World Journal of Pharmaceutical Sciences
ISSN (Print): 2321-3310; ISSN (Online): 2321-3086
Published by Atom and Cell Publishers
Available online at: http://www.wjpsonline.com/
Original Article

Studying the effect of dispersed drug crystal in the organic phase on the encapsulation by solvent evaporation technique
(3) Independent models as tools for studying the drug release profiles

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Received: 18-03-2014 / Revised: 29-03-2014 / Accepted: 30-03-2014

ABSTRACT

Aspirin dissolution profiles from different particle size ranges of Eudragit RS100 microcapsules were studied in relation to the studied microcapsule structures. The results showed that there is no burst effect and the total amount of drug released from different particle size ranges prepared with the same or different TDC are more than 80% during 12 hr. The release data indicated the closest of the dissolution profile in every case. The values of standard deviation at every time unit were also used as an indication for the release data distribution around the mean of drug release. The model independent methods were used to prove the dissolution profile similarity of Aspirin from different particle size ranges microcapsules prepared by using the same theoretical drug content. Accordingly the mean dissolution profile of Aspirin from different particle size ranges of Eudragit RS100 prepared by using the same TDC was used to represent the drug release profile and also to study the effect of increasing TDC. The mean release data showed the closest of the dissolution profiles from different products prepared by using different TDC. Again the independent models were used to prove the similarity of the dissolution profile of Aspirin from different Eudragit RS100 microcapsules prepared on using different TDC. Accordingly it was concluded that the overall Aspirin dissolution profile can be used to represent the drug release profile from different particle size ranges of Eudragit RS100 microcapsules prepared by using the same or different TDC.

Key words: Division mechanism, Dissolution profile, independent models, Eudragit RS100, Aspirin crystal.

INTRODUCTION

Drug release is the process by which a drug leaves a drug product and is subjected to absorption, distribution, metabolism and excretion, eventually becoming available for pharmacological action [1]. In vitro dissolution has been recognized as an important element in drug development. Under certain conditions it can be used as a surrogate for assessment of bioequivalent [2]. Dissolution profile is a graphical representation, in terms of concentration verses time, of complete release of active substance from a dosage form in an appropriate selected dissolution medium. It reflects the drug release under selected condition which helps for optimization of the dosage form by comparing the dissolution profile of various formulas. In recent year, more emphasis has been placed on dissolution testing within the pharmaceutical industry and corresponding, by regulatory authorities. Indeed the comparison of dissolution profile has extensive application throughout the product development process and can be used to: Develop in vitro-in vivo co-relation, which can help to reduced costs, speed-up product development and reduced the need of perform costly bioavailability human volunteer studies. Also establish final dissolution specification for the pharmacological dosage form and establish the similarity of pharmaceutical dosage forms, for which composition, manufacture site, scale of manufacture, manufacturing process and/or equipment may have changed within defined limits [3].

The methods of approach to investigate the kinetics of drug release from controlled release formulation can be classified into 3 categories: Statistic methods, Model independent methods and Model dependant methods [4]. Exploratory data analysis

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method is one of statistic methods including Simple parameter read on the curve or drug release data like initial and total amount of drug release. Although they are not endorsed by FDA, the method is useful in obtaining an improved understanding of the dissolution data and therefore is recommended to be used. They are used in the first step to compare the dissolution data in both graphical and numerical manner. The dissolution profile data are illustrated graphically by plotting the mean dissolution profile date for each formulation with an error bars extending to two Standard errors at each dissolution time point [4, 5]. Other statistic methods based on the analysis of variance or t-student test are single time point dissolution and multipoint time dissolution [6].

Model-independent methods can be further differentiated as ratio tests and pair-wise procedures. The ratio tests are relations between parameters obtained from the release assay of the reference formulation and the release assay of the test product at the same time and can go from a simple ratio of percent dissolved drug ($t_{x\%}$) to a ratio of area under the release curve (AUC) or even to a ratio of mean dissolution time (MDT) [2]. MDT is a measure of the rate of the dissolution process: the higher the MDT, the slower the release rate [7-9]. Although Costa et al [2] used dissolution efficiency (DE) as an other release parameter to characterize the drug release profile rate and not with the release profile comparison method; it will be used here also for comparison with the independent method [10, 11]. The dissolution efficiency of a pharmaceutical dosage form is defined as the area under the dissolution curve up to a certain time [12, 13]. The values of MDT and DE were used as an indication of the efficient control of drug release as a result of increasing the values of MDT and decreasing the values of DE [7-9].

The pair-wise procedures include the difference factor and the similarity factor [14] and the Rescigno index [15]. The difference factor (f_1) measures the percent error between two curves over all time points. The similarity factor (f_2) is a logarithmic transformation of the sum-squared error of differences between the test and reference products over all time points [2]. There are a lot of literature which used the values of F1 and F2 as an indication for the similarity or dissimilarity of the dissolution profiles [7, 10, 16, 17, 18]. Rescigno proposed a bioequivalence index to measure dissimilarity between a reference and a test product based on plasma concentration as a function of time. This Rescigno index can also be used based on drug dissolution concentrations.

The aim of this work is trying to use the independent models as tools to study the similarity or dissimilarity of the drug release profile of different particle size microcapsules products prepared by using different theoretical drug content.

MATERIALS AND METHODS

Materials: Acetylsalicylic acid crystals (ADWIC, Egypt), Eudragit RS100 (Rohm Pharma, Germany), Gelatin (Pharma Production, Austria). All other chemicals were of analytical grades.

