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A NEW MATHEMATIC METHOD FOR CALCULATION OF PEPPAS-SAHLIN MODEL CONSTANTS AND INTERPRET THE RESULTS IN RELATION TO ZERO ORDER, HIGUCHI, KROSMEYER-PEPPAS MODELS AND MICROCAPSULE STRUCTURE IMAGE.

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ABSTRACT

It was tried to calculate the constants values of Peppes-Sahlin model (k_1&k_2) using software packet and a mathematic matrix method for aspirin release data from Eudragit RS100 microcapsules. Then discuss the values of the constants as tool for the drug release mechanisms determination in relation to the physico-chemical microcapsule structure suggested by the author. In addition, applying the new mathematic method suggested by the author as a trial to have an image about the drug release mechanism(s) and the violet of each at every unit time from the microcapsules. The calculation of the Peppes-Sahlin constants (k_1&k_2) were done at fixed **m** value for Fickian drug diffusion from the spheres, at **m** value determined by the software packet and at **m** value equal to the exponent **n** value of Krosmeyer-Peppas model. The results showed the inability of using both fixed (**m**) value for Fickian diffusion from spheres and that calculated by software packet. The using of (**m**) value equal to (**n**) value showed the contribution of Fickian diffusion and polymer chain relaxation on the drug release process which is in agreement with the microcapsule structure but sometimes did not in agreement with the overall drug release mechanism. In addition the results cannot used for calculation the percent of drug released by each mechanism at each unite time of the drug release. The application of a new mathematic method using **m** value equal to **n** value led to calculate the percent of drug released by each mechanism at each unite time. Also showed the overlap, alternate, predominate and combination of drug release mechanisms at each unite time.

KEYWORDS: New mathematic method, Krosmeyer-Peppas model, Peppas-Sahlin model, Zero order kinetic, Higuchi model.

INTRODUCTION

Drug release is the process by which a drug leaves the dosage form and is subjected to absorption, distribution, metabolism and excretion, eventually becoming available for pharmacological action[1]. In vitro dissolution has been recognized as an important element in drug development. Under certain conditions it can be used as a surrogate for assessment of bioequivalent[2]. During the journey of the pharmaceutical technology development, there were continuous suggestion of different models to interpret the mechanisms of the drug release. One of the most popular is Higuchi model. It describes drug release as a diffusion process based in the Fick's law, square root time dependent. Higuchi model was simplified as, $\mathbf{Q = K_H\ t^{1/2}}$ where $\mathbf{K_H}$ is the Higuchi dissolution rate constant. For diffusion controlled process, plotting the amount of drug released in time per unit area versus square root of time is linear.[3-4] This relation can be used to describe the drug dissolution from several types of modified release pharmaceutical dosage forms[2].

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-Peppas and Korsmeyer- Peppas[5-7]. The equation is represented as: $\mathbf{M_t / M_\infty = K\ t^n}$. The logarithm form of the equation could be written as: $\mathbf{Log\ (M_t / M_\infty) = Log\ k + n\ Log\ t}$ where $(\mathbf{M_t / M_\infty})$ 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 $\mathbf{t^{-n}}$) incorporating structural and geometric characteristics of the delivery system. The release exponent **n** is ≤ 0.5 for Fickian diffusion and › 0.5 - › 1 for non-Fickian diffusion (Anomalous Transport) from slab respectively. A value of **n** is 1 actually means that, the drug release is independent of time regardless of the geometry (Case II transport, Zero order release). If the value of **n** is higher than 1, then the drug release transport is Super Case II transport. The value of **n** ≤ 0.43 for Fickian diffusion and › 0.43 - › 0.85 for non-Fickian diffusion from spheres, respectively. A value of **n** is 0.85 actually means that, the drug release is independent of time regardless of the geometry (Case II transport, Zero order release). If the value of **n** is higher than 0.85 then the drug release transport is Super Case II transport. This equation can be used to analyze only first 60% of release, regardless of geometric shapes[2, 9-10].

