International Research Journal of Pharmaceutical and Applied Sciences (IRJPAS)
Available online at **www.irjpas.com**
Int. Res J Pharm. App Sci., 2013; 3(6):56-69

Research Article

MECHANISMS AND PERCENT OF DRUG RELEASE OF EACH *NEW MATHEMATIC APPROACH*

Omar Mady,Ph.D.
Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Tanta, Tanta, Egypt.

*Corresponding Author: Omar Mady; Email: Omer.Mady@gmx.at

Abstract: Peppas and Sahlin model accounts for the coupled effects of Fickian diffusion and case II transport. By using the exponent coefficient (n) from Krosmeyer-Peppas model and substitution in Peppas-Sahlin model, the constants (K1&K2) could be calculated using different calculation methods. Matrix method is widely used for calculation of the kinetic constants which lead to calculate one constant value for each mechanism, for the whole drug release process. It was proved about the unacceptable points on using the kinetic constants (K1&K2) calculated by matrix solution method for comparison and also for calculation of the Fickian fraction release. Another mathematic method was applied for calculation of the kinetic constants (K1&K2) which is substitution method. The use of the substitution method gives the chance for calculation of the kinetic constants (K1&K2) at each unites time. As a result it could be calculate the amount of drug release % by each mechanism at each unites time and there is no need for further calculation for comparison like the Fickian fraction release. Also the substitution method may be, indicate the role of each drug release mechanism at each point especially because the comparison would be between the amount of drug release % by each mechanism at each unites time. Not only that but also the overlap, alternate, predominate and also combination of all drug release mechanisms at each unites time can be clearly observed which bring us to the realty of the drug release process which is a dynamic complex one.

Key words: drug release mechanism, matrix solution, substitution solution, kinetic constant

INTRODUCTION

In the development of the pharmaceutical dosage forms, the providing of a particular drug release profile is highly desirable. Under certain conditions it can be used as a surrogate for the assessment of bioequivalence. Several theories/kinetics models describe drug dissolution from immediate and modified release dosage forms. The quantitative interpretation of the values obtained in the dissolution assay is facilitated by the usage of a generic equation that mathematically translates the dissolution curve in function of some parameters related with the pharmaceutical dosage forms[1].

Different factors related to the drug can influence its release like kind of drug, its polymorphic form, crystallinety, particle size, solubility and its amount in the pharmaceutical dosage form[2-4].

A water soluble drug incorporated in a matrix is released mainly by diffusion, while for a low water soluble drug the self erosion of the matrix will be the principle release mechanism[1]. To compare dissolution profiles between two drug products, model dependent (curve fitting), statistic analysis and model independent methods can be used.

Numerous methods are available to elucidate the dissolution data as a function of time but its dependence on the dosage form properties can be best deduced by using equations which mathematically translates the dissolution curves in the function of other parameters related to the delivery device. The best model for drug dissolution / release can be selected based on different criteria. The most common method used is the correlation coefficient r^2 to assess the fitting of a model equation[3].

Krosmeyer et al[5], derived a simple relationship which described the drug release from a polymeric system. This relationship is very frequently used to describe the drug release from several different pharmaceutical modified release dosage forms[1]. To find out the release mechanism of the drug, the first 60 % of the drug release data should be fitted in the Krosmeyer-Peppas model. The drug release exponent (**n**) value is used to characterize different drug release mechanism. From cylinder shape matrices, when the value of (**n**) is 0.45 or less the drug release mechanism will be corresponding to Fickian diffusion mechanism. If value of (**n**) is < 0.85, the drug release mechanism will be considered as non-Fickian one and if it is exact 0.89 then the drug release is case II transport. In case of (**n**) is higher than 1 the release mechanism will be considering super case II transport [1].

An interesting model was developed by Peppas and Sahlin. This model accounts for the coupled effects of Fickian diffusion and case II transport [6-7]. By using the exponent coefficient (**n**) from Krosmeyer-Peppas model and substitution in Peppas-Sahlin model, the constants ($\mathbf{K_1}$&$\mathbf{K_2}$) can be calculated. The values of $\mathbf{K_1}$ indicates the contribution of diffusion (Fickian or case 1 kinetics) while the value of $\mathbf{K_2}$ is associated with the dissolution as well as relaxation of the polymer chains[8].

It was reported that if the values of $\mathbf{K_1}$ and $\mathbf{K_2}$ are available, it can calculate the percent of drug release due to Fickian mechanism and also the ratio of relaxation to the Fickian contribution [9-11].

Accordingly, the aim of this work is trying to apply the algebra mathematic methods to calculate the values of ($\mathbf{K_1}$&$\mathbf{K_2}$) of Peppas-Sahlin model and determinate the percent of drug release by each mechanism of drug release in relation to the exponent drug release mechanism value of Krosmeyer-Peppas model.

Theoretical Aspect:

To quantify and materialize the amount of drug released by Fickian diffusion and by polymer relaxation, the release data can be treated based on the Peppas-Sahlin equation, which accounts for the coupled effects of Fickian diffusion and case II transport [6].

$$\frac{\mathbf{Mt}}{\mathbf{M}\infty} = \mathbf{K_1\, t^m + K_2\, t^{2m}} \quad \text{.....(1)}$$

Where $\mathbf{Mt/M}\infty$ is the fraction of drug release at time **t**. The first and the second terms on the right hand side of the equation (1) represent the Fickian diffusion and the case II relaxation contributions respectively[6,8]. $\mathbf{K_1}$ and $\mathbf{K_2}$ are kinetic constants. To calculate the kinetic constants, the release data treated as a system of non-linear equations[8,12].

In mathematics, a system of linear or nonlinear equations is a collection the same set of variables. The theory of linear or nonlinear systems is the basis and a fundamental part of linear algebra. A system of equation just means more than one equation. This pair of equations is called a system of linear or nonlinear equations because we are solving more than one equation simultaneously. A solution to the system consists of an ***x***-value and ***y***-value that satisfy both equations at the same time. A system of linear or nonlinear equations can be solved by many different ways e.g. Substitution, Elimination, Matrices, and Graphing [13].

Graphical Solution of a System of linear or nonlinear equations is done by graph the first equation and then graph the second equation. At the point of intersection of the two equations **x** and **y** have the same values for each. Elimination method of a System of linear or nonlinear equations involves removing variables from the equations. Variables are removed until only a single last variable is left, i.e. until there is one equation with one unknown. This equation is then solved for this unknown. Then the other unknown can be deduced.

Substitution method of a System of linear or nonlinear equations involves expressing one variable in terms of another until there is a single equation in one unknown. This equation is then solved for that one unknown. The result is then used to solve for the variable which was expressed in terms of the variable whose solution has just been found.

To calculate the values of $\mathbf{K_1}$ and $\mathbf{K_2}$ as two variables using substitution method, it is essential to use the cumulative amount ($\mathbf{Q_1}$ & $\mathbf{Q_2}$) of drug release at two following measured times ($\mathbf{t_1}$ & $\mathbf{t_2}$).
The amount of drug released at $\mathbf{t_1}$ is ($\mathbf{Q_1}$) and can be written as the following:

$$\mathbf{Q_1 = K_1\,(t_1)^m + K_2\,(t_1)^{2m}} \quad \text{.....(2)}$$

$$\mathbf{K_1 = [\,Q_1 - K_2\,(t_1)^{2m}]\,/\,(t_1)^m} \quad \text{.....(3)}$$

and the amount of drug released at $\mathbf{t_2}$ is ($\mathbf{Q_2}$) and can be written as the following:

$$\mathbf{Q_2 = K_1\,(t_2)^m + K_2\,(t_2)^{2m}} \quad \text{.....(4)}$$

From (3) and (4); we get

$$\mathbf{K_2 = [\,Q_2\,(t_1)^m - Q_1\,(t_2)^m]\,/\,[(t_2)^{2m}\,(t_1)^m - (t_1)^{2m}\,(t_2)^m]} \quad \text{.....(5)}$$

and the value of $\mathbf{K_1}$ can then be calculated from equation (3).

