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LETTER TO THE EDITOR

FAST ANALGESIC ACTIVITY FROM RECRYSTALLIZED NIMESULIDE AND ITS SOLID DISPERSION

Sir,

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Nimesulide (chemically 4-nitro-methane-sulphanilide), an acidic NSAID, is virtually insoluble in aqueous fluids. The poor solubility and wettability of the drug gives rise to difficulties in pharmaceutical formulation and leads to variable bioavailability (1). Studies have already been carried out to increase its aqueous solubility by complexation (2), crystallization (3) and solid dispersions (4). However, no reports are available regarding the effect of increased solubility on the onset of pharmacological action. Hence, presently an attempt has been made to increase the solubility of nimesulide by recrystallization followed by solid dispersion and to correlate the improved solubility with onset of analgesic activity.

Nimesulide (Courtesy, M/s Shilpa Antibiotics Ltd., Raichur, India) crystals were obtained by solvent change method at different temperature conditions. Nimesulide (1 g) was dissolved in 130 ml absolute alcohol. To this solution, 400 ml distilled water was added at room temperature, 50°C and 70°C separately and crystals were collected after filtration. Crystals obtained at room temperature, 50°C and 70°C were labeled as NRT, N50 and N70 respectively. Crystals obtained at 70°C (N70) were recrystallized by dissolving in alcohol and adding distilled water containing 1% or 2% tween 20 (labeled as NT1 and NT2 crystals respectively). Solid dispersion of NT1 crystals with PVP (drug and PVP in the ratio of 10 : 1) was prepared by solvent evaporation method (labeled as NTP). Solubility and *in vitro* dissolution rate studies were carried out in 0.1N hydrochloric acid according to reported methods (4). Percentage yield of the crystals was determined by weighing the resulted crystals. IR spectra were recorded for parent nimesulide and its crystal forms on Shimadzu FTIR-8300 Infrared Spectrophotometer. Analgesic activity was conducted by tail flick and hot plate method (5) using Swiss Albino mice, weighing 25–30 g (4–6 weeks old), after oral administration of 12.5 mg/kg body weight of parent nimesulide, NT1 and NTP. The cut off time for analgesic activity in hot plate and tail flick method was 15 and 10 seconds respectively. The values are expressed as mean ± standard error (SE) and statistical significance was analyzed by means of student's t-test. The p value less than 0.05 was considered as significant. The sample size 'n', in solubility, practical yield

determination and dissolution rate studies was 6. In analgesic activity, the number of animals in each group was 6.

Since solubility and dissolution rate of nimesulide crystals obtained at 70°C (N70) was increased by 5 folds compared to parent nimesulide, this temperature was found to be favorable for crystallization. To improve the solubility, N70 crystals were recrystallized in presence of 1% and 2% tween 20 (NT1 and NT2). These crystals showed almost 11 times increase in solubility and dissolution rate compared to parent nimesulide. Further improvement in the dissolution rate of nimesulide was observed with the solid dispersion of NT1 crystals with PVP. The results of solubility, practical yield, dissolution rate studies and analgesic activity are shown in Table I and II. IR spectra of crystals obtained at 70°C, recrystallized nimesulide (NT1) and solid

TABLE I: Result of practical yield, solubility and *in vitro* dissolution rate studies for parent nimesulide and its crystal forms.

Sample	*Practical yield (%)*	*Solubility (mg/L)*	*Percentage dissolution rate (in 1 h)*
Nimesulide	–	9.72±0.41	10.81±0.93
NRT	83.60±1.29	22.98±0.19	16.56±1.21
N50	81.72±1.13	24.23±0.08	19.02±0.94
N70	80.92±0.95	49.22±0.28	30.82±0.43
NT1	76.86±1.58	108.91±0.06	35.18±0.54
NT2	72.85±1.34	113.93±0.21	37.13±0.53
NTP	94.33±1.17	112.46±0.72	37.02±0.46

Parent nimesulide and its crystal forms (NRT, N50, N70, NT1, NT2 and NTP) were evaluated for solubility, percentage yield determination and *in vitro* dissolution rate studies following reported methods. The sample size 'n' is 6 and values are expressed as mean ± SE.
NRT-Nimesulide crystals obtained at room temperature by solvent change method.
N50-Nimesulide crystals obtained at 50°C by solvent change method.
N70-Nimesulide crystals obtained at 70°C by solvent change method.
NT1-Crystals obtained by recrystallization of N70 in presence of 1% tween 20.
NT2-Crystals obtained by recrystallization of N70 in presence of 2% tween 20.
NTP-Solid dispersion of NT1 crystals in presence of PVP.