An interesting model based on logic concepts was developed by Peppas-Sahlin to quantify and materialize the amount of drug released by Fickian diffusion and polymer relaxation. This model accounts for the coupled effects of Fickian diffusion and case II transport[11-12]. $\mathbf{M_t/M_\infty = K_1\ t^m + K_2\ t^{2m}}$ where **Mt/M∞** is the fraction of drug release at time **t.** The first and the second terms on the right hand side of the equation represent the Fickian diffusion and the case II relaxation contributions respectively[11-13]. $\mathbf{k_1}$ and $\mathbf{k_2}$ are kinetic constants. To calculate the kinetic constants, the release data treated as a system of non-linear equations using special soft wares[13, 14]. Matrix method is widely used to calculate the kinetic constants by soft wares which lead to calculation of one constant value for each mechanism of the whole drug release process. Omar Y. Mady, proved about the unacceptable points of using one value for the kinetic constants ($\mathbf{k_1}$&$\mathbf{k_2}$) of the whole drug release time for comparison and also for calculation the Fickian fraction release especially the drug release mechanism is a dynamic process. Another mathematic method suggested by Mady O.,and it was applied for calculation of the kinetic constants ($\mathbf{k_1}$&$\mathbf{k_2}$) which is substitution method. The use of the substitution method gives the chance for calculation of the kinetic constants ($\mathbf{k_1}$&$\mathbf{k_2}$) at each unite time. As a result, it could be calculate the amount of drug release % by each mechanism at each unite 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 unite time. Not only that but also the overlap, alternate, predominate and also combination of all drug release mechanisms at each unite time indicate the dynamic complex drug release process which is in agreement with the logic concept of the drug release[15].

The reasons for all suggested drug release models may be due to the full information's about the physico-chemical properties of both drugs and polymers which would be summarized in the Preformulation process in addition to the high development in the pharmaceutical technology processes. For example, the using of instrumental analysis methods like I.R., X-ray diffraction, DSC and extra help in the explanation of the method of drug entrapment in the matrix during the formulation process and if there is any physical or chemical interaction between the drug and excipients. In addition to the reported mechanisms of drug release from certain polymers like swelling of certain kinds of celluloses, solubility of the polymer which may be depends on the pH of the dissolution media and also release through pores from others like Eudragit RS100 & RL100. Overall of the above, the intelligence of the researchers

with the helping of the information's collected from the above ways, will lead to creation of an image about the forms of the drug entrapped in the pharmaceutical dosage form[16-18]. Also the using of computer system with different mathematic software played an important role in the suggesting of different models. As an example to what stated above, Omar Y. Mady, tried to solve the low drug entrapment in the microcapsule structure prepared by using solvent evaporation technique[16-19]. The author suspended Aspirin crystal in the organic phase containing dissolved Eudragit RS100 with different drug-polymer ratios before pouring into 0.1 N HCl containing gelatin as an aqueous phase. The mean actual drug content was markedly higher than the theoretical one. Based on scientific and logic concepts which supported with references, the findings were explained according to the division of the emulsified microcapsule during preparation by what is named division mechanism[19]. XRPD, DSC and FTIR scans were used for inspection of the crystallinity properties and any possible interaction between the drug and the polymer[20]. Mady O., tried to use XRPD and DSC as tools for studying the method of drug entrapment in the microcapsule structure. The results helped to have an image about the drug entrapment methods which found to be more than one form. At the first, the drug entrapped as a solid solution form. Increasing the theoretical drug content leads to an increasing in the amount of the drug crystal form. Between these two forms another minute form may be formed as a result of increasing the theoretical drug content or /and certain kind of physic- chemical interaction between the drug and the polymer. It was concluded that all analysis results supported what is suggested mechanism during microcapsules formation (Division Mechanism) as a result of appearances or disappearances of drug crystals in addition to its effect on actual drug content[21]. The dissolution profiles of Aspirin from different particle size ranges of Eudragit RS100 microcapsules prepared with the same or different theoretical drug content were studied in relation to the suggested microcapsule structures. The results again supported the image about microcapsule structure suggested as a result of instrumental analysis discussed[22]. Mady O., tried to use different dependent models (kinetics and mechanisms) 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 methods of drug entrapment. It was found that the drug release kinetic obeys zero order and Higuchi models. Higuchi model had a large application in the polymeric matrix systems but zero order is an ideal to coated dosage forms. Both two entrapment forms are found to be the structure of Eudragit RS100 microcapsules entrapped the drug[21]. The good fitting of the drug release to Korsmeyer-Peppas model, which can be used as a decision parameter between the above two

