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A comprehensive computer program for the study of drug release kinetics from compressed matrices

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The article presents details of ZOREL, a software developed for the purpose of studying drug release kinetics from compressed matrics. The program, written in FORTRAN, uses raw dissolution data for input. It initially corrects the dissolution data for drug and/or volume losses occurring at the time of sampling and on the basis of the weight of the dosage form and the drug content, estimates the values of amount and percent drug released at various times for each formulation unit. The values of log mean fraction released are computed and regressed against log time to yield the values of kinetic constant (k) and release exponent (n) and subsequently calculations are made for mean dissolution time (MDT). For swelling matrices, the respective contributions of the diffusion and the polymer relaxation along with the constants of k_1 and k_2, are also computed. Based on the phenomenological analysis, the software predicts the type of release *viz* Fickian, non-Fickian (anomalous) or zero-order. In addition, the values of mean (±SD) percent released are calculated and regressed against square root of time up to various observations. The values of rate of drug release and $t_{50\%}$, $t_{60\%}$, up to $t_{90\%}$ of the drug release are computed using the program.

COMPUTERS are finding increasing application in handling and treatment of data generated during pharmaceutical research. Numerous computer programs with diverse pharmaceutical applications have been developed by different workers.[1-6] owing to ever increasing complexity of the pharmaceutical professional's work patterns, the need for newer user-interactive software, however remains. Only a couple of these software[7-8] are meant to evaluate drug release from different oral dosage forms. the first[7] deals with the application of Weibull equation on dissolution data, while the second[8] is a Macintosh-compliant software.

Of all the approaches known for control of drug release, the compressed matrices continue to receive maximum attention, as these devices incur the lowest fabrication costs and high possibility of incorporating optimum levels of therapeutically active agent in them[9]. Compressed matrices, in fact, are recognized as simplest approach in the modified formulation design.

We present here a computer program that is meant to evaluate drug release from compressed matrices. The software, ZOREL, encompasses most steps as are employed, in general for evaluation of drug release from compressed matrices. It is ideally suited for use in developmental and preformulation studies.

THEORETICAL BASIS

In compressed matrix formulations, the drug is dispersed in a matrix of inert retardant material(s), which is then compressed into tablets. The release of drug is controlled by several physical processes which include

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permeation by water, leaching (extraction or diffusion) out of the drug from the matrix and erosion of the matrix material. Several models were developed by Higuchi[10] to describe the kinetics of drug release from both homogeneous and heterogeneous matrix systems. A simplified equation that describes the release of poorly water soluble drug from surface of a planar tablet is :

$$Q = k \sqrt{t} \quad (1)$$

where Q is the total amount of drug released per unit surface in time *t*, and *k* is a kinetic constant incorporating structural and geometric characteristics of the controlled delivery device.

Equation 1 is alternatively described as :

$$M_t/M_\infty = k. \sqrt{t} \quad (2)$$

where M_t/M_∞ is the fractional release of drug at time t. In a still more general form, Eqn. 2 is expressed as

$$M_t/M_\infty = k. t^n \quad (3)$$

The value of n in Eqn. 3 represents the diffusional exponent for drug release indicating the type of release mechanisms[11]. The value of n=0.5 (Eqn. 2) is representative of a system where release is controlled entirely by Fickian diffusion mechanism and rate of drug transport from the system is proportional to $t_{1/2}$. For some matrices, e.g., those containing swellable polymers as excipients, departure from Fickian mechanism is seen and the behaviour of drug release is termed as non-Fickian. It arises from coupling of the diffusion (Case I) and molecular relaxation (Case II) phenomena[12]. Case II transport is characterized by the zero-order release kinetics and a unity value of n. The release is also characterized through mean dissolution time (MDT), a parameter obtainable from *k* and *n* values through the following relationship[13].

