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Original Article

Studying the Effect of Dispersed Drug Crystal in the Organic Phase on the Encapsulation by Solvent Evaporation Technique; (4) Dependent models as tools for studying the drug release

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ABSTRACT

Different dependent models (kinetics and mechanisms) were used to study the Aspirin release from different particle size ranges of Eudragit RS100 microcapsules prepared with the same or different theoretical drug content in relation to the method of drug entrapment. The drug release kinetic obeys zero order kinetic and Higuchi model. Higuchi model had a large application in the polymeric matrix systems but zero order is an ideal to coated dosage forms. Both two forms are found to be the structure of Eudragit RS100 microcapsules entrapped drug. The good fitting of the drug release to Korsmeyer-Peppas model, which can be used as a decision parameter between the above two models, indicates the mechanism of the drug release in every case is either Case II or supper Case II. The above results are also supported by the good fitting of the dissolution data to Hixson-Crowel model since Eudragit RS100 is a swellable and non soluble polymer. The application of Weibull model again support the above results since the value of b > 1 in every case which indicating that the drug release mechanism is case II. Application of first order equation to the whole release data showed no fitting but the graphic representation showed bi-phase release data with one point transition time between the two phases which is after 2 hrs. There is no good fitting between Baker-Lansodale model and drug release data in every case but good fitting in every case was found with Hopfenberg model.

Key words: Dependent models, drug release, division mechanism, drug entrapment, Aspirin crystal, Eudragit RS100, Solvent evaporation technique.

INTRODUCTION

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 [1]. The model dependant methods can be classified into kinetics models and mechanisms models. The drug dissolution from solid dosage forms has been described by some kinetic models which include zero-order kinetics, first order kinetics, Higuchi model and Hixson-Crowel model. The mechanisms of drug release from a solid dosage form can be interpreted using these models: Weibull model, Baker-Lansodale model, Korsmeyer-Peppas & Ritger-Peppas model and Hopfenberg model [2-5]. Zero order is the ideal method of drug release in order to achieve a prolonged pharmacological action. It describes the systems where the drug release rate is independent on its concentration. Zero order is expressed as:

$$C = k_0 t$$

where C is the amount of drug release at time t , K_0 is zero-order rate constant. A plot of the amount of drug released versus time will be linear for zero-order kinetic [2]. On the opposite of that, the first order describes the release of drug from system where release rate is concentration dependent. The drug release is first order if it obeys the equation:

$$Log\ C_0 - Log\ C_t = k_1\ t / 2.303$$

where, C_t is the amount of drug released in time t, C_0 is the initial concentration of drug and K_1 is first order constant. The graphical representation of the log cumulative percent of the drug remaining versus time will be linear with a negative slope [6]. Higuchi describes drug release as a diffusion process based in the Fick's law, square root time dependent. Higuchi model was simplified as,

$$Q = K_H t^{1/2}$$

where K_H is the Higuchi dissolution constant. For diffusion controlled process, plotting the amount of

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drug released in time per unit area versus square root of time is linear [2-3].

On the opposite of Higuchi model, Hixson-Crowel cube root law is used by assuming that the drug release rate is limited by the drug particles dissolution rate and not by the diffusion [2]. It describes the release from systems where there is a change in surface area and diameter of particles or tablets [7-8]. Hixson-Crowel equation is:

$$(Q_0)^{1/3} - (Q_t)^{1/3} = K_{HC}\, t$$

where, Q_t is the remaining amount of drug in the dosage form at time t, Q_0 is the initial amount of the drug in tablet and K_{HC} is the rate constant of Hixson-Crowell rate equation. A graphical representation of the cube root of the amount of drug remaining versus time will be linear if the equilibrium condition is not reached and if the geometrical shape of the dosage form diminishes proportionally overtime [9].

An empirical equation to analyze both Fickian and non-Fickian release of drug from swelling as well as non- swelling polymeric delivery systems was developed by Ritger and Peppas and Korsmeyer and Peppas [10-14]. The equation is represented as:

$$M_t / M_\infty = K\, t^{n}$$

The logarithm form of the equation could be written as:

$$Log\ (M_t / M_\infty) = Log\ k + n\ Log\ t$$

where M_t / M_∞ is fraction of drug released at time t, n is diffusion exponent indicative of the transport mechanism of drug through the polymer, K is kinetic constant (having units of t^{-n}) incorporating structural and geometric characteristics of the delivery system. The release exponent n = 0.5 and 1.0 for Fickian and non-Fickian diffusion from slab and n = 0.45 and 0.89 for Fickian and non-Fickian diffusion from cylinders, respectively. A value of n = 1 actually means that, the drug release is independent of time regardless of the geometry. This equation can be used to analyze only first 60% of release, regardless of geometric shapes. The value of n = 0.5 is for $(time)^{1/2}$ kinetics and n = 1 for zero-order release [14].

The Weibull model expresses the accumulated fraction of drug m in solution at time t. The equation can be rearranged as:

$$Log\ [\ ln\ -\ (\ 1 - m\ )] = b\ Log\ (\ t - T_i) - log\ a$$

where m is accumulated fraction of drug in solution at time t, a is the scale parameter which defines the time scale of the process. T_i is the location parameter, represents the lag time before the onset of the dissolution or release process and in most of the cases will be zero. The shape parameter b characterizes the curves as either exponential ($b=1$), s - shaped ($b>1$) or parabolic ($b<1$) [15]. A graphic representation of link side versus time t gives a linear relation. Shape parameter (b) is obtained from the shape of the line and the scale parameter (a) can be estimated from the ordinate value ($1/a$) at time $t = 1$[15].

Baker-Lonsdale developed a model from the Higuchi model which describes the controlled release of drug from a spherical matrix [16]. Baker-Lonsdale model could be redefined as:

$$3/2\ [1 - (1 - M_t / M_\infty)\ 2 / 3] - M_t / M_0 = k\ t$$

where M_t is the amount of drug released at time t and M_∞ is the amount of drug released at an infinite time and k is the release constant corresponds to the slope. The graphic representation of the left side of the equation versus time will be linear if the established conditions were fulfilled. This equation can be used to the linearization of the release data from several formulations of microcapsules [17].

Hopfenberg and Katzhendler et al developed a general mathematical equation describing drug release from slabs, spheres and infinite cylinders displaying heterogeneous erosions as:

$$M_t / M_\infty = 1 - [1 - k_0\, t / C_0\, a_0\ ]\ n$$

where M_t is the amount of drug dissolved in time t, M_∞ is the total amount of drug dissolved when the dosage form is exhausted, M_t / M_∞ is the fraction of drug dissolved, k_0 is the erosion rate constant, C_0 is the initial concentration of drug in the matrix and a_0 is the initial radius for sphere or cylinder or the half-thickness for a slab. The value of n is 1, 2, and 3 for a slab, cylinder and sphere respectively [18, 19].