models (Higuchi and Ritger-Peppes), indicates the mechanism of the drug release in every case is either Case II or supper Case II in addition for few case anomalous one. 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[23]. According to what stated above, the aim of this work is try calculate the constants values of Peppes-Sahlin ($\mathbf{k_1}$&$\mathbf{k_2}$) using software packet (DDSolver) and matrix method suggested by the author[15]. Then discuss the values of the constants as tools to the drug release mechanisms and the physico-chemical microcapsule structure suggested also by the author. In addition, applying the new mathematic method suggested by the author as a trial to have an image about the drug release mechanism(s) and the violet of each at every unit time from the microcapsules.

MATERIALS AND METHODS

The materials and methods used are the same as in reference published by the author[23]. TDC is % of theoretical drug content and ADC is % of actual drug content.

RESULTS AND DISCUSSION

In the literature it was found that Peppes et al[14] used the value of **m** for Peppes-Sahlin equation on studying the effect of the hydrogel structure and synthesis condition on the drug delivery with two values, one of both calculated using special software and the second is fixed at 0.5. It was also reported that when the exponent value is 0.5 for hydrogel membrane then the release mechanism is Fickian diffusion one and if it is lower than 0.5 then the transport mechanism is less Fickian diffusion one[24]. Accordingly, first it will try to calculate the values of the model constants ($\mathbf{k_1}$ and $\mathbf{k_2}$) suggested by Peppes-Sahlin model using fixed **m** value at 0.43 for spheres, matrix method for calculation[23] and the results are represented in table (1). From the table it can be noticed that the correlation coefficient value ($\mathbf{r^2}$) in every case is higher than 0.98 which is high enough to evaluate the drug dissolution behavior by Peppes-Sahlin equation. Also the values of $\mathbf{k_2}$ are very high comparing to the values of $\mathbf{k_1}$ which are also negative i.e. there is no Case I drug release (Fickian diffusion) and the drug release mechanism follows case II relaxation. These results are in agreement with what is reported by Mady O[23] who studied the drug release kinetics and found that the drug release kinetic obeys zero order kinetic. At the same time these results are disagreement with the obeying of the drug release data to Higuchi model since there is no role for Fickian diffusion on the drug release process according to the application of Peppas-Sahlin model. Higuchi model had a large application in the polymeric matrix systems but the zero order models

becomes the ideal to describe coated dosage forms or membrane controlled dosage forms[3]. Both two forms are found to be the structure of Eudragit RS100 microcapsules entrapped Aspirin[16, 18].

Table (1): Calculated values of Peppes-Sahlin constant on using fixed m value (0.43).

TDC	**20%**			**33%**			**50%**		
Microcp. PS	**500-400**	**400-315**	**315-80**	**800-500**	**500-400**	**315-80**	**800-500**	**500-400**	**315-80**
k_1	-7.599	-5.646	-9.092	-2.621	12.180	-7.155	-7.060	-5.622	-3.975
k_2	15.832	14.140	14.716	12.381	17.420	15.218	15.509	14.487	13.626
m	0.430	0.430	0.430	0.430	0.430	0.430	0.430	0.430	0.430
r^2	0.991	0.992	0.978	0.994	0.988	0.993	0.990	0.990	0.985
TDC	66%			80%					
Microcp. PS	**800-500**	**500-400**	**315-80**	**800-500**	**500-400**	**315-80**			
k_1	-4.180	-8.254	-4.991	-2.551	-3.699	-5.001			
k_2	13.888	15.244	13.415	13.055	13.190	13.452			
m	0.430	0.430	0.430	0.430	0.430	0.430			
r^2	0.990	0.984	0.989	0.993	0.994	0.994			

