
Effect of Surfactants on the Solubility and Dissolution Rate of Nimesulide from Tablets

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The effect of two surfactants, sodium lauryl sulfate (SLS) and Tween 80, on the aqueous solubility and dissolution rate of nimesulide from tablets, formulated employing starch paste and polyvinylpyrrolidone (PVP) as binders, was studied. A marked increase in the solubility as well as dissolution rate of nimesulide was observed with both the surfactants. When there was no surfactant tablets formulated employing PVP as binder exhibited higher dissolution rates than those formulated with starch paste as binder. Incorporation of SLS and Tween 80 in the tablets formulated with starch paste as binder has markedly enhanced the dissolution rate of nimesulide. An 8.85 and 8.17 fold increase in the dissolution rate was observed with SLS and Tween 80 respectively. In the case of tablets formulated with PVP as binder, there was only a marginal increase in the dissolution rate when these surfactants were incorporated. Dissolution of nimesulide from the tablet formulations followed first order kinetics.

Nimesulide, chemically 4-nitro-2-phenoxy methane sulphanilamide, is a non-steroidal anti-inflammatory analgesic drug¹. It is widely used for the treatment of inflammatory conditions associated with rheumatoid arthritis, respiratory tract infections, soft tissue and oral cavity inflammations. Nimesulide is practically insoluble in water and aqueous fluids. Its solubility is reported as 0.01 g/l in water², 0.12 g/l in 0.1 N hydrochloric acid³ and 0.10 g/l in phosphate buffer³ of pH 7.5. As such its oral absorption is dissolution rate limited. The very poor aqueous solubility of the drug gives rise to difficulties in the formulation of dosage forms and may lead to variable dissolution rates and bioavailabilities. Surfactants have been reported earlier to improve the dissolution rate of poorly soluble drugs such as hydrocortisone⁴, tolbutamide⁵, sulphathiazole⁶, griseofulvin⁷, frusemide⁸, amphotericin-B⁹, sulfamethoxazole¹⁰ and piroxicam¹¹. In the present investigation the possibility of using surfactants to improve the solubility and dissolution rate of nimesulide from compressed tablets was studied.

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EXPERIMENTAL

Nimesulide (gift sample from M/s. Aristo Pharmaceuticals Ltd., Mumbai), sodium lauryl sulfate (BDH), Tween 80(BDH), polyvinylpyrrolidone (PVP, K-30), potato starch (Loba-chemie), lactose, I.P., talc I.P. magnesium stearate, I.P., sodium hydroxide (Qualigens), boric acid (Qualigens), potassium chloride (Qualigens) were used. Two commercial formulations of nimesulide were also included in the study for comparison purpose.

Estimation of Nimesulide:

An U.V. spectrophotometric method based on measurement of absorbance at 230 nm in alkaline borate buffer of pH 8.4 was used for the estimation of nimesulide. The method was validated for linearity, accuracy, precision and interference. The method obeyed Beers law in the concentration range of 0-10 µg/ml ($r=0.998$). When a standard drug solution was repeatedly assayed ($n=6$), the relative error and coefficient of variation were found to be 1.25% and 1.6% respectively. No interference by the excipients used in the study was observed.

Solubility Determination:

The solubility of nimesulide in water and water containing various concentrations of SLS and Tween 80 (1, 1.5, 2 and 3%) and PVP (1%) was determined. Excess nimesulide (50 mg) was added to 15ml of each fluid taken in a 25 ml stoppered conical flask and the mixtures were shaken for 24 h at room temperature ($28\pm 1^\circ$) on a rotary flask shaker. After 24 h of shaking 1 ml aliquots were withdrawn at 1 h interval and filtered immediately using a 0.45μ disc filter. The filtered samples were diluted suitably and assayed for nimesulide by U.V. Spectrophotometric method. Shaking was continued until two consecutive estimations are the same. The solubility experiments were conducted in triplicate.

Preparation of Tablets:

Compressed tablets of nimesulide each containing 100 mg were prepared by conventional wet granulation method as per the formulae given in Table - 1. PVP and starch paste were used as binders at 3% concentration in the formula and potato starch at 15% concentration as disintegrant. Tablet granulations were compressed into tablets to a hardness of 5-6 kg/sq.cm. on a Cadmach single punch tablet machine.

Evaluation of Tablets :

Tablets were tested for uniformity of weight as per I.P. (1996). Disintegration times were determined in a

Themonic tablet disintegration test machine, USP, using distilled water as the fluid. Hardness of the tablets was tested using a Monsanto hardness tester. Friability of the tablets was determined in a Roche friabilator. Nimesulide content of the tablets was estimated by the spectrophotometric method described above.