The selection of a suitable model for fitting dissolution data is essential, not only for quantitative evaluation of drug release characteristics but also for comparison of dissolution profiles using model-dependent approaches. 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 provides a number of statistical criteria for evaluating the goodness of fit of a model, including the correlation coefficient (***R_obs–pre***), the coefficient of determination (***Rsqr, R^2, or COD***), the adjusted coefficient of determination (***Rsqr_adj or $R^2_{adjusted}$***), the mean square error (***MSE***), the standard deviation of the residuals (***MSE_root or Sy.x***), ***SS***, ***WSS***, the Akaike Information Criterion (***AIC***), and the Model Selection Criterion (***MSC***). Among these criteria, the most popular ones in the field of dissolution model identification are the $R^2_{adjusted}$, the ***AIC*** and the ***MSC*** [20]. For release models with the same number of parameters, the coefficient of determination (R^2) can be used to discriminate the most appropriate model [20-22]. Singh et al reported that the SSR/R^2 is better than relying only

on R^2 as goodness of fit value and this shall also not be considered that equation having best R^2 value always have best SSR value. These both if used in some relationship may give more genuine justification about choice of equations, but individually these may be misleading in formulation development [13]. However, when comparing models with different numbers of parameters, the adjusted coefficient of determination should be used:

$$R^2_{\text{adjusted}} = 1 - \frac{n-1}{n-p} \cdot \left(1 - R^2\right)$$

where ***n*** is the number of data points and ***p*** is the number of parameters in the model. This is because R^2 will always increase as more parameters are included, whereas R^2 adjusted may decrease when over-fitting has occurred. Therefore, the best model should be the one with the highest R^2 adjusted, rather than that with the highest R^2 [15]. The Akaike information Criterion has been used for selecting optimal models for more than 35 years [23]. Its general applicability and simplicity make it an excellent and popular criterion for various purposes, including drug dissolution data analysis [24]. The AIC as defined below is dependent on the magnitude of the data as well as the number of data points:

$$\text{AIC} = n \cdot \ln(\text{WSS}) + 2 \cdot p$$

where ***n*** is the number of data points, ***WSS*** is the weighted sum of squares, and ***p*** is the number of parameters in the model. When comparing two models with different numbers of parameters, the model with a lower ***AIC*** value can be considered to be the better model, but how much lower the value needs to be to make the difference between the models statistically significant cannot be determined because the distribution of the ***AIC*** values is unknown. It should be noted that when a comparison is made, the weighting scheme used in each model must be the same [20].

The MSC provided by MicroMath Corporation [20] is another statistical criterion for model selection which is attracting increasing attention in the field of dissolution data modelling [25, 26]; it is defined as:

$$= \ln\left(\frac{\sum_{i=1}^{n} w_i \cdot \left(y_{i\_\text{obs}} - \bar{y}_{\_\text{obs}}\right)^2}{\sum_{i=1}^{n} w_i \cdot \left(y_{i\_\text{obs}} - y_{i\_\text{pre}}\right)^2}\right) - \frac{2p}{n}$$

where w_i is the weighting factor, which is usually equal to 1 for fitting dissolution data, y_{i_obs} is the ***ith*** observed ***y*** value, y_{i_pre} is the ith predicted ***y*** value, y_{obs} is the mean of all observed ***y***-data points, ***p*** is the number of parameters in the model, and ***n*** is the number of data points. The ***MSC*** is a modified reciprocal form of the ***AIC*** and has been normalized so that it is independent of the scaling of the data points. When comparing different models, the most appropriate model will be that with the largest ***MSC***. It is, therefore, quite easy to develop a feeling for what the ***MSC*** means in terms of how well the model fits the data. Generally, a ***MSC*** value of more than two to three indicates a good fit [27]. Although all the criteria mentioned above can be calculated by DDSolver to assess the goodness of fit of dissolution models, it should be noted that when mechanistic models are evaluated, model selection should be based, not only on the goodness of fit but also on the mechanistic plausibility of the model.

The aim of this work is to apply different dependent models (kinetics and mechanisms) to study the drug release from different particle ranges Eudragit RS100 microcapsules prepared by using different or the same TDC (theoretical drug content). The selection of the most suitable model for fitting dissolution data would be based on the calculating values of R^2, R^2_{adje}, AIC and MSC using DDSolver soft ware. The drug release study has also to be in relation to the physco-chemical drug entrapment mechanism which occurred as a result of the division mechanism suggested by the author.

MATERIALS AND METHODS

Materials and methods are the same in reference [28].

RESULTS AND DISCUSSION

The kinetic and mechanism of drug released was studied using different dependent models. The models were transformed into straight-line equations and the best fitness of the model was chosen on the bases of the values of R^2, $R^2_{adj.}$, ***AIC*** and ***MSC***. Table (1A) shows goodness of fitness of the drug dissolution data of all different particle size microcapsules prepared with the same or different theoretical drug content (TDC) to zero order kinetic since the values of R^2 and $R^2_{\text{adjust.}}$ are high enough to consider good fitting. Also closing the values of MIC and the values of MSC which is between 2 and 4 support also the fitting of the dissolution profiled to zero order kinetic. From table (1B) it can be noticed the closest of zero order dissolution rate constant from all products which is in agreement with the similarity of the dissolution profiles [28]. The alternative negative values between **Tlag** (lag time of drug release) and $\mathbf{F_0}$ (initial drug release which is the intercept with the

y axis) interpretate each other because if there is a lag time of drug release then $\mathbf{F_0}$ should has negative sign and vice versa. The lag time of the dissolution profile is related to the drug solubility in the dissolution media and the method of drug entrapment. The presence of lag time in the dissolution profile of particle size ranges 500-400 µm and 315-80 µm of microcapsules prepared by using 20 % and 33.33% TDC may be due to the molecular dispersion and minute drug crystal entrapment mechanisms [29]. At the same time the absence of lag time from the dissolution profile of particle size range 800-500 µm microcapsules prepared by 33.33% TDC may be due to the size of the microcapsules which need long time till complete evaporation of the organic phase (dichloromethane). This led to molecular dispersion of the drug in interior the microcapsule structure as a result of using 0.1N HCL as an aqueous phase which has the minimal solubility of the drug. This method was used as a tool to increase the amount of drug entrapment in the microcapsules prepared by solvent evaporation technique [30, 31]. The dissolution profile of 800-500 µm particle size range of microcapsules prepared by using 50% TDC showed double lag time than that from 500-400 µm particle size range of the same product. That is may be due to the amount of drug crystal in the first is more than the second one [29]. The absence of lag time from the dissolution profile of 315-80 µm particle size range may be due to increase the surface area as a result of the smallest microcapsules and the high concentration of molecular dispersed drug in the microcapsule structure [29]. At the same time increase the drug crystal in the microcapsule as a result of increasing TDC used and also the particle size range may led to decrease the thickness the polymer film. This led to increase the lag time 50% in case 800-500 µm particle size range of microcapsules prepared on using 66.66% than that from product prepared on using 80% TDC of the same size range which has the opposite effect on the value of F_0.

Table (1C) shows the secondary parameters of zero order kinetics which are the time required to release 25%, 50%, 75%, 80% and 90% of drug. From the table it can be notice the closest of data to each other's which again in agreement with the similarity of the different dissolution profiles [28]. This could be also noticed from the values of standard deviation at each time. Table (2A) shows the first order kinetic data which indicates the values of R^2 and $R^2_{adjested}$ are not high enough to consider a good fitting with first order kinetics on application the whole release data all-over the dissolution time. In addition the values of AIC look high although the values of MSC are between 2 and 3 in most cases. At the same time the graphic representation of the dissolution data according to the first order equation (figure 1A-D) shows bi-phase dissolution profile for every particle size ranges prepared with same or different TDC [32, 33]. Accordingly, the extend of the two phase was determined according the value of calculated correlation coefficient $\boldsymbol{R^2}$. It was found (table 2b) that the first phase is between 0-2 hrs and the second one is between 2- 8 hrs. Also there is a together rate change point which is the point at which the drug dissolution rate changed from one rate to another i.e. there is no phase transition state. It is at 2hr. From table (2B) it can be noticed that the first phase dissolution rate constant from products can be arranged in the following order 20% < 33.33% < 50% > 66.66 % > 80%TDC. That is may be due to the molecular dispersion of the drug in the product prepared on using 20% TDC which decreased with increasing TDC [29]. Decreasing the drug crystal content and increasing the polymer content in the product prepared on using 66.66% TDC than that of 80TDC[28] may be responsible about increasing the release rate constant on using 66.66% TDC than that on using 80% TDC. That is may be due to prolongation of the diffusion route of the drug [34, 35]. At the same time, table (2B) shows the closest of the dissolution rate constant of the drug in the second phase from all different particle size ranges microcapsules prepared on using the same or different TDC with nearly the same intercept. That is may be due to that, after 2 hrs dissolution time the drug release occurred mainly from the drug crystal entrapped in the microcapsule structure.