At the same time the application of Krosmeyer-Peppes model indicated the drug release mechanisms from the microcapsules prepared on using different TDC with different particle size ranges are Case II and Super case II except that from the smallest particle size range of microcapsules prepared on using of 20%, 50 %, 66% TDC and the biggest particle size range of microcapsules prepared on using 66% TDC since the value of the exponent (**n**) is lower than 0.85 indicating the release mechanism is anomalous[23]. The application of Krosmeyer-Peppas model results are in agreement with the image of microcapsules structure as a result of instrumental analysis[21]. But these results are not again in agreement with that obtained from the application of Peppes-Sahlin equation at fixed m value at 0.43 (table 1) which indicates there is no roll for Fickian diffusion in drug release in all cases. Accordingly it can be concluded the inability of using fixed value for (**m**) in Peppas-Sahlin equation.

Table 2: Calculation the % of drug released by different mechanisms from Eudragit RS100 microcapsules prepared by using 20% TDC & the calculated (K_1&K_2) at fixed m value.

PS µm	500-400				400-315			
Time	**diffusion**	**Erosion**	**total(calcu.)**	**total(det.)**	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**
0.5	-5.56	8.48	2.92	8.49	-4.13	7.58	3.44	8.40
1	-7.60	15.83	8.23	9.01	-5.65	14.14	8.49	10.01
1.5	-9.12	22.80	13.68	10.26	-6.78	20.37	13.59	11.68
2	-10.38	29.54	19.16	17.11	-7.71	26.39	18.67	13.39
3	-12.46	42.56	30.10	25.59	-9.26	38.01	28.75	26.79
4	-14.18	55.13	40.95	41	-10.54	49.24	38.70	38.09
5	-15.68	67.39	51.72	56.68	-11.65	60.19	48.54	53.06
6	-17.02	79.41	62.39	63.64	-12.65	70.92	58.28	60.44
7	-18.24	91.23	72.99	75.99	-13.55	81.48	67.92	68.95
8	-19.37	102.88	83.51	79.24	-14.39	91.88	77.49	74.39

PS µm	315-80			
Time	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**
0.5	-6.66	7.89	1.23	9.39
1	-9.09	14.72	5.62	9.51
1.5	-10.91	21.20	10.29	9.81
2	-12.42	27.46	15.04	12.59
3	-14.91	39.55	24.65	16.55
4	-16.97	51.24	34.28	28.75
5	-18.76	62.64	43.88	45.35
6	-20.36	73.81	53.45	59.8
7	-21.82	84.80	62.97	66.08
8	-23.18	95.62	72.45	69.68

On trying to estimate the percent of drug release by different mechanisms at each time intervals, the amount of drug release % could be calculated using the values of coefficient constants ($\mathbf{k_1}$&$\mathbf{k_2}$) which calculated at fixed **m** value and then substituted in Peppes-Sahlin equation[15]. The results of this substitution are summarized in tables (2-6). From the tables, it can be noticed that, the amount of drug release % by diffusion mechanism from different particle size ranges microcapsules prepared by using the same or different TDC are negative. This indicates that there is no contribution for the Fickian diffusion mechanism in the drug release process but it is only a pure polymer chain relaxation predominant mechanism. That is may be due to that, the negative values of $\mathbf{k_1}$ calculated as a result of using fixed value of **m**. Also from the tables it can be noticed that the determined amount of drug release % after half an hour, which represents in this case the initial drug release and indicates if there is burst effect or not, in every case is markedly higher than that calculated one. In addition, it can be noticed that the calculated total % of drug release which is the summation of the amount % of drug released by diffusion and dissolution are not completely similar to the experimental determined total percent of drug release even that till 6 hours release time which represent the time for 60% drug release[15].

Table 3: Calculation the % of drug released by different mechanisms from Eudragit RS100 microcapsules prepared by using 33% TDC & the calculated (K_1&K2) at fixed m value.