Equipment: Mechanical stirrer (Heidolph,RZR-2000,Germany),UV/visible spectrophotometer (Perkin-Elmer, Lambda 1,USA),Vibrating set of sieves (VEB /letalweberei Neustadt, Orla, Germany).

Methods

Preparation of microcapsule: Microcapsules were prepared by solvent evaporation technique. The aqueous solution was 200 ml of 0.1N HC1 containing 0.5 gm of gelatin as an antiaggregating agent. The organic phase was composed of a constant volume of dichloromethane (20 ml) containing the required weight of Eudragit RS100. The required weight of drug was dispersed with stirring in the organic phase until a homogeneous dispersion was obtained. Then, the prepared homogeneous organic phase was poured onto the stirred aqueous phase at 500 rpm. Stirring was continued until complete evaporation of the dichloromethane. The microcapsules were collected by filtration and air dried. In every case, the total amount of polymer and drug was 10 gm. Microcapsules containing 20%, 33.33%, 50%, 66.66% and 80% theoretical drug content were prepared.

Product size analysis: The mean particle sizes of the microspheres were determined by sieving method. A definite weight of Eudragit RS100 microspheres containing drug was placed on a set of standard sieves and shaken for 10min using mechanical sieve shaker. The resulting fractions remaining on the sieves were used for further study.

Determination of the actual drug content: After standardization of the method of drug analysis in dichloromethane, an accurate weight (100 mg) of each product was dissolved in 100 ml of dichloromethane. The produced dichloromethane solution was measured spectrophotometrically at 241 nm using dichloromethane as a blank. The procedure was carried out in triplicates.

Drug release from the microspheres: An exact weight of the prepared microspheres equivalent to 100 mg Aspirin was added to a flask (200 ml capacity), 100 ml of phosphate buffer pH 7.2 was added. The bottle was shaken at 100 rpm at 37°C (±0.5). Samples were withdrawn at different time intervals. The drug content of the sample was determined spectrophotometrically at 229 nm. Three replicates were conducted.

RESULTS AND DISCUSSION

Dissolution profile is a graphical representation, in terms of concentration versus time, of complete drug release from the dosage form in an appropriate selected dissolution medium. It reflect the release pattern of the drug under selected condition sets which help for optimizing the dosage formula by comparing the dissolution profile of various formulas of the same drug. The description of drug release profile from the dosage form was suggested to be done as the following [19]:

Simple parameter read on the curve or drug release data like initial and total amount of drug release in addition to the drug release rate: Table (1) shows the drug release from all Eudragit RS100 microcapsules prepared with different Aspirin crystal theoretical drug content (TDC) and different particles size ranges. The mean amount of drug released percent of the whole product (the sum of the amount of drug release from different particle size ranges prepared with the same TDC) at time intervals with standard deviation values were also reported. From the table it can be noticed that the amount of drug released after half an hour from every product prepared with different TDC is around 10% indicating the absence of the burst effect which is one of the problems facing nearly all products prepared by solvent evaporation technique [20-23]. Also as a general it can be concluded that, the drug release rate from different particle size ranges microcapsules of the same or different products prepared with different TDC decreased with decreasing the particle size ranges. In addition the total amount of drug released, which is the second problem facing all products prepared by solvent evaporation technique [20-23], is around 80% of the actual drug content (ADC). Also the total amount of drug released from different particle size ranges after 24 hrs of the same product decreased with decreasing the particle size range. On comparing the total amount of drug released after 24 hrs from the same particle size range of different products prepared on using different TDC, it can be concluded that increasing TDC led to decreasing the total amount of drug released. An interesting finding is the total amount of drug released after 24 hrs from particle size range 500-400 µm of the products prepared on using either 20% or 33% TDC is markedly higher than that from particle size range 315-80 µm of the same products. The smallest particle size ranges released the same total amount of drug from the product prepared on using 20% and 80% TDC while the highest particle size ranges released the same total amount of drug from products prepared on using 33.33% and 50% TDC. At the same time there is nearly homogenous difference in the total amount of drug released from the different particle size ranges of product prepared on using 66.66% TDC.

Mady O.[24], reported that, The drug entrapment mechanism in the microcapsules prepared with either 20% or 33.33% TDC and having particle size range (315-80 µm) is a solid solution form in addition to minute drug crystal form while in the higher particle size ranges may be only as solid solution. The molecular dispersion of the drug may be led to more readily drug release than from a particulate form and initiates rate-controlled delivery with higher drug delivery efficiencies [25]. The presence of the minute drug crystal in the microcapsule structure in the size range 315-80 µm may be responsible about the markedly decrease in the total amount of drug released comparing to that from higher particle size ranges. That is due to the fact that the crystal form of the drug needs to be dissolved then diffused from the microcapsules. This could be explaining what is reported before about the drug release from products prepared on using 20% and 33.33% TDC concerning with the rate and total amount of drug released. Mady O. [24], reported also that increasing TDC led to increasing the amount of drug crystals in the microcapsule structure. The x-ray diffraction patterns showed increasing the drug crystallinety with increasing both TDC used and the particle size ranges of the microcapsules prepared by using 50%, 66.66% and 80% TDC. Based on the fact that the drug solubility (which is the first step in the drug release process) would be increased with decreasing its particle size range, it could be expected that the rate and total amount of drug released from products prepared by using 50%, 66.66% and 80% TDC will be decreased with increasing TDC. This theoretical explanation is completely in agreement with what is reported above about decreasing the rate and total amount of drug released with increasing TDC which is due to increasing the amount of drug crystal in the microcapsule structure. Again Mady O.[26], reported that for the same product prepared with the same TDC, decreasing the particle size range on using 50%, 66.66% and 80% TDC led to decreasing the actual drug content (ADC) and increasing the actual polymer content (APC) in the microcapsule structure. Eudragit RS100 is a copolymer of ethyl acryl ate, methyl methacrylate

and a low content of meth acrylic acid ester with quaternary ammonium groups. The ammonium groups are present as a salt and make the polymer permeable. It was also reported that the rate of drug release from the microcapsules decreased with an increasing in the polymer concentration due to prolongation of the diffusion route of the drug [27, 28]. This could be explain what is reported above about decreasing the rate and total amount of drug released with decreasing the particle size ranges from products prepared on using 50%, 66.66% and 80% TDC.