The above substitution calculation will be used to calculate the values of $\mathbf{K_1}$ and $\mathbf{K_2}$ for the amount of drug released at $\mathbf{t_1}$. To calculate the same values at $\mathbf{t_2}$, it has to use the cumulative drug release at $\mathbf{t_2}$ and $\mathbf{t_3}$,....etc. To carry out this complex calculation Microsoft excels was used after self programmed. The advantage of this method is, it can calculate the values of $\mathbf{K_1}$ & $\mathbf{K_2}$ at each time interval and then can calculate the amount of drug released by each mechanism at each release time interval which may give an indication about the behaviour of the formulation matrix.

Matrix Solution of a System of linear or nonlinear equations can also used to calculate the kinetic constants [14]. If listed the model of each data it will be:

$$m x_1 + c = y_1$$

$$m x_2 + c = y_2$$ and in matrix form $$\begin{vmatrix} X_1 & 1 \\ X_2 & 1 \\ X_n & 1 \end{vmatrix} \times \begin{vmatrix} m \\ c \end{vmatrix} = \begin{vmatrix} Y_1 \\ Y_2 \\ Y_n \end{vmatrix}$$

$$m x_n + c = y_n$$

Suppose the matrix name $\mathbf{A} = [\mathbf{x} \quad \mathbf{1}]$, vector $\mathbf{B} = \begin{vmatrix} m \\ c \end{vmatrix}$, vector $\mathbf{Y} = \begin{vmatrix} Y_1 \\ Y_2 \\ Y_n \end{vmatrix}$ vector $\mathbf{X} = \begin{vmatrix} X_1 \\ X_2 \\ x_n \end{vmatrix}$

The equation above can be written in more simple way $\mathbf{A} \times \mathbf{B} = \mathbf{Y}$.

The object is to find $\mathbf{B} = \begin{vmatrix} m \\ c \end{vmatrix}$ for a given matrix **A** and vector **Y**.

In case of matrix **A** is not square in general it cannot find its inverse.

To solve this problem, it needs a *generalized inverse.* The trick is to multiply matrix A with its transpose (either from left or from right) and the result of this multiplication will be square matrix that can find its inverse.

When $\mathbf{A} \times \mathbf{B} = \mathbf{Y}$ then multiply the two side with $\mathbf{A^t}$, then it will be

$$(\mathbf{A^t} \times \mathbf{A})\, \mathbf{b} = \mathbf{A^t}\, \mathbf{Y}$$ where $\mathbf{A^t}$ is transpose **A**

then multiply the side of the equation with $(\mathbf{A_t} \times \mathbf{A})^{-1}$ to get the following

$$(\mathbf{A^t} \times \mathbf{A})^{-1} (\mathbf{A^t} \times \mathbf{A})\, \mathbf{b} = (\mathbf{A^t} \times \mathbf{A})^{-1} \mathbf{A^t}\, \mathbf{Y}$$

Since multiplication of a matrix with its inverse produce identity matrix, the result will be:

$\mathbf{b} = (\mathbf{A^t} \times \mathbf{A})^{-1} \mathbf{A^t Y}$ and

$\mathbf{L} = (\mathbf{A^t} \times \mathbf{A})^{-1} \mathbf{A^t}$ which called left generalized inverse of matrix of A. Multiply with $(\mathbf{A^t} \times \mathbf{A})$, the result will be

$$\mathbf{A^t} \times \mathbf{A} = \begin{vmatrix} \sum \mathbf{X^2} & \sum \mathbf{X} \\ \sum \mathbf{X} & \mathbf{n} \end{vmatrix}$$

And multiply $\mathbf{A^t} \times \mathbf{Y}$ the result will be

$$\mathbf{A^t} \times \mathbf{Y} = \begin{vmatrix} \sum \mathbf{xy} \\ \sum \mathbf{y} \end{vmatrix}$$

Which are the values of $\mathbf{K_1}$ and $\mathbf{K_2}$.

Then, it is clear that from the matrix solution, there is only one general value for each kinetic constant ($\mathbf{K_1}$ & $\mathbf{K_2}$) for all release process. Microsoft excels was also used to carry out this kind of calculations. In addition from knowing the value of the kinetic constants $\mathbf{K_1}$ and $\mathbf{K_2}$, it could be theoretically calculate the amount of drug release via diffusion and/or by other mechanism from cumulative amount of drug released % at any time.

MATERIALS AND METHODS

The materials and methodes used are the same as in refrance published by the author[15].

RESULTS AND DISCUSSION

The 1st part of this work, it was possible to successfully prepare paracetamol (as a model drug) granules to modify its property from non-compressible to compressible drug using thermoplastic granulation technique. The used granulating agents are Stearic acid and glyceryl mono stearate which are mixed with the drug in cold state then the temperature increased above the melting point of the granulating agent and then decreased to room temperature while stirring. Mady [17] discussed the mechanism of the granulation of each granulating agent. The author reported that when stearic acid (SA) particle soften or melted it will be rounded with drug particles (immersion nucleation) which led to formation of powder with small mean particle size and the formed particles will have irregular surface. At the same time glyceryl monostearate (GMS) has the chance to produce nucleation by both immersion and distribution mechanism. The coalescence of the produced nuclei will be optimal and the nuclei have residual surface liquid to promote a successful fusion which led to deformation of nuclei surface for coalescence as well as promoting the rounding of granulation. These two different mechanisms led to different physical properties of the produced granules, tablet and the drug release. Mady also reported that the drug release mechanism is non-Fickian mechanism which was expected as a result of the granulation mechanism. To quantify and materialize the amount of drug released by Fickian diffusion and by polymer relaxation, the drug released data is treated based on the Peppas-Sahlin equation[6].

The values of the kinetic constants $\mathbf{K_1}$ and $\mathbf{K_2}$ (calculated from matrix method) along with correlation coefficient $\mathbf{r^2}$ values are presented in table (1).

Table 1: Drug release parameters from Krosmeyer-Peppas equation (matrix solution):

	SA %				GMS %			
Conc.	5%	10%	15%	20%	5%	10%	15%	20%
K_1	6.772825	2.085316	0.014523	1.971812	2.729905	2.75968	3.681749	1.490367
K_2	0.059277	0.299214	1.664541	0.187746	0.035759	-0.00191	-0.05236	-0.02392
r^2	0.997352	0.987084	0.989281	0.981908	0.97673	0.983071	0.97779	0.971844

From table (1), it can be noticed that, the value of $\mathbf{r^2}$ is high enough to evaluate the release data according to Peppas-Sahlin model. In case of using SA as a granulating agent, an interpretable values of the diffusion contribution $\mathbf{K_1}$ can be noticed indicating Fickian or case I kinetic part of the drug release and $\mathbf{K_2}$ which is associated with the dissolution as well as relaxation of polymer chains[8]. These results are in agreement with what reported by the author about the drug release mechanism from tablets pressed from granules prepared by using SA as a granulating agent (anomalous release mechanism)[15]. Also, it can be noticed that, the value of $\mathbf{K_1}$ decreased with increase SA concentration and then increased again in case of using 20% SA. Opposite results can be noticed with the values of $\mathbf{K_2}$ which indicate that, there is an alternative predominate exchange release function between the two mechanisms although both, as can be noticed from the values of $\mathbf{K_1}$ and $\mathbf{K_2}$, worked at the same time with different violent. In addition the value of diffusion contribution $\mathbf{K_1}$ in case of using 5% SA is markedly higher comparing to that of $\mathbf{K_2}$ which is very low. This is not in agreement with the reported finding of the exponent release value **n** on application of Peppas-Krosmeyer equation which is 0.6618 indicating anomalous release mechanism[15]. This finding may be explained as the following: Stearic acid is a saturated waxy solid fatty acid with an 18-carbon chain and its water solubility is 3mg/l at 20°C[17].

