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**“ENHANCEMENT OF DISSOLUTION AND BIOAVAILABILITY OF  
SOME POORLY SOLUBLE ACTIVE PHARMACEUTICAL  
INGREDIENTS AND DEVELOPMENT OF THEIR FORMULATION”**

Summary report for thesis to be submitted to  
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## Summary and Conclusions of the work

Dissolution of water insoluble drugs has always been problem for formulation with pharmaceutical industries and the realization of the fact that formulation factors are significant in affecting the biological availability of a drug in a dosage form has led to continuous development and expansion of novel drug delivery systems.

For orally administered solid particles containing the drug, the dissolution process is the rate limiting process with respect to absorption process. It is because dissolution is going to exert an effect on the rate and amount of drug appearing in the body. The poor dissolution characteristics of relatively insoluble drugs have been a problem to pharmaceutical industry.

**Chapter 1** of the thesis exemplifies introduction to the problem. Various techniques used for dissolution rate enhancement are mentioned in introduction. It also gives literature reviewed for the different methods available. Of these all the available techniques some promising techniques are studied in the present work with different excipients to improve dissolution pattern of lower aqueous solubility drugs which are carbamazepine, oxcarbamazepine and gabapentin. The techniques studied are formulation of Self Emulsifying Drug Delivery Systems, Liquisolid Systems and their comparative evaluation with Solid Dispersions and Microcrystals.

The work was carried out with different drugs, carbamazepine, oxcarbamazepine and gabapentin, all having bioavailability problems. Objectives of the work achieved and profiles of CBZ, OCBZ and GPN are pointed out in introduction part. It is hypothesized that drug in solution state gives maximum rate of dissolution as well as complete dissolution. In present work, this hypothesis was studied by using two different techniques, SEDDS systems and liquisolid systems. Dissolution studies showed that SEDDS gave fine emulsion on dilution of the system with USP SGF. Liquisolid systems gave disaggregated particles in which the drug was retained in solution state. Another approach of dissolution rate enhancement is conventional particle size reduction. However conventional milling or cutting results in particle size reduction but at the sacrifice of loss of material flowability (static charges developed), increase in particle size on storage (recrystallization of drug). In present work two more drug delivery systems solid dispersion and microcrystals were prepared where after particle size reduction the amorphous material was stabilized in polymer matrix.

**Chapter 2** is designated to entire Experimental section. Wherein subchapters give information about the different formulations like SEDDS, Liquisolid systems, Solid dispersion systems and Microcrystals prepared. It illustrated the materials and methods of preparation for each drug delivery system.

**Brief overview of each drug delivery system developed and evaluated.****Self Emulsifying Drug Delivery Systems**

SEDDS formulations for CBZ, OCBZ and GPN were designed using simplex centroid mixture design. Each mixture was analyzed for particle size, visual inspection of self emulsification and drug dissolution studies.

All the formulations of experimental design for CBZ, OCBZ and GPN were assessed for *in vitro* drug dissolution studies. Dissolution studies were carried out in USP XXIV type II dissolution apparatus (Veego, Mumbai, India) with a 400 mL Schott Duran beaker as a dissolution vessel. Samples of GPN SEDDS dissolution studies were analyzed using HPLC. The purpose of carrying out dissolution studies in 250 mL dissolution medium was to get discriminatory results for drug dissolution pattern. Preliminary studies in 900 mL dissolution medium yielded inequitable results.

The values for experimental levels of components of mixture design along with their corresponding response values are tabulated. Contour graphs (ternary phase diagrams) for particle size and percent drug dissolved were constructed for the analyzed model. Particle size data analysis was performed using Malvern zetasizer.

The coefficient and standard error values of model analyzed for response particle size and percent drug dissolved helped analyze the model and identify the optimum values for SEDDS components.

Accelerated Stability studies for CBZ OCBZ and GPN SEDDS systems were performed and the results were extrapolated for shelf-life calculation SEDD systems.

