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Tablet Formulation of Piroxicam Containing PVP K-30 and Sodium Lauryl Sulphate

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Piroxicam, a non-steroidal antiinflammatory agent is widely used as a first line drug in the symptomatic relief of rheumatoid arthritis and osteoarthritis. Major problem with this drug is its very low solubility in biological fluids, which results into poor bioavailability after oral administration. Therefore, tablet formulation of piroxicam with polyvinyl pyrolidone K-30 and sodium lauryl sulphate was prepared with a view to increase its water solubility. The dissolution profile of promising batch T1 was compared with marketed preparation (MP-dispersible tablet). Batch T1 gave far better dissolution than the marketed product, which released only 55% drug in 30 min while batch T1 released 86% drug in 30 min. Comparison of *in vitro* dissolution profile of batch T1 with that of cycladol (solid dispersion with β cyclodextrin) showed no significant difference in % dissolution efficiency except time for 50% dissolution (t_{50}) for cycladol was 4.41 min while for batch T1 it was 9.29 min. Batch T1 was considered better than cycladol as far as the cost of raw materials used in the product is concerned. Selected formulation (batch T1) was subjected to stability studies. The formulation was found to be stable for 4 w at 45° with insignificant change in the hardness, disintegration time and *in vitro* drug release pattern.

Piroxicam (PXM) is used as a first line drug in the treatment of rheumatoid arthritis and osteoarthritis and has less incidence of side effects[1]. It is practically insoluble in water and peak blood level reaches between 1-3 h and its bioavailability is between 45-75% after oral administration[1]. It shows erratic dissolution profile in gastric and intestinal fluid due to its poor water solubility. Rate of absorption and/ or extent of bioavailability for such insoluble hydrophobic drug is controlled by rate of dissolution in gastro-intestinal fluids. The peak plasma concentration (C_{max}) and the time taken to reach C_{max} (t_{max}) depend upon extent and rate of dissolution of drug *in vivo* respectively. Hence the present work was aimed at increasing the rate of dissolution of piroxicam and to minimize the erratic dissolution profile of drug. Dissolution of poorly soluble drugs can be increased by solid dispersion techniques[2,3]. Numbers of drugs have been shown to improve their dissolution character when converted to solid dispersions[2,4-8]. To date some reports on formulation of these systems have appeared[1,9-16]. Dissolution of drug can be increased by inclusion of surfactant in solid dispersions of drug with hydrophilic carriers[17]. So far there are only few reports in the literature on the dissolution study of solid dispersions containing surfactants[18-20], but no reports in the literature on the dissolution study of tablet dosage forms of solid dispersion containing surfactant and their comparison with its conventional and marketed solid dispersion tablets. Solid dispersions can be prepared by various methods such as solvent evaporation and melting method[21,22]. Hence attempts were made in the present investigation to enhance the dissolution rate of piroxicam by including sodium lauryl sulphate (SLS) in the solid dispersions of piroxicam and polyvinyl pyrolidone K-30 (PVP K-30) using solvent evaporation method.

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MATERIALS AND METHODS

Lactose was purchased from Vikas Pharmaceuticals,

Mumbai. Microcrystalline cellulose was purchased from Maruti Chemicals, Ahmedabad. Piroxicam USP was obtained as a gift sample from Cadila Healthcare, Ahmedabad. Polyvinyl pyrolidone K-30 was obtained as a gift sample from Helios Pharmaceutical, Ahmedabad. Sodium lauryl sulphate, Span-40 and Span-60 were purchased from S.D. Fine Chemicals, Ahmedabad. Crossed linked PVP was purchased from GAF Chemical Corporation, Mumbai. Chloroform was purchased from Laser Chemicals, Ahmedabad. All other materials used were of pharmaceutical grade.