From above it can be stated that, the molecular dispersion of aspirin crystal in the Eudragit RS100 microcapsule structure, if present, has the major rule in the drug release but the presence of the drug as crystal form, the polymer content and the drug solubility have the rate limiting factor of the drug release. This is may be due to the reported finding of drug crystal dispersion in the microcapsule structure using Electron Scanning Microscope [26] which is also supported by x-ray and DSC analysis results [24].

The Standard Deviation is a measure of how spreads out numbers are. Its value is bigger when the differences are more spread out. Accordingly, the effect of the structure of the microcapsules which is formed as a result of the suggested division mechanism, on the drug release, could be also observed from the values of Standard Deviation of the mean of the amount of drug released from different particle size ranges at time intervals. From table (1) it can be noticed that the value of Standard Deviation of the mean drug release form the microcapsules with different particle size ranges and prepared on using 20% and 33.33% TDC for 1.5 hr is lower than one indicating the homogeneity of the drug release from these microcapsules. That is may be due the release of molecularly dispersed drug in the microcapsule structure. After 1.5 hrs it can be noticed the high values of Standard deviation in both cases. That is may be due to the drug release, in addition form molecularly dispersed drug, from the minute drug crystal in the microcapsule structure. The release of the drug from the crystal which is encapsulated in the microcapsules is controlled by many factors. These Factors create difference in the drug release and which will be reflected on the values of standard deviation. On the other side it can be noticed that the lower and homogeneity of Standard Deviation values of the mean drug release from different microcapsules prepared on using 50%, 66.66% and 80% TDC with exception points. That is may be also indicate the drug release occurred mainly from one encapsulated form which is the drug crystal entrapped in the microcapsule structures [24 & 26]. All of the above results are in agreement with the entrapment method of the drug which was discussed by the author as a result of x-ray diffraction patterns and DSC analysis [24] which is also in agreement with the role of the suggested division mechanism on the microcapsule formation [26].

Calculated parameters like MDT (Mean Dissolution Time), DE (Dissolution Efficiency) and Ratio Test Procedures: They are Model independent methods [29-34] which rely on the individual characterization of each curve. They promote direct comparison of the dissolution data and do not rely in the choice of model functions that sometimes may prove artificial. The objective is essentially to translate either the profile or profile differences into a single value [33]. The mean in vitro dissolution times, MDT are given from a release ***M(t)*** by [29]

$$MDT = \frac{\int_0^\infty t \, dM(t)}{\int_0^\infty dM(t)}$$

where the denominator corresponds to the total amount dissolved, $M(\infty)$. A fraction of drug release, $M(t)/M(\infty)$ is related to the number of molecules of drug substance released from the dosage form up to the time ***t*** and can be regarded as a cumulative function ***F(t)*** in the statistical sense [33]. In practice, the integrals in the above equation are computed numerically, yielding,

$$MDT = \frac{\sum_i \bar{t}_i \, \Delta M_i}{\sum_i \Delta M_i}$$

Where $\bar{t}_i$ is the midpoint of the time period during which the fraction ΔM_i of the drug has been released from the dosage form [29]. Other similar formula gives the moments of dissolution times of order ***k***

$$m_k = \frac{\sum_i \bar{t}_i^{\,k} \, \Delta M_i}{\sum_i \Delta M_i}$$

One of the advantages of this method is that the comparison is based on a physically significant quantity, of widespread use for establishing in vitro /in vivo correlations. It is also possible to characterize the profiles with statistical moments such as ***MDT***, its relative dispersion (***RD***) and the variance associated with the ***MDT*** (***VT***) [33]. The method may require, however, the knowledge of the time at which the plateau, i.e. full dissolution, is attained. Variance of dissolution times are estimated from the following formula:

$$VT = \frac{\sum_i (\bar{t}_i - MDT)^2 \, \Delta M_i}{\sum_i \Delta M_i}$$

The relative dispersion of dissolution times (***RD***) is given by [33].

$$RD = \frac{VT}{MDT^2}$$

The dissolution efficiency (DE) is defined as the area under the dissolution curve up to a certain time ***(t)*** expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time [12,13].

DE was calculated from the following equation;

$$DE = \left[\frac{\int_0^t y \, .dt}{y_{100} \, .t} \right] \times 100\%$$

Where, ***y*** is the drug percent dissolved in the time ***t***. Dissolution efficiency (DE) can have a range of values depending on the time interval chosen. However, while comparing a set of data a constant time interval should be selected.