Higuchi model was also applied to the dissolution data (Table 3a). Goodness of fit of dissolution data by Higuchi model ($\mathbf{R^2}$**&** $\mathbf{R^2_{adje}}$) is high enough to evaluate the dissolution behaviour. Also the values of AIC are nearly similar and the values of MSC are between 2-3 which indicating better fitting [27]. The mean Higuchi rate constants of different particle size ranges prepared by using 20%, 33.33% and 50% TDC are equal while that from microcapsules prepared on using 66.66% TDC are lower than that from 80% TDC (able 3b). That is may be due the mechanism of drug entrapment in the microcapsules prepared on using 20%, 33.33% and 50% TDC which are combination of molecular dispersion, drug crystal and another form of interaction between the drug and the polymer [29]. Increasing the drug crystal in the microcapsule structure prepared on using 80% TDC more than that in 60% TDC may be responsible about decreasing the Higuchi dissolution rate. Using the two functions (Tlag & F_0) which are automatically calculated and provided by DDSolver (table 3b), it can be noticed that, the mean Tlag of products

prepared by using 20% TDC is equal to that of 33.33% TDC and both are higher than that of 50% and 66.66% TDC which are also equal. The mean Tlag of the product prepared on using 80%TDC is the lowest one. This observed finding from the dissolution data is completely against the fact that decrease the drug particle size and the drug molecular dispersion have high dissolution rate than the form of drug bigger particle size one. That is in agreement with what is reported by the author about the presence some kind of interaction between the molecular dispersed drug and the polymer which may be responsible about the above result. The author also reported that this interacted form needs further IR explanation [29].

Hixson-Crowel model was also applied since Eudragit RS100 is water insoluble but water swellable polymer. Accordingly, it can be concluded that the change in total microcapsule surface will be regularly and occurred only as a result of swelling of the polymer especially there is no drug crystal observed attached to the microcapsule surface [36]. Then it can be expected that the drug release will depend on the drug particles dissolution rate [2 9] and the method of drug entrapment in the microcapsule structure.

Table (4) shows the goodness of fit of the dissolution data to the Hixson-Crowel model which support the hyposis before. Also from the same table the best-fit values show the closest of the Hixson-Crowel dissolution rate constant (K_{HC}) as a general to each other which again supports the presences of certain interaction between the drug dispersed molecule and the polymer. This is because the presence of the drug in the molecular dispersed form (in products prepared by using 20%, 33% and 50% TDC) should release the drug faster than that when the drug present as a crystal form (in products prepared by using 66% and 80% TDC) [29] in case of there is no interaction between the drug and the polymer.

Korsmeyer – Peppas model was also applied to the dissolution data from different particle size ranges microcapsules prepared by using the same or different TDC. Although the fitting data are not ideal but it can be consider as good fitting specially there is no value for either R^2 or R^2_{adj} lower than 0.9 (table 5). Also from the table it can be noticed there are some variability in the values of the model kinetics constant (K_{KP}). That is may be due to its incorporation in the structural and geometric characterization of the delivery system which could be expected to change during the dissolution process [5]. The release exponent (n) is an indicative of the mechanism of release because it indicates relative rates of diffusion and polymer relaxation. For spherical particles, a Fickian-diffusion controlled release is implied when n is 0.43 (Case I in which the rate of diffusion is much smaller than the rate of relaxation). Accordingly, $0.43 < n < 0.85$ is an indication of both diffusion controlled release and swelling controlled release (also known as anomalous transport), while a value of n equal to 0.85 indicates case-II transport where the diffusion process is much faster than the relaxation process, system controlled by relaxation[37, 38]. Occasionally, values of $n > 1$ have been observed, which are regarded as Super Case II kinetics [39, 40]. From table (5) it can be noticed that, the values of n of all different particle size microcapsules prepared by using the same or different TDC indicating that the drug release mechanism is case II or super case II. That is means the drug release rate does not change over the time and the drug is released according to zero order mechanism which is in agreement with what stated before about the zero order release kinetics. This phenomenon can generally attributed to structure changes induced in the polymer by the penetrate [41].

Cox et al [42] and Saki et al [43] stated that super case-II transport mechanism is a relaxation release by which the drug transport mechanism associated with stresses and state transition in hydrophilic glassy polymers which swell in water or biological fluids. This process also involves polymer disentanglement and erosion.

Peppas et al. [44, 45], reported that the dynamic swelling behaviour of hydrogels is dependent on the relative contribution of penetrate diffusion and polymer relaxation. In the ionic hydrogels, the polymer relaxation is affected by the ionisation of functional groups. An increase in the degree of ionization results in the electrostatic repulsion between ionized functional groups, leading to chain expansion, which in turn affects macromolecular chain relaxation. Thus, the swelling mechanism becomes more relaxation-controlled when the ionization of hydrogel increases. Also Gierszewska et al [46] reported that the swelling of chitosan, chitosan- and chitosan-sodium alginate depend on the pH of the dissolution media. Increasing the pH of swelling solution from 3.5 to 9.0 cause a decrease of protonation of chitosan amine groups and simultaneously a deprotonation of alginate carboxylic acid groups or increase of degree of ionization of low-molecular pentasodium tripolyphosphate. Therefore, the swelling mechanism becomes more relaxation-controlled as ionization of sodium alginate and pentasodium tripolyphosphate becomes prominent. As a result the values of n values increased.

Eudragit® RS 100 is a copolymer of ethyl acrylate, methyl methacrylate and a low content of methacrylic acid ester with quaternary ammonium groups. The ammonium groups are present as chloride salts and make the polymers permeable. In basic dissolution medium the polarity of the ammonium groups will be increased which associated with stresses and state transition in hydrophilic glassy of the polymer. As a result the swelling mechanism becomes more relaxation-controlled as ionization of the quaternary ammonium groups prominent. As a result the values of ***n*** increased. The molecular dispersion of aspirin may be led to increase the polarity in the microcapsule structure as a result of certain of interaction [47, 48] with polymer which led to increase the value on ***n***. This theoretical explanation can be supported with the ***n*** values of particle size ranges 500-400, 400-315 and 315-80 which are 0.956, 0910 and 0.810 respectively where in the bigger particle size ranges microcapsules the drug entrapped as solid solution form with certain interaction with the polymer. On decreasing the microcapsules particle size ranges, it was found that the drug entrapped, in addition to solid solution with certain drug polymer interaction, also minute drug crystal [29].

Hopfenberg model was also applied on the drug release data of all different particle size Eudragit RS100 microcapsules prepared by using different TDC (Table 6). From the table it can be concluded that the value of R^2 in every case is high enough to apply the Hopfenberg model for the release data. The other values like R^2_{adj}, ***AIC*** and ***MSC*** also support the same conclusion. From the table it can be noticed that the initial curves fitting using Hopfenberg model over range of 0 to 80% drug release, yielded values for **n** are ***1*** in every case. Accordingly the model for slab was therefore used. On trying to use (***n*=3**) manually because the products are microcapsule, the value of R^2, R^2_{adj}, ***AIC*** and ***MSC*** are markedly decreased.

