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Effect of Selected Binders and Disintegrants on the Dissolution Rate of Nimesulide from Tablets

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Much variations in the disintegration and dissolution characteristics were observed when the effect of seven commonly used binders namely starch paste, acacia, sucrose, poly vinyl pyrrolidone (PVP), hydroxy propyl methyl cellulose (HPMC), methyl cellulose and gelatin and four disintegrants namely potato starch, micro crystalline cellulose (MCC), pregelatinized starch (PGS) and Primogel on the dissolution rate and other qualities of nimesulide tablets was studied. ANOVA of dissolution efficiency (DE_{30}) values and Duncan's Multiple Range Test were used to compare the performance of various binders and disintegrants. Based on DE_{30} values the order of performance of binders and HPMC>PVP> sucrose>acacia>starch paste>methyl cellulose>gelatin and that of disintegrants was Primogel>PGS> potato starch>MCC. Tablets formulated employing PVP-potato starch, HPMC-potato starch, starch paste-Primogel, PVP-PGS and PVP-Primogel as binder-disintegrant gave much higher dissolution rate and efficiency values than other, both formulated and commercial. The above tablets also fulfilled all other official requirements.

Nimesulide, is a relatively new non-steroidal antiinflammatory analgesic drug[1]. It is widely used for the treatment of inflammatory conditions associated with rheumatoid arthritis, respiratory tract infections, soft tissue and oral cavity inflammations. It is not yet official in any pharmacopoeia. Nimesulide is practically insoluble in water and aqueous fluids. Its solubility is reported as 0.01 g/l in water[2], 0.12 g/l in 0.1 N hydrochloric acid[3] and 0.10 g/l in phosphate buffer[3] 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. Though nimesulide tablets and suspensions are available commercially, no work was reported on the pharmaceutical formulation aspects of nimesulide. In the present work the effect of seven commonly used binders and four disintegrants on the dissolution rate of nimesulide from compressed tablets was studied. The results are reported in the present communication.

Nimesulide (gift sample from M/s. Aristo Pharmaceuticals Ltd., Mumbai), poly vinyl pyrrolidone (PVP, K-30) hydroxy propyl methyl cellulose (having a viscosity

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of 50 cps in a 2% weight aqueous solution at 20°; HPMC), potato starch (Loba - Chemie), acacia, gelatin (Oxoid), methyl cellulose, sucrose, Primogel, (Sodium starch glycollate) micro crystalline cellulose (Avicel, FMC Type pH 205; MCC), pregelatinized starch (prepared in the laboratory by a known method[4]), lactose, I.P. talc, I.P., magnesium stearate, I.P., sodium hydroxide (Qualigens), boric acid (Qualigens), potassium chloride (Qualigens) were used.

The following commercial formulations of nimesulide were also included in the study for comparison purpose. NISE (Nimesulide tablets) 100 mg, M/s Dr. Reddy's Laboratories, Hyderabad, Batch No. 2 NSO 6319, Mfg. Date : Jan, 1999, Exp. Date : Dec 2001; NIMEGESIC (Nimesulide tablets), 100 mg, M/s. Alembic Chemical works, Mumbai, Batch No. 82304, Mfg. Date : Nov., 1998, Exp. Date : Oct., 2001.

An U.V. spectrophotometric method based on the 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 mcg/ml (r = 0.998). When a standard drug solution was repeatedly assayed (n=6), the relative error and co-efficient of variation were found to be 1.25% and 1.6% respectively. No interference by the excipients used in the study was observed.

Compressed tablets of nimesulide each containing 100 mg were prepared by conventional wet granulation method as per formulae given in Table-1. One series of tablets (T1-T7) were formulated with different binders and potato starch (15%) as disintegrant and 2% of each of talc and magnesium stearate as lubricants. All the binders were used at 3% concentration of the formula in the form of either an aqueous solution or mucilage of suitable strength. A 2-5% is the usual concentration range for all the binders used[5]. Another series of tablet (T8-T13) were formulated with different disintegrants in their effective concentrations using starch paste and PVP as binders. Tablet granulations were compressed into tablets to a hardness of 5-6 kg/sq.cm. on a Cadmach single punch tablet machine.