Results for SEDDS of CBZ with labrasol showed incredible increase in *in vitro* dissolution of CBZ when compared with pure drug. OCBZ SEDDS also showed considerable increase in percent drug dissolution when compared with their pure drug counterparts. However GPN SEDDS did not show increase in drug dissolution to the extent that previous systems of CBZ and OCBZ showed.

**Liquisolid systems**

Liquisolid systems for CBZ, OCBZ and GPN were prepared using Avicel PH 103 as carrier powder and Aerosil as coating material. CBZ and OCBZ were dissolved in PEG 600 (used as the liquid vehicle to prepare the liquid medication of different drug concentrations) with different drug conc. in liquid medication (15 – 30 % w/w). Effect of tween 80 was studied on CBZ and OCBZ liquisolid systems. Effect of Gelucire was studied on liquisolid systems of GPN. Key formulation aspects of prepared liquisolid systems like Excipient ratio, Liquid load factor ( $L_f$ ), Fraction of molecularly dispersed drug ( $F_M$ ) in the liquid medication of liquisolid systems and Drug dissolution rate for first 10 min of dissolution studies ( $D_R$ ) were determined and tabulated.

To study the effect of amount of dissolution medium on percent drug dissolution of liquisolid systems dissolution studies were conducted in 3 different dissolution medium volumes i.e. 450 mL, 600 mL and 900 mL. The dissolution study was conducted in USP XXVII simulated gastric fluid (without enzymes) having pH  $1.2 \pm 0.02$  as dissolution media. Liquisolid systems were placed in cloth pouches to avert floating of them on dissolution media surface.

The higher CBZ dissolution rates displayed by the liquisolid systems compared to marketed conventional tablets were clearly observed. The dissolution rate ( $D_R$  in mg of drug dissolved per min) observed during the first 10 min of the dissolution process was plotted against the volume of dissolution medium. Since the liquisolid tablets contain a solution of the drug in PEG 600 (17% w/w), the drug surface available for dissolution is tremendously increased. Admittedly, the relatively small amounts of liquid vehicle (PEG 600) contained per liquisolid system, are not sufficient to increase the overall saturation solubility of drug in the aqueous dissolution medium. The consistent and higher dissolution rates displayed by liquisolid systems may also imply enhanced oral bioavailability.

Since the drug is completely in solution in the liquid medications of PEG 600, it presented improved dissolution properties. However, the solubilization state of the drug in the liquid vehicle of the liquisolid systems does not entirely justify the initial drug release patterns observed. The drug concentration in the liquid medication ( $C_d$  ranging from 15 to 25% w/w) has an apparent effect on the CBZ 10 min dissolution rates displayed by the liquisolid systems of PEG 600, as shown in Figure 2.2.7. However, at the same dissolution conditions, systems containing liquid medications with increasing  $C_d$  values exhibited declining *in vitro* release properties until reaching a minimum plateau dissolution rate displayed by the liquisolid systems containing about more than 20% w/w of drug in their liquid medications. Such differences in the drug dissolution rates of the PEG 600 liquisolid systems possessing different  $C_d$  values, observed in Figure 2.2.7, may be justified using the previous hypothesis of the available drug surface effects on dissolution.

In case of CBZ and OCBZ liquisolid systems the solubilization and molecular dispersion states of the drug in liquisolid systems were different. When dissolution rates obtained from PEG 600 liquisolid systems possessing different  $C_d$  values were plotted against their corresponding  $F_M$  values it was observed that after remaining at a minimum plateau level for  $F_M$  values.

For GPN liquisolid systems Liquid load factor was studied in the range of 0.44 to 0.87. All the liquisolid systems of GPN prepared exhibited good flow properties.