$$MDT = n/(n+1)\, k^{(1/n)} \quad \ldots\ldots (4)$$

The non-Fickian release behaviour of swellable matrices is further analyzed using an equation wherein the diffusion and polymer relaxation mechanisms of transport are considered simultaneously :

$$M_t/M_\infty = k_1.t^m + k_2. t^{2m} \quad \ldots\ldots (5)$$

where the first term on the right hand side is the Fickian contribution and the second term is the Case-II relaxation contribution. The constants, k_1 and k_2, express the respective contributions of the diffusion and the polymer relaxation mechanisms, allowing quantitative evaluation of their importance on overall release. The coefficient *m* is purely Fickian diffusion coefficient for a device of any shape and its determination is based on the aspect ratio, *2a/l*, where a is the radius and *l* is the thickness (height) of the device[12]. The percentages of the Fickian (*F*) and relaxational (*R*) drug release may be determined using Eqns. 6 and 7.

$$F = 1/[1+(k_2/k_1)\, t^m] \quad \ldots\ldots (6)$$

$$F/R = (k_2/k_1)\, t^m \quad (7)$$

The semi-empirical Eqn. 3, and Eqns. 4 and 5 are applied to phenomenological analysis of any release behaviour from matrix systems and hence are advantageously used to approach the constant release of drug during development of heterogeneous matrix formulations. A number of reports cite the use of these equations for the evaluation of drug release[14-18].

Program Structure

The program has been written in Microsoft FORTRAN (version 5.0) and debugged of syntactical and run-time errors using an IBM-compatible PC (Pentium PC 60 MHz, Microcare, Chandigarh, 16 MB RAM). The program is menu-driven, user-friendly and gives an elaborate, well formatted and illustrated output. The flow chart in Fig. 1 highlights its menu hierarchy.

The algorithm of ZOREL assumes treatment of data in accordance with Eqns. 1-7. Initially, depending upon the sampling technique employed, the raw absorbance (or concentration) data from dissolution studies is appropriately corrected for the loss of drug during sampling using the mathematical correction factors reported recently by the authors[19]. Subsequently, the values of amount, fraction and percent drug released at various times for each dosage form unit are calculated. The calculations are further made for mean (± S.D.) of percent drug released and logarithm of mean fraction released at various times. The rate of drug release (mean±S.D.) at the corresponding mid-points of time intervals and overall rate of drug release (±S.D.) are also computed. The relative magnitude of the latter provides a positive clue regarding regulation of drug release. A small value indicates the constant release desirable for sustained

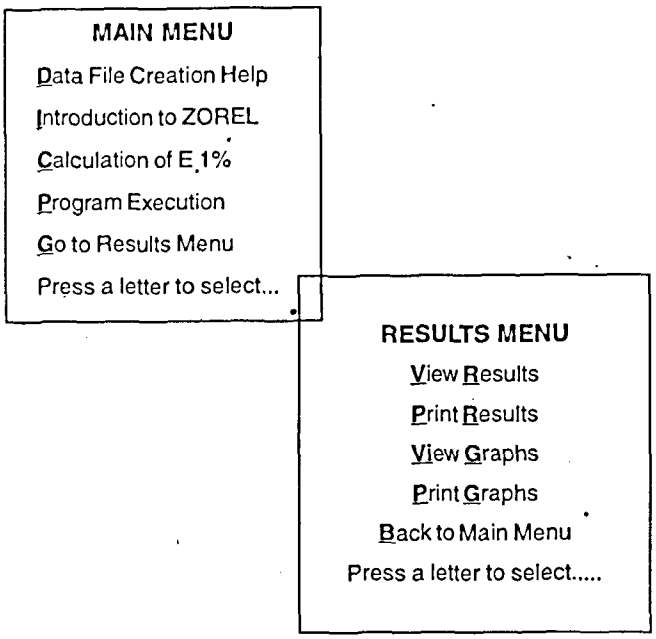

Fig. 1. Menu hierarchy of ZOREL software

action products, while higher values construe the significant presence of either initial burst effect or subsequent fluctuations in drug release rate.