Preparation of solid dispersions of piroxicam containing PVP K-30:

Solid dispersions containing piroxicam and PVP K-30 in various ratios were prepared by the solvent evaporation method. Five hundred milligrams of piroxicam was dissolved in 10 ml chloroform in a beaker and then PVP K-30 was added and mixed to dissolve. A 10 g mixture of lactose-MCC (4:1) was added to the above solution and mixed. Chloroform was evaporated at room temperature and resulting mass was passed through # 60. The granules were dried at room temperature for 1 h and then dried at 65° for 6 h in a hot air oven. The dried granules were stored at room temperature. The composition of various batches is shown in the Table 1.

TABLE 1: COMPOSITION OF BATCHES CONTAINING PVP K-30

Batch Code	Piroxicam (g)	PVP K-30 (g)	Lactose-MCC (4:1) (g)
B1	0.5	0.5	10.0
B2	0.5	1.0	10.0
B3	0.5	1.5	10.0
B4	0.5	2.0	10.0
B5	0.5	2.5	10.0

***In vitro* dissolution study:**

Quantity of granules equivalent to 20 mg of piroxicam was filled in hard gelatin capsule by hand filling method. Dissolution study of capsule was carried out using USP type 1 dissolution apparatus in a 900 ml of simulated gastric fluid[23] (pH-1.2), maintained at 37±0.5° at a speed of 50 RPM. Five ml of samples were withdrawn at time intervals of 5, 10, 20, 30, 45, 60, 90 and 120 min. The volume of dissolution fluid was adjusted to 900 ml by replacing each 5 ml aliquot withdrawn with 5 ml of simulated gastric fluid, pH 1.2. The concentration of piroxicam in the samples was determined by measuring absorbance at 333 nm.

TABLE 2: FORMULATIONS OF DIFFERENT BATCHES FOR FACTORIAL DESIGN

Batch Code	Real Values		Transformed Values	
	Parts of PVP K30 per part of piroxicam	Parts of SLS per part of piroxicam		
	X1	X2	X1	X2
C1	3	0.15	-1	-1
C2	4	0.15	0	-1
C3	5	0.15	+1	-1
C4	3	0.20	-1	0
C5	4	0.20	0	0
C6	5	0.20	+1	0
C7	3	0.25	-1	+1
C8	4	0.25	0	+1
C9	5	0.25	+1	+1

X1: Levels of PVP K-30, X2: Levels of SLS.

Surfactant inclusion in solid dispersion:

To study the combined effect of PVP K-30 and sodium lauryl sulphate on the dissolution of the piroxicam, a 3^2 full factorial design was adopted[24]. Each of the factor and level was transformed in such a way that the high level of each factor was +1 and low level was -1. The real values and transformed values of different batches are shown in Table 2. Nine batches of the solid dispersion were prepared according to scheme shown in Table 3. The drug was dissolved in the chloroform and PVP K-30 was added to the prepared solution and shaken to dissolve PVP K-30. To that solution SLS was added and shaken to disperse it uniformly. To that lactose-MCC (4:1) was added and mixed well. Chloroform was evaporated at room temperature and resulting mass was passed through # 60. The granules were dried at room temperature for 1 h and then dried at 65° for 6 h in a hot air oven. The dried granules were stored at room temperature. *In vitro* dissolution study was conducted by the method described earlier.

Formulation, preparation and evaluation of tablets of piroxicam-PVP K-30 solid dispersion containing sodium lauryl sulphate:

Two formulations were developed for preparation of tablet dosage form of piroxicam-PVP K-30 solid dispersion containing SLS using two different disintegrating agents, SSG (batch T1) and CLP (batch T2) at a level of 4% concentration of the total tablet weight. The total weight of tablet was 334 mg. All the ingredients were mixed intimately and the mixture was compressed into tablets (334 mg weight) using a single punch tablet machine. Compressed tablets were then evaluated for hardness[25] and disintegration[26]. *In vitro* dissolution study was conducted by the method described earlier. Table 4 shows the formulation and evaluation of tablets of piroxicam.