It was reported that, Hoffenberg's model can be applied to surface eroding polymer matrices where a zero-order surface detachment of the drug is the rate limiting release step. The equation is valid for spheres, cylinders and slabs [49]. Eudragit RS 100 microcapsules containing Aspirin as model drug are spherical in shape which may be in some cases irregular due to high drug crystal content [36]. Accordingly, the value of ***n*** should be ***3*** and not ***1*** as calculated by DDSolver soft ware. The same result had Pillay and Fassihi [50] who proposed negligible erosion for calcium alginate pellets based on the low erosion constant values obtained in their study using the Hopfenberg model. The value of ***n*** was **3** in the Hopfenberg equation, the data in the present study also demonstrated poor linearity (r2 =0.8596). The author explained the finding as a result of the absence of perfectly spherical shape of the pellets which is a prerequisite for obtaining best –fit for this equation. At the same time Arschia et at [50] found that a gradual erosion of the micropellets was observed during dissolution. Also Hixson-Crowell Cube Root Law indicates a change in surface area with progressive dissolution of the matrix with time with poor fit (R^2 =0.8937) which was again contradicting our observation. The author, as a trial to explain the result, used the same equation in two parts i.e., 0-4 hrs study and 4-8hrs study since alginate is insoluble in acidic pH and more soluble in pH > 7.0 As assumed, best fit with R^2 = 0.9976 (K_{hc} = 0.0134) and 0.9490 (K_{hc} = 0.0038). In this study, application of Hixson-Crowel model showed good fitting for the dissolution data from different particle size Eudragit RS100 prepared by using the same or different TDC.

It was also reported that, Hopfenberg [15] is an empirical mathematical erosion models of the system; assumed that the rate of drug release from the erodible system is proportional to the surface area of the device which is allowed to change with time. All mass transfer processes involved in controlling drug release are assumed to add up to a single zero-order process (characterized by a rate constant, k_0) confined to the surface area of the system. This zero-order process can correspond to a single physical or chemical phenomenon, but it can also result from the superposition of several processes, such dissolution, swelling, and polymer chain cleavage. A good example for systems Hoffenberg's model can be applied to surface eroding polymer matrices where a zero-order surface detachment of the drug is the rate limiting release step. Hopfenberg derived the following, general equation, which is valid for spheres, cylinders and slabs:

$$\frac{M_t}{M_\infty} = 1 - \left(1 - \frac{k_0 \cdot t}{c_0 \cdot a}\right)^n$$

M_t and M_∞ are the cumulative amounts of drug released at time t and at infinite time, respectively; C_0 denotes the uniform initial drug concentration within ***a*** is the radius of a cylinder or sphere or the half-thickness of a slab; ***n*** is a 'shape factor' representing spherical (**n**=3), cylindrical (**n**=2) or slab geometry (**n**=1). The model ignores edge and erodible end effects. From the above Hopfenberg model it is clear that slabs lead zero-order drug release kinetics, whereas spheres and cylinders exhibit declining release rates with time [51, 52].
Again, it was also reported that the release models with major applications and best describing drug release phenomenon are the Higuchi model, zero

order kinetics, Weibull model and Korsmeyer-Peppas model. The Higuchi and zero order models represent two limit cases in the transport and drug release phenomena and the Korsmeyer-Peppas model can be a decision parameter between these two models. While the Higuchi model had a large application in the polymeric matrix systems, the zero order models becomes the ideal to describe coated dosage forms or membrane controlled dosage forms [53]. Mady O., reported that the Aspirin was entrapped in the microcapsule structure as solid solution form, minute drug crystal and pure crystal form which again in agreement with the above reported [29]. Accordingly, from above it can concluded that, since it was found that the drug release obey zero order kinetics and also the application of Korsmeyer-model indicated the drug release mechanism is super case II, it can be concluded that the above finding about the value of (n = 1) is due to the drug release zero order kinetics which lead to, on application of Hopfenberg model, that value of n is 1 although the products are microcapsules. Also from table (6) it can be noticed the value of Hopfenberg rate constant (k_{HC}) is nearly equal one which is in agreement with the similarity of the drug dissolution profile from different particle size microcapsules prepared with different or the same TDC [28] specially it was reported that the rate constants values for Hopfenberg model decreased as the content of guar gum increased in matrix granules which indicated that the differing proportion of gum granules mixed with matrix granules could control and modulate the drug release[54].

Baker-Lonsdale is usually used to linearization of the release data from several formulations of microcapsules and microspheres [55, 56]. On application of Baker-Lonsdale model on the Aspirin release data from different particle size of Eudragit RS100 microcapsules prepared with the same or different TDC, from table (7), it can be noticed that there is no liner fitting between the release data and the model. It was reported that a linear relationship is found with the application of diffusion based Baker-Lonsdale kinetic models. This is indicating that the drug release behaviour is mainly governed by diffusion mechanism [57-60]. That is may explain the reason by which the failure on application of Baker-Lonsdale model on the dissolution data of Aspirin from different Eudragit RS100 microcapsules prepared on using the same or different TDC. At the same time that is support with what stated before about the drug release mechanism.

The general empirical equation described by Weibull was adapted to the dissolution/ release process. It is successfully applied to almost all kind of dissolution curves. The results of Weibull model are listed in table (8). The values of R^2, R^2_{adj}, AIC and MSC are indicating the good fitting of the drug release data from different particle size Eudragit RS100 microcapsules prepared by using the same or different TDC with Weibull model. Also from the table it can be noticed that the value of b > 1 in every case which indicating that the drug release mechanism is case II and the dissolution curve is S-shaped with upward curvature followed by a turning point [15]. The parameter, a, can be replaced by the more informative dissolution time, T_d, that is defined by $a = (T_d)^b$ and is read from the graph as the time value corresponding to the ordinate $-ln\ (1-m)=1$. Since $-ln\ (1-m)=1$ is equivalent to m = 0.632, T_d represents the time interval necessary to dissolve or release 63.2% of the drug present in the pharmaceutical dosage form [15]. From the table (8) it was also concluded that the time necessary to dissolve 63.2% of the drug entrapped in different particles size Eudragit RS100 microcapsule structure is nearly equal. These results again supported what stated before about the similarity of the drug dissolution profile from all products [28] and also support the effect of the drug crystal dispersed in the organic phase on the microcapsules formation which occurred as a result of division mechanism suggested the author [36].

CONCLUSION

From above it can be concluded that, the different dependent models can be applied as tools to study the drug release kinetics as well as the drug release mechanism. At the same time it well better to correlate the release both kinetics and mechanism to the physiochemical structure of the microcapsules. Since the outcomes of the drug release models may be, at sometimes, are not in agreement with the actual entrapment method it is recommended that the outcome of all models should be interpretate in relation to the method of drug entrapment in the microcapsule structure.

Table 1a: Goodness of fit of dissolution data of zero order kinetic:

	20 % TDC			33.33 % TDC		
Parameter	500-400	400-315	315-80	800-500	500-400	315-80
Rsqr	0.983	0.984	0.956	0.988	0.976	0.987
Rsqr_adj	0.981	0.982	0.950	0.987	0.973	0.985
AIC	52.199	49.871	59.193	45.337	55.789	49.094
MSC	3.666	3.725	2.722	4.039	3.332	3.907
	50 % TDC			66.66% TDC		
Parameter	800-500	500-400	315-80	800-500	500-400	315-80
Rsqr	0.980	0.979	0.970	0.981	0.967	0.979
Rsqr_adj	0.977	0.977	0.966	0.978	0.963	0.976
AIC	53.560	52.978	56.056	51.869	57.370	51.674
MSC	3.495	3.474	3.104	3.544	3.026	3.443
	80 % TDC					
Parameter	800-500	500-400	315-80			
Rsqr	0.986	0.989	0.988			
Rsqr_adj	0.984	0.988	0.986			
AIC	48.246	45.450	46.354			
MSC	3.860	4.103	3.989			

Table 1B: Best fit values of the dissolution data of zero order kinetics:

	20 % TDC					33.33 % TDC				
Parameter	500-400	400-315	315-80	Mean	SD	800-500	500-400	315-80	Mean	SD
k_0	10.694	9.810	9.336	9.947	0.689	9.169	10.793	10.353	10.105	0.840
Tlag	0.181	0.077	0.292	----	----	-0.112	0.443	0.189	----	----
F_0	-1.936	-0.757	-2.726	----	----	1.024	-4.783	-1.953	----	----
	50 % TDC					66.66 % TDC				
Parameter	800-500	500-400	315-80	Mean	SD	800-500	500-400	315-80	Mean	SD
k_0	10.493	10.087	9.731	10.103	0.381	9.888	9.982	9.301	9.723	0.369
Tlag	0.112	0.063	-0.085	-----	-----	-0.075	0.209	-0.010	-----	-----
F_0	-1.177	-0.632	0.828	-----	-----	0.744	-2.091	0.093	-----	-----
	80 % TDC									
Parameter	800-500	500-400	315-80	Mean	SD					
k_0	9.690	9.526	9.409	9.542	0.141					
Tlag	-0.145	-0.055	0.039	-----	-----					
F_0	1.409	0.522	-0.364	-----	-----					

Table 1c: The secondary parameter of zero order kinetic:

	20 % TDC					33.33 % TDC				
Parameter	500-400	400-315	315-80	Mean	SD	800-500	500-400	315-80	Mean	SD
T25	2.519	2.626	2.970	2.705	0.236	2.615	2.759	2.603	2.659	0.087
T50	4.857	5.174	5.648	5.226	0.398	5.341	5.076	5.018	5.145	0.172
T75	7.194	7.723	8.325	7.747	0.566	8.068	7.392	7.433	7.631	0.379
T80	7.662	8.232	8.861	8.252	0.600	8.613	7.855	7.916	8.128	0.421
T90	8.597	9.252	9.932	9.260	0.668	9.704	8.782	8.882	9.122	0.506
	50 % TDC					66.66 % TDC				
Parameter	800-500	500-400	315-80	Mean	SD	800-500	500-400	315-80	Mean	SD
T25	2.495	2.541	2.484	2.507	0.030	2.453	2.714	2.678	2.615	0.141
T50	4.877	5.020	5.053	4.983	0.093	4.982	5.218	5.366	5.189	0.194
T75	7.260	7.498	7.622	7.460	0.184	7.510	7.723	8.054	7.762	0.274
T80	7.737	7.994	8.136	7.956	0.203	8.016	8.224	8.592	8.277	0.292
T90	8.690	8.985	9.164	8.946	0.240	9.027	9.226	9.667	9.306	0.327
	80 % TDC									
Parameter	800-500	500-400	315-80	Mean	SD					
T25	2.435	2.570	2.696	2.567	0.130					
T50	5.015	5.194	5.353	5.187	0.169					
T75	7.595	7.818	8.010	7.808	0.208					
T80	8.111	8.343	8.541	8.332	0.215					
T90	9.143	9.393	9.604	9.380	0.231					

Table 2A: Goodness of fit of dissolution data of first order kinetics data.

	20% TDC			33.33% TDC			50% TDC		
Parameter	500-400	400-315	315-80	800-500	500-400	315-80	800-500	500-400	315-80
Rsqr	0.897	0.923	0.868	0.957	0.874	0.909	0.892	0.910	0.905
Rsqr_adj	0.897	0.923	0.868	0.957	0.874	0.909	0.892	0.910	0.905
AIC	68.138	63.433	68.14	56.29	70.42	66.196	68.278	65.64	65.585
MSC	2.072	2.368	1.828	2.943	1.868	2.197	2.023	2.208	2.151
	66.66% TDC			80% TDC					
Rsqr	0.904	0.872	0.910	0.951	0.950	0.943			
Rsqr_adj	0.904	0.872	0.910	0.951	0.950	0.943			
AIC	65.833	69.086	64.06	58.76	58.53	59.633			
MSC	2.148	1.855	2.204	2.808	2.795	2.661			

Table 2B: Best fitting values of the two phases dissolution data of first order kinetics:

20% TDC	Phase1			Phase2		
PS range	K 1	inter	r2	K1	inter	r2
500-400	-0.107	2.17	0.983	-0.115	2.22	9.888
400-315	-0.090	2.13	0.996	-0.093	2.15	0.997
315-80	-0.086	2.15	0.971	-0.094	2.21	0.994
50 % TDC	**Phase1**			**Phase2**		
PS range	K 1	inter	r2	K1	inter	r2
800-500	-0.009	1.96	0.991	-0.111	2.20	0.979
500-400	-0.009	1.97	0.905	-0.098	2.15	0.976
315-80	-0.008	1.95	0.897	-0.096	2.15	0.968
80% TDC	**Phase1**			**Phase2**		
PS range	K 1	inter	r2	K1	inter	r2
800-500	-0.026	1.97	0.920	-0.089	2.111	0.996
500-400	-0.026	1.98	0.922	-0.083	2.115	0.992
315-80	-0.024	1.98	0.886	-0.083	2.115	0.991

33 % TDC	**Phase1**			**Phase2**		
PS range	K 1	inter	r2	K1	inter	r2
800-500	-0.019	1.97	0.992	-0.078	2.09	0.997
500-400	-0.025	1.99	0.970	-0.117	2.24	0.967
315-80	-0.024	1.99	0.970	-0.096	2.15	0.976
66 % TDC	**Phase1**			**Phase2**		
PS range	K 1	inter	r2	K1	inter	r2
800-500	-0.017	1.96	0.915	-0.101	2.161	0.964
500-400	-0.017	1.97	0.930	-0.100	2.184	0.971
315-80	-0.008	1.96	0.878	-0.088	2.141	0.976

Table 3a: Goodness of fit of dissolution data by Higuchi model:

	20 % TDC			33.33 % TDC		
Parameter	**500-400**	**400-315**	**315-80**	**800-500**	**500-400**	**315-80**
Rsqr	0.947	0.949	0.891	0.965	0.918	0.957
Rsqr_adj	0.941	0.942	0.878	0.961	0.908	0.952
AIC	63.440	61.391	68.228	56.076	68.075	60.599
MSC	2.541	2.573	1.819	2.965	2.103	2.757
	50 % TDC			66.66% TDC		
Parameter	**800-500**	**500-400**	**315-80**	**800-500**	**500-400**	**315-80**
Rsqr	0.931	0.944	0.925	0.935	0.912	0.925
Rsqr_adj	0.923	0.937	0.916	0.926	0.901	0.916
AIC	65.725	62.908	65.147	64.042	67.362	64.189
MSC	2.278	2.481	2.195	2.327	2.027	2.192
	80 % TDC					
Parameter	**800-500**	**500-400**	**315-80**			
Rsqr	0.958	0.958	0.951			
Rsqr_adj	0.953	0.953	0.945			
AIC	59.120	58.677	60.100			
MSC	2.773	2.780	2.615			

Table 3b: Best fit values of Higuchi model:

	20 % TDC					33.33 % TDC				
Parameter	500-400	400-315	315-80	Mean	SD	800-500	500-400	315-80	Mean	SD
k_H	38.006	34.877	32.635	35.173	2.698	32.812	37.897	36.924	35.878	2.700
Tlag	1.346	1.311	2.198	1.619	0.502	1.217	2.314	1.351	1.627	0.598
F_H	-30.615	-27.088	-26.769	-28.157	2.134	-23.97	-32.887	-29.954	-28.938	4.543
	50 % TDC					66.66 % TDC				
Parameter	800-500	500-400	315-80	Mean	SD	800-500	500-400	315-80	Mean	SD
k_H	37.037	35.853	34.410	35.767	1.316	34.945	35.081	32.738	34.255	1.315
Tlag	1.371	1.318	1.292	1.327	0.040	1.323	1.430	1.358	1.370	0.055
F_H	-28.853	-27.691	-24.951	-27.165	2.003	-25.41	-28.139	-24.273	-25.943	1.986
	80 % TDC									
Parameter	800-500	500-400	315-80	Mean	SD					
k_H	34.582	33.951	33.426	33.986	0.579					
Tlag	1.219	1.264	1.316	1.266	0.049					
F_H	-24.841	-25.198	-25.571	-25.203	0.365					