Dissolution Rate Study:

The dissolution rate of nimesulide from the tablets, both formulated and commercial was studied in 900 ml of alkaline borate buffer¹² (pH 8.4) using the USP XXI 3-station dissolution rate test apparatus (Model DR-3, M/s. Campbell Electronics) with a paddle stirrer. One tablet containing 100 mg of nimesulide, a speed of 50 rpm and a temperature of $37\pm 1^\circ$ was used in each test. Samples of dissolution medium (5 ml) were withdrawn through a filter at different time intervals, suitably diluted and assayed for nimesulide by measuring absorbance at 230 nm. The dissolution experiments were conducted in triplicate. From the dissolution data dissolution efficiency (DE) was calculated as suggested by Khan¹³.

Statistical Analysis:

DE_{30} values, calculated based on dissolution data, were statically analysed by Analysis of Variance (ANOVA) and Duncan's Multiple Range Test to test the significance of the observed differences due to binders and surfactants at 5% level of significance.

TABLE 1 : FORMULAE OF NIMESULIDE TABLETS PREPARED

Ingredient (mg/tablet)	Formulation					
	T1	T2	T3	T4	T5	T6
Nimesulide	100	100	100	100	100	100
Potato Starch (dry)	75	75	75	75	75	75
Lactose	290	285	285	290	285	285
Starch (as mucilage)	15	15	15	-	-	-
Poly vinyl pyrrolidone (K-30) (as aqueous solution)	-	-	-	15	15	15
Sodium lauryl sulfate	-	5	-	-	5	-
Tween 80	-	-	5	-	-	5
Talc	10	10	10	10	10	10
Magnesium stearate	10	10	10	10	10	10
Total Weight	500	500	500	500	500	500

RESULTS AND DISCUSSION

The solubility of nimesulide in water was increased in the presence of surfactants (Table-2). The solubility increased linearly as the concentration of surfactant increased with both SLS ($r=0.999$) and Tween 80 ($r = 0.997$). SLS gave higher increase in the solubility of nimesulide when compared to Tween 80. The solubility of nimesulide was increased by 17.7 and 9.1 fold at 1.0% concentration and 53.2 and 23.7 fold at 3.0% concentration respectively with SLS and Tween 80. The higher solubility of nimesulide observed with SLS is due to the more number of micelles formed when compared to Tween 80 at a given concentration as it is reported¹⁴⁻¹⁶ that the surfactant molecules per micelle are 62 and 132 respectively for SLS and Tween 80.

The effect of surfactants on the dissolution rate of nimesulide was studied in two series of tablets, one prepared with starch paste as binder and the other prepared with PVP as binder. SLS and Tween 80 were included in the tablets formulations at 1.0% concentration in the formula. All the tablets prepared were found to contain nimesulide within $100\pm 5\%$ of the labelled claim. All batches of tablets prepared fulfilled the official (I.P.) test for uniformity of weight. Hardness of the tablets in all the batches was found to be in the range of 5-7 kg/sq.cm and was satisfactory. The percentage weight loss in the friability test was less than 1.0%. All the tablets formulated fulfilled the official (I.P.) specification for disintegration time (Table - 3).

TABLE 2 : SOLUBILITY OF NIMESULIDE

Surfactant Concentration (w/v)	Solubility (mg/100 ml)		
	SLS	Tween 80	PVP
0	0.86	0.86	0.86
1.0	15.20	7.84	12.30
1.5	23.36	11.55	-
2.0	30.63	14.36	-
3.0	45.76	20.12	-

Solubility of nimesulide in water was determined in the presence of surfactants such as SLS and Tween 80 and PVP

TABLE 3 : DISINTEGRATION AND DISSOLUTION PARAMETERS OF VARIOUS NIMESULIDE TABLETS

Formulation	DT (min)	T ₅₀ (min)	K' $\times 10^2$ (min ⁻¹)	DE ₃₀ (%) ($\bar{x}\pm s.d$)
T1	1.75	43	1.56 (9.984)*	16.04 \pm 4.37
T2	2.25	6	14.16 (0.989)	75.62 \pm 0.87
T3	1.50	10	13.08 (0.952)	61.11 \pm 1.25
T4	10.00	14	7.30 (0.984)	51.9 \pm 11.05
T5	4.00	10	8.80 (0.969)	51.24 \pm 1.55
T6	1.50	9	11.60 (0.984)	67.16 \pm 2.68
C1	1.50	10	4.58 (0.988)	52.16 \pm 4.50
C2	3.50	51	1.296 (0.981)	25.44 \pm 3.70

C1 and C2 are two commercial brands of nimesulide tablets obtained.