Logically, it can be expected that SA has no solubility in the dissolution media which is 0.1N HCl. According to the previously suggested granulation mechanism reported by the author [16] the drug is exposed to the dissolution medium. Since the drug has high solubility in the dissolution medium, it can be expected the dissolution occurred through the drug molecules on the tablet surface which may be responsible about the above finding[1]. Also the retarding effect is due to the tablet surface area (low surface area) and the captures effect of SA to the drug particles by sticking which increased with increasing the SA concentration. Increase SA concentration leads to increasing its capture effect to the drug particles which led to a decrease in drug concentration exposed to dissolution medium. As a result the value of $\mathbf{K_1}$ is markedly decreased with increase SA concentrations from 5% to 10% to 15 % which is very low (table 1). Increase the value of $\mathbf{K_1}$ again on using 20 % SA than that on using 15% may be due to the high concentration of SA which normally used as sustained release matrix with special drug release mechanism suggested by Riza et al[8]. Such mechanism may be responsible about the presence dissolution mechanism $\mathbf{k_2}$ with different values depending on the concentrations of SA used. Naser et al[18] stated that, because the value of **n** is markedly exceed the value of 0.5 corresponding to diffusion controlled release and furthermore together with the good fitting of the zero- order model indicate significant contribution of erosion. Further analysis by Peppas and Sahlin model showed higher values of the relaxation constant $\mathbf{K_2}$, compared with the diffusion constant $\mathbf{K_1}$, combined with the low solubility of drug, reflect the prevalence of the erosion as a mechanism for drug release versus swelling mechanism.

Makai et all [9], found the diffusion exponent (n=0.635) signified a non-Fickian mechanism of drug release but the drug dissolution occurring via Fickian diffusion proved to be essential because the diffusion rate

constant $\mathbf{K_1}$ is much higher than relaxation rate constant $\mathbf{K_2}$. The author reported that the Fickian contribution to the overall release process decreased with increasing the amount of drug release, hence the relaxation of the polymer chains became more pronounced. These results can be explained with simultaneous water up-take during the dissolution process with enables polymer relaxation. The presence of drug particles on the surface can easily accessible to the dissolution medium.

On using GMS as a granulating agent, from table (1) it can be noticed that, in case of using 5% GMS, the value of $\mathbf{K_1}$ is much higher than $\mathbf{K_2}$. Mady [15] reported that the drug release mechanism is anomalous according to the value of drug release exponent (n = 0.6749). These results are in agreement with what stated by Makai et al[9]. Also from table (1), it can be noticed that, although the drug release mechanism from tablet pressed from granules prepared on using 10 % GMS is anomalous (n = 0.6181) [15] the value of $\mathbf{K_2}$ is extreme low comparing with that of $\mathbf{K_1}$, not only that but also it is negative. Ghosal et al [10] reported that the n values were higher than 1, which may be regarded as super case II kinetics arising from a reduction in the attractive forces between polymer chains. According to the Peppas-Sahlin model, a negative value of $\mathbf{K_1}$ was obtained. The author reported the insignificant effect of Fickian diffusion on drug release compared to the relaxation process.
Reza et al[8] found that cetostearyl alcohol matrix system released the drug via non-Fickian release mechanism (n = 0.6211). Although the value of $\mathbf{K_2}$ is negative, the author reported that some level of polymer relaxation and swelling occurred which support its tendency to release the drug by non-Fickian kinetics.

From above it may be concluded that, the value of the kinetic constant (**n**) from Krosmeyer-Peppas equation has a predominate effect on determination and interpretation of the drug release kinetics and values of $\mathbf{K_1}$ and $\mathbf{K_2}$ of Peppas-Sahlin model have to be explain in correlation to the kinetic exponent constant (**n**). In case of using 15% GMS, from table (1), the value of $\mathbf{K_1}$ and $\mathbf{K_2}$ are increased than that form other used concentrations, the value of $\mathbf{K_1}$ is remarkable higher than that of $\mathbf{K_2}$ which has also negative value. This is also in agreement with the reported value of exponent drug release by the author (n = 0.4526). Again when GMS used at 20% concentration, the value of $\mathbf{K_1}$ is the lowest comparing with other GMS concentrations and $\mathbf{K_2}$ has also negative value. Both should be considered because the drug release kinetic is non-Fickian (n=0.6553)[15]. These results can be explained according to the suggested granulation mechanism of GMS in addition to the surface activity and the method of drug entrapment in the granules [15].

On trying to estimate the percent of drug release by different mechanisms at each time intervals, the amount of drug release % and the values of coefficient constants ($\mathbf{K_1}$&$\mathbf{K_2}$) which calculated from matrix solution are used in the equation (1). The results of this substitution are summarized in table (2). From table (2), it can be noticed that, the amount of drug released % by diffusion is higher than that by dissolution in case of using 5% SA. The difference will be smaller in case of using 10% SA and will be opposite on using 15% SA. The effect of high SA concentration used can be noticed from the difference between two mechanisms in case of using 20%. The release mechanisms started with high diffusion mechanism than dissolution one, then this difference will start to decrease till 40 minutes and then would be opposite. Makai et al[9], from the value of exponent (n), K_1 and K_2 reported that the Fickian contribution to the overall release process decreased with increasing the amount of drug release hence, the relaxation of the polymer chains became more pronounced as result of simultaneous water up-take during the dissolution process with enables polymer relaxation. This theoretical explanation would be clear from the experimental values in table (2) in case of using 20% SA which is also in agreement with the suggested drug release mechanism from SA by Riza et al[8]. Also in every case there is no complete similarity between the calculated and experimentally determinate total percent of drug released. But 60% drug released which are theoretically calculated from matrix solution, are to some extend closed to the experimentally determinate ones. After that the theoretically calculated drug release % will be markedly higher than that determinate ones which is in agreement with what stated by Krosmeyer-Peppas model about the using of only 60% of the release data.

At the same time the application of Peppas-Sahlin equation to the release data from tablets pressed from granules prepared by using GMS, from table (3), it can be noticed that, the contribution of both diffusion and dissolution mechanisms on the drug release can be noticed although the diffusion mechanism at the begin is markedly higher than the second. Then, the big difference started to decreased. Also the contribution of dissolution mechanism on the drug release is negligible in case of using 10% GMS and can be noticed on using 15% GMS and remarkable on using 20% GMS and in every case is negative. In addition it begins with lower value and ended with higher one[9].

Mady [15], reported that the release mechanism on using 5% and 10% GMS follows non-fickian mechanism (diffusion-dissolution). But in case of 15% GMS it is pure diffusion mechanism which will be again non-Fickian on using 20% GMS. The above reported finding is now also supported with the calculated value % of drug by diffusion and dissolution mechanisms. The high positive values % of drug released by diffusion and the lower values of the percent of drug released by dissolution in case of using 5% GMS can be explained according to the reported structure of the granules prepared on using 5%GMS (coalesces of the aggregated drug crystals but it can be also distinguish the drug crystals which indicate the change on its surface)[16]. This observed structure gives the chance for both mechanisms to work simultaneously. Increase the concentration of GMS to 10 % led to denser coalescence of the drug crystal which cannot be distinguish [16] and then reflected on the drug release. Using 10 % GMS was considered to be a transition physical drug entrapment stat[15]. This observed structure give the chance for the drug released by both mechanisms although the value of dissolution one is

minimal and also has negative value. On using 15% GMS it would be expected that the granules surfaces will be denser and the drug release will be done only by diffusion mechanism especially GMS has no solubility in water[19] which is in agreement with what stated before.

Table 2: Calculation the % of drug released by different mechanisms using the calculating (K_1&K_2) from matrix solution and the release data of tablets prepared using different concentrations of SA:

Time (min)	5 % SA				10 % SA			
	Amount % released by		Total % released		Amount % released by		Total % released	
	Diffusion	Dissolution	Calculated	Determined	Diffusion	Dissolution	Calculated	Determined
5	18,27	0,43	***18,70***	**12,43**	5,64	2,19	***7,83***	**8,25**
10	28,01	1,01	***29,03***	**20,75**	8,66	5,15	***13,81***	**10,98**
15	35,97	1,67	***37,64***	**32,66**	11,12	8,51	***19,63***	**18,61**
20	42,95	2,38	***45,34***	**51,45**	13,28	12,14	***25,43***	**25,79**
30	55,15	3,93	***59,08***	**66,52**	17,07	20,04	***37,11***	**39,39**
40	65,86	5,60	***71,46***	**76,68**	20,39	28,61	***48,99***	**50,12**
60	84,56	9,24	***93,80***	**88,00**	26,20	47,22	***73,42***	**72,14**
80	100,98	13,18	***114,15***	**93,91**	31,29	67,39	***98,68***	**89,49**
100	115,87	17,35	***133,22***	**96,82**	35,92	88,79	***124,72***	**99,10**
Time (min)	15 % SA				20 % SA			
	Amount % released by		Total % released		Amount % released by		Total % released	
	Diffusion	Dissolution	Calculated	Determined	Diffusion	Dissolution	Calculated	Determined
5	0,03	7,14	***7,18***	**7,34**	5,66	1,55	***7,21***	**7,33**
10	0,04	13,38	***13,42***	**10,97**	8,92	3,84	***12,75***	**11,27**
15	0,05	19,31	***19,36***	**18,46**	11,63	6,53	***18,16***	**17,91**
20	0,06	25,06	***25,12***	**25,87**	14,04	9,52	***23,56***	**25,25**
30	0,07	36,17	***36,24***	**38,95**	18,32	16,20	***34,51***	**34,59**
40	0,08	46,93	***47,01***	**47,60**	22,12	23,62	***45,73***	**45,27**
60	0,09	67,74	***67,84***	**66,43**	28,85	40,18	***69,03***	**69,04**
80	0,11	87,90	***88,00***	**79,43**	34,83	58,58	***93,41***	**82,69**
100	0,12	107,57	***107,69***	**93,76**	40,31	78,48	***118,80***	**96,05**

At the same time in case of using 20% GMS the surface of the particle can be expected to extreme denser and the drug release has to be only by diffusion mechanism but according to the value of the exponent (**n**), $\mathbf{K_1}$ and $\mathbf{K_2}$, the drug release mechanism is anomalous. That is may be due the surface activity of GMS which may be led to some drug to be eroded from the granules.

From tables (2&3), it can be also noticed an interesting finding which is the calculated total % of drug release (in case of using different SA concentrations and 5% GMS) which the summation of the amount % of drug released by diffusion and dissolution is not completely similar to the experimental determinate total percent of drug released. At the same time the calculated total % of drug release in case of using 10%, 15% &20% GMS, is the result of substation of the amount of drug release % by dissolution from that by diffusion. Not only that but also, the value of the total % of drug release is closer (also in many cases equal) to experimental determinate total percent of drug released. These non-logic results may be due to the mathematic process in which the matrix inverse has to be calculated. The inverse of the matrix in many cases may lead to create a negative sign for the value which may responsible about the above results specially it could not imagine the reabsorption of the amount of drug release. This may be the reason by which the value of $\mathbf{K_1}$ and $\mathbf{K_1}$ should be considered only for 60% drug released and their interpretation should be occurred in correlation to the exponent coefficient (n) of Krosmeyer-Peppas model.

Figure 1, is a representative curve for the data in table 2 which indicates the amount of drug release by each mechanism and the relation between the calculated and determinate total drug release % at each time interval. From figure (1) it could be noticed the role of SA concentration on the difference of drug release mechanisms. It looks smooth and applicable ones which may be due to constant change variable during the application of the release data. This variable is the time. But there are some unacceptable points concerning the use of matrix solution which are:

1. It could not imagine there is a fixed percent drug release which calculated form fixed constants ($\mathbf{K_1}$&$\mathbf{K_2}$) even that for 60% drug release because drug release process is a complex process. The release process is a dynamic process depends on different factors which can change at every unit of time. These factors are related to the drug, matrix,

dissolution medium and the matrix-drug preparation technique. Accordingly it could be expected that at every time unite both mechanisms work together with equal ratios or one is predominate or only one worked which lead to some extend an alternative effect which can exchange like zigzag structure except that from hydrogell matrix and the drug is in the solid state solution form. The above logic statements is in agreement with what state by Maki et al [9] who reported that the Fickian contribution to the overall release process decreased with increasing the amount of drug release hence, the relaxation of the polymer chains became more pronounced as result of simultaneous water up-take during the dissolution process with enables polymer relaxation.

2. Increase the calculate total % drug release than that of experimental one gives no confidence even on using 60% drug release specially the calculation process from the beginning used as a percent.
3. The above results give also an indication about the only use of the kinetic constants ($\mathbf{K_1}$&$\mathbf{K_2}$) for comparisons which reported by many authors and determination the ratio of release mechanisms (fraction ratio) are not the correct way because the difference from determination of percent of drug release is only the multiplication with ($\mathbf{t^m}$).

Table 3: Calculation the % of drug released by different mechanisms using the calculating (K_1&K_2) from matrix solution and the release data of tablets prepared using different concentrations of GMS:

Time (min)	5 % GMS				10 % GMS			
	Amount % released by		Total % released		Amount % released by		Total % released	
	Diffusion	Dissolution	Calculated	Determined	Diffusion	Dissolution	Calculated	Determined
5	8,09	0,31	***8,40***	**12,74**	7,46	-0,01	***7,45***	**8,37**
10	12,91	0,80	***13,71***	**14,43**	11,45	-0,03	***11,42***	**10,23**
15	16,98	1,38	***18,36***	**17,82**	14,72	-0,05	***14,66***	**12,28**
20	20,62	2,04	***22,66***	**25,94**	17,58	-0,08	***17,50***	**16,81**
30	27,11	3,53	***30,63***	**31,73**	22,59	-0,13	***22,46***	**24,36**
40	32,91	5,20	***38,11***	**34,13**	26,98	-0,18	***26,80***	**28,21**
60	43,27	8,99	***52,26***	**47,40**	34,67	-0,30	***34,37***	**34,25**
80	52,55	13,25	***65,80***	**69,76**	41,42	-0,43	***40,98***	**40,70**
100	61,09	17,91	***78,99***	**83,61**	47,54	-0,57	***46,97***	**46,74**
Time (min)	15 % GMS				20 % GMS			
	Amount % released by		Total % released		Amount % released by		Total % released	
	Diffusion	Dissolution	Calculated	Determined	Diffusion	Dissolution	Calculated	Determined
5	7,63	-0,22	***7,40***	**6,90**	4,28	-0,20	***4,08***	**2,55**
10	10,44	-0,42	***10,02***	**8,87**	6,74	-0,49	***6,25***	**4,71**
15	12,54	-0,61	***11,93***	**11,34**	8,79	-0,83	***7,96***	**7,03**
20	14,29	-0,79	***13,50***	**13,88**	10,61	-1,21	***9,40***	**9,73**
30	17,16	-1,14	***16,03***	**16,13**	13,84	-2,06	***11,78***	**12,37**
40	19,55	-1,48	***18,07***	**19,77**	16,72	-3,01	***13,71***	**15,21**
60	23,49	-2,13	***21,36***	**21,65**	21,80	-5,12	***16,68***	**17,28**
80	26,75	-2,76	***23,99***	**23,47**	26,33	-7,46	***18,86***	**18,23**
100	29,60	-3,38	***26,21***	**25,87**	30,47	-10,00	***20,47***	**20,21**

Figure 1: Drug release by different mechanisms calculated using matrix method from table 2.