Table 4: Goodness of fit and best fit parameters of dissolution data of Hixson-Crowel model:

Best-fit Values									
	20%TDC			33%TDC			50%TDC		
Parameter	500-400	400-315	315-80	800-500	500-400	315-80	800-500	500-400	315-80
Rsqr	0.942	0.957	0.907	0.978	0.895	0.949	0.936	0.948	0.941
Rsqr_adj	0.942	0.957	0.907	0.978	0.895	0.949	0.936	0.948	0.941
AIC	62.372	57.753	64.706	49.385	68.600	60.320	63.000	60.154	60.792
MSC	2.648	2.937	2.171	3.634	2.051	2.785	2.551	2.757	2.631
Best-fit Values									
Parameter	500-400	400-315	315-80	800-500	500-400	315-80	800-500	500-400	315-80
kHC	0.042	0.043	0.039	0.041	0.047	0.046	0.042	0.046	0.045
Goodness of Fit									
	66%TDC			80%TDC					
Parameter	800-500	500-400	315-80	800-500	500-400	315-80			
Rsqr	0.946	0.916	0.945	0.971	0.971	0.963			
Rsqr_adj	0.946	0.916	0.945	0.971	0.971	0.963			
AIC	60.207	64.850	59.188	53.399	53.245	55.238			
MSC	2.710	2.278	2.692	3.345	3.323	3.101			
Best-fit Values									
Parameter	800-500	500-400	315-80	800-500	500-400	315-80			
kHC	0.046	0.044	0.042	0.045	0.043	0.041			

Table 5: Goodness of fit and best fit parameters of dissolution data of Korsmeyer-Peppas model:

Goodness of Fit

	20% TDC			33% TDC			50% TDC		
Parameter	500-400	400-315	315-80	800-500	500-400	315-80	800-500	500-400	315-80
Rsqr	0.966	0.965	0.913	0.981	0.952	0.983	0.941	0.963	0.931
Rsqr_adj	0.962	0.960	0.902	0.978	0.946	0.981	0.934	0.958	0.922
AIC	59.097	57.687	68.428	50.218	62.687	51.340	64.163	58.808	64.362
MSC	2.976	2.943	1.799	3.551	2.642	3.683	2.434	2.891	2.274

Best-fit Values

	20% TDC			33 % TDC			50% TDC		
Parameter	500-400	400-315	315-80	800-500	500-400	315-80	800-500	500-400	315-80
k_{KP}	10.482	10.635	13.274	10.911	8.931	9.264	11.789	10.988	12.662
n	0.956	0.910	0.810	0.891	1.013	1.026	0.872	0.912	0.813

Goodness of Fit

	66% TDC			80 % TDC		
Parameter	800-500	500-400	315-80	800-500	500-400	315-80
Rsqr	0.946	0.923	0.930	0.972	0.975	0.968
Rsqr_adj	0.940	0.913	0.922	0.968	0.972	0.964
AIC	62.054	66.013	63.457	55.252	53.643	55.727
MSC	2.525	2.162	2.265	3.160	3.284	3.052

Best-fit Values

	66% TDC			80 % TDC		
Parameter	800-500	500-400	315-80	800-500	500-400	315-80
k_{KP}	12.728	10.647	11.797	12.242	11.272	10.603
n	0.823	0.886	0.814	0,854	0.881	0.894

Table 6: Goodness of fit and best fit parameters of dissolution data by Hopfenberg model:

Goodness of Fit

	20%TDC			33%TDC			50%TDC		
Parameter	500-400	400-315	315-80	800-500	500-400	315-80	800-500	500-400	315-80
Rsqr	0.981	0.984	0.952	0.988	0.967	0.985	0.979	0.979	0.970
Rsqr_adj	0.979	0.981	0.946	0.986	0.963	0.983	0.976	0.976	0.966
AIC	53.069	50.045	60.050	45.830	59.065	50.284	53.849	53.067	56.168
MSC	3.579	3.707	2.637	3.989	3.004	3.788	3.466	3.465	3.093

Best-fit Values

K_{HC}	0,103	0.097	0,088	0.094	0.099	0.100	0.103	0.100	0.099
N	1	1	1	1	1	1	1	1	1

Goodness of Fit

	66%TDC			80%TDC		
Parameter	800-500	500-400	315-80	800-500	500-400	315-80
Rsqr	0.980	0.965	0.979	0.985	0.989	0.988
Rsqr_adj	0.978	0.961	0.976	0.983	0.987	0.986
AIC	52.007	57.983	51.677	48.936	45.579	46.411
MSC	3.530	2.965	3.443	3.791	4.090	3.983

Best-fit Values

K_{HC}	0.100	0.096	0.093	0.099	0.096	0.093
N	1	1	1	1	1	1

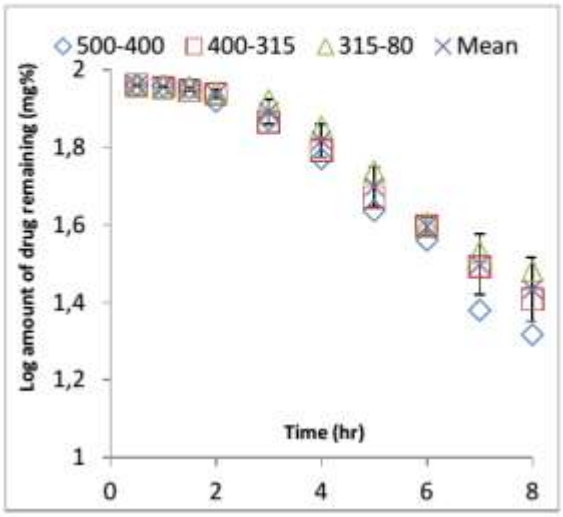
Table 7: Goodness of dissolution data by Baker-Lonsdale model:

	20% TDC			33.33% TDC			50% TDC		
Parameter	500-400	400-315	315-80	800-500	500-400	315-80	800-500	500-400	315-80
Rsqr	0.336	0.391	0.259	0.478	0.147	0.350	0.299	0.369	0.372
Rsqr_adj	0.336	0.391	0.259	0.478	0.147	0.350	0.299	0.369	0.372
AIC	86.756	84.156	85.421	81.229	89.515	85.857	86.960	85.117	84.444
MSC	0.210	0.296	0.099	0.449	-0.041	0.231	0.155	0.260	0.266
	66.66% TDC			80% TDC					
Rsqr	0.344	0.264	0.340	0.453	0.434	0.402			
Rsqr_adj	0.344	0.264	0.340	0.453	0.434	0.402			
AIC	85.092	86.573	83.953	82.820	82.789	83.111			
MSC	0.222	0.106	0.215	0.403	0.369	0.313			