PS µm	800-500				500-400			
Time	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**
0.5	-1.92	6.64	4.72	7.99	-8.92	9.33	0.42	6.48
1	-2.62	12.38	9.76	10.28	-12.18	17.42	5.24	7.83
1.5	-3.15	17.83	14.69	11.9	-14.62	25.09	10.47	10.93
2	-3.58	23.10	19.52	15.54	-16.64	32.51	15.87	14.07
3	-4.30	33.28	28.98	28.41	-19.97	46.82	26.85	24.65
4	-4.89	43.11	38.22	40.7	-22.73	60.66	37.93	35.78
5	-5.41	52.70	47.30	49.05	-25.13	74.15	49.02	41.6
6	-5.87	62.10	56.23	59.28	-27.28	87.37	60.09	61.55
7	-6.29	71.34	65.05	64	-29.24	100.38	71.14	78.28
8	-6.68	80.45	73.77	71.53	-31.05	113.19	82.15	81.13
PS µm	315-80							
Time	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**				
0.5	-5.24	8.16	2.92	5.98				
1	-7.15	15.22	8.06	7.79				
1.5	-8.59	21.92	13.33	11.11				
2	-9.77	28.40	18.62	18.41				
3	-11.73	40.90	29.17	26.94				
4	-13.35	52.99	39.64	42.41				
5	-14.76	64.78	50.02	45.7				
6	-16.02	76.33	60.31	66.19				
7	-17.18	87.69	70.52	71.5				
8	-18.24	98.89	80.65	77.85				

Table 4: Calculation the % of drug released by different mechanisms from Eudragit RS100 microcapsules prepared by using 50% TDC & the calculated (K_1&K_2) at fixed m value.

PS µm	800-500				500-400			
Time	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**
0.5	-5.17	8.31	3.14	10.39	-4.12	7.76	3.65	7.86
1	-7.06	15.51	8.45	11.36	-5.62	14.49	8.86	11.28
1.5	-8.47	22.34	13.87	11.99	-6.75	20.87	14.12	12.99
2	-9.64	28.94	19.30	13.06	-7.68	27.03	19.35	13.61
3	-11.57	41.69	30.11	27.4	-9.22	38.94	29.72	28.14
4	-13.17	54.00	40.83	42.01	-10.49	50.45	39.96	41.71
5	-14.57	66.02	51.45	49.16	-11.60	61.67	50.07	46.7
6	-15.81	77.79	61.98	67.15	-12.59	72.66	60.07	66.85
7	-16.95	89.36	72.42	73.04	-13.50	83.48	69.98	71.58
8	-18.00	100.78	82.78	81.39	-14.33	94.14	79.81	76.26
PS µm	315-80							
Time	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**				
0.5	-2.91	7.30	4.39	11.03				
1	-3.98	13.63	9.65	12.7				
1.5	-4.77	19.63	14.86	12.88				
2	-5.43	25.43	20.00	13.73				
3	-6.52	36.63	30.11	27.88				
4	-7.42	47.45	40.03	42.11				
5	-8.20	58.00	49.80	44.69				
6	-8.90	68.35	59.44	66.74				
7	-9.54	78.52	68.97	70.41				
8	-10.13	88.54	78.41	75.88				

An exploratory data analysis was also done for the calculated % of drug release by different mechanisms from Eudragit RS100 microcapsules prepared by using different or similar TDC & the calculated (k_1&k_2) at fixed **m** value. This is done by plotting the dissolution data from tables (2-6) which will be figures (1-5). The figures indicate the amount of drug release by each mechanism and the relation between the calculated and determined total drug release % at each time interval. From the figures it can be noticed that the amount of drug released as a result of the polymer relaxation mechanism, in every case, is higher than the total amount released either determined or calculated. Also the negative drug released as a result of Fickian diffusion mechanism which is responsible about the higher value of that release by polymer relaxation mechanism should not be considered. That is may be due that it can not be imagine there is a reabsorption of the drug from the dissolution media although in literature such phenomena can be found but on using plain polymer immersed in drug solution [25].

Table 5: Calculation the % of drug released by different mechanisms from Eudragit RS100 microcapsules prepared by using 66% TDC & the calculated (K_1&K_2) at fixed m value.