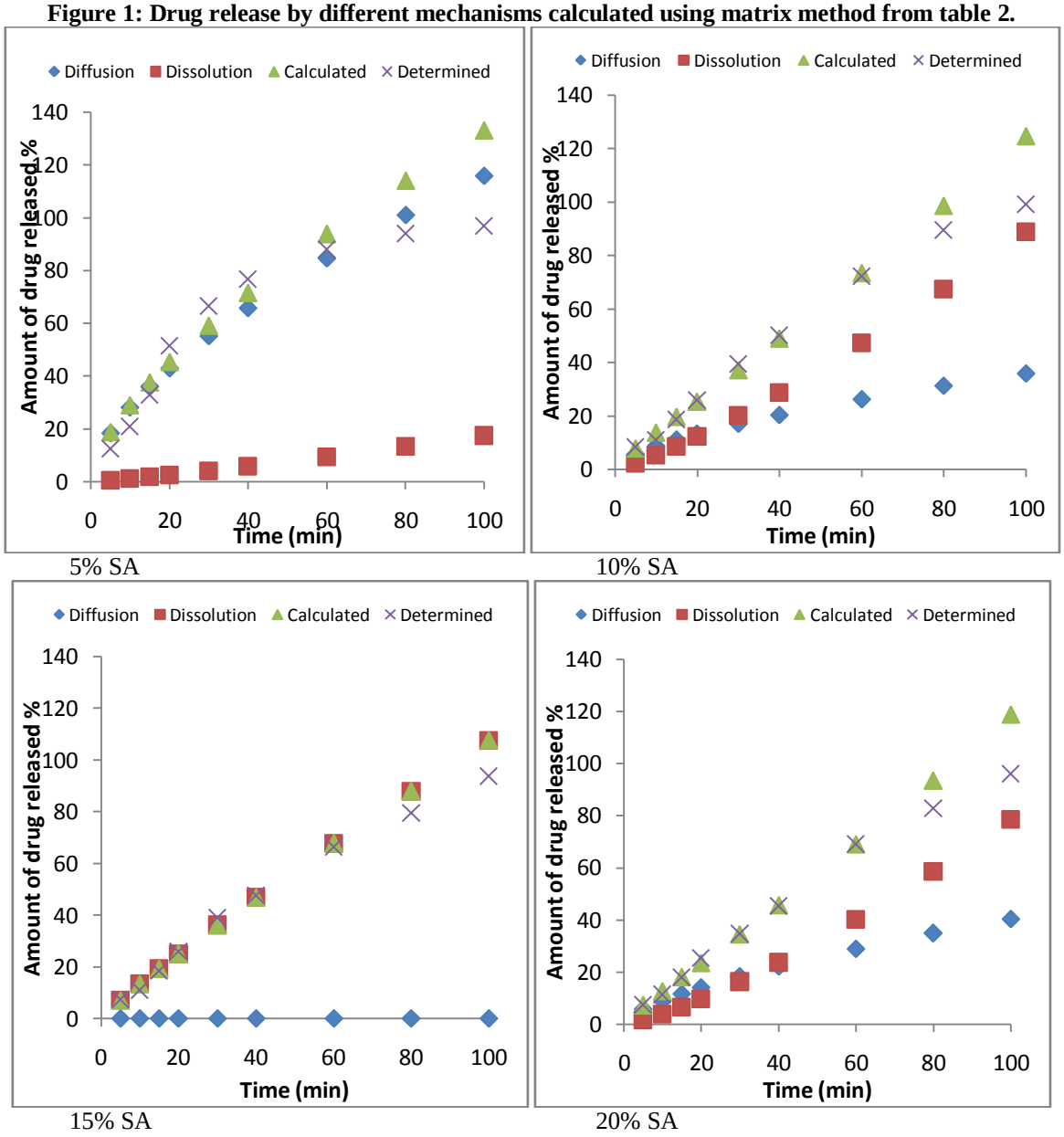
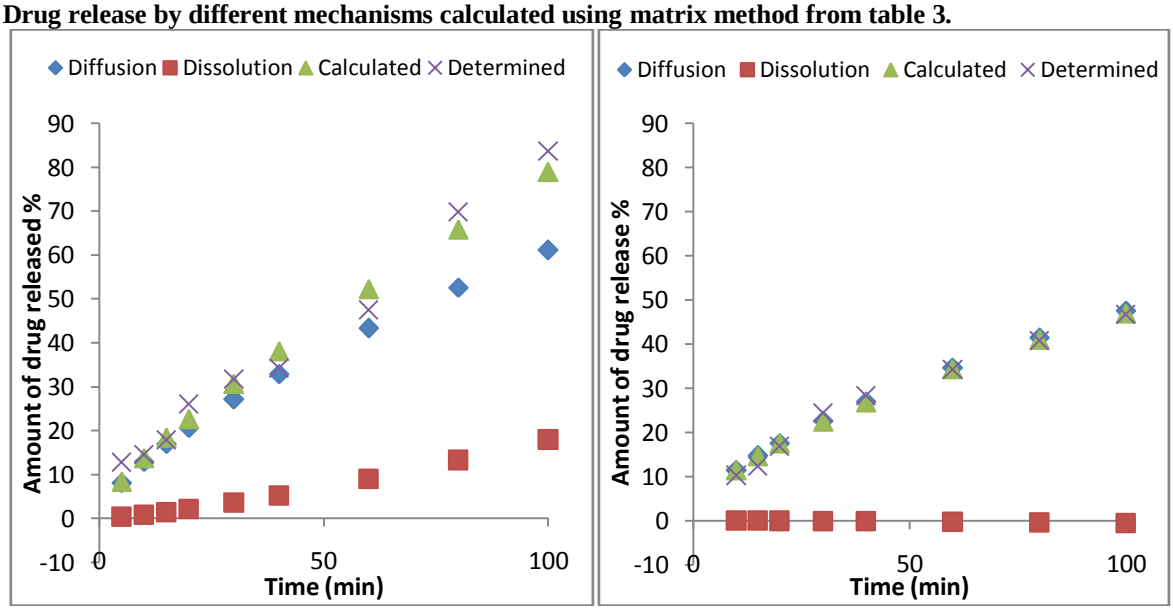
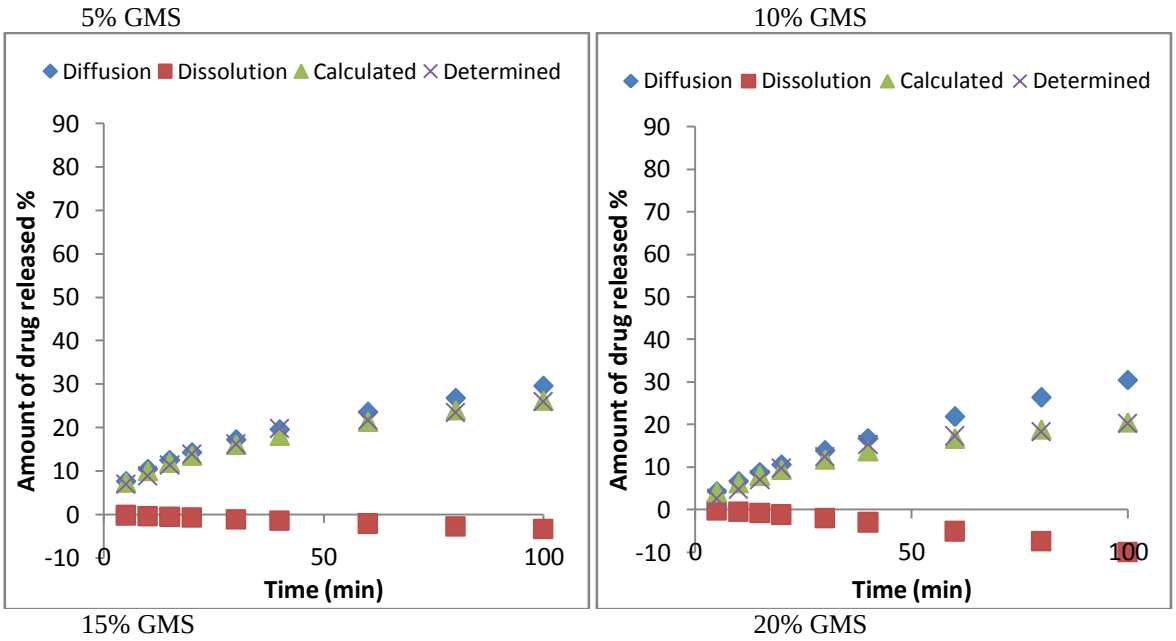


Figure 2: Drug release by different mechanisms calculated using matrix method from table 3.





The second method used for determination of the value of K_1 and K_2 is the substitution method. The advantage of this method is that, there is no general value for kinetic constants (K_1& K_2) for the release time like that on using matrix solution method but for every interval time. Accordingly, it is possible to calculate the amount of drug released by each mechanism at each release time which may give an indication about the behaviour of the formulation matrix. The values of K_1 and K_2 at every interval dissolution time were calculated according equation (5) and the results are used in equation (1) to the determination the percent of drug release by each mechanism. The results are summarized in table (4&5) for the using of different concentrations of SA and GMS respectively.

From both tables it can be noticed that, in both cases on using either SA or GMS at different concentrations, the values of the calculated total % released are completely equal to the determinate total % released. Also when the value of one mechanism is unusual high and has positive sign, the second has negative sign which led to reduce the calculated total % released to be equal the determinate total % released. Not only that but also both (calculated total % released and determinate total % released) are lower than 100 % which is in agreement with the use of drug release as percent from the beginning.

