2. PLAN OF WORK AND RESEARCH ENVISAGED

A drug delivery scientist encounters complex numerical and statistical reckoning on mathematical modelling of data generated during drug release kinetics, pharmacokinetics and DoE optimization of oral DDS. Manual data analysis in such cases being an impracticable and gruelling task, invariably calls for access to the pertinent computer software. The latter is considered nearly indispensable as it effectively lessens the expenditure of time, manpower, operational effort, mental input, finances, and potential errors during proletarian computations. The diminutive number of computer programs developed so far are either specific to attain the constrained objective(s) or are beyond the affordability and accessibility of the most. Accordingly, with increasing complexity of drug delivery research, the need for versatile and user-interactive software remains.

2.1. Development of Definitive Computer Software

Computer programs would be written in a suitable high-level language interface on the basis of documented algorithms on VAX mainframe and IBM-PC equipped with numeric co-processor (e.g., Pentium IV PC) with sizable RAM and disk space. The source codes were planned to be compiled using appropriate compiler(s), and subsequently debugged of various syntactical, logical and run-time errors. Programs would be designed to run on any IBM-compatible PC, requiring minimal hard disk space and execution time. Application programs would be written as menu-driven and user-friendly software, yielding elaborate and well-formatted elegant outputs (include the pertinent scatter plots) quickly and accurately, ready to be incorporated into reports or dissertations or manuscripts. Whole of the input information was planned to be entered through an ASCII file, the help for creating the same would be encompassed in the software. Hence, attempts would be made to develop versatile software not only suited for use in the developmental studies on CR drug delivery devices but even for the conventional oral solid dosage forms too.

The current plan of work would encompass development of computer software for (i) analysis and modeling of drug release kinetics from oral CRDDS, (ii) optimization of drug delivery using RSM, (iii) compartmental and noncompartmental pharmacokinetic analysis from plasma and urine level data, (iv) plasma protein binding and effect of pH and temperature on it, (v) modeling of oral bioavailability data obtained after cross-over studies, and (vi) nonparametric inferential statistical analysis.

2.1.1. Modelling of Drug Release Kinetics: With advancements in polymer science and supramolecular chemistry, design of oral CRDDS has been becoming increasingly intricate. Accordingly, the series of calculations involved during the kinetic processes have also become complicated, and the task of subsequent interpretation from the numeric results as incredibly demanding. As an obligatory step towards simulating real life experiments in the realm of CR drug delivery, research needs to be refurbished to
numerically develop and solve the general continuum kinetic models. Drug release kinetics being the cornerstone of drug delivery development, the acute need of the hour is to translate such models into apposite executable computer programs. Only mathematical modelling of drug release kinetics together with numerical simulation can provide the insight to the experimentalist, thus distinctly reducing the number of studies needed to obtain the desired CR profile(s). The algorithm of software would assume treatment of data in accordance with various popular approaches proposed like Higuchi model, Korsemeyer & Peppas model, Peppas & Sahlin model, Hixon & Crowell cube root model, Weibull, zero-order, first-order and second-order kinetic models. The basic input data for the program would be raw spectrophotometric absorbance or drug concentration values measured at various times during a dissolution run for “n” number of dosage forms units. Also, program(s) may be written for comparison of dissolution profiles using established approaches. Computer algorithms would also be generated for correction of drug release data for drug and/or volume losses observed during WR or WOR sampling during multi-sample dissolution runs and the computer program would be written based on such derived pseudo-codes.

2.1.2. Systematic Optimization of Drug Delivery Systems: The application of planned optimization studies using DoE is an established strategy to perk up the quality and efficacy of formulations on one hand, and improve the development economics in terms of time, cost and effort on the other. Software for implementing optimization using suitable experimental designs, like factorial design, central composite design, simplex design, etc. would be developed. The method of computing the coefficients of the polynomial equations would be based upon the popular algorithms of contrasts and MLRA, while the significance of the coefficients would be determined using the Yates’ ANOVA and the Student’s t-test. Further, the programs would also be authored for determining the optimum formula based upon grid search method and/or desirability function and generating data for constructing subsequent graphics viz. 3-D response surface plots and 2-D contour plots. Also, help features may be included to propose an apt experimental design for a specific drug delivery problem.