Tablets were tested for uniformity of weight as per I.P. (1996). Disintegration time in distilled water was determined using a Thermonic Tablet Disintegration Test Machine, USP. 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.

The dissolution rate of nimesulide from the tablets, both formulated and commercial was studied in 900 ml of alkaline borate buffer (pH 8.4) using 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±1° were 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 Khan[6].

DE_{30} values, calculated based on dissolution data, were statistically analysed by Analysis of Variance (ANOVA) and Duncan's Multiple Range Test to test the significance of the observed difference due to various binders and disintegrants.

All the tablets prepared were found to contain nimesulide within 100±5% of the label claim. All batches 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 507 kg/sq.cm and was satisfactory. The percentage weight loss in the friability test was less than 1.0%. Tablets formulated with gelatin as binder did not fulfil the official (I.P.) disintegration test of uncoated tablets. Though the tablets formulated with all other binders fulfilled the official (I.P.) specification for disintegration time, variations were observed in their disintegration times in the range 1.5-12.0 min.

Dissolution profiles of various tablets are shown in Table-2. Dissolution of nimesulide from the tablets followed first order kinetics. The correlation coefficient (r) between log per cent undissolved and time was in the range of 0.882-0.999 with various tablet formulations. The dissolution of nimesulide from one of the commercial products was much higher than that from the other (Table 2). This observed difference in the dissolution profiles of the commercial products may be due to formulation variables.

Much variations were observed in the dissolution characteristics of the tablets formulated with various bind-

TABLE 1 : FORMULAE OF NIMESULIDE TABLETS PREPARED

Ingredient (mg/Tablet)	FORMULATION												
	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12	T13
Nimesulide	100	100	100	100	100	100	100	100	100	100	100	100	100
Potato Starch (Dry)	75	75	75	75	75	75	75	-	-	-	-	-	-
MCC	-	-	-	-	-	-	-	75	-	-	75	-	-
PGS	-	-	-	-	-	-	-	-	75	-	-	75	-
Primogel	-	-	-	-	-	-	-	-	-	20	-	-	20
Starch Paste	15	-	-	-	-	-	-	15	15	15	-	-	-
Acacia	-	15	-	-	-	-	-	-	-	-	-	-	-
Surcose	-	-	15	-	-	-	-	-	-	-	-	-	-
PVP-K-30	-	-	-	15	-	-	-	-	-	-	15	15	15
HPMC	-	-	-	-	15	-	-	-	-	-	-	-	-
Methyl cellulose	-	-	-	-	-	15	-	-	-	-	-	-	-
Gelatin	-	-	-	-	-	-	15	-	-	-	-	-	-
Lactose	290	290	290	290	290	290	290	290	290	345	290	290	345
Talc	10	10	10	10	10	10	10	10	10	10	10	10	10
Magnesium Stearate	10	10	10	10	10	10	10	10	10	10	10	10	10
Total Weight (mg)	500	500	500	500	500	500	500	500	500	500	500	500	500

TABLE 2 : DISSOLUTION CHARACTERISTICS OF NIMESULIDE TABLETS FORMULATED

Formulation	Cumulative per cent dissolved at 4 times (min)				De_{30} (%) X±s.d	k_1 (min-1)
	10	30	60	120		
T1	7.9	32.5	69.1	82.8	16.0±4.3	0.016
T2	11.5	44.8	76.5	94.5	20.1±5.0	0.024
T3	14.6	43.6	62.7	89.4	22.7±2.9	0.018
T4	37.6	85.5	98.8	98.7	51.9±11.0	0.070
T5	35.2	89.3	96.0	97.4	54±1.4	0.033
T6	3.5	14.7	25.8	44.0	7.9±2.7	0.004
T7	3.3	8.0	14.4	21.0	4.1±0.6	0.002
T8	8.3	9.6	13.4	20.2	7.3±0.1	0.001
T9	9.8	35.3	56.3	70.2	18.3±2.8	0.010
T10	35.0	78.5	99.3	99.9	55.8±10	0.050
T11	1.2	2.9	5.0	7.5	1.6±0.1	0.001
T12	59.4	82.5	91.7	95.3	60±4.2	0.031
T13	65.7	92.8	97.5	99.6	64.7±2.7	0.060
C1	50.2	74.3	85.0	96.7	52.1±45	0.045
C2	21.05	42.1	55.6	79.2	25.4±3.7	0.012