### **Solid Dispersion Systems**

In case of SDs poorly soluble drug are dispersed in an inert hydrophilic polymer or matrix by melting, solution formation or solvent melting to yield solid dispersion. Literature survey revealed that certain hydrophilic swellable polymers like Na-CMC, HPMC and

chitosan have still been unexplored for their potential to form solid dispersion in order to improve dissolution properties of poorly soluble drugs. Solid dispersions were prepared with modified solvent evaporation technique. In present work solid dispersions for carbamazepine and oxcarbamazepine using three different polymers Na-CMC, HPMC and Chitosan individually, were prepared by pouring the drug solution at once in polymer suspension.

To study all the possible combinations of individual polymer and drug, solid dispersions of CBZ and OCBZ were prepared according to three levels full factorial design ( $3^2$ ). For experimental design the dependent variables measured were percent drug dissolved at various time points and particle size of solid dispersion.

Solubility Determination for all the SDs was performed. *In vitro* dissolution study for all the solid dispersions of experimental design for CBZ and OCBZ with Na-CMC, HPMC and chitosan were performed using USP XXVII simulated gastric fluid (SGF) without enzymes having pH 1.2.

SEM photographs for pure drugs and their SDs with Na-CMC, HPMC and chitosan were taken with scanning electron microscope (JSM-5610LV, Jeol Corporation., Japan).

In case of SDs of CBZ and OCBZ it was found that quadratic terms of experimental design ( $x_1$  and  $x_2$ ) had significant positive effect on percent drug dissolved. the response surface plots for percent drug dissolved from SDs in SGF of Na-CMC, HPMC and chitosan at 30 minutes ( $Q_{30}$ ) was plotted. Response surface shows that higher the amount of polymer, significant is the dissolution enhancement. In order to assess comparative extent of dissolution rate enhancement from its SDs mean dissolution time (MDT) was calculated.

Particle sizes of pure drug and SDs were determined using Malvern Mastersizer (Malvern Mastersizer, UK) with petroleum ether as dispersion medium for sample.

SDs of polymers Na-CMC and chitosan for CBZ and OCBZ showed increase in dissolution rate on increase in amount of polymer. Whereas in case of HPMC solid dispersions increase in amount of polymer upto certain level led to enhanced drug dissolution but further addition of polymer resulted in decrease of dissolution of drug.

SDs of CBZ and OCBZ with Na-CMC showed promising drug dissolution results; hence they were subjected to accelerated stability studies. Stability studies data was extrapolated to determine the shelf life of product.

To conclude, MLR analysis of results of experimental design illustrated that SD of CBZ and OCBZ when prepared with hydrophilic swellable polymers showed marked increase in percent drug dissolution in SGF without enzymes which was illustrated with the help of mean dissolution time. SDs prepared with Na-CMC showed the highest drug dissolution compared to HPMC and chitosan owing to its optimum wetting properties by gelatinization and control over particle size of drug.

## Microcrystals

Microcrystals of CBZ and OCBZ were prepared using Na-CMC, HPMC and chitosan. For the experiments performed as per design coded and actual values of independent variables are depicted in table 1. Two levels -1 and 1 were used for study and for centre points a third level was set at '0' for all the independent variables (drug concentration, chitosan concentration, feed rate, inlet temperature and percent aspiration). Table 2 shows the experiments performed as per the fractional factorial design. Whereas percent drug dissolved, wettability time, flowability in terms of angle of repose and particle size were designated as response variables.

The present study was performed with fractional factorial design of resolution 5 (with all 2 factor interaction) for the screening of drug concentration, chitosan concentration, feed rate, inlet temperature and percent aspiration for spray drying. Whereas percent drug dissolved, wettability time, flowability in terms of angle of repose and particle size were designated as response variables.

Microcrystals of CBZ and OCBZ were prepared using solvent change method. The formed microcrystals were grown naturally in medium and spray dried to completely dry the microcrystal product and not for formation of the particles or microcrystals. Spray drying parameters like feed rate, inlet temperature and percent aspiration decide the quality of final product like particle size, flow properties as well drug loading capacity of the system.

Prepared microcrystals were characterized for particle size measurements *in vitro* Dissolution studies and wettability Studies.