The mean percent drug released data are regressed against square root of time values up to various observations. The regression parameters including coefficient of determination (r^2), standard error of estimate (s), the significance of regression (F ratio) and amount of explained variance are determined according to the standard formula[20]. The calculation of regression parameters of Higuchian plot up to various times helps one to determine deviation from Higuchi ideal, if any. A positive deviation means marked contribution to release rates by erosion, while a negative deviation in the later stages of profile denotes depletion of the drug from the matrix[21].

The program next calculates the kinetic constant (k) and release exponent (n) values for each dosage form unit pertaining to Eqn. 3, through regression of log fraction released values versus log time data. The regression parameters of the log mean fraction released versus log time plot up to various readings are also determined, to yield the change in behaviour of kinetic constant and release exponent values with passage of time during the dissolution run. The approach was successfully employed by Bavija *et al.*[15], in achieving zero-order release from a matrix system. The mean dissolution time (*MDT*) values are calculated as per Eqn. 4 and listed along with the values of k and n.

The profile reported in literature[12] between aspect ratio and diffusion coefficient was adapted in the program and the value of Fickian diffusion coefficient (m, Eqn. 5) for any value of aspect ratio is determined by cubical spline interpolation. The values of constants k_1 and k_2 are calculated by solving Eqn. 5 while the F and R values are determined as per Eqns. 6 and 7. In addition, the program lists the values of $t_{50\%}$, $t_{60\%}$, $t_{70\%}$, $t_{80\%}$, and $t_{90\%}$ of drug release. A comment on the overall mechanism of drug release is included towards the end.

Input and Output

The input attributes and variables for the ZOREL program are listed in Table 1. The basic input data for the program are raw absorbance (or concentration) values measured at various times during a dissolution run. The data are simultaneously accepted for n number of dosage forms units forming part of the study. Whole of the input information is entered through an ASCII file, required to be created by the user. The help for creating an input file is provided in the software.

A typical computer output includes the results in tablular form and some graphics. The graphic output comprises the scatter plots of mean percent released *versus* time, mean percent released *versus* square root of time (Higuchian plot) and mean rate of drug release *versus* mid point time intervals.

General Features

The earlier version of the software[1,22] written by the authors has been well-tested over several years through hands-on-use by different groups of drug formulation scientists in research and industry. It has proved to be a versatile tool in providing a store-house of information, far more rapidly and conveniently than that can be obtained by either manual means or use of handheld calculators or electronic spreadsheet packages. The program provides the calculated parameters in well-formatted tables, ready to be incorporated into a report or dissertation.

Table 1
Input Attributes, Constants and Variables of ZOREL program

	1. Logical Attributes	
1.	Measured Entity	• Absorbance • Concentration
2.	Dissolution run	• Same medium throughout the study • Change in medium during the study
3.	Sampling Technique	• Automated with sample return • Manual with sample replacement • Manual without sample replacement
4.	Matrix type	• Swellable • Non-swellable
	2. Qualitative Attribute	
1.	Identification code	
	3. Quantitative Constants	
1.	Mean ratio of drug content to mass of dosage form unit	
2.	Total number of dosage form units	
3.	Total number of observations	
4.	Total volume of dissolution medium	
5.	Volume of sample withdrawn (applicable only to non-automatric studies)	
6.	E 1% of drug in dissolution media (applicable only when raw data are absorbance values)	
7.	Diameter of device (Applicable in case of swellable matrices)	
8.	Height or thickness of device (applicable in case of swellable matrices)	
	4. Quantitative Variables	
1.	Mass of each dosage form device	
2.	Measured absorbance or concentration data at various times	

It runs on any IBM/compatible PC, 80386 or higher, under DOS 3.3 or later, and requires only 400 KB of hard disk space. The execution time on a 80486 DX2 PC with 8 MB RAM is < 5 s. The program has been modified to run on a machine even without a numeric co-processor.

Availability

A soft copy of the program can be obtained *ex-gratis* from the authors within six months of publication of this paper by sending a blank formatted 3.5" floppy diskette in a floppy mailer. For the convenience of the users, a model format of an input file, text of the data file creation help, and result output of ZOREL software would also be supplied along with the software.

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