As a trial to understand these phenomena, the mathematical procedure which is used according to equation (5) was followed up and it was found that it is due to mathematical calculation process. Since the addition or subtraction (depending on the sign of each) of diffusion and dissolution values lead to produce calculated total % value completely equal to the determinate total % release, the value of calculated total % release can be considered as a product of ratios (ratio of the value of diffusion part and ratio of the value of dissolution one) and the sign of each should be neglected (absolute value).

Table 4: Calculation the % of drug released by different mechanisms using the calculating (K_1&K_2)from Substation method and the release data of tablets prepared using different concentrations of SA :

Time (min)	5 % SA				10 % SA			
	Amount % released by		Total % released		Amount % released by		Total % released	
	Diffusion	Dissolution	Calculated	Determined	Diffusion	Dissolution	Calculated	Determined
5	10,36	2,07	***12,43***	**12,43**	10,30	-2,05	***8,25***	**8,25**
10	4,25	16,50	***20,75***	**20,75**	-1,33	12,31	***10,98***	**10,98**
15	-21,06	53,72	***32,66***	**32,66**	3,32	15,29	***18,61***	**18,61**
20	50,20	1,25	***51,45***	**51,45**	8,68	17,11	***25,79***	**25,79**
30	78,39	-11,87	***66,52***	**66,52**	26,22	13,18	***39,39***	**39,39**
40	105,36	-28,68	***76,68***	**76,68**	28,96	21,16	***50,12***	**50,12**
60	136,20	-48,20	***88,00***	**88,00**	57,91	14,24	***72,14***	**72,14**
80	158,56	-64,65	***93,91***	**93,91**	110,86	-21,37	***89,49***	**89,49**

100	176,25	-79,43	***96,82***	**96,82**	180,70	-81,59	***99,10***	**99,10**
Time (min)	**15 % SA**				**20 % SA**			
	Amount % released by		**Total % released**		**Amount % released by**		**Total % released**	
	Diffusion	**Dissolution**	**Calculated**	**Determined**	**Diffusion**	**Dissolution**	**Calculated**	**Determined**
5	5,50	1,84	***7,34***	***7,34***	7,64	-0,31	***7,33***	**7,33**
10	-10,82	21,79	***10,97***	***10,97***	3,19	8,08	***11,27***	**11,27**
15	-12,13	30,59	***18,46***	***18,46***	3,47	14,45	***17,91***	**17,91**
20	-6,65	32,52	***25,87***	***25,87***	21,07	4,18	***25,25***	**25,25**
30	18,55	20,40	***38,95***	***38,95***	20,58	14,01	***34,59***	**34,59**
40	9,39	38,21	***47,60***	***47,60***	20,11	25,17	***45,27***	**45,27**
60	42,71	23,72	***66,43***	***66,43***	71,74	-2,70	***69,04***	**69,04**
80	29,34	50,09	***79,43***	***79,43***	80,84	1,85	***82,69***	**82,69**
100	156,12	-62,36	***93,76***	***93,76***	152,13	-56,08	***96,05***	**96,05**

Table 5: Calculation the % of drug released by different mechanisms using the calculating (K_1&K_2) from Substation method and the release data of tablets prepared using different concentrations of GMS

Time (min)	**5 % GMS**				**10 % GMS**			
	Amount % released by		**Total % released**		**Amount % released by**		**Total % released**	
	Diffusion	**Dissolution**	**Calculated**	**Determined**	**Diffusion**	**Dissolution**	**Calculated**	**Determined**
5	18,95	-6,21	12,74	12,74	11,57	-3,20	8,37	8,37
10	17,24	-2,81	14,43	14,43	12,56	-2,33	10,23	10,23
15	1,25	16,56	17,82	17,82	3,08	9,20	12,28	12,28
20	31,69	-5,75	25,94	25,94	9,27	7,54	16,81	16,81
30	48,61	-16,88	31,73	31,73	28,23	-3,86	24,36	24,36
40	28,05	6,09	34,13	34,13	33,66	-5,45	28,21	28,21
60	0,48	46,92	47,40	47,40	35,16	-0,92	34,25	34,25
80	56,48	13,28	69,76	69,76	40,58	0,12	40,70	40,70
100	77,20	6,42	83,61	83,61	50,97	-4,23	46,74	46,74
Time (min)	**15 % GMS**				**20 % GMS**			
	Amount % released by		**Total % released**		**Amount % released by**		**Total % released**	
	Diffusion	**Dissolution**	**Calculated**	**Determined**	**Diffusion**	**Dissolution**	**Calculated**	**Determined**
5	141,56	-134,66	6,90	6,90	1,78	0,77	2,55	2,55
10	-36,07	44,93	8,87	8,87	2,49	2,22	4,71	4,71
15	-27,93	39,27	11,34	11,34	2,06	4,97	7,03	7,03
20	-39,64	53,52	13,88	13,88	10,53	-0,80	9,73	9,73
30	-31,05	47,18	16,13	16,13	11,27	1,11	12,37	12,37
40	-43,04	62,80	19,77	19,77	21,66	-6,45	15,21	15,21
60	-35,12	56,78	21,65	21,65	27,83	-10,54	17,28	17,28
80	-32,39	55,86	23,47	23,47	23,12	-4,90	18,23	18,23
100	-32,16	58,03	25,87	25,87	27,11	-6,90	20,21	20,21

Accordingly, the amount of drug release by either diffusion or dissolution can be estimated for each time intervals. The results of these estimation processes for the release data from the tablet pressed from granules of either SA or GMS at different concentrations are summarized in tables (6&7). From tables (6,7) it can concluded that there is an alternative predominate exchange release function between the two mechanisms although both, as can be noticed from the amount drug release % by diffusion and that by dissolution, worked at the same time with different violent.

Table (6): Estimation the amounts of drug release via each mechanism at each time intervals from release data of tablet pressed from granules prepared by using different concentrations of SA:

Time (min)	5 % SA				10 % SA			
	Amount % released by		Total % released		Amount % released by		Total % released	
	Diffusion	Dissolution	Calculated	Determined	Diffusion	Dissolution	Calculated	Determined
5	10,36	2,07	***12,43***	**12,43**	6,88	1,37	***8,25***	**8,25**
10	4,25	16,50	***20,75***	**20,75**	1,07	9,91	***10,98***	**10,98**
15	9,20	23,46	***32,66***	**32,66**	3,32	15,29	***18,61***	**18,61**
20	50,20	1,25	***51,45***	**51,45**	8,68	17,11	***25,79***	**25,79**
30	57,77	8,75	***66,52***	**66,52**	26,22	13,18	***39,39***	**39,39**
40	60,27	16,41	***76,68***	**76,68**	28,96	21,16	***50,12***	**50,12**
60	65,00	23,00	***88,00***	**88,00**	57,91	14,24	***72,14***	**72,14**
80	66,71	27,20	***93,91***	**93,91**	75,03	14,46	***89,49***	**89,49**
100	66,74	30,08	***96,82***	**96,82**	68,27	30,83	***99,10***	**99,10**
Time (min)	15 % SA				20 % SA			
	Amount % released by		Total % released		Amount % released by		Total % released	
	Diffusion	Dissolution	Calculated	Determined	Diffusion	Dissolution	Calculated	Determined
5	5,50	1,84	***7,34***	**7,34**	7,05	0,28	***7,33***	**7,33**
10	3,64	7,33	***10,97***	**10,97**	3,19	8,08	***11,27***	**11,27**
15	5,24	13,22	***18,46***	**18,46**	3,47	14,45	***17,91***	**17,91**
20	4,39	21,48	***25,87***	**25,87**	21,07	4,18	***25,25***	**25,25**
30	18,55	20,40	***38,95***	**38,95**	20,58	14,01	***34,59***	**34,59**
40	9,39	38,21	***47,60***	**47,60**	20,11	25,17	***45,27***	**45,27**
60	42,71	23,72	***66,43***	**66,43**	66,54	2,50	***69,04***	**69,04**
80	29,34	50,09	***79,43***	**79,43**	80,84	1,85	***82,69***	**82,69**
100	66,99	26,76	***93,76***	**93,76**	70,18	25,87	***96,05***	**96,05**