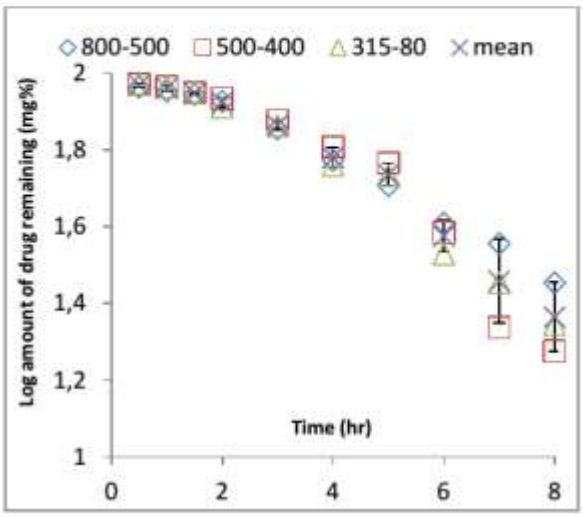
Table 8: Goodness of fit and best fit parameters of dissolution data of Weibull model:

	20%TDC			33%TDC			50%TDC		
Parameter	500-400	400-315	315-80	800-500	500-400	315-80	800-500	500-400	315-80
Rsqr	0.959	0.958	0.891	0.982	0.936	0.974	0.934	0.953	0.924
Rsqr_adj	0.954	0.953	0.877	0.979	0.928	0.971	0.926	0.947	0.915
AIC	60.859	59.394	68.277	49.683	65.636	55.683	65.254	61.095	65.326
MSC	2.800	2.772	1.814	3.604	2.347	3.249	2.325	2.663	2.177
Best-fit Values									
Parameter	500-400	400-315	315-80	800-500	500-400	315-80	800-500	500-400	315-80
α	9.204	9.031	11.026	9.909	10.964	10.437	8.150	8.734	7.519
β	1.192	1.116	1.308	1.232	1.249	1.250	1.104	1.130	1.021
Td	6.435	7.190	6.266	6.438	6.802	6.529	6.687	6.808	7.210
Goodness of Fit									
	66%TDC			80%TDC					
Parameter	800-500	500-400	315-80	800-500	500-400	315-80			
Rsqr	0.934	0.916	0.923	0.964	0.979	0.960			
Rsqr_adj	0.926	0.905	0.913	0.959	0.976	0.955			
AIC	64.119	66.899	64.467	57.732	52.073	58.125			
MSC	2.319	2.073	2.164	2.912	3.441	2.812			
Best-fit Values									
Parameter	800-500	500-400	315-80	800-500	500-400	315-80			
α	7.488	9.069	8.107	7.766	9.602	9.050			
β	1.039	1.095	1.005	1.062	1.233	1.087			
Td	6.946	7.493	8.022	6.888	6.258	7.589			

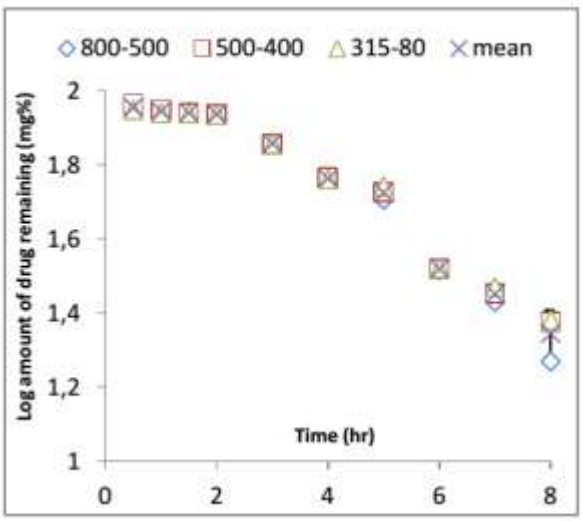
Figure 1: First order dissolution kinetics of Aspirin from different particle size ranges microcapsules prepared by using different TDC.



