

DESIGN AND DEVELOPMENT OF AN UNIQUE USER FRIENDLY SOFTWARE FOR INTERPRETATION OF DISSOLUTION DATA

Bijan Kumar Gupta*¹, Seemanchala Rath², Surajit Goon², Nripendra Nath Bala²

¹ Department of Pharmaceutical Technology, Jadavpur University, Kolkata – 700032, India

² BDCA College of Pharmacy and Technology, Barasat, Kolkata – 700127, India

E-mail address of the author for correspondence - bijangupta@gmail.com, bcda_principal@yahoo.co.in

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ABSTRACT

Generally dissolution data were interpreted by Microsoft excel, which is time consuming and tedious. So in the present study an attempt has been made to create Dissolution.exe software using C language for determining percentage of drug released, log (percentage of amount remaining to be released) and other parameters for fitting them into different mathematical models such as zero order, first order, Higuchi, Hixson-Crowell & Korsmeyer Peppas. Quincy and koolpot were used as IDE and graphics package for operating the software and drawing two dimensional graphs respectively. Telmisartan tablets were subjected to dissolution for running the software. The software returned 5 graphs along with their linear regression equations and R^2 values in a very less time than from Microsoft excel. All the mathematical values obtained from the treated data and graphs were exactly same as obtained from Microsoft excel. In conclusion operation and execution of the software was very easy and less time consuming as compared to Microsoft excel on any Microsoft enabled Operating System.

KEY WORDS: Dissolution software, First order, Higuchi, Mathematical models, Regression equation, Zero order

INTRODUCTION

In vitro dissolution study is an important parameter to be considered during development of a dosage form, for quality control and to assist with the determination of bioequivalence¹. Dissolution testing not only gives the amount of drug released from the dosage form but also about the kinetic and mechanism of drug release pattern. Generally dissolution data were

interpreted by Microsoft excel, which is time consuming and tedious. So in the present study an attempt has been made to create **dissolution.exe** software using C language^{2,3} for determining the parameters such as amount of drug released, % drug released, log (% of amount remaining to be released) as a function of time. The software also helps in fitting the dissolution data into different types of mathematical models such as zero order

model⁴, first order model⁴, Higuchi model⁵, Hixson-Crowell model¹ & Korsmeyer Peppas model⁵. Dissolution is pharmaceutically defined as a process in which a solid substance solubilizes in a given solvent that is mass transfer from a solid surface into the dissolution medium or solvent under standardized conditions of liquid/solid interface, temperature, pH and solvent composition. It is a dynamic process that changes with time and explains the process by which a homogenous mixture of a solid or a liquid can be obtained in a solvent. Dissolution rate is defined as the mass transfer from a solid surface into the dissolution medium or solvent per unit time under standardized conditions of liquid/solid interface, temperature, pH and solvent composition⁶.

MATERIALS AND METHODS

Materials

Quincy IDE which is freeware open-source software to develop C/C++ programme, Telmisartan (Tel) was obtained as a gift sample from Torrent Pharmaceuticals, Baddi, H.P., India. Telmisartan tablets (Telday 40) were purchased from the market and hydrochloric acid (HCl) was purchased from Merck Pvt. Ltd. Double distilled water (DDW) was prepared in the laboratory from demineralized water. All the reagents used were of analytical grade and were used as received.

Software development

An executable (exe) software was developed using C which is a high level language, can generate machine independent exe and code which can be successfully executed on any Microsoft enabled Operating System^{2, 3}. To develop the software we used Quincy as IDE⁷ (Integrated development environment). Quincy⁸ is a simple programming environment for C or C++ on Windows. It contains an editor, a compiler, a debugger and graphics toolkits. To generate the graphs koolplot⁹ was used as graphics package. Koolplot is very simple to use software library for drawing 2 – dimensional graphs from C or C

++ programs. It comes pre-installed and ready to use with Quincy.