TABLE II: Analgesic activity of parent nimesulide and its crystal forms.

Time (min)	*Reaction time (s) in hot plate method (Reaction time in tail flick method)*			
	Control	*Parent nimesulide*	*NT1*	*NTP*
0	3.08±0.89 (3.28±0.65)	3.33±0.82 (3.15±0.21)	3.08±0.59 (3.22±0.72)	3.28±0.14 (3.35±0.19)
10	3.24±0.28 (3.12±0.62)	4.01±0.39 (3.28±0.28)	3.94±0.61 (3.19±0.69)	4.15±0.80 (3.40±0.71)
20	3.01±0.34 (3.29±0.69)	5.78±0.96* (4.22±0.43)	6.28±0.81** (5.18±0.21)*	6.03±1.19* (5.02±0.33)*
30	3.24±0.62 (3.30±0.54)	8.02±0.81*** (6.03±0.18)***	9.13±0.62*** (7.55±0.18)***	8.96±0.36*** (7.51±0.62)***
45	3.38±0.41 (3.38±0.71)	9.47±0.12*** (7.28±0.29)***	12.67±0.13*** (8.69±0.34)***	11.55±1.01*** (8.10±0.47)***
60	3.21±0.32 (3.10±0.92)	9.20±0.65*** (8.83±0.82)***	11.92±0.36*** (10.83±0.65)***	11.03±0.96*** (9.81±0.09)***

*P<0.05, **P<0.01 and ***P<0.001 compared to control
Parent nimesulide and its crystal forms (NT1 and NTP) were evaluated for analgesic activity following hot plate and tail flick methods. Each group contained 6 animals. The values are expressed as mean ± SE and p value was computed by Student's t-test.

dispersion of recrystallized nimesulide (NTP) showed that there was no change in the peaks of nimesulide when compared to parent nimesulide. The presence of additional peaks in IR spectra of NT1 and NTP could be due to the presence of adsorbed surfactant and PVP on the crystal surface. This may suggest the absence of any chemical change upon the treatment of nimesulide at higher temperature or with tween 20 and PVP. Hence the improvement in the solubility may be attributed to the physical changes due to recrystallization and solid dispersion. The higher energetic state of the crystals that were obtained at elevated temperature could be the reason for the improvement in solubility of nimesulide. The improved solubility of nimesulide from the crystals obtained by recrystallization in presence of tween 20 may be due to the increased wettability by the adsorption of surfactant onto the hydrophobic surface of the drug crystals. This may also be due to the defect caused in the crystal structure because of the presence of surfactant during crystallization and crystal would become thermodynamically unstable and dissolve faster. The possibility of formation of a solid solution of water soluble surfactant in drug crystal might also enhance dissolution (3, 6). Further improvement in the dissolution rate of nimesulide from solid dispersion may be due to the adsorption of water soluble polymer PVP on the crystal surface (3). In analgesic activity, even though p value for most of the groups was found to be significant compared to the control group, the reaction time was moderately increased with recrystallized nimesulide (NT1) and solid dispersion of nimesulide (NTP). This may suggest better onset of analgesic activity from recrystallized nimesulide and its solid dispersion than that of parent nimesulide, which could be due to increased solubility and dissolution rate of nimesulide from these crystals.

Present study showed that recrystallization of nimesulide in presence of tween 20 and its solid dispersion with PVP considerably improved the solubility and dissolution rate. The onset of analgesic activity was moderately rapid with recrystallized nimesulide and its solid dispersion. However bioavailability and pharmacokinetic studies are necessary to confirm these results. The study further revealed the usefulness of increased solubility to get rapid onset of pharmacological action.

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