Formulation and Dissolution Studies of Solid Dispersions of Nimesulide

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Nimesulide, a highly water insoluble drug, exhibited poor dissolution pattern which perhaps is the reason for its poor absorption. Solid dispersions of nimesulide were prepared by fusion method using different carriers such as poloxamer PF-127, PEG 4000, citric acid, PVP, urea and mannitol. The ratio of drug:carrier chosen was 1:5 after initial trials with different ratios. They were evaluated for drug content, intactness of the drug in the formulations and dissolution. The drug content in the formulations varied from 76-84%. There was no interacton between the drug and the carriers as seen by their TLC. From the cumulative percent drug release data obtained by carrying out dissolution studies for a period of 3 h in 0.1 N HCl medium and the control study using 0.1% sodium lauryl sulphate, it was observed that the release rate constant of the formulations (0.289 to 561 h^{-1}) were significantly greater than that of the drug (0.065 h^{-1}) and the control (0.111 h^{-1}). Poloxamer PF-127 was found to be the best carrier followed by PEG 4000 and urea.

NIMESULIDE, a newer generation NSAID is very effective in the treatment of rheumatoid arthritis and other associated conditions[1]. It is reported to have terminal half life between 1.64-4.95 h. C_{max} values ranging from 1.98-9.85 mg/L were achieved within 1.67-3.17 h after oral administration of 50-200 mg tablets. The drug is extensively bound (99%) to human plasma proteins and it undergoes extensive metabolism in the liver[2]. Nimesulide has a lower risk of duodenal lesions in comparison with most NSAIDs[3]. It exhibits poor water solubility (0.01 mg/ml)[4] which may pose dissolution related absorption problems. Solid dispersions, one of the pharmaceutical techniques to improve the dissolution of poorly water soluble drugs[5] play an important role in increasing rate of dissolution, absorption and therapeutic efficacy of drugs. Thus, the formulation of solid dispersions of nimesulide was taken up in the present study.

Solid dispersions of nimesulide were prepared using the carriers[6] poloxamer PF-127, PEG 4000, citric acid, mannitol, PVP and urea by fusion method[7]. After initial trials with different ratios of the carriers, the drug carrier ratio of 1:5 which gave considerable release in all the products was chosen.

The drug content in the solid dispersions was determined by extracting the drug by suitable solvents from the sample equivalent to 100 mg of nimesulide and estimating the drug by spectrophotometry at 393 nm[4]. The solvent used for extraction of drug from citric acid and mannitol solid dispersions was chloroform, from poloxamer PF-127 solid dispersion was PEG 400 and from the PEG 4000, PVP and urea solid dispersions was methanol.

The intactness of the drug in the formulations was evaluated by TLC using chloroform:methanol (9.5:0.5) as the solvent system and pure nimesulide as the reference sample. The drug was detected by exposing the TLC plates to iodine vapours.

Dissolution studies of the pure drug (20 mg) and formulations (equivalent to 20 mg of drug) were carried out in a USP dissolution test apparatus at 50 rpm and 37 ±0.5° using 900 ml of 0.1 N HCl (pH 1.2). A control study was also carried out for pure drug using 0.1% sodium lauryl sulphate (SLS) in the dissolution medium.

1 ml samples were withdrawn at the interval of 0.5 h for 3 h and filtered[8]. The filtrates were assayed spectrophotometrically at 393 nm, after suitable dilution.

Table-1 : T_{50} and Dissolution rate constant of pure drug and solid dispersions

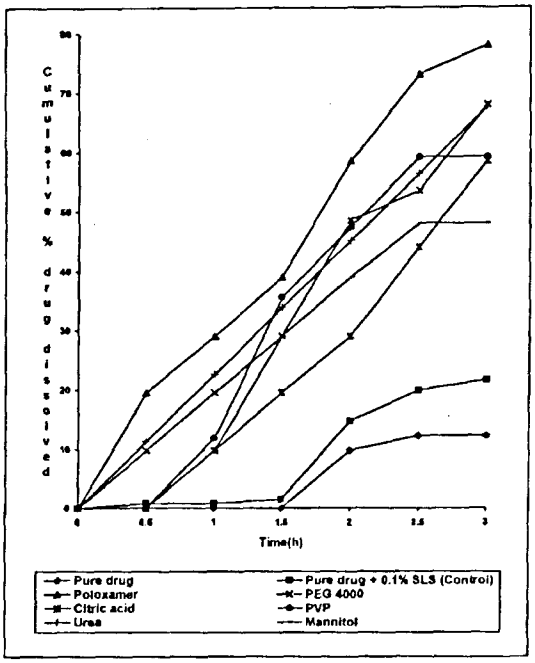
Sample	t_{50} (min)*	Dissolution Rate constant* (K) (h^{-1})
Pure drug	-	0.065
Pure drug+0.1% SLS	-	0.111
Poloxamer PF-127 S.D	106.5	0.561
PEG 4000 S.D	129.7	0.408
Citric acid S.D	163.5	0.340
PVP S.D	133.3	0.390
Urea S.D	132.0	0.400
Mannitol S.D	-	0.289

Note: S.D=Solid Dispersion, *-Average of three determinations.