Features of Dissolution.exe

It requires the data in a triplicate manner. It calculates parameters for all the 3 replicates along with their average & standard deviation (sd) values. It displays 5 graphs along with their R² values & linear Regression equation by method of least square. It calculates the amount of drug loss due to sampling. It imports all the data (input & output) into a text file (output.txt) automatically.

In vitro dissolution study

For the dissolution of tel tablets (Telday 40) United States Pharmacopeia (USP) apparatus-1 (LABINDIA, DISSO.) was used. Dissolution was carried out in 900 ml. of 0.1N HCl at 37±0.5°C and the basket was rotated at 50 rpm. Samples were withdrawn at an interval of 5 minutes from the starting of dissolution. Each time 5ml. of sample withdrawn was diluted up to 25ml. with 0.1N HCl and analysed for the amount of Tel released, in an UV-visible spectrophotometer (SHIMADZU 1700) at 228 nm taking 0.1N HCl as blank. Dissolution was carried out in a triplicate manner.

RESULTS AND DISCUSSION

Operation of Dissolution.exe:

Step 1

Initially the software requires number of absorbencies to be input, which may be generated by any suitable analytical method (here UV-visible spectrophotometric method was used) followed by the values of c, m, df, f and dc. Where, c= y-intercept of the standard curve of the active pharmaceutical ingredient (in this case telmisartan), m= slope of the standard curve, $df = (V_d \times V) / 1000 \times V_s$, where df=dilution factor, V_d=volume of the sample diluted up to in ml, V=volume of the dissolution fluid in ml & V_s=volume of the sample withdrawn in ml, $f = V_d / 1000$ = loss factor. Loss factor was introduced to calculate the amount of drug loss due to sampling, dc= Drug content of the dosage form in

mg and time = sampling time in minutes from the starting of dissolution.

Step 2

Absorbance values for Replicate I obtained after analyzing the dissolution samples were given. Then dissolution .exe displayed time, dr, logarr, logd, w, sqroot and logt (fig. 1), where dr = % of drug released, logarr = common logarithmic transformation of % of amount remaining to be released (%ARR), logd = common logarithmic transformation of % of drug released (%DR), $w = W_0^{1/3} - W^{1/3}$, where $W_0 = \text{ARR}$ in mg & $W = \text{dc}$, sqroot = square root of the time, logt = common logarithmic transformation of time.

Step 3

Absorbance values for Replicate II obtained after analyzing the dissolution samples were given. Then dissolution .exe displayed time, dr, logarr, logd, w, sqroot and logt for the data of replicate II. Similarly the data of replicate III were also interpreted as shown in fig. 2. Then the software generated the average and standard deviation values of the triplicate data automatically (fig. 3), where per dr = dr, lgarr = logarr, lgd = logd, lgt = logt and sd represents the standard deviation (n = 3). Regression equations along with the R^2 values of different mathematical models such as zero order model, first order model, Higuchi model, Hixson Crowell model & Korsmeyer Peppas model was also displayed simultaneously as shown in fig. 4. After displaying the regression equations & R^2 values of the 5 mathematical models, the zero order plot was automatically generated by dissolution.exe. Then the remaining plots were shown one by one simply by pressing the right arrow key. All the plots were shown in fig. 5a – 5e. The software was also able to generate an output file (output.txt) by default in the program file where the software was installed containing all the input and output data in it, shown in fig 6.

All the average and standard deviation values of the triplicate dissolution data were shown in table 1 and table 2. All the mathematical values obtained from the treated data and graphs were

exactly same as obtained from Microsoft excel. Dissolution of Tel tablet was best fitted to first order model (R^2 value = 0.9643). Mechanism of drug release was found to be both diffusion and polymer relaxation^{10, 11} (slope of Korsmeyer Peppas model = 0.5924).

CONCLUSIONS

The dissolution.exe software was successfully developed to calculate % drug released, log (% of amount remaining to be released) and all other dissolution parameters that are essential to fit the dissolution data into different mathematical models. Linear regression equations along with their R^2 values were also determined by the software. Operation of the software was very easy and less time consuming as compared to Microsoft excel. So it can be employed for research as well as industrial quality control and assurance purposes.