*Figures in parentheses are correlation coefficient of log percent undissolved and time.

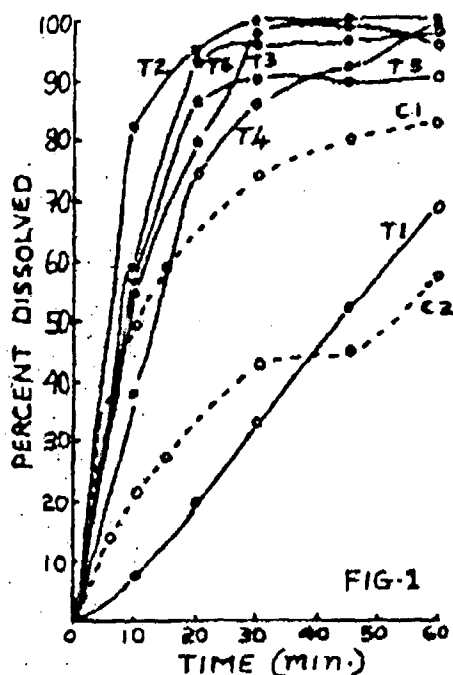


Fig. 1 : Dissolution Profiles of Nimesulide Tablets

Dissolution studies were performed using various formulated tablets (T1, T2, T6) (o — o) and two brands of commercial tablet C1 and C2 (o — o).

Dissolution of nimesulide from the tablets formulated as well as commercial products was studied in alkaline borate buffer of pH 8.4. Alkaline borate buffer of pH 8.4 provided satisfactory sink condition needed for the dissolution rate testing of nimesulide with good discriminating power. The solubility of nimesulide in this fluid was 43.9 mg/100 ml, where as it was 0.86 and 4.2 mg/100 ml respectively in water and phosphate buffer of pH 7.4. Dissolution profiles of various tablets are shown in Fig. 1. Dissolution of nimesulide from the tablets followed first order kinetics. The correlation coefficient (r) between log percent undissolved and time was in the range 0.952-0.989 with various tablet formulations (Table - 3).

The dissolution parameters of various tablets are summarised in Table - 3. When there was no surfactant included, tablets formulated with PVP as binder (T4) gave much higher dissolution rate and efficiency values than those formulated with starch paste (T1). The higher dissolution rate and efficiency values observed with tablet formulation T4 is due to the solubilizing effect of PVP on nimesulide. It was found that the solubility of nimesulide in water was increased by 14.3 fold when PVP was present at 1% concentration (Table - 2) ANOVA of DE_{30}

values and Duncan's multiple range test indicated that the differences observed in the dissolution characteristics of the formulations due to surfactants were significant ($p < 0.05$) in both the series formulated employing starch paste and PVP as binders. Incorporation of surfactants markedly enhanced the dissolution rate and efficiency values of nimesulide in the case of tablets prepared with starch paste as binder. An 8.85 and 8.17 fold increase in the dissolution rate of nimesulide was observed with tablet formulations containing SLS (T2) and Tween 80 (T3) respectively when compared to formulation T1. Whereas in the case of tablets formulated with PVP as binder, there was only a marginal increase in the dissolution rate and efficiency of nimesulide when the surfactants were included. As tablet formulation containing PVP as binder (T4) itself gave higher and faster dissolution of nimesulide due to its solubilizing effect on nimesulide, the effects of surfactants are nullified in formulations containing combination of PVP and surfactant and hence only a marginal increase in the dissolution was observed with these formulations. The increase in the dissolution rate was 1.20 and 1.29 fold with formulations containing SLS (T5) and Tween 80 (T6) respectively when compared to formulation T4. The higher dissolution rates observed with the tablet formulations containing SLS and Tween 80 are due to the solubilizing effect of these surfactants on nimesulide observed in the present study and also due to the improved wetting of hydrophobic drug particles during the process of disintegration and dissolution. The dissolution rate and efficiency values of tablets formulated employing SLS and Tween 80 were also higher than those of the commercial formulations tested (Table - 3).

Thus as SLS and Tween 80 were found to enhance both the solubility and dissolution rate of nimesulide, these surfactants could be used in tablet formulations to improve the dissolution rate of nimesulide, a poorly water soluble drug.

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