CHAPTER 5

S U M M A R Y

SUMMARY

Solid dispersion is one of the most widely used techniques now a days, either to enhance the action or prolong the action of drugs. This study involves the first aspect of its application. Careful study of comprehensive literature reveals still a good scope of work in this direction.

Nifedipine, Phenytoin and Ketoprofen, poorly water soluble drugs, administration of which may result in lower and variable bioavailability were chosen as model drugs. Therefore, the study aims at reducing this bioinequivalence on one hand and increasing the overall bioavailability of drugs on other hand. Apart from common highly water soluble excipients, excipients like polyoxyl-40-stearate, poloxamer 188 and poloxamer 407, were also evaluated for their efficacy to improve the dissolution behaviour and bioavailability of the selected drugs.

Solid dispersions were prepared using fusion method at slightly higher temperature than the melting point of the corresponding excepients followed by quenching to about 4°C.

On the preliminary investigation of dissolution behaviour of various solid dispersions of Nifedipine, solid dispersions reflected good improvement in the dissolution characteristics of drug, the minimum and maximum rate of

dissolutions being about 4 and 29 times the dissolution rate of drug at two reference points in the entire length of dissolution profile i.e. 2 hr. The observed improved dissolution behaviour could not solely be due to the solubilising power of these excepients as manifested in the solubility studies in which Poloxamer 407 was most effective; which could be substantiated by dissolution study of physical mixtures.

After analysing above results, two best rated systems namely Nfd- PEG 6000 solid dispersions and Nfd - Poloxamer 188 solid dispersions, were further investigated for their dissolution behaviour by yet another method, i.e. tape method as suggested by Goldberg et al (1965)

Both the systems showed good improvement in their dissolution behaviour but the results could not be quantitated, as the drug itself did not dissolve to yield detectable amount in solution, though the relative dissolution behaviour could be observed in terms of relative dissolution rates and cube root dissolution rate constants, which reflected the effect of compositions of solid dispersions in terms of drug to excipient ratio; the lower the ratio, better was the release.

The underlying mechanism to bring about this improved dissolution behaviour of drug, was investigated using various techniques like x-ray diffraction patterns, photomicropraphs, hot stage microscopy for construction of phase diagrams and IR spectrophotometery. The chief

reason for the improved dissolution behaviour of the selected test preparations, was found to be their amorphous form which is associated with greater amount of energy than the crystalline form.

These two solid dispersions viz. Nfd-PEG 6000 (1: 19), Nfd-Pololoxamer 188 (1:19), Adalat capsule and Nfd tablet (Sarabhai Chemicals Ltd., India), were evaluated to assess their bioavailability. The results of their bioavailability after being analysed by suitable statistical (multiple variance test) method, reflected slight superiority of Adalat capsule in terms of high plasma concentration of drug of 1 hr. than the two solid dispersions. Two solid dispersions appeared to be bioequivalent and were definitely superior to Nfd. Tablet in terms of rate and extent of absorption.

Therefore, solid dispersions appeared to enhance the gastro intestinal absorption of Nifedipine which was the ultimate objective.

Phenytoin, a widely used antiepileptic drug, having considerable bioinequivalence and a narrow therapeutic range; and whose bioavailability depends upon its dissolution behaviour was the second choice in this study.

Preliminary in-vitro dissolution study revealed, a marked improvement in the dissolution behaviour of drug from its solid dispersions. The minimum and maximum dissolution

rates being 0.81 and 2 times the dissolution rate of Phenytoin only (MSZ) at two reference points in the entire length of dissolution profile.

Improved wettability, reduction of crystallite size and presence of high concentrations of excepients around the drug particle in general; and in particular high microenvironmental concentration of urea around the drug particles and reduction of crystallite size in case of Pheny - urea and Pheny-POS solid dispersion respectively, may be the reasons for the observed improved dissolution behaviour of drug from the solid dispersions.

The two selected test preparations viz. Pheny-Urea and Pheny-POS solid dispersions were chemically stable under normal room temperature and humidity conditions, for a period of two years, but Pheny-Urea solid dispersion aged resulting in decrease in dissolution rate of drug within relatively short span of the period, which excluded it from bioavailability study.

IR spectra also did not yield any evidence suggesting any chemical interaction.

The bioavailability study (excretion rate study) of two test preparations viz. Pheny-POS (1:3) solid dispersion and Phenytoin, revealed the superiority of solid dispersion in terms of both rate and extent of absorption as reflected by higher excretion rates of Phenytoin from solid dispersion

than Phenytoin itself, even though the dose of drug in solid dispersion is 2/3rd of the Phenytoin used as such. Thus, the improved bioavailability of Phenytoin from such a solid dispersion system may offer clinical advantage in terms of achieving the required therapeautic level of drug in epileptic patients and help reduce the intersubject variations.