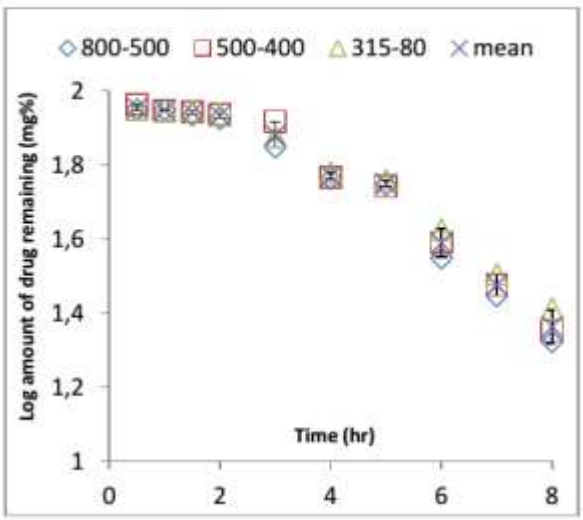
A: 20 % TDC



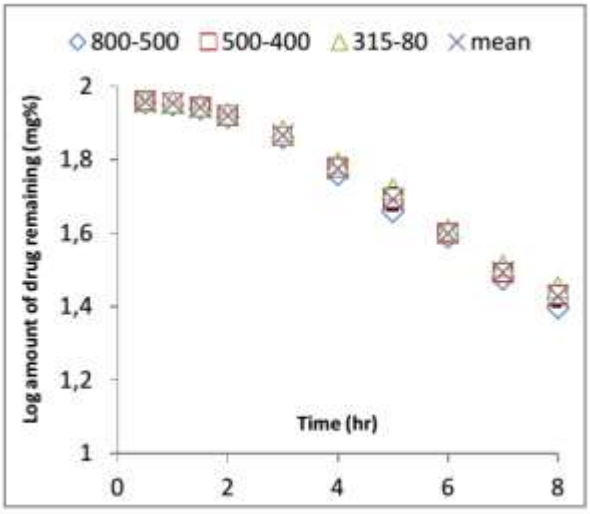
B: 33.33 % TDC



C: 50 % TDC



D: 66.66 % TDC



E: 80 % TDC

REFERANCES

1. Dash S. et al, Kinetic modelling on drug release from controlled drug delivery systems, Acta Poloniae Pharmaceutica-Drug research 2010; 67:(3)217-223.
2. Kalam M. et al, Continental J. Pharm Sci 2007; 1: 30-35.
3. Ofoefule S. and Chukwu A., Sustained release dosage forms: design and evaluation of oral products, Enterprises, Lagos 2002; 91-120.
4. Shah S. et al, Pak. J., Pharm. Sci. 2011; 24(2): 183-192.
5. Chime S. et al, Kinetics mechanisms of drug release from swellable and non swellable matrix, RJPBCS 2013; 4(2): 97-103.
6. Kabir A. Et al, Dhaka Univ J Pharm Sci 2009; 8(1): 23-30.
7. Hixson A. and Crowell J. Ind Eng Chem 1931; 23:923-931.
8. Shoaib H. Et al, Pak J Pharm Sci 2006; 19(2): 119- 124.
9. Rahman M. et al, Int J Pharm Biomed Res 2011; 2(1): 7-12.
10. Korsmeyer R. and Peppas N. J Control Rel 1983; 1:89-98.
11. Ritger P. and Peppas N. J Cont Rel 1987; 5:23-36.
12. Ritger P. and Peppas N. J Cont Rel 1987; 5: 37-42.
13. Singh J. et al, Prediction of *in vitro* Drug Release Mechanisms from Extended Release Matrix Tablets using SSR/R^2 Technique. *Trends in Applied Sciences* Research 2011; 6: 400-409.
14. Ford J. et al, Importance of drug type, tablet shape and added diluents on drug release kinetics from hydroxypropyl methyl celluloce matrix tablets. Int. J. Pharm. 1987; 40: 223-234.
15. Costa P. And Sousa L., Modeling and comparison of dissolution profiles and Eur J Pharm Sci 2001; 13:123-133.
16. Baker R. And Lonsdale H., Controlled release: mechanisms and rates. In: Taquary AC, Lacey RE. (Eds.), Controlled Release of Biologically Active Agents. New York: Plenum Press 1974; 15-71.
17. Shukla A, and Price C., Pharm Res 1991; 8:1369-1400.
18. Hopfenberg H., In: Paul DR, Haris FW. (Eds.). Controlled Release Polymeric Formulations. ACS Symposium Series. 33. Washington. DC: American Chemical Society 1991; 26-31.
19. Katzhendler I et al. J Pharm Sci; 1997, 86:110-115.
20. Zhang Y. et al, An introduction to the approaches used by DDSolver, Electronic supplementary material (doi: 10.1208/s12248-010-9185-1).
21. Syed A. et al, Modulating the release behaviour and kinetic evaluation of diclofenac sodium from natural polymers, international journal oc ChemTech research 2010; 2(2):834-841.
22. Jovita K. et al, Optimaization of methods for the preparation of famotidine floating microspheres, Der Pharmazie letter 2011; 3(6): 68-76:
23. Aaike H. A new look at the statistical model identification, IEEE Trans Automat Control. 1974; 19:716–23
24. Costa F. O, Sousa JJ, Pais AA, Formosinho SJ. Comparison of dissolution profiles of Ibuprofen pellets. J Control Release, 2003;89:199–212.
25. Koizumia T, Ritthidej GC, Phaechamud T. Mechanistic modelling of drug release from chitosan coated tablets. J Control Release. 2001;70:277–84
26. Mollo AR, Corrigan OI. Effect of poly-hydroxy aliphatic ester polymer type on amoxycillin release from cylindrical compacts.Int J Pharm. 2003;268:71–9.
27. Mayer B. et al., Pharmacokinetic-pharmacodynamic profile of systemic nitric oxide-synthase inhibition with L-NMMA in humans. Br J Clin Pharmacol. 1999;47:539–44
28. Mady O., 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, World J Pharm Sci 2014; 2(4): 409-421.
29. Mady O., Studying the Effect of Dispersed Drug Crystal in the Organic Phase on the Encapsulation by Solvent Evaporation Technique. (2) X-ray diffraction and DSC as tools to study the microcapsule structure in relation to the suggested division mechanism, accepted for publication in international journal of Pharmaceutical sciences and Research, 2014; 5(07)July.
30. Korsatko B. et al, Third European congress of bio pharmaceutics and pharmacokinetics, proceeding volume 1, bio pharmaceutics 1987; 243-251.
31. Mady O., The effect of surfactant and plasticizer on Eudragit RS100 microspheres prepared by solvent evaporation technique, Journal of Global Pharmaceutical Sciences 2013; 1,01-11
32. Dredan J. et al, Evaluation of mathematical models describing drug release from lipophilic matrices, Int. J. of Pharmaceutics 1996; 145: 61-64.
33. Mady O., Contribution of waxes on granulation and compression of non-comprisable drug: Tableting, drug release and physic-chemical structure, Int. Res J Pharm. App Sci. 2013; 3(5):94-104.
34. Sinha V. et al, Chitosan microspheres a a potential carrier for drugs, int. J. Pharm. 2004; 274(1-2):1-33.
35. Ghulam M. et al, Evaluation of cefixime loaded chitosan microsphere: Analysis of dissolution data using DDSolver, Dissolution technologies, may 2012.
36. Mady O., Studying the Effect of Dispersed Drug Crystal in the Organic Phase on the Encapsulation by Solvent Evaporation Technique. (I) Effect of Drug Loading Extent on the Product Size Analysis, Morphology and Drug content, Accepted for publication in international journal of Pharmaceutical sciences and Research 2014; 5(07)July.
37. Winston W. et al, On spray drying of uniform silica-based microencapsulates for controlled release, Soft Matter 2011; 7.
38. Drużyńska M. and Czubenko J, Mechanism of water diffusion into non crosslinked and ionically crosslinked chitosan membranes, Progress on Chemistry and Application of Chitin and Its ..., 2012, volume XVII.
39. Ranga R. et al, Cellulose matrices for zero‐ order release of soluble drugs. Drug Dev Ind Pharm, 1988; 14: 2299‐ 2320.
40. Munday D. and Cox P, Compressed xanthan and karaya gum matrices: hydration, erosion and drug release mechanisms. Int J Pharm 2000; 203: 179‐ 192.
41. Patel J. et al, Formulation and evolution of transdermal path of meloxicam, Pharma science monitor 2011;2(4): 89-102.
42. Cox P. et al, Development and evaluation of multiple unit oral sustained releases dosage form for *S* (+)-ibuprofen: preparation and release kinetics. Int.J.Pharm. 1999; 193: 73-84.
43. Saki Sultana, Development and evaluation of in-vitro release kinetics of sustained release pellets of gliclazide using combinations of cellulose polymers, J Pharm Educ Res 2012; 3(1):1-9.
44. Khare A. and Peppas N., Swelling/deswelling of anionic copolymer gels. Biomaterials 1995; 16: 559‐ 567.

45. Kim B. et al, Dynamic swelling behavior of pH‐ sensitive anionic hydrogels used for protein delivery. J Appl Polym Sci 2003;89:1606‐ 1613.
46. Gierszewska-Drużyńska M. and Ostrowska-Czubenko J., Progress on Chemistry and Application of Chitin and Its ..., 2012, Volume XVII, 66.
47. Mady O., Ph.D. 1994, Thiesis, Faculty of pharmacy, Tanta University, Tanta, Egypt.
48. Mady, O.Y. and Mabrouk, M., Studying the Effect of Surfactant on Eudragit RS100 Microspheres Prepared by Solvent Evaporation Technique, Mansura Journal of Pharmaceutical Sciences 1997; 13 (1): 30.
49. Yao F. and Weiyuan K., Drug Release Kinetics and Transport Mechanisms of Non-degradable and Degradable Polymeric Delivery Systems, Drug Deliv. 2010; 7(4): 429–444
50. Arshia S. et al, Entrapment of andrographolide in cross-linked alginate pellets: 1. Formulation and evaluation of associated release kinetics; Pak. J. Pharm. Sci. 2007; 20(1), 1-9.
51. Siepmann J. and Gopferich A., Mathematical modeling of bioerodible, polymeric drug delivery systems, Advanced Drug Delivery Reviews 2001; 48: 229–247.
52. Gopferich A. and Tessmar J., Polyanhydride degradation and erosion, Advanced Drug Delivery Reviews 2002; 54: 911–931.
53. Kalam A. et al, Release kinetics of modified pharmaceutical dosage forms: a review, continental J. Pharmaceutical Sciences 2007; 1: 30 – 35.
54. Chavda H. et al, Preparation and in vitro evaluation of guar gum based triple-layer matrix tablet of diclofenac sodium , Research in Pharmaceutical Sciences, February 2012; 7(1): 57-64.
55. Polleto F., et al, Int. J. Pharm 2007; 345: 70.
56. Fuentes G., Lat. Am. Appl. Res. 2005; 35: 9.
57. Celebi N. et al, The preparation and evaluation of salbutamol sulphate containing poly(lactic acid-co-glycolic acid) microspheres with factorial design-based studies, Int. J. Pharm.1996; 13689–100.
58. Pardakhty A., In vitro study of polyoxyethylene alkyl ether niosomes for delivery of insulin, Int. J. Pharm. 2007; 328: 130–141.
59. Shifeng Y. et al, Layer-by-layer assembly of poly(L-glutamic acid)/chitosan microcapsules for high loading and sustained release of 5-fluorouracil; European Journal of Pharmaceutics and Biopharmaceutics 2011 ;78:336–345.
60. Shifeng Y. et al, Nanoporous multilayer poly(l-glutamic acid)/chitosan microcapsules for drug delivery, International Journal of Pharmaceutics 2012; 427: 443– 451.