DDSolver is a menu-driven add-in program for Microsoft Excel written and is capable of performing most existing techniques for comparing drug release data. DDSolver could be served as a useful tool for dissolution data analysis. The results data are represented in table (2). From the table it can be noticed the high values of AUC and ABC of all drug release profiles. That is may be due to the nature of calculation methods for determination of AUC and ABC. But when the calculations depend on the concentrations of drug molecules the results showed the closing of the calculated data to each other like in case of calculation of MRT and MDT. The values of VDT (variance of the dissolution time), $\mathbf{m_k}$ (moments of dissolution time of order k) and RD (relative dispersion of the dissolution time) may indicate the variation of drug release mechanism in every case which is completely in agreement with what stated before about the drug release percent and its relation to the drug entrapment mechanism. Also from the same table it can be noticed the similarity of the dissolution efficiency (DE) from all products calculated by the DDSolver.

A ratio test procedure is model-independent approach for comparing dissolution profiles; these can be further classified into ratio test of percent dissolved and mean dissolution time. The percent dissolved is discussed before and also used for calculation for mean dissolution time at each point. Since most of drug has been dissolved, then calculation of MDT ratio can be considered as meaningful [34]. For such calculation it is essential to have the dissolution data for test and standard. To evaluate the observed similarity of dissolution profile from different particle size ranges microcapsules prepared by using the same TDC, the dissolution profile of each particle size range will compared with the mean profile of all particle size ranges prepared with the same TDC. The results are tabulated in table (3). From the table it can be noticed that the calculated MDT ratios values are approximately 1 which may indicate local sameness and also for over all dissolution profile [34]. To assure the similarity of the dissolution profile of drug from different particle size prepared with the same TDC another procedures were also applied using the mean drug released from different particle size ranges as a reference for comparison.

Pair-wise procedures: Pair-wise procedures are the most widely used method for assessing the similarity between a pair of dissolution data. The distinction of this method is that the similarity can be evaluated using a single statistical index estimated from the individual raw data (or mean data) of two profiles. These indices include the difference factor f_1, the similarity factor f_2 [14] and the two Rescigno indices [15].

Difference factor and similarity factor: The difference factor f_1 is a measure of the relative error between two curves, while the similarity factor f_2 is a measure of the similarity in the percent of dissolution between two curves. These two factors can be respectively defined by:

$$f_1' = \left[\frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} (R_t + T_t)/2} \right] \times 100$$

$$f_2 = 50 \cdot \log\left\{ \left[1 + \frac{1}{n} \sum_{t=1}^{n} (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\}$$

where R_t, T_t are the percentage dissolved of the reference and test profile respectively at time point t and n is the number of sampling points. For the profiles to be considered "similar", f_1 should be close to 0, and f_2 should be close to 100. Current FDA guidelines [34] suggest that two profiles can be considered similar if f_1 is less than 15 (0–15) and f_2 is greater than 50 (50–100), which is equivalent to an average difference of 10% at all sampling time points.

Table (4) shows the DDSolver calculated values of F_1, F_2, Rescigno $index_{1\&2}$ for all drug release profiles. From the table it can be noticed that all F_1 values are lower than 9% indicating that the average difference between of drug release from any particle size range prepared with the same TDC and the mean drug release of the whole product are

lower than 10 % at all sampling time points. Also the value of F_2 are greater than 50% suggesting that the drug release profile from any particle size ranges which prepared using the same TDC can be considered similar to the mean of drug release of the whole product prepared with the same TDC.

Rescigno index: which was originally proposed for evaluating the bioequivalence of two formulations based on plasma-concentration versus time curves, has also been used to compare dissolution profiles [34]. It is defined as:

$$\xi_j = \left(\frac{\int_0^t |R_i - T_i|^j \, dt}{\int_0^t |R_i + T_i|^j \, dt} \right)^{1/j}$$

where R_i and T_i are the percentage of drug dissolved at the i-t h time point for the reference and test formulations respectively, and j is 1 and 2 for the first- ($\xi 1$) and second-order ($\xi 2$) Rescigno index respectively. The Rescigno index, which can be calculated using the trapezoidal rule, takes on values from zero (which indicates no difference between the reference and test formulations) to one (which indicates complete dissolution of one formulation before the other begins to dissolve). A major difference between f_1, f_2 and the Rescigno index is that the first two take into account only the n sampling times when determining the profile differences, whereas the Rescigno index also takes into account the spacing between successive sampling times by evaluating integrals over time (34). From table (4) it can be noticed that the values of Rescigno index of the products are closed to zero which indicates no drug release difference from different particle size ranges and the mean of drug release prepared with the same TDC.

The similarity of the DE and the closest of the MDT values, which reflect the retarding effect of the dosage form, and the similarity of different pair-wise tests of dissolution data from different particle size ranges of the same product prepared by using the same TDC leading to plotting the mean of the dissolution data from different particle size ranges prepared by using the same TDC (figure 1, A-E). The error bars represent the deviation of drug release from different particle size ranges from the mean which again shows what stated before on studying the drug release from table (1). All dissolution profiles were fitted using polynomial 3 with correlation coefficient (r^2) higher than 0.99.

As a result from above, the mean of drug release percent from different particle size ranges prepared by using the same TDC was used to study the effect increasing TDC on the drug release (table 5). From the table it can be noticed the closest of the release data which is supported from the values of SD. The parameters values of the mean dissolution profile of Aspirin from Eudragit RS100 Microcapsules (table 6) showed the closest values of MRT, MDT and RD indicating the similarity of drug release. At the same time it can be noticed that the values of VDT and m_k of the mean different products are not closed to each other. That is may be due to the different drug release mechanisms as a result of different drug entrapment mechanisms as stated before. In addition it can be also noticed the high similarity values of dissolution efficiency from the mean of all products prepared with different TDC.