Ketoprofen, a propionic acid derivative, is commonly used anti-inflammatory drug. It also has low aqueous solubility which may result in bioinequivalence.

Basic investigations on the dissolution behaviour of drug from solid dispersions employing two successful excipients namely PEG 6000 and Poloxamer188 resulted in improved dissolution of drug from solid dispersions in comparision to Ketoprofen only. The minimum and maximum dissolution rates of drug from these solid dispersions were 1.6 and 8.0 times the dissolution rates using two reference points (10 min. & 60 min.). Physical mixtures also displayed superior dissolution characteristics in relation to drug. In fact, keto-PEG 6000 SD and keto-PEG 6000 PM, do not differ much in terms of their dissolution rates, which became a notable feature for the later to be used as a test preparation in bioavailability trial.

These two systems were also analysed for their dissolution behaviour by tape method (Goldberg, et al, 1965).

The results suggested excellent correlation between dissolution rates obtained by USP method and the tape method, in terms of the improvement of dissolution behaviour from these two systems. Cube root dissolution rate constants were also computed which were about 10 and 4 times the rate constant of Ketoprofen for Keto-Poloxamer 188 solid dispersion and its physical mixture respectively. It was about 2 times for keto-PEG 6000 physical mixture in comparision to Ketoprofen only.

It has been theorised that the systems investigated follow a mixed mathematical model comprising of planar surface dissolution and particulate dissolution model.

Apart from the limited role of particle size reduction, the factors which may contribute to observed increase in the dissolution characteristics are (i) reduction in aggregation and agglomeration of drug (ii) the existence of high concentrations of excipients in the vicinity of drug particle (iii) possible micellar solubilization of drug at concentration higher than the critical micelle concentrations of excipients.

The selected samples were stable chemically and did not show any change in their dissolution behaviour when stored under normal temperature and humidity conditions for a reasonable length of time.

Bioavailability (excretion rate of Ketoprofen) of four test preparations viz. Keto-Poloxamer 188 (1:9) SD, Keto-PEG 6000 (1:9) PM, Keto capsule and Keto capsules (M & B) , was evaluated using a suitable trial design. The results after being subjected to suitable statistical analysis (multiple variance test), revealed bioequivalency between Keto-Poloxamer 188 SD and Ketoprofen only, however equal clinical efficacy or broad based trial, might provide a further conclusive evidence. But still Keto-Poloxamer 188 SD was found to be superior to both Keto-PEG 6000 PM and Ketocaps (M&B). The poor bioavailability of Keto-PEG 6000 PM is inexplicable at this juncture, but poor availability of Keto caps (M&B) could be attributed to the lower observed dissolution rate of drug as a result of the use little compaction pressure on the powder mix of the above mentioned capsules and the possible formulation factors. In Keto capsule, no such pressure was used and the drug was filled in a bigger capsule, which resulted in better dissolution rates than Keto caps (M&B).

The use of such a solid dispersion may serve well in achieving faster action and at the same time minimise bioinequivalency problem to some extent.

While working with these excepients, some useful features observed are (i) Use of Polyoxyl-40-stearate resulted in much improved dissolution behaviour of Phenytoin here in this study and with other studies too

(not reported) but the waxy nature of this excipient poses a great problem in handling this specially when seiving Finer granules which still may improve the dissolution behaviour, can't be obtained particularly in tropical climate like that of our country. Therefore, if it is to be used, it should be used under carefully controlled temperature.
(ii) Use of Poloxamer 188 and Poloxamer 407 as excipients in solid dispersions yielded good results especially when using Poloxamer 188. But one common feature of Poloxamer 407, has been observed in case of Nifedepine, Phenytoin and Nitrofurtanoin (unreported) that as the concentration of Poloxamer 407 in solid dispersion is decreased, there is corresponding increase in the dissolution rates of these drugs from solid dispersions. However, still lower concentrations of this were not evaluated in the current study but it is hoped that this may serve as a versatile excipient in such studies particularly with the added advantage of using lower concentration. At the same time both these Poloxamers have proved to be good solubility enhancers. Therefore, this potential also can be tapped in a suitable manner.

Incorporating these Poloxamers with drug having lower melting point like Ketoprofen (m.P. 96°C) in solid dispersions, results in solid which is difficult to pass through finer seives, but when using with drug having high melting front like Nifedipine or Phenytoin, this problem is not so severe. This once again suggests

the use of controlled temperature for achieving better results.

Summing up, the use of solid dispersions appeared to be beneficial in the context of achieving faster action, better bioavailability and minimising the bioinequivalence problem along with its possible utility in industry in which the working environment can be suitably controlled and monitored. Also is its added utility for controlling the release of drugs, finds a wide spectrum of area to work at.