PS µm	800-500				500-400			
Time	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**
0.5	-3.06	7.44	4.38	11	-6.04	8.17	2.13	8.21
1	-4.18	13.89	9.71	11.16	-8.25	15.24	6.99	11.54
1.5	-5.02	20.00	14.99	13.84	-9.91	21.96	12.05	12.34
2	-5.71	25.92	20.21	15.88	-11.28	28.45	17.17	13.85
3	-6.85	37.33	30.48	29.55	-13.53	40.97	27.44	17.35
4	-7.80	48.36	40.56	42.02	-15.40	53.08	37.68	41.6
5	-8.62	59.12	50.49	44.09	-17.03	64.89	47.86	44.79
6	-9.36	69.66	60.30	64.65	-18.49	76.46	57.97	61.05
7	-10.03	80.03	69.99	72.03	-19.81	87.84	68.03	70.15
8	-10.65	90.25	79.59	78.95	-21.04	99.06	78.02	77.53

PS µm	315-80			
Time	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**
0.5	-3.65	7.19	3.54	10.86
1	-4.99	13.41	8.42	11.11
1.5	-5.99	19.32	13.33	11.76
2	-6.82	25.03	18.21	13.31
3	-8.18	36.06	27.87	24.85
4	-9.31	46.71	37.40	39.86
5	-10.30	57.10	46.81	42.68
6	-11.18	67.29	56.11	57.73
7	-11.98	77.30	65.32	67.99
8	-12.72	87.17	74.45	74.2

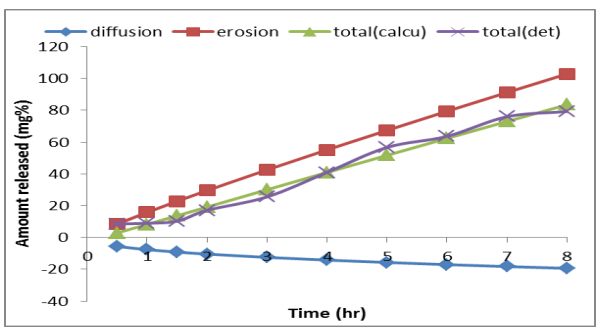
The calculated total amount of drug released looks like as a fitting one for the determined total amount of drug released. Also from the figures it can be concluded the role of the polymer and the method of drug entrapment on the drug release mechanisms. They looked smooth and applicable ones which may be due to a constant change variable during the

application of the release data. Comparing the data from the tables and the equation used for the calculations it can be stated that this variable is the time, accordingly it can be understand the description of the figures (1-5) stated before[15].

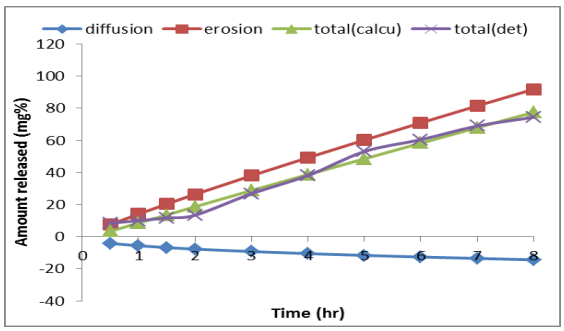
Table 6: Calculation the % of drug released by different mechanisms from Eudragit RS100 microcapsules prepared by using 80% TDC & the calculated (k_1&k_2) at fixed m value.

PS µm	800-500				500-400			
Time	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**
0.5	-1.87	7.00	5.13	9.74	-2.71	7.07	4.36	8.81
1	-2.55	13.05	10.50	10.94	-3.70	13.19	9.49	9.89
1.5	-3.06	18.80	15.74	13.15	-4.44	19.00	14.56	12.35
2	-3.48	24.36	20.88	17.55	-5.05	24.61	19.56	16.68
3	-4.18	35.09	30.91	27.54	-6.06	35.45	29.39	26.8
4	-4.76	45.46	40.70	42.51	-6.90	45.93	39.03	40.1
5	-5.26	55.57	50.31	54.41	-7.63	56.15	48.51	50.41
6	-5.71	65.48	59.77	61.17	-8.28	66.16	57.87	60.24
7	-6.12	75.22	69.10	70.18	-8.88	76.00	67.12	68.95
8	-6.50	84.83	78.33	75.1	-9.43	85.71	76.28	72.98
PS µm	315-80							
Time	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**				
0.5	-3.66	7.21	3.55	8.49				
1	-5.00	13.45	8.45	9.34				
1.5	-6.00	19.38	13.37	11.29				
2	-6.83	25.10	18.27	15.79				
3	-8.20	36.16	27.96	24.53				
4	-9.33	46.84	37.51	38.3				
5	-10.32	57.26	46.94	47.59				
6	-11.20	67.47	56.27	59.38				
7	-12.01	77.51	65.51	67.55				
8	-12.75	87.41	74.66	71.65				

Mady O.**,** discussed some objections about the use of drug mechanisms constants of Peppes - Sahlin model (**k_1&k_2**) for comparison or for determination the mechanism of drug release. These objections are again found in this study with the same proves. That is may be the reason by which the model suggested researchers (Peppas-Sahlin) were not using the constant values of (**k_1&k_2**) for further calculation of the amount of drug released by each mechanism at each unit time and used instead what they called fractional contribution of each drug release mechanism.



(A)



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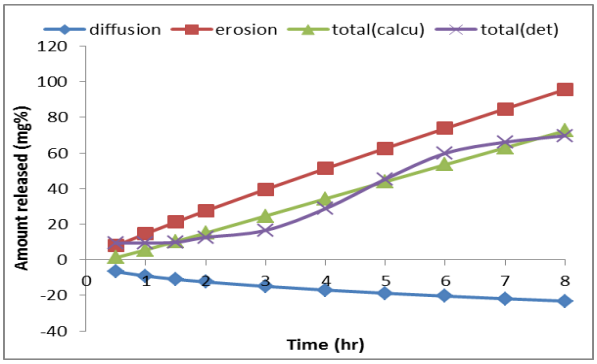
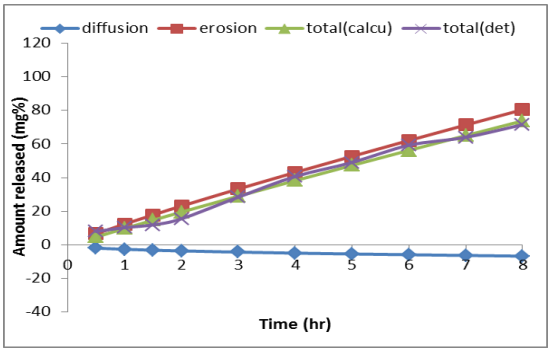


(C)

Figure (1): Drug release by different mechanisms calculated using matrix method and fixed m value from microcapsules prepared by using 20% TDC and:

(A) 500-400 µm microcapsules
(B) 400-315 µm microcapsules
(C) 315-80 µm microcapsules

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



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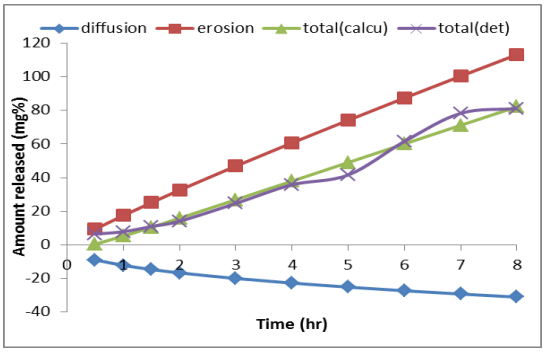

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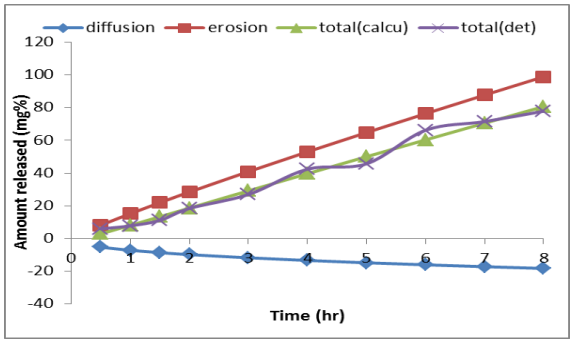