T_{50} values were calculated from the plot of cumulative % drug dissolved vs time.

K values were calculated from the linear regression analysis of the dissolution data.

Fig. 1 : Dissolution profiles of pure drug, control and formulations



The values obtained are the average values of three determinations

The cumulative percent drug dissolved at various time intervals were found out from which the values of t_{50} were determined. The release rate constant was calculated by the linear regression analysis of the data. All the solid dispersions were found to be free flowing. The drug content varied from 76 to 84%. All the products resolved into clear spots with R_f value similar to that of pure drug (0.88). No extra spots were detected which indicated that there was no interaction between the pure drug and the carriers. From the results it can be seen that all the solid dispersions showed rapid dissolution of drug as compared to the nimesulide pure drug as well as nimesulide in presence of 0.1% SLS. Poloxamer PF-127 was found to be the best carrier (Figure 1 and Table 1) as seen by the dissolution rate constant which is nearly 10 times when compared to the pure drug and 5 times when compared to the control followed by PEG 4000 and urea. The same results are confirmed by their t_{50} values.

The efficiency of carriers in improving the dissolution of nimesulide is in the following order :

poloxamer PF-127>PEG 4000>urea>PVP>citric Acid>mannitol.

Hence, it can be concluded that the solid dispersions improved the dissolution characteristics of nimesulide.

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Quantitative Determination of Bacoside by HPLC

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High pressure liquid chromatographic method for quantitative determination of Bacoside-A_3 the main active constituent of the saponin fraction having facilitatory effect on learning is described. A C_{18} column was used for the separation with acetonitrile:water (40:60) as mobile phase. the lowest quantitation limit was 26 µg/ml. The intra-day relative standard deviations and deviation from actual concentration values are less 6% and ±8% respectively, which showed good reproducibility and accuracy of the method.

BACOPA monniera L (Syn:*Herpestis monniera* L., HB & K), BRAHMI, is used as a reputed nervine tonic in the traditional system of medicine[1]. Its alcoholic extract was found to improve the performance of rats in several learning tests as manifested by better aquisition, consolidation and retention of newly acquired behavioural responses[2,3]. The activity has been localised in the saponin fraction designated as bacosides[4]. A traditional remedy developed by us from the plant *Bacopa monniera* containing bacosides as the active constituents is already marketed as *Memory Plus*. Earlier a U.V. spectrophotometeric method for quantitative determination of bacosides was developed[5]. In this communication, a HPLC method for the estimation of bacoside A_3[6], the main constituent of the bacosides is described.

Standard sample of bacoside A_3 was obtained from the Medicinal Chemistry Division of CDRI, acetonitrile and methanol both were of HPLC grade and were procured form E. Merck (India) Ltd., Bombay and used without further purification. All other reagents were of analytical grade and used without further purification. Aerial part of *Bacopa monniera* L. was collected from West Bangal, India. A voucher specimen is deposited in the Herbarium of CDRI. The air dried and powdered plant material was processed as reported earliar[7].

The HPLC system consisted of a Perkin Elmer 250 solvent delivery system, a Rheodyne (Cotati, CA, USA) model 7125 injector with a 20 µL loop and a Perkin Elmer model 235 diode array detector with a G.P. 100 printer plotter. Separation was carried out on a ODS E. Merck column (250 mm x 4 mm, ID, and 5 µm particle size). The column effluent was monitored at 215 nm. Chromatography was performed at 27+-3° at a flow rate of 1 ml/min of the mobile phase consisting acetonitrile:water (40:60). the mobile phase was filtered and degassed before use.

Stock standard solution containing 260 ug/ml of bacoside, A_3 was prepared by dissolving 2.6 mg of standard bacoside A_3 in 0.5 ml of methanol and then making up the volume upto 10 ml with mobile phase. Working standard solutions were prepared form the stock solution in the concentration range 26 to 260 µg/ml, using mobile phase. The sample (active fraction) solution containing 500 µg/ml was prepared by dissolving 5 mg of sample in 1 ml of

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