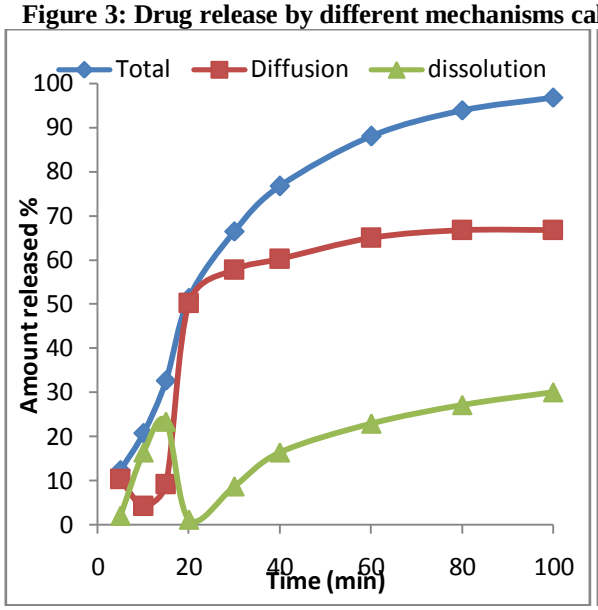
This alternative and combined release effect can be easily observed from figures (3&4) which looks in agreement with the solubility of the drug in the dissolution medium, the physicochemical properties of the SA and GMS, the suggested granulation mechanism of the used granulating agent, the method of entrapment of drug and the effect of the concentration of either SA or GMS used.

Table (7): Estimation the amounts of drug release via each mechanism at each time intervals from release data of tablet pressed from granules prepared by using different concentrations of GMS:

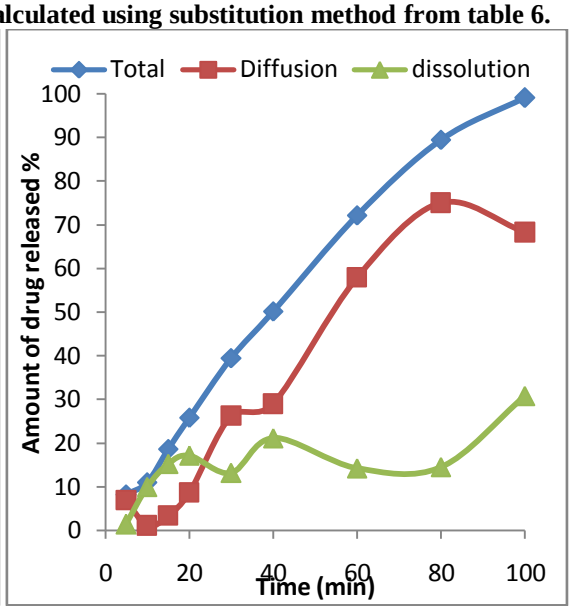
Time (min)	5 % GMS				10 % GMS			
	Amount % released by		Total % released		Amount % released by		Total % released	
	Diffusion	Dissolution	Calculated	Determined	Diffusion	Dissolution	Calculated	Determined
5	9,60	3,14	***12,74***	**12,74**	6,56	1,81	***8,37***	**8,37**
10	12,41	2,02	***14,43***	**14,43**	8,62	1,60	***10,23***	**10,23**
15	1,25	16,56	***17,82***	**17,82**	3,08	9,20	***12,28***	**12,28**
20	21,96	3,98	***25,94***	**25,94**	9,27	7,54	***16,81***	**16,81**
30	23,55	8,18	***31,73***	**31,73**	21,43	2,93	***24,36***	**24,36**
40	28,05	6,09	***34,13***	**34,13**	24,28	3,93	***28,21***	**28,21**
60	0,48	46,92	***47,40***	**47,40**	33,38	0,87	***34,25***	**34,25**
80	56,48	13,28	***69,76***	**69,76**	40,58	0,12	***40,70***	**40,70**

100	77,20	6,42	***83,61***	**83,61**	43,15	3,58	***46,74***	**46,74**
Time (min)	**15 % GMS**				**20 % GMS**			
	Amount % released by		**Total % released**		**Amount % released by**		**Total % released**	
	Diffusion	**Dissolution**	**Calculated**	**Determined**	**Diffusion**	**Dissolution**	**Calculated**	**Determined**
5	3,54	3,37	***6,90***	**6,90**	1,78	0,77	***2,55***	**2,55**
10	3,95	4,92	***8,87***	**8,87**	2,49	2,22	***4,71***	**4,71**
15	4,71	6,62	***11,34***	**11,34**	2,06	4,97	***7,03***	**7,03**
20	5,91	7,97	***13,88***	**13,88**	9,04	0,69	***9,73***	**9,73**
30	6,40	9,73	***16,13***	**16,13**	11,27	1,11	***12,37***	**12,37**
40	8,04	11,73	***19,77***	**19,77**	11,72	3,49	***15,21***	**15,21**
60	8,28	13,38	***21,65***	**21,65**	12,54	4,75	***17,28***	**17,28**
80	8,61	14,86	***23,47***	**23,47**	15,04	3,18	***18,23***	**18,23**
100	9,22	16,65	***25,87***	**25,87**	16,11	4,10	***20,21***	**20,21**

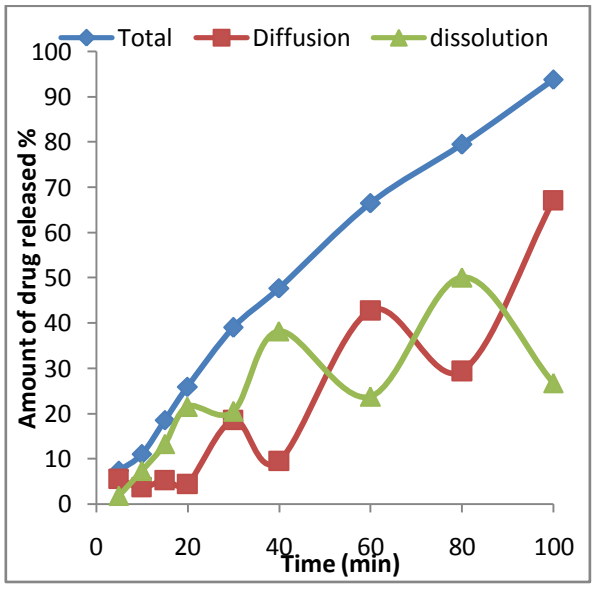
Figure 3: Drug release by different mechanisms calculated using substitution method from table 6.