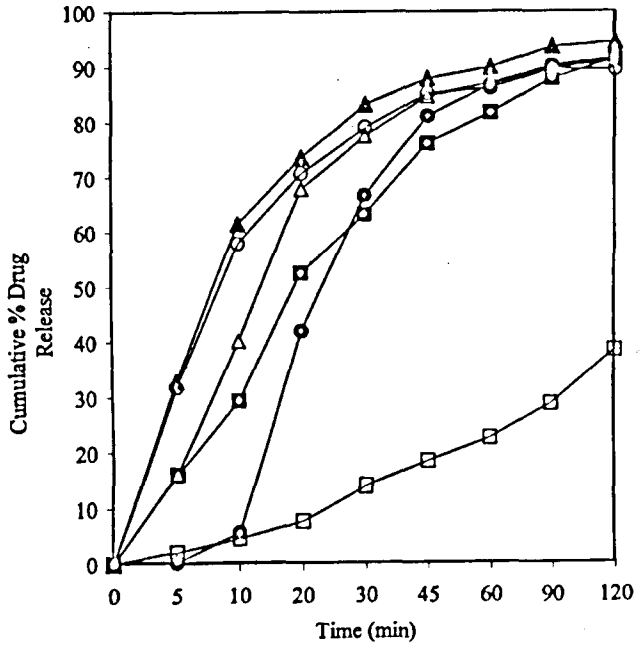

Fig. 1: Comparative *In vitro* release profile of piroxicam from solid dispersion containing PVP K-30.

Different ratios of PXM: PVP K-30 used were, 1:0 (-□-), 1:1 (-■-), 1:2 (-△-), 1:3 (-○-),1:4 (-▲-),and 1:5 (-●-).

TABLE 3: COMPOSITION OF FACTORIAL BATCHES

Batch Code	Piroxicam (mg)	PVP K-30 (g)	SLS (mg)	Lactose-MCC(4:1) (g)
C1	500	1.5	75	3.25
C2	500	2.0	75	3.25
C3	500	2.5	75	3.25
C4	500	1.5	100	3.25
C5	500	2.0	100	3.25
C6	500	2.5	100	3.25
C7	500	1.5	125	3.25
C8	500	2.0	125	3.25
C9	500	2.5	125	3.25

TABLE 4: FORMULATION AND ELALUATION OF TABLETS OF PIROXICAM

Batch	Solid Dispersion (mg)	SSG (mg)	CLP (mg)	Hardness (kg/cm^2)	Disintegration time (s)
T1	320	14	-	5.8	88
T2	320	-	14	6.2	102

SSG: Sodium starch glycolate, CLP: Cross-linked PVP.

TABLE 5: RESULTS OF LINEAR MULTIPLE REGRESSION ANALYSIS

Batch Code	X1	X2	X1X2	X1X1	X2X2	t_{50} (min)
C1	-1	-1	1	1	1	11.33
C2	0	-1	0	0	1	7.66
C3	1	-1	-1	1	1	26.24
C4	-1	0	0	1	0	8.38
C5	0	0	0	0	0	7.45
C6	1	0	0	1	0	23.71
C7	-1	1	-1	1	1	8.49
C8	0	1	0	0	1	7.54
C9	1	1	1	1	1	23.78

MODEL	R-Square value
Full model	0.9946
If X1 omitted	0.3469
If X2 omitted	0.9854
If X1X2 omitted	0.9946
If X1X1 omitted	0.6606
If X2X2 omitted	0.9909