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TABLES

Table1

Time in minutes	(Time) ^{1/2}	Log (Time)	% DR	Log (%ARR)	Log (%DR)	W ₀ ^{1/3} - W ^{1/3}
5	2.2361	0.699	26.463	1.8665	1.4225	0.3327
10	3.1623	1	56.6262	1.6371	1.753	0.8302
15	3.873	1.1761	68.622	1.4965	1.8364	1.0948
20	4.4721	1.301	74.3549	1.4087	1.8713	1.2459
25	5	1.3979	78.0083	1.3422	1.8921	1.354
30	5.4772	1.4771	85.5737	1.1563	1.9323	1.6268
35	5.9161	1.5441	92.2053	0.8893	1.9647	1.9585

Table1: Average values of the triplicate dissolution data

% DR = Percentage of drug released,

% ARR = Percentage of amount of drug remaining to be released,

W₀ = Drug content in mg, W = ARR in mg.

Table2

Sl.No	% DR	Log (% ARR)	Log (% DR)	W ₀ ^{1/3} - W ^{1/3}
1	0.7435	0.0044	0.0123	0.0104
2	1.0167	0.0101	0.0078	0.0201
3	1.0223	0.0141	0.0065	0.0251
4	1.1328	0.0194	0.0066	0.0322
5	0.5057	0.0100	0.0028	0.0158
6	1.9882	0.0613	0.0101	0.0835
7	1.0449	0.0569	0.0049	0.0642