To evaluate the observed similarity of dissolution profiles from microcapsules prepared by using different TDC, the dissolution profile of each will compared with the overall mean profile of all products prepared with different TDC. The results are tabulated in table (7). From the table it can be noticed that the calculated MDT ratios values are approximately 1 which may indicate local sameness and also for over all dissolution profile [34].

To assure the similarity of the mean of the dissolution profile of drug from all products prepared by using different TDC, pair-wise procedures were also applied using the overall mean drug released as a reference for comparison (table 8). From the table it can be noticed that all F_1 values are lower than 4.2% indicating that the average difference between of drug release from any whole product prepared with difference TDC and the overall mean drug release of the whole products are lower than 10 % at all sampling time points. Also the values of F_2 are greater than 50% suggesting that the mean drug release profile from any product can be considered similar to the drug release profile of the overall mean of the whole products prepared with the different TDC. Also, from table (8) it can be noticed that the values of Rescigno index of the products are closed to zero which indicate no drug release difference from different products and the overall mean of drug release prepared with different TDC.

The similarity of the DE, the closest of the MDT values and the similarity of different pair-wise tests of dissolution data of different products prepared by using different TDC leading to plotting the overall mean of the dissolution data from different products prepared by using different TDC (figure 2). The error bars represent the deviation of drug release from different products from the overall mean of drug release. Accordingly, it can be consider the overall mean of the dissolution profile

as dissolution profile of drug from microcapsules prepared by using any TDC and also have any particle size range.

CONCLUSION

From above it can be concluded the similarity of Aspirin release from different particle size ranges of Eudragit RS100 microcapsules prepared using the same TDC dispersed in the organic phase. The mean of drug released from different particles size ranges prepared using the same TDC showed the similarity of drug release from all products prepared by using different TDC. At the end it was concluded that the overall mean of the drug release from all products prepared by using different TDC can be used to represent the drug release profile from every microcapsule with any particle size range and prepared by using different TDC. The independent models were used to reach to this finding.

Table 1: Aspirin dissolution data from different particle size of Eudragit RS100 microcapsules prepared by using different TDC:

	20% TDC					33.33% TDC				
	Particle size ranges					Particle size ranges				
Time(hr)	500-400	400-315	315-80	Mean	±SD	800-500	500-400	315-80	mean	±SD
0.5	8.490	8.400	9.390	**8.760**	*0.547*	7.990	6.480	5.980	**6.817**	*1.046*
1	9.010	10.010	9.510	**9.510**	*0.500*	10.280	7.830	7.790	**8.633**	*1.426*
1.5	10.260	11.680	9.810	**10.583**	*0.976*	11.900	10.930	11.110	**11.313**	*0.516*
2	17.110	13.390	12.590	**14.363**	*2.412*	15.540	14.070	18.410	**16.007**	*2.207*
3	25.590	26.790	16.550	**22.977**	*5.598*	28.410	24.650	26.940	**26.667**	*1.895*
4	41.000	38.090	28.750	**35.947**	*6.400*	40.700	35.780	42.410	**39.630**	*3.442*
5	56.680	53.060	45.350	**51.697**	*5.787*	49.050	41.600	45.700	**45.450**	*3.731*
6	63.640	60.440	59.800	**61.293**	*2.057*	59.280	61.550	66.190	**62.340**	*3.522*
7	75.990	68.950	66.080	**70.340**	*5.099*	64.000	78.280	71.500	**71.260**	*7.143*
8	79.240	74.390	69.680	**74.437**	*4.780*	71.530	81.130	77.850	**76.837**	*4.880*
24	96.900	81.750	82.480	**87.043**	*8.544*	87.630	87.130	78.940	**84.567**	*4.879*

	50% TDC					66.66% TDC				
	Particle size ranges					Particle size ranges				
Time(hr)	800-500	500-400	315-80	Mean	±SD	800-500	500-400	315-80	mean	±SD
0.5	10.390	7.860	11.030	**9.760**	*1.676*	11.000	8.210	10.860	**10.023**	*1.572*
1	11.360	11.280	12.700	**11.780**	*0.798*	11.160	11.540	11.110	**11.270**	*0.235*
1.5	11.990	12.990	12.880	**12.620**	*0.548*	13.840	12.340	11.760	**12.647**	*1.073*
2	13.060	13.610	13.730	**13.467**	*0.357*	15.880	13.850	13.310	**14.347**	*1.355*
3	27.400	28.140	27.880	**27.807**	*0.375*	29.550	17.350	24.850	**23.917**	*6.153*
4	42.010	41.710	42.110	**41.943**	*0.208*	42.020	41.600	39.860	**41.160**	*1.145*
5	49.160	46.700	44.690	**46.850**	*2.239*	44.090	44.790	42.680	**43.853**	*1.075*
6	67.150	66.850	66.740	**66.913**	*0.212*	64.650	61.050	57.730	**61.143**	*3.461*
7	73.040	71.580	70.410	**71.677**	*1.318*	72.030	70.150	67.990	**70.057**	*2.022*
8	81.390	76.260	75.880	**77.843**	*3.077*	78.950	77.530	74.200	**76.893**	*2.438*
24	86.030	86.730	83.740	**85.500**	*1.564*	87.210	82.560	79.610	**83.127**	*3.832*