2.1.3. Pharmacokinetic Analysis and Modelling: The indispensable use of pertinent computer software for pharmacokinetic data analysis is well recognized. Computer programs would be developed for analyzing and modeling the data obtained from biopharmaceutical and pharmacokinetic domains associated with bioavailability determination of oral drug delivery devices. The software may offer a multitude of options of computing pertinent pharmacokinetic parameters, viz. $k_a$, $K$, $Cl$, $Cl_{renal}$, $V_{d appellent}$, $t_{1/2}$, $t_{1/2(absorption)}$, $(AUC)_a$ etc. from plasma/serum/saliva levels of drug using the standard Wagner-Nelson, Loo-Riegelman or feathering techniques, and of $k_a$, $K$, $ke$, $Cl_{renal}$, $V_{d appellent}$, $t_{1/2}$, $t_{1/2(absorption)}$, etc. using the standard Sigma-minus, Wagner-Nelson or rate-residual techniques from urinary excretion studies. Software would also be written for noncompartmental pharmacokinetic analysis facilitating the computation
of pharmacokinetic parameters like MRT, MAT, VRT, \((AUMC)_{OT}\), etc. employing various integration techniques like trapezoidal, log-trapezoidal, cubical spline, Lagranges, parabola-through-the-origin (PTTO), and the hybrid approaches. Plus, the software may also be authored for analyzing and comparing bioavailability of two or more formulations by multivariate crossover analysis of variance, as per the authentic algorithms of the experimental design and federal guidelines. The latter software may also include the facility of multiple comparison tests like Newmann's test, Dunet's test, Duncan's multiple range test, Tukey's test, and least significant difference tests, and the help features for creating data files and designing protocols, e.g., of bioavailability experiments. Owing to immense pharmacokinetic implications of protein binding, it was also proposed to include computational facilities to model and calculate varied drug binding parameters, and study the effect of pH, temperature, drug concentration, protein concentration, etc. on protein binding.

2.1.4. Inductive nonparametric statistical evaluation: Often data for scientific reporting of kinetic modelling data has to be supplemented with the results of pertinent statistical analyses. Such “distribution-free” nonparametric tests have invariably been employed during evaluation of various pharmacokinetic, biopharmaceutical, and drug release studies, when several assumptions of normality of data, sample size, etc. are not met with. The outcome of most of the pharmaceutical research has to tested using inferential statistics incorporating the nonparametric tests like chi-square test, sign test, randomness (run) test, Mann-Whitney test, Friedman test, Kruskal Wallis test, Wilcoxon signed rank sum test, Spearman’s rank correlation, etc. Data analysis using computers is not only quicker, more accurate and convenient, but results in greater elegant outputs too. Above all, a pharmaceutical scientist can surmount the hiccups of data analyses himself with little help of the statisticians. Although the facility for basic statistical computation is customarily available through statistical packages and spreadsheets, yet for multitude of reasons, the requirement of dedicated software for nonparametric inductive statistics stays on. The software may offer facility to analyse the data based on one or more of the aforesaid statistical techniques in an interactive manner through pop-up menus.

2.2. Validation of Computer Software for Oral Drug Delivery

Ultimately, the validity, utility and accuracy of the authored computer software would be verified through their application on the diverse data raised on the development of diverse oral drug delivery devices. The software would be initially validated using the theoretical test data generated intuitively, debugged for any errors (logical, grammatical or run-time), recompiled and re-executed. Subsequently, the source codes would be validated using the real test data generated experimentally and/or that reported in literature. The programs would be later prepared to run on IBM-compatible PC's by recompiling them on the in-house machines. The aesthetic effects and help features would be encompassed particularly for creating the input data files. Finally, the
programs would be combined together using either C routines or Norton's batch enhancing techniques in the form of the user-friendly and menu-operative software.

Developed software would also be validated using the *in vitro* drug release data generated experimentally using different oral DDS like hydrophilic and hydrophobic matrices, buccoadhesives and mucoadhesives, solid dispersions and inclusion complexes, microspheres, hydrodynamically balanced systems, etc., employing drugs on the basis of their physicochemical, biopharmaceutical and pharmacokinetic characteristics, using blends of polymers/carriers based on their release rate controlling potential, biodegradability, cost, availability, etc. Drug release data obtained through dissolution studies using type I or II USP apparatus would be employed for the purpose. Initial formulations studies, carried out as a prelude to the optimization studies, would ostensibly identify the polymers as the factors and their concentrations as factor levels. Subsequently, comprehensive kinetic modelling would be carried out on drug release kinetic data obtained from the formulations prepared as per the chosen design (2-factor multiple level FD or CCD) using the in-house built software. Response mapping using contour plots and response surfaces would be conducted with the help of software written for the purpose and otherwise. Optimal formulations would be located using programs based upon feasibility and grid searches and finally validation of drug release kinetic modelling and optimization would be carried out by comparing the release performances of the optimized formulations with that predicted using DoE optimization. The theoretical rationale and experimental validity of the proposed correction formulae would also be explored using drug dissolution data obtained from conventional and CR formulations.

Pharmacokinetic data analysis would be conducted to validate the computer programs using *in vivo* experimental data from blood, saliva and urine levels observed in man or laboratory animals generated using various oral treatments of drugs and drug products. Also, programs on cross-over ANOVA and multiple comparisons would be tested for comparisons of bioavailability profiles using the experimental data and the data reported in literature. Attempts may also be made to develop linear IVIVC and IVIVR using pertinent data obtained from *in vitro* drug release and *in vivo* pharmacokinetic studies. Software on protein binding may be tested using *in vitro* binding studies as a function of varied drug concentrations, protein concentrations, temperature(s), and/or pH. The genuineness of the software for applying varied nonparametric test(s) may be verified using the data reported in the authentic literature.