ers (Table 2). Based on DE_{30} values the order of performance of binders was found to be HPMC> PVP> sucrose> acacia> starch paste> methyl cellulose> gelatin. Analysis of variance (ANOVA) of DE_{30} values indicated highly significant ($P<0.01$) differences in the dissolution characteristics of tablets due to binders. Duncan's Multiple Range Test was used to compare the performance of various binders. Tablets formulated with PVP and HPMC exhibited significantly higher dissolution rates and efficiency values among all. Tablets formulated with starch paste, acacia and sucrose as binders exhibited similar dissolution behaviour. The differences observed among these tablets were not significant. Tablets formulated with methyl cellulose and gelatin as binders gave very low dissolution rate and efficiency values. though the tablets formulated with PVP and HPMC exhibited longer disintegration times, they gave rapid and higher dissolution of nimesulide. The rapid and higher dissolution observed with these binders may be due to their strong hydrophilic nature.

The effect of four disintegrants namely potato starch, MCC, PGS and Primogel on the dissolution rate of nimesulide was studied in two series of tablets prepared with starch paste and PVP as binders. Based on DE_{30} values the order of performance of disintegrants was found to be Primogel>PGS>Potato starch>MCC with both the binders starch paste and PVP.

When starch paste was used as the binder, tablets formulated with Primogel gave much higher dissolution rate and efficiency values than the others. Tablets formulated employing potato starch and PGS as disintegrants exhibited similar dissolution behaviour. When PVP was used as the binder, tablets formulated employing potato starch, PGS and Primogel as disintegrants gave similar dissolution. The observed differences in the DE_{30} values of these tablets were not significant. With both the binders starch paste and PVP, tablets formulated with MCC as disintegrant gave very poor dissolution of nimesulide. Among all the tablets prepared, formulation T4 (PVP/potato starch), T5 (HPMC/potato starch), T10 (starch paste/Primogel), T12 (PVP/PGS) and T13 (PVP/Primogel) gave much higher dissolution rates and efficiency

values than others, both formulated and commercial. Hence the corresponding binder - disintegrant combinations were considered suitable for nimesulide tablets. The above tablets also fulfilled all the other official requirements.

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Visible Spectrophotometric and HPLC Methods for Estimation of Suprofen from Bulk Drug Samples

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One visible spectrophotometric and one HPLC method have been developed for estimation of suprofen from bulk drug sample. Developed visible spectrophotometric method is based on formation of chloroform extractable coloured complex of drug with copper (II) acetate in presence of potassium chloride and acetate buffer pH 5.8. The coloured complex shows absorbance maxima at 682.0 nm. Beer's law was obeyed in the concentration range of 0-10 mg/ml of suprofen. Developed HPLC method was a reverse phase chromatographic method using Inertsil C_{18} column and acetonitrile:water::35:65 pH 2.7 as mobile phase with detection at 254 nm. Caffeine was used as internal standard for HPLC method. Linearity was observed in concentration range of 20-250 µg/ml of suprofen. Results of analysis for both the methods were validated statistically.

Suprofen, chemically α-methyl-4-(2-thienylcarbonyl) benzene acetic acid is an anti-inflammatory agent[1]. Few analytical methods for estimation of suprofen from biological fluids, including one GC[2], one HPTLC[3] and three HPLC[4-6] are reported. One HPLC[7] method is reported for determination of suprofen in drug substance and capsules. However no spectrophotometric method is reported for the estimation of the drug from pharmaceuticals or bulk drug sample. An attempt has been made in the present study to develop a simple visible spectrophotometric and an HPLC method for analysis of suprofen from bulk drug sample.

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A Jasco UV/visible recording spectrophotometer with 1 cm matched quartz cells and Shimadzu delivery module LC-10AD with UV SPD-10A detector and Chromatopac C-R7A integrator were used for present study.

For colorimetric method standard drug solution in chloroform (10 mg/ml) was diluted with the same so as to give several dilutions in the concentration range of 0-7 mg/ml of suprofen. To 5 ml of each dilution taken in