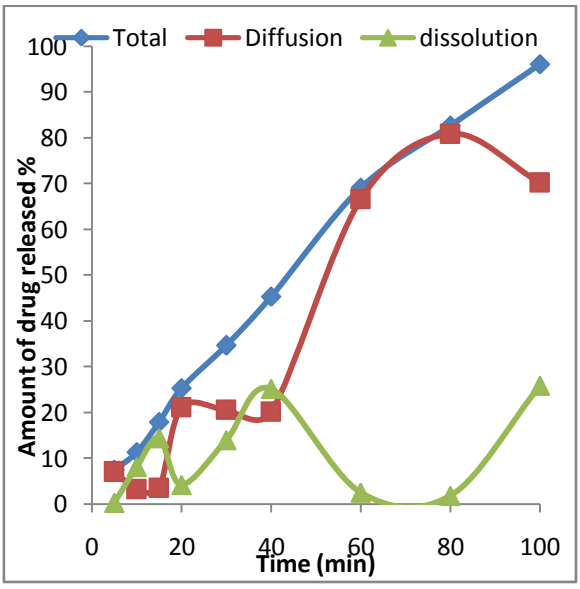
5% SA



10% SA

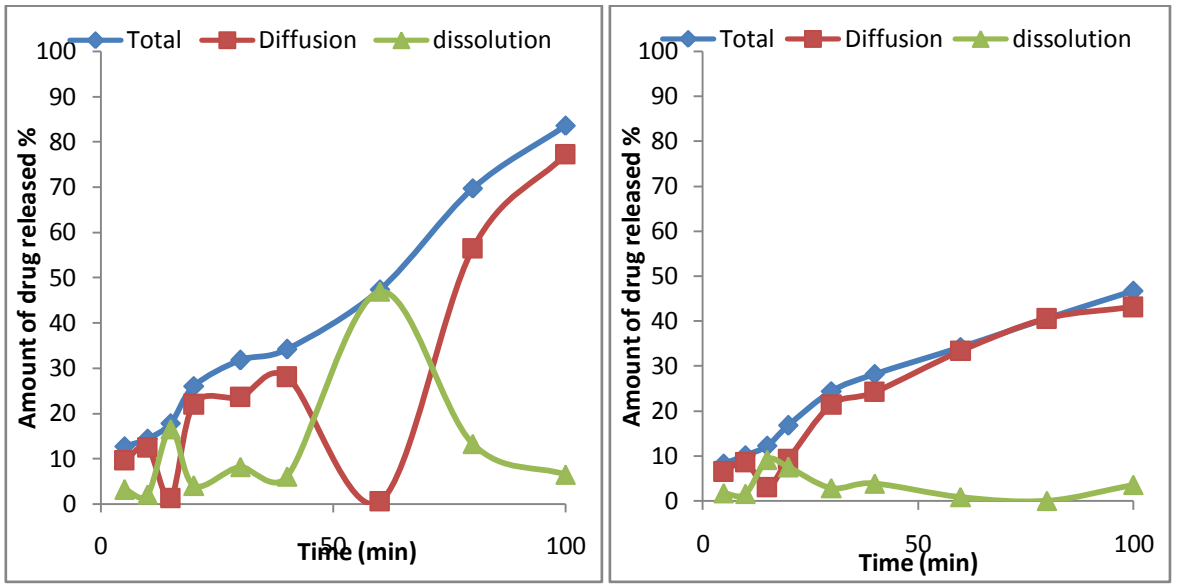


15% SA

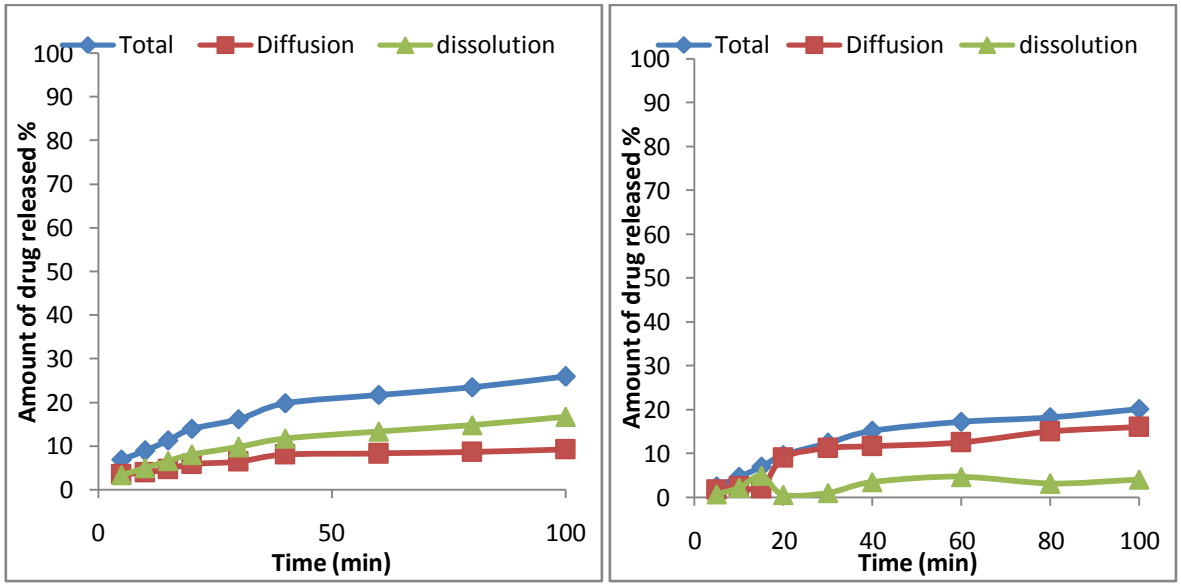


20% SA

Figure 4: Drug release by different mechanisms calculated using substitution method from table 7.



5% GMS **10% GMS**



15% GMS **20% GMS**

CONCLUSION:

Peppas and Sahlin model accounts for the coupled effects of Fickian diffusion and case II transport. By using the exponent coefficient (**n**) from Krosmeyer-Peppas model and substitution in Peppas-Sahlin model, the constants (K_1&K_2) could be calculated using matrix method. It was proved about the unacceptable points on using the kinetic constants (K_1&K_2) for comparison and also for calculation the Fickian fraction released. The use of the substitution method for calculation of the kinetic constants give the chance for calculation the kinetic constants at each unite time which may be indicate the role of each drug release mechanism at each point. Also the amount of drug release percent by each mechanism at each unite time can be also calculated.

References:

1. Costa P., Lobo J., Modelling and comparison of dissolution profiles, *European j. Of Pharma. Sci*., **2001**,13, 123-133.
2. El-arinin S., Leuenberger H., Modelling of drug release from polymer matrices: effect of drug loading , *Int. J. Pharm. Sci*., **1995**, 121, 141-148.
3. Lokhandwala H., Deshpande A. And Deshpande S., Kinetic modelling and dissolution profiles comparison: an overview, *Int. J. Pharm. Bio. Sci*., **2013**, 4(1): 728-737.
4. Aluton M., Pharmaceutics, the science of dosage form design, Churchill Livingstone edition, **1998**, 154-165.

5. Krosmeyer R., Doelker E., Buri P., Peppas N., mechanisms of solute release from porous hydrophilic polymers, *Int. J. Pharm. Sci*., **1983**, 15,25-35.
6. Peppas N. and Sahlin J., A simple equation for the description of solute release, III Coupling of diffusion and relaxation , *Int. J. Pharma. Sci.*, **1989**, 57, 169-172.
7. Siepmann J. and Peppas N., Modelling of drug release from delivery systems based on hydroxypropyl methylcellulose, *Advanced drug delivery reviews*, **2001**, 48, 139-157.
8. Abdul Qudir M., Rahaman M., Karim M., Akter S, Awkat M.and Reza S., evaluation of hadrophobic materials as matrices for controlled-release drug delivery, *Pakistan Journal of Pharmaceutical Sciences* **2003**; 16(2):17-28.
9. Szepes A., Makai Z., Blümer C., Mäder K., Kasa P. And Revesz P., Characterization and drug delivery behaviour of starch-based hydrogels prepared via isostatic ultrahigh pressure, *Carbohydrate polymers*, **2008**, 72, 571-578.
10. Ghosal K. and Ray S., Alginate/hydrophilic particulate systems: New matrix for specific and controlled drug delivery, *Brazilian Journal of Pharmaceutical Sciences*, **2011**, 47(4), 833-844.
11. Sanots H., Veiga F., Pina M: and Sousa J., Comaction, Compression and drug release properties of diclofenac sodium and ibuprofen pellets compressing xanthan gum as a sustained release agent, *Int. J. of Pharmaceutics***, 2005**, 295, 15-27.
12. Serra L., Domenech J., Peppas N., Drug transport mechanisms and release kinetics from molecularly design poly(acrylic acid-g-ethylene glycol) hydrogels, Biomaterials **2006**, available online at www.science direct.com.
13. http://www.wtamu.edu/academic/anns/mps/math/mathlab/col_algebra/col_alg_tut52_nonlinear_sys.htm
14. Derf A, Advanced matrix theory for science test and engineering, johan Wiley & sohn, ny, **1982.**
15. Mady O., Contribution of Waxes on granulation and compression of non compressible drug: tableting, drug release and physic-chemical structure, *Int. Res J Pharm. App Sci*., **2013**; 3(5):94-104.
16. Mady O., Contribution of Waxes on granulation and compression of non compressible drug: particle size distribution as a tool for studying the granulation process, *Int. Res J Pharm. App Sci*., **2013**; 3(5):127-134
17. http://en.wikipedia.org/wiki/Stearic_acid.
18. Hashem F., Shaker D., Nasr M., Saad I., Ragaey R., Guar gum and hydroxy propyl methylcellulose compressed coated tablets for colonic drug delivery: in vitro and in vivo evaluation in healthy human volunteers, *Drug Discoveries & Therapeutics*. **2011**; 5(2):90-95.
19. http://en.wikipedia.org/wiki/Glycerol_monostearate.