	80% TDC				
	Particle size ranges				
Time(hr)	800-500	500-400	315-80	Mean	±SD
0.5	9.740	8.810	8.490	**9.013**	*0.649*
1	10.940	9.890	9.340	**10.057**	*0.813*
1.5	13.150	12.350	11.290	**12.263**	*0.933*
2	17.550	16.680	15.790	**16.673**	*0.880*
3	27.540	26.800	24.530	**26.290**	*1.568*
4	42.510	40.100	38.300	**40.303**	*2.112*
5	54.410	50.410	47.590	**50.803**	*3.427*
6	61.170	60.240	59.380	**60.263**	*0.895*
7	70.180	68.950	67.550	**68.893**	*1.316*
8	75.100	72.980	71.650	**73.243**	*1.740*
24	84.440	78.400	77.190	**80.010**	*3.884*

Table 2: The parameters values of dissolution profile of Eudragit RS100 Microcapsules prepared using:

	20 % TDC				33.33 % TDC			
Parameter	500-400	400-315	315-80	mean	500-400	400-315	315-80	mean
AUC	1738.35	1558.73	1492.45	1596.51	1577.23	1651.68	1572.23	1600.38
ABC	587.25	403.27	487.07	492.53	525.90	439.44	322.33	429.22
MRT	5.03	7.92	7.69	7.04	7.02	6.92	8.37	7.45
MDT	6.06	4.93	5.91	5.66	6.00	5.04	4.08	5.08
VDT	25.39	16.13	22.13	21.70	26.40	12.93	6.37	16.14
m2	62.12	40.46	57.00	53.72	62.42	38.36	23.04	41.90
RD	0.69	0.66	0.63	0.68	0.73	0.51	0.38	0.63
DE	0.72	0.65	0.62	0.67	0.66	0.69	0.66	0.67
	50 % TDC				66.66 % TDC			
Parameter	500-400	400-315	315-80	mean	500-400	400-315	315-80	mean
AUC	1665.48	1623.30	1595.33	1628.04	1651.01	1580.86	1527.54	1586.47
ABC	399.24	458.22	414.43	423.96	442.04	400.58	383.10	408.57
MRT	7.22	7.13	7.65	7.34	7.04	7.74	8.21	7.69
MDT	4.64	5.28	4.95	4.96	5.07	4.85	4.81	4.92
VDT	11.82	19.57	16.84	16.15	17.07	12.44	13.81	14.51
m2	33.35	47.48	41.34	40.74	42.76	35.99	36.96	38.67
RD	0.55	0.70	0.69	0.66	0.66	0.53	0.60	0.60
DE	0.69	0.68	0.66	0.68	0.69	0.66	0.64	0.66
	80 % TDC							
Parameter	500-400	400-315	315-80	mean				
AUC	1599.76	1522.07	1490.30	1537.37				
ABC	426.80	359.54	362.26	382.87				
MRT	7.56	8.44	8.55	8.21				
MDT	5.05	4.59	4.69	4.79				
VDT	18.96	13.83	13.99	15.72				
m2	44.50	34.86	36.01	38.62				
RD	0.74	0.66	0.64	0.69				
DE	0.67	0.63	0.62	0.64				

AUC, area under the dissolution curve
ABC, area between the drug dissolution curve and its asymptote
MRT, mean residence time of the drug substance molecules in the dosage form
MDT, mean dissolution time
VDT, variance of dissolution time
m_k, moments of dissolution times of order k
RD, relative dispersion of dissolution time, CV^2 (coefficient of variation)
DE, dissolution efficiency

Table 3: Ratio of MDT of dissolved drug from different particles size range prepared using:

	20%			33.33%			50%		
Time(hr)	500-400	400-315	315-80	800-500	500-400	400-315	800-500	500-400	400-315
0.5	0.969	0.969	1.072	1.172	0.951	1.000	1.065	0.805	1.130
1	0.947	0.947	1.000	1.191	0.907	1.000	0.964	0.958	1.078
1.5	0.969	0.969	0.927	1.052	0.966	1.000	0.950	1.029	1.021
2	1.191	1.191	0.877	0.971	0.879	1.000	0.970	1.011	1.020
3	1.114	1.114	0.720	1.065	0.924	1.000	0.985	1.012	1.003
4	1.141	1.141	0.800	1.027	0.903	1.000	1.002	0.994	1.004
5	1.096	1.096	0.877	1.079	0.915	1.000	1.049	0.997	0.954
6	1.038	1.038	0.976	0.951	0.987	1.000	1.004	0.999	0.997
7	1.080	1.080	0.939	0.898	1.099	1000	1.019	0.999	0.982
8	1.065	1.065	0.936	0.931	1.056	1.000	1.046	0.980	0.975
24	1.113	1.113	0.948	1.036	1.030	1.000	1.006	1.014	0.979
	66.66%			80 %					
Time(hr)	800-500	500-400	400-315	800-500	500-400	400-315			
0.5	1.097	0.819	1.083	1.081	0.977	0.942			
1	0.990	1.024	0.986	1.083	0.983	0.929			
1.5	1.094	0.976	0.930	1.081	1.007	0.921			
2	1.107	0.965	0.928	1.074	1.000	0.947			
3	1.236	0.725	1.039	1.061	1.019	0.933			
4	1.021	1.011	0.968	1.057	0.995	0.950			
5	1.005	1.021	0.973	1.060	0.992	0.937			
6	1.057	0.998	0.944	1.054	1.000	0.985			
7	1.028	1.001	0.971	1.044	1.001	0.981			
8	1.027	1.008	0.965	1.039	0.996	0.978			
24	1.049	0.993	0.958	1.041	0.980	0.965			

Table 4: DDSolver calculated values of F_1, F_2 & Rescigno index (1&2) for the drug release profiles:

	20% TDC			33% TDC			50% TDC		
PS range	500-400	400-315	315-80	800-500	500-400	315-80	800-500	500-400	315-80
f1	8.759	3.990	8.551	6.446	6.194	6.194	2.262	1.417	2.205
f2	66.812	80.678	67.859	72.987	73.675	79.354	88.266	93.930	90.298
¦Î1	0.043	0.017	0.034	0.028	0.024	0.020	0.012	0.008	0.011
¦Î2	0.045	0.023	0.034	0.029	0.024	0.025	0.015	0.008	0.012
	66% TDC			80% TDC					
PS range	500-400	400-315	315-80	800-500	500-400	315-80			
f1	4.942	2.725	4.018	4.224	0.787	3.732			
f2	77.753	81.647	82.914	81.791	97.229	84.942			
¦Î1	0.020	0.006	0.020	0.020	0.005	0.016			
¦Î2	0.021	0.010	0.020	0.021	0.007	0.016			

F1 is Differenace factor
F2 is Similarity factor
¦Î1 Rescigno index 1
¦Î2 Rescigno index 2

Table 5: Mean amount of drug released % from different microcapsules prepared by using different TDC:

Time (hr)	20%	33.33%	50%	66.66%	80%	Mean	±SD
0.5	8.760	6.817	9.760	10.023	9.013	**8.875**	*1.262*
1	9.510	8.633	11.780	11.270	10.057	**10.250**	*1.283*
1.5	10.583	11.313	12.620	12.647	12.263	**11.885**	*0.906*
2	14.363	16.007	13.467	14.347	16.673	**14.971**	*1.322*
3	22.977	26.667	27.807	23.917	26.290	**25.531**	*2.011*
4	35.947	39.630	41.943	41.160	40.303	**39.797**	*2.322*
5	51.697	45.450	46.850	43.853	50.803	**47.731**	*3.398*
6	61.293	62.340	66.913	61.143	60.263	**62.391**	*2.634*
7	70.340	71.260	71.677	70.057	68.893	**70.445**	*1.090*
8	74.437	76.837	77.843	76.893	73.243	**75.851**	*1.925*
24	87.043	84.567	85.500	83.127	80.010	**84.049**	*2.669*

Table 6: The parameters values of the mean dissolution profile of Aspirin from Eudragit RS100 Microcapsules prepared using:

Parameter	**20%**	**33%**	**50%**	**66%**	**80%**	**Mean**
AUC	1596.51	1600.38	1628.04	1586.47	1537.37	1589.75
ABC	492.53	429.22	423.96	408.57	382.87	427.43
MRT	7.04	7.45	7.34	7.69	8.21	7.56
MDT	5.66	5.08	4.96	4.92	4.79	5.09
VDT	21.70	16.14	16.15	14.51	15.72	16.99
m2	53.72	41.90	40.74	38.67	38.62	42.85
RD	0.68	0.63	0.66	0.60	0.69	0.66
DE	0.67	0.67	0.68	0.66	0.64	0.66

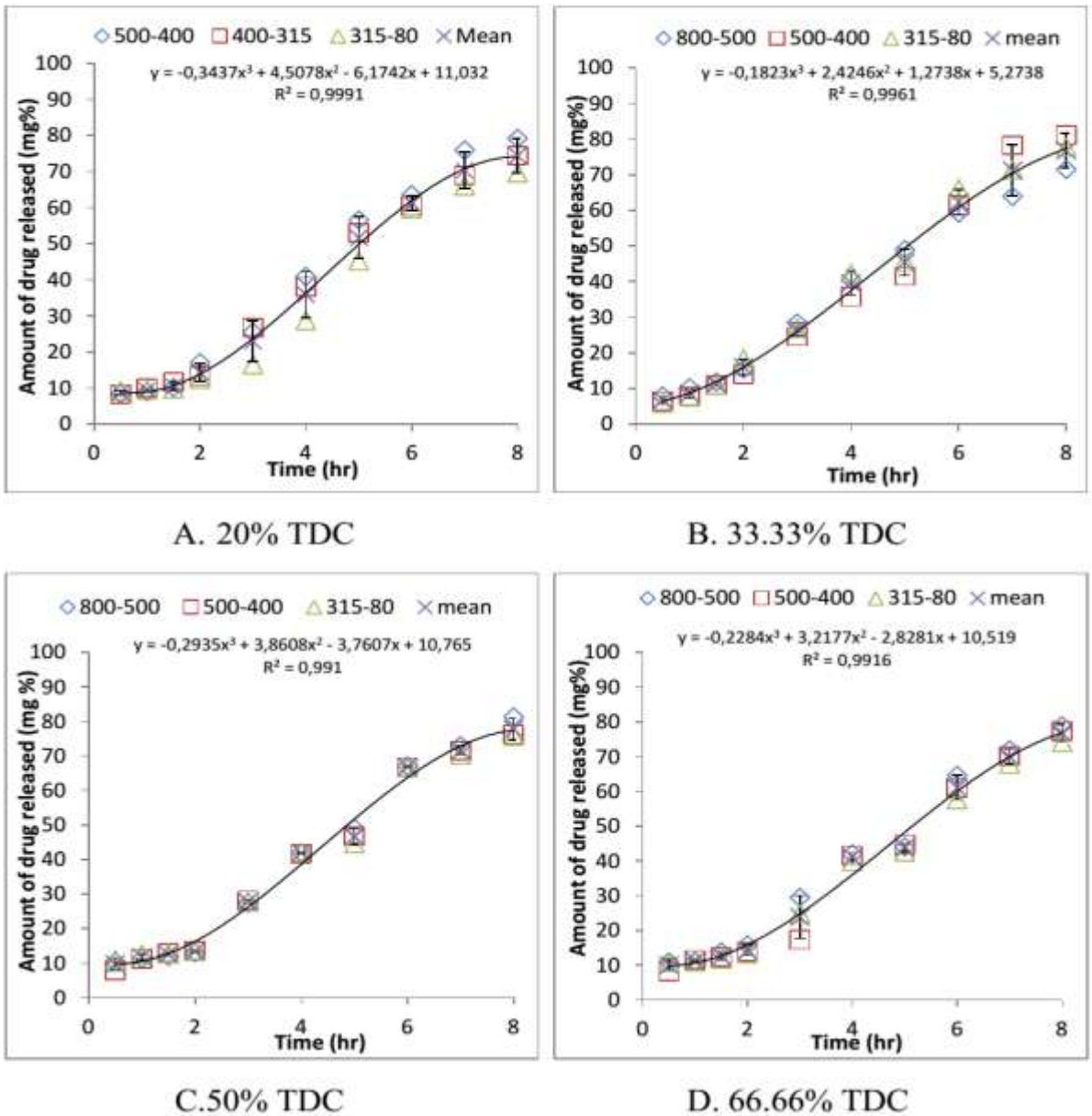
Table 7: Ratio of MDT of dissolved drug from all Products prepared using different TDC:

Time	20%	33.33%	50%	66.66%	80%
0.5	1.000	1.000	1.000	1.000	1.000
1	0.913	1.120	1.059	0.963	0.952
1.5	0.868	1.273	0.890	0.916	1.061
2	1.044	1.279	0.674	0.794	1.134
3	0.966	1.065	1.048	0.923	0.983
4	0.988	1.000	1.001	1.027	0.983
5	1.117	0.966	0.945	0.927	1.025
6	1.008	1.013	1.028	1.002	0.946
7	1.019	1.020	0.981	1.013	0.968
8	1.000	1.018	0.992	1.028	0.960
24	1.113	0.998	0.975	0.966	0.941

Table 8: DDSolver calculated values of F_1, F_2 and Rescigno index (1&2) for the mean drug release profiles of all products prepared by using different TDC:

	20%	33.33%	50%	66.66%	80%
f1	4.149	2.486	4.240	3.101	3.780
f2	81.072	89.984	82.421	86.691	82.641
¦Î1	0.015	0.006	0.013	0.008	0.021
¦Î2	0.016	0.007	0.013	0.009	0.021

Figure 1: Mean drug released % from different particle size ranges of Eudragit RS100 microcapsules prepared by using the same TDC.

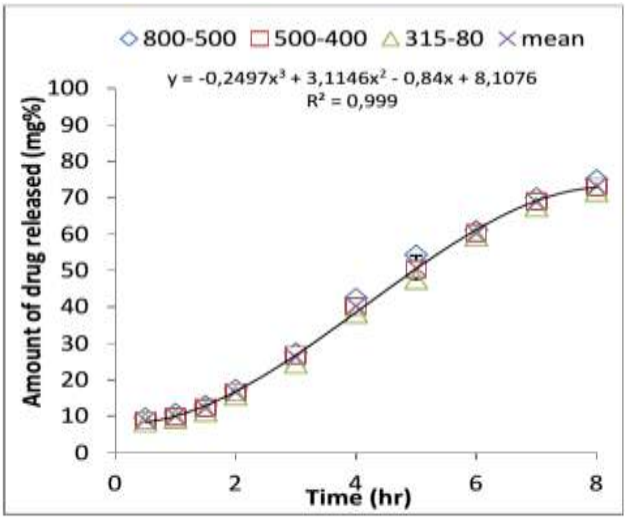


A. 20% TDC

B. 33.33% TDC

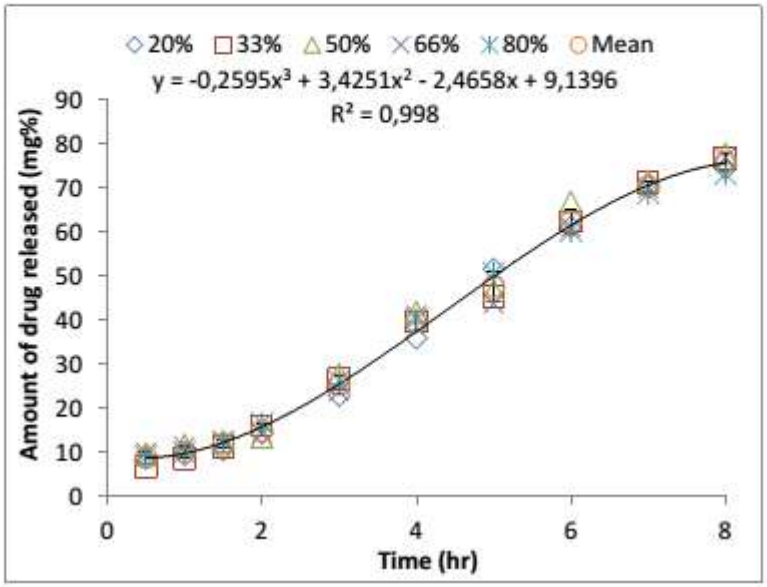
C.50% TDC

D. 66.66% TDC



E.80% TDC

Figure 2: The overall mean of the dissolution profile of Aspirin from all Eudragit RS100 microcapsules prepared using different TDC:



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