Table2: Standard deviation values of the triplicate dissolution data

FIGURES

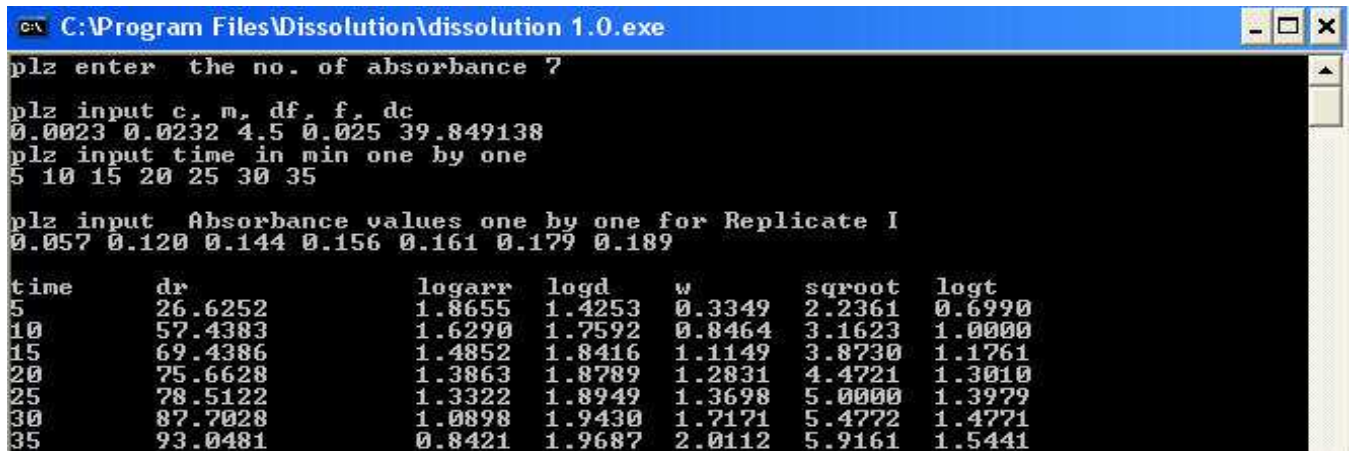


Fig. 1: Screen short of the software showing the values for Replicate I

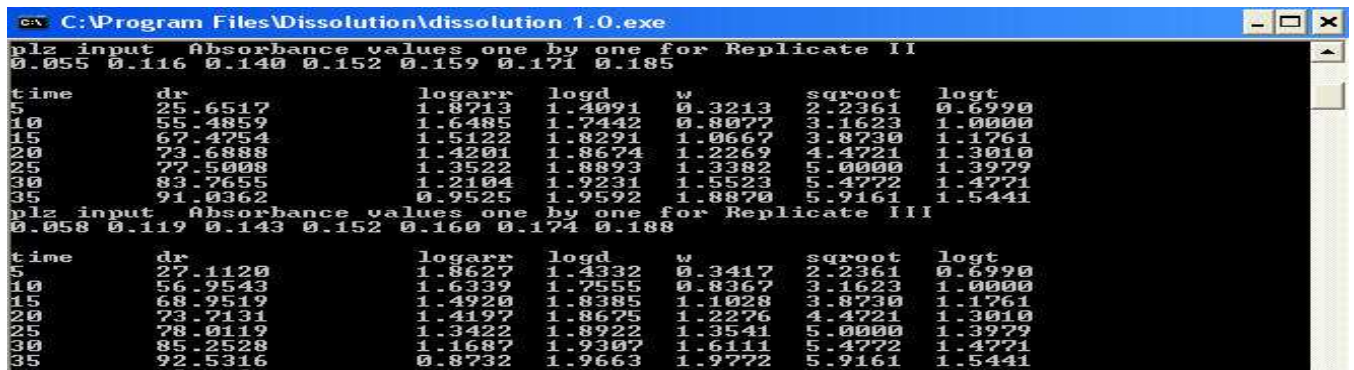


Fig. 2: Screen short of the software showing the values for Replicate II and III

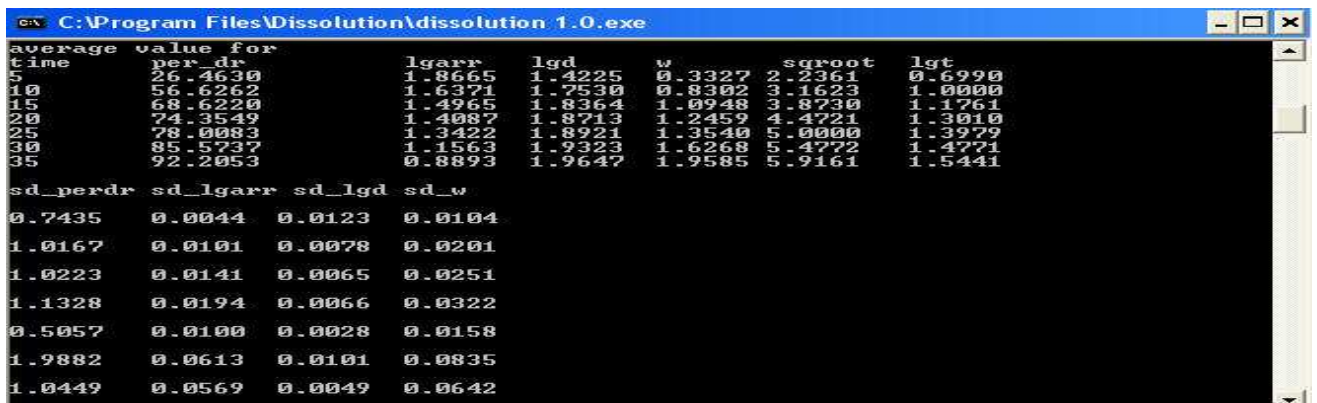


Fig. 3: Screen short of the software showing the average and standard deviation values

