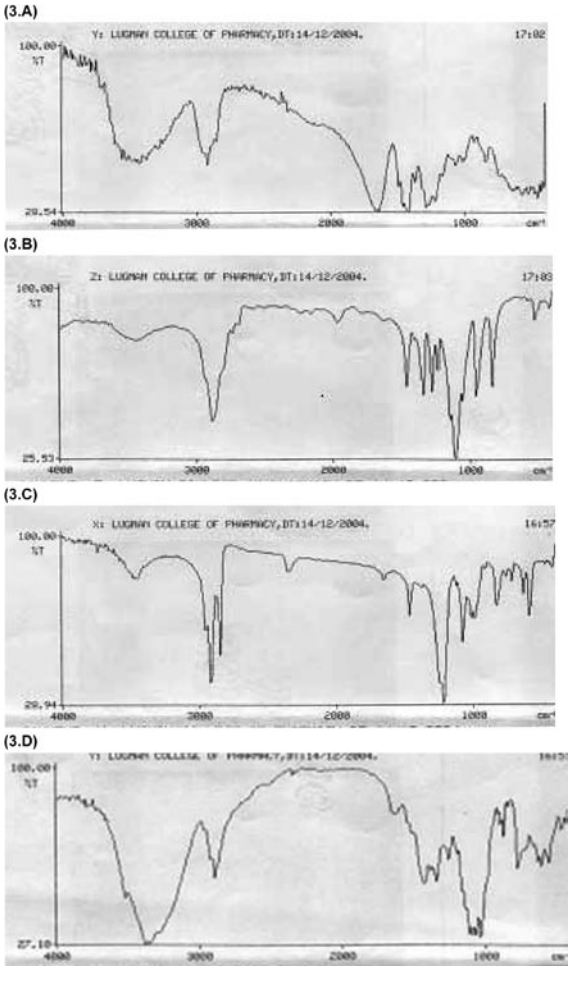

Figure 3. Figure 3. FT-IR spectrum of (A) meloxicam; (B) polyethylene glycol 6000; (C) sodium lauryl sulphate; (D) meloxicam PEG 6000 and SLS formulation (experiment run number 54).

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