RESULTS AND DISCUSSION

Fig. 1 shows the comparative *in vitro* release profile of various solid dispersions of piroxicam with PVP K-30 having different weight fractions of PVP K-30 such as 1, 2, 3, 4, and 5 for 1 part of piroxicam. From the release profile it can be seen that dissolution of piroxicam increases with increase in PVP K-30 up to 1:4 ratio of drug: PVP K-30. This may be attributed to the increase in drug wetability, solubilization of the drug due to hydrophilic carrier. After this particular ratio with further increase in the amount of PVP K-30, the dissolution was decreased. This decrease in dissolution may be due to increased viscosity. Surfactants can be used to enhance the dissolution rate of the drug because they reduce the surface tension, increase the wetability of the drug particles, and thereby enhance the dissolution rate[17-20]. In the present investigation Span-60, Span-40 and SLS were tried to enhance the dissolution rate. From the preliminary studies it was observed that SLS was more effective amongst the three surfactants used. To study the combined effect of PVP K-30 and SLS on the dissolution of the piroxicam, factorial design was adopted[24]. A 3^2 full factorial design was used to optimize process variables that were thought to affect the release of piroxicam from solid dispersion. The response selected for the present optimization set was time for 50% drug dissolution (t_{50}). Interactive statistical model was utilized in order to evaluate the response t_{50}=bo+b1X1+b2X2+b12X1X2+b11X1X1+b22 X2X2. Where, bi is the coefficient for the factor i. A polynomial equation was generated by linear multiple regression that quantitatively explain the effect of different variables on the dissolution. The equation derived was Y=6.8877+7.58833*X1-0.9033*X2+0.095*X1*X2+ 9.4383*X1*X1+0.9933*X2*X2. To identify the important parameters affecting t_{50} value, the stepwise multiple regression analysis of the data was carried out. The results

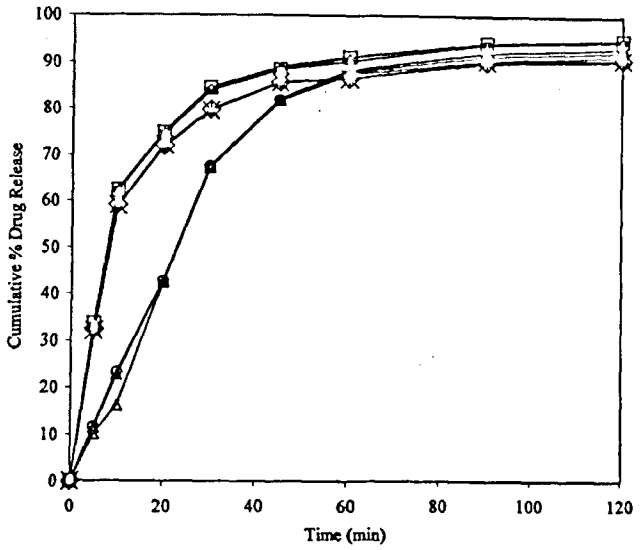

Fig. 2: Comparative *in vitro* release profile of piroxicam from factorial batches.

Different ratios of PXM: PVP K-30:SLS used were,1:3:0.15 (-●-), 1:4:0.15 (-▣-),1:5:0.15 (-△-), 1:3:0.20 (-◇-), 1:4:0.20 (-♦-), 1:5:0.20 (-○-), 1:3:0.25 (-x-), 1:4:0.25 (-□-) and 1:5:0.25 (-▲-).

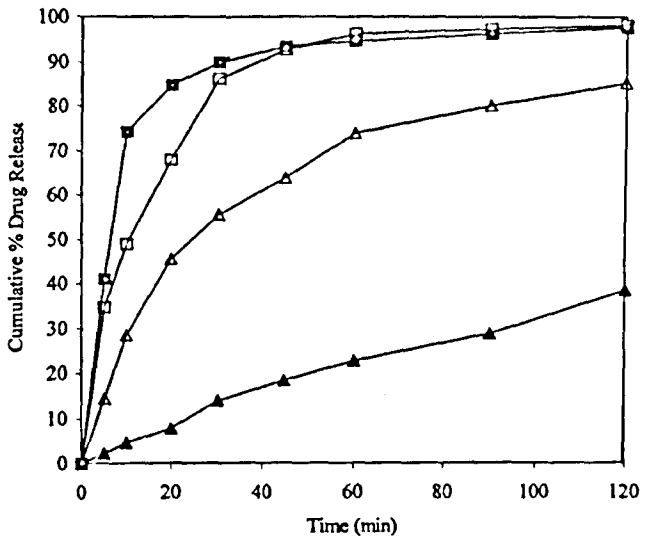

Fig. 3: Comparative *in vitro* release profile of formulated tablets and market products.