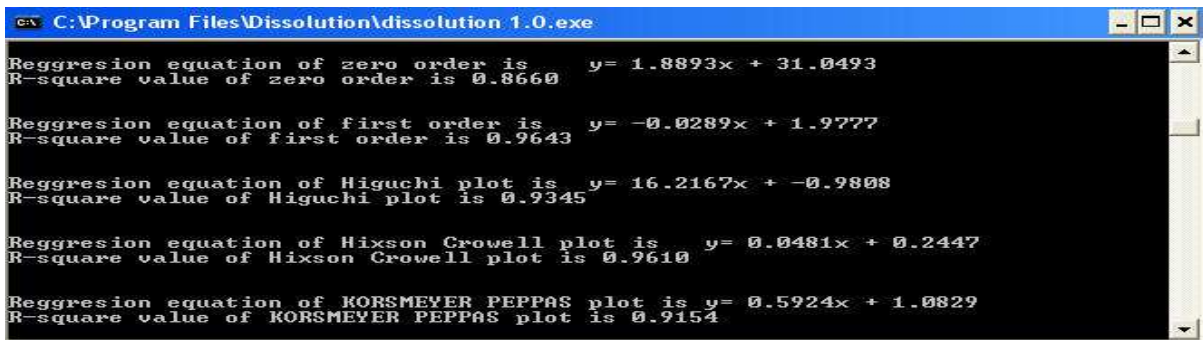


Fig. 4: Screen short of the software showing the regression equations and R^2 values of different mathematical models

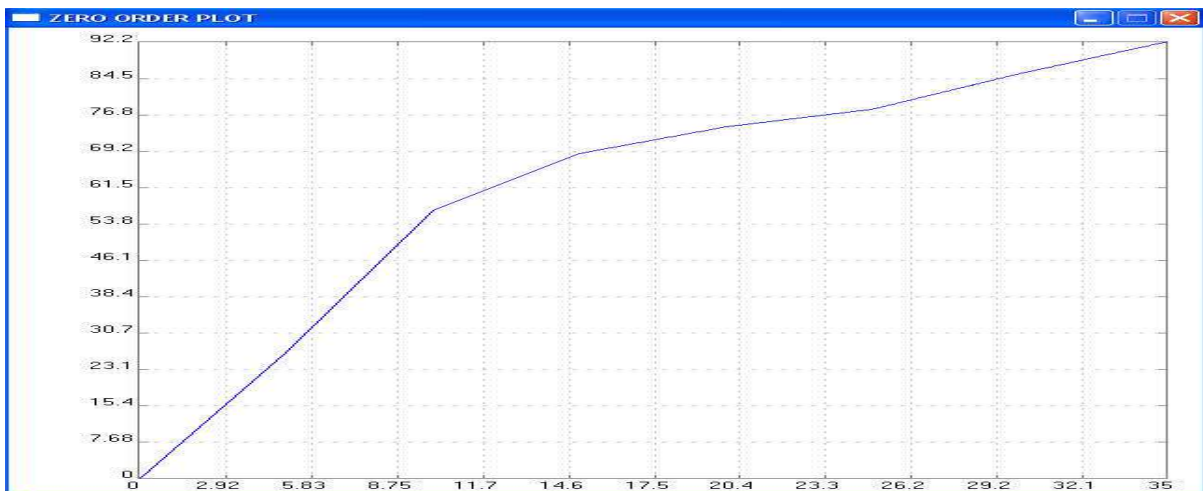


Fig. 5a: Zero order dissolution profile of telmisartan tablet

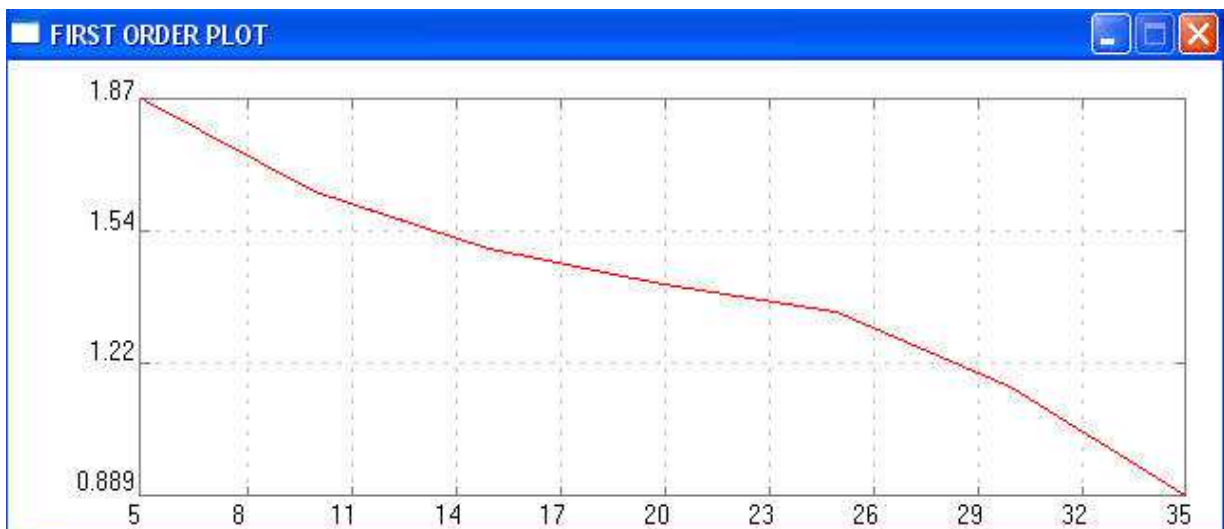


Fig. 5b: First order dissolution profile of telmisartan tablet

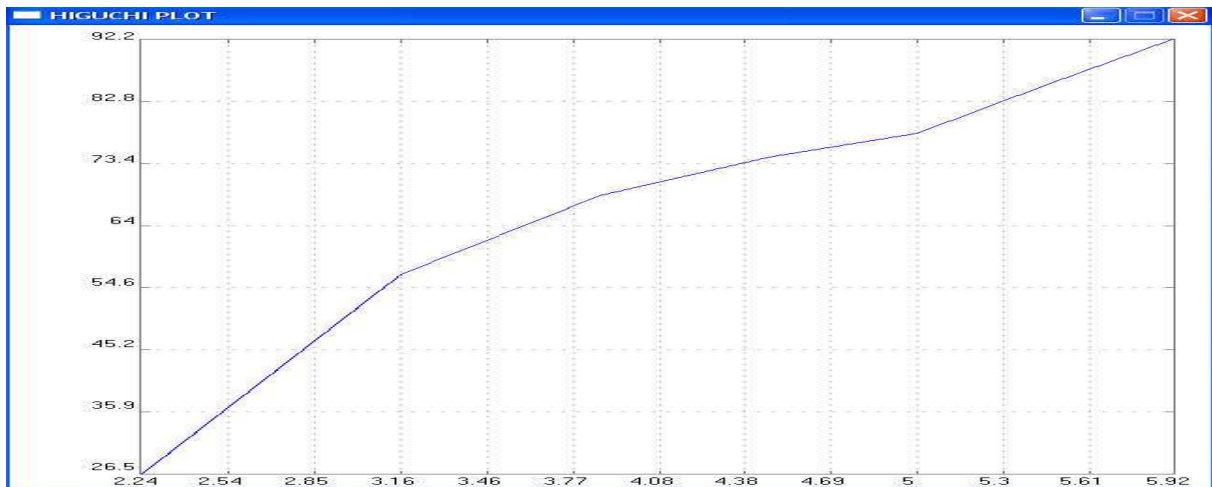


Fig. 5c: Dissolution profile of telmisartan tablet (Higuchi plot)

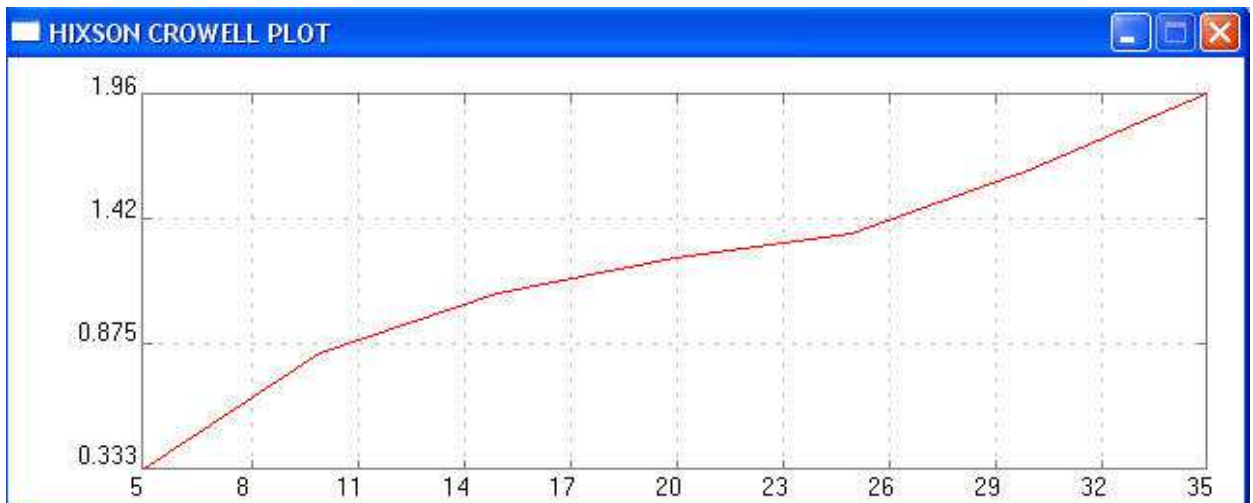


Fig. 5d: Dissolution profile of telmisartan tablet (Hixson Crowell plot)

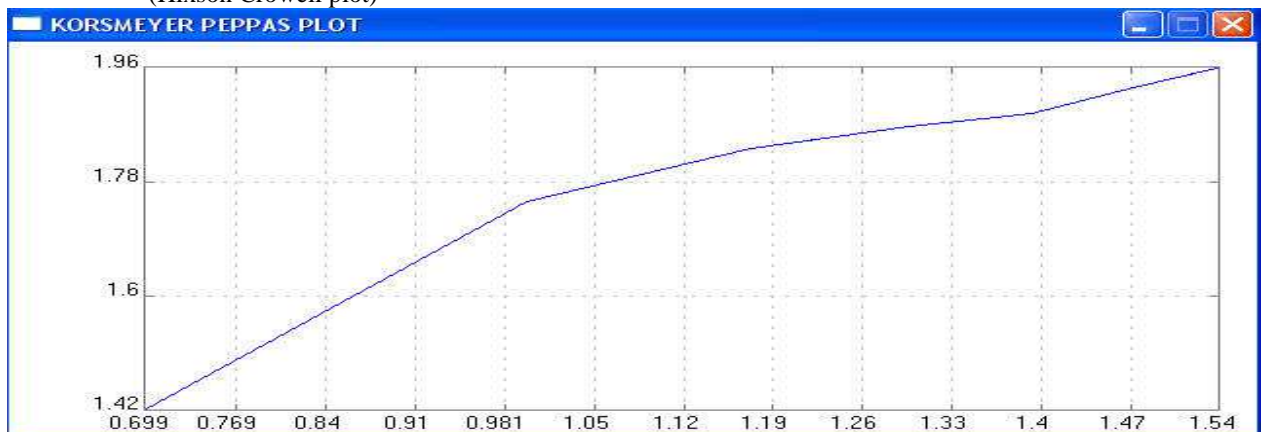


Fig. 5e: Dissolution profile of telmisartan tablet (Korsmeyer Peppas plot)

Fig. 6: Output file generated by Dissolution.exe

Input values of c, m, df, f, dc are:-
 0.002300 0.023200 4.500000 0.025000 39.849138

Input time in min one by one
 5 10 15 20 25 30 35

Absorbance values for Replicate I
 0.057000 0.120000 0.144000 0.156000 0.161000
 0.179000 0.189000

time	dr	lgarr	lgd	w	sqrt	lgt
5	26.6252	1.8655	1.4253	0.3349	2.2361	0.6990
10	57.4383	1.6290	1.7592	0.8464	3.1623	1.0000
15	69.4386	1.4852	1.8416	1.1149	3.8730	1.1761
20	75.6628	1.3863	1.8789	1.2831	4.4721	1.3010
25	78.5122	1.3322	1.8949	1.3698	5.0000	1.3979
30	87.7028	1.0898	1.9430	1.7171	5.4772	1.4771
35	93.0481	0.8421	1.9687	2.0112	5.9161	1.5441

Absorbance values for Replicate II
 0.055000 0.116000 0.140000 0.152000 0.159000
 0.171000 0.185000

time	dr	lgarr	lgd	w	sqrt	lgt
5	25.6517	1.8713	1.4091	0.3213	2.2361	0.6990
10	55.4859	1.6485	1.7442	0.8077	3.1623	1.0000
15	67.4754	1.5122	1.8291	1.0667	3.8730	1.1761
20	73.6838	1.4201	1.8674	1.2269	4.4721	1.3010
25	77.5008	1.3522	1.8893	1.3382	5.0000	1.3979
30	83.7655	1.2104	1.9231	1.5523	5.4772	1.4771
35	91.0362	0.9525	1.9592	1.8870	5.9161	1.5441

Absorbance values for Replicate III
 0.058000 0.119000 0.143000 0.152000 0.160000
 0.174000 0.188000

time	dr	lgarr	lgd	w	sqrt	lgt
5	27.1120	1.8627	1.4332	0.3417	2.2361	0.6990
10	56.9543	1.6339	1.7555	0.8367	3.1623	1.0000
15	68.9519	1.4920	1.8385	1.1028	3.8730	1.1761
20	73.7131	1.4197	1.8675	1.2276	4.4721	1.3010
25	78.0119	1.3422	1.8922	1.3541	5.0000	1.3979
30	85.2528	1.1687	1.9307	1.6111	5.4772	1.4771
35	92.5316	0.8732	1.9663	1.9772	5.9161	1.5441

average value for

time	per_dr	lgarr	lgd	w	sqrt	lgt
5	26.4630	1.8665	1.4225	0.3327	2.2361	0.6990
10	56.6262	1.6371	1.7530	0.8302	3.1623	1.0000
15	68.6220	1.4965	1.8364	1.0948	3.8730	1.1761
20	74.3549	1.4087	1.8713	1.2459	4.4721	1.3010
25	78.0083	1.3422	1.8921	1.3540	5.0000	1.3979
30	85.5737	1.1563	1.9323	1.6268	5.4772	1.4771
35	92.2053	0.8893	1.9647	1.9585	5.9161	1.5441

sd_perdr	sd_lgarr	sd_lgd	sd_w
0.7435	0.0044	0.0123	0.0104
1.0167	0.0101	0.0078	0.0201
1.0223	0.0141	0.0065	0.0251
1.1328	0.0194	0.0066	0.0322
0.5057	0.0100	0.0028	0.0158
1.9882	0.0613	0.0101	0.0835
1.0449	0.0569	0.0049	0.0642

Regression equation of zero order is $y = 1.8893x + 31.0493$
 R-square value of zero order is 0.8660

Regression equation of first order is $y = -0.0289x + 1.9777$
 R-square value of first order is 0.9643

Regression equation of Higuchi plot is $y = 16.2167x + -0.9808$
 R-square value of Higuchi plot is 0.9345

Regression equation of Hixson Crowell plot is $y = 0.0481x + 0.2447$
 R-square value of Hixson Crowell plot is 0.9610

Regression equation of KORSMEYER PEPPAS plot is $y = 0.5924x + 1.0829$
 R-square value of KORSMEYER PEPPAS plot is 0.9154