Leverage plots of predicted and actual values for the experimental design with percent drug dissolved, particle size, wettability time and angle of repose as responses for microcrystals of CBZ with Na-CMC, HPMC and Chitosan respectively were generated for getting better idea about their effect. The optimization parameters for spray drying process also had significant effect on product quality, such as increasing in feed rate increases particle size of product considerably. However it did not show any statistically significant effect on percent drug dissolution. However increase in inlet temperature also showed decrease in percent drug dissolution.

Since particle size has direct relationship with drug dissolution, decrease in particle size led to increased drug dissolution due to increase in surface area available for wetting.

Results also showed that increase in feed rate increased the particle size of microcrystals. Increase in feed rate for spray drying promoted particle growth because of excessive liquid supply and larger droplet size. Increase in inlet temperature of inlet air during spray drying decreased the particle size of microcrystals formed since the moisture content of spraying solution was also decreased due to rapid evaporation of liquid. CBZ Na-CMC showed the most narrow particle size distribution.

Results for Contact angle of pure drug powder and optimized batch of microcrystals showed that there was significant improvement in hydrophilicity of microcrystals produced.

DSC Thermogram of CBZ Na-CMC and OCBZ microcrystals suggested significant reduction in crystallinity of pure drug.

SEM studies for CBZ and OCBZ microcrystals formed in various batches of experimental design revealed significant changes in particle shape and surface topography due to impact of spray drying process.

CBZ and OCBZ microcrystals systems were subjected to accelerated stability studies. The accelerated stability data was extrapolated for shelf-life calculation of CBZ and OCBZ Na-CMC microcrystals.

Controlled crystallization poorly water soluble drugs in presence of carriers like Na CMC, HPMC and chitosan (which are rendered as a protective hydrophilic polymers) using spray-drying technique effectively enhance the drug dissolution. Controlled crystallization of drug in presence of carrier leads to formation of molecularly dispersed form of drug which has significantly reduced particle size.

**Chapter 3** is pharmacokinetic studies in rabbits. The formulation with best *in vitro* performance was selected from other formulations for studying *in vivo* behaviour in rabbits. The study investigated the pharmacokinetics of Carbamazepine, oxcarbamazepine and gabapentin in rabbits. The protocol was approved by the Institutional ethical committee at the M. S. University of Baroda at Vadodara, India. The experiments were conducted as per CPCSEA (committee for prevention, control and supervision of experimental animals) guidelines.

HPLC methods for the determination of carbamazepine, oxcarbamazepine and gabapentin from formulation as well as plasma were developed. The methods were validated for accuracy, precision, selectivity and recovery studies.

The extraction efficiency was calculated by adding known amount of CBZ, OCBZ and GPN (0.5, 1 and 1.5 µg/ml; n = 5 per concentration) to 0.5 ml of blank rabbit plasma. The CBZ and OCBZ were extracted into 5 ml of chloroform.

The control (conventional tablets) and SEDDS of CBZ (5 mg/kg) were administered into the oral cavity of each rabbit. Three groups of rabbits were undertaken for study. Blood samples were collected from the marginal ear vein at 0.25, 0.5, 0.75, 1, 2, 4, 6, 12 and 24 hrs after CBZ, OCBZ and GPN. Plasma samples collected from the rabbits were analyzed using developed reverse phase HPLC method and the drug plasma concentration values were determined from the calibration curve.

On observing the different *in vivo* pharmacokinetic parameters tabulated it is clear that CBZ SEDDS systems with labrasol showed improved oral bioavailability over CBZ Vit E

SEDDS and marketed conventional tablets. Pharmacokinetic study of OCBZ revealed that OCBZ SEDDS showed more bioavailability than conventional marketed tablets. Pharmacokinetic study of GPN exposed that GPN SEDDS also showed more bioavailability when compared with conventional marketed tablets. However the increment in percent bioavailability was not to the extent showed by CBZ and OCBZ SEDD systems.