Batch TI (-□-), MP (-△-), Cycladol (-▣-) and Piroxicam (-▲-).

of stepwise regression are shown in table 5. The results obtained from the factorial design revealed that PVP K-30 alone is more effective in enhancing the dissolution rate than SLS alone, but in combination with PVP K-30, SLS give some additional contribution to enhance the dissolution rate. Fig. 2 shows the comparative release profile of factorial batches. Batch C5 was considered as the best batch because it has minimum t_{50} value (7.45 min) and also it contains less amount of SLS. So it was selected for the formulation of tablet dosage form. The results of disintegration test revealed that batch T1 (88 s) has faster disintegration than batch T2 (102 s). *In vitro* dissolution revealed that there was no significant difference of batch T1 and batch T2 for % dissolution efficiency[27] (% DE) and time for 50% dissolution (t_{50}). Hence batch T1 was considered superior than batch T2 because of faster disintegration. Fig. 3 compares the *in vitro* release profiles of pure drug and batch T1 with market product -300 mg dispersible tablet (MP) and cycladol (piroxicam:β-cd solid dispersion marketed by Ranbaxy). The % dissolution efficiencies of pure drug, market product (MP), cycladol and best batch (batch T1) are shown in the Table 6. It is very clearly evident that batch T1 is a far better formulation than the market product (MP). In comparison with cycladol, batch T1 has same % dissolution efficiency as that of cycladol except slight higher t_{50}. The *in vitro* release profile of batch T1 was compared with conventional market product and cycladol for similarity factor (f_2) and dissimilarity factor (f_1). The values (Table 7) show that there is good similarity in *in vitro* dissolution of batch T1 with cycladol. So batch T1 was considered better than cycladol as far as the cost of the raw materials used in the product is concerned. Hence it can be concluded that the faster dissolution of piroxicam can be achieved by solid dispersion with PVP K-30 and sodium lauryl sulphate. In order to determine the change in *in vitro*

TABLE 6: COMPARISON OF BEST BATCH WITH THE MARKET PRODUCT

Product	% Dissolution Efficiency	Time for 50% drug release(t_{50}) (min)
PURE DRUG	14.82	>120
MP	39.83	27.8
CYCLADOL	49.31	4.41
BATCH TI	48.58	9.29

TABLE 7: COMPARISON OF *IN VITRO* DISSOLUTION PROFILES BY F_1 AND F_2 TESTS

Time (min)	Cumulative % drug release		
	Batch TI	Market product (MP)	Cycladol
0	0	0	0
5	36.64	14.37	40.15
10	50.82	28.44	69.26
20	69.83	45.55	81.25
30	88.1	55.4	87.25
45	92.62	63.77	93.27
60	96.09	73.72	94.48
90	97.21	79.94	96.18
120	98.09	85.11	97.42
Similarity factor (f_2)[29]		32.61	56.44
Dissimilarity factor (f_1)[29]		41.02	9.31

TABLE 8: RESULTS OF STABILITY STUDY

Time (min)	CPR (initial)	CPR (after storage at 45° for 30 d)
0	0	0
5	34.6	32.7
10	48.8	46.2
20	67.8	65.5
30	86.1	85.5
45	92.0	92.8
60	91.1	96.4
90	97.2	97.2
120	98.1	97.8
MEAN	69.0	68.2
Tcal : 0.048905		
Ttab : 1.7458		

CPR : Cumulative percent drug release.

release profile on storage, stability study of batch T1 was carried out at 45° for 4 w. Tablets of batch T1 were withdrawn at the end of 4 w. The tablets were then evaluated for change in *in vitro* drug release pattern, hardness and disintegration time. Not much change in the physical characteristics and the release profile was observed at the end of 4 w. The student's t-test[28] was applied to study the effect of storage. It is evident from the Table 8 that the effect of storage is insignificant at 5% level for batch T1. Hardness, disintegration time as well as *in vitro* release pattern of piroxicam from batch T1 were almost the same before and after storage for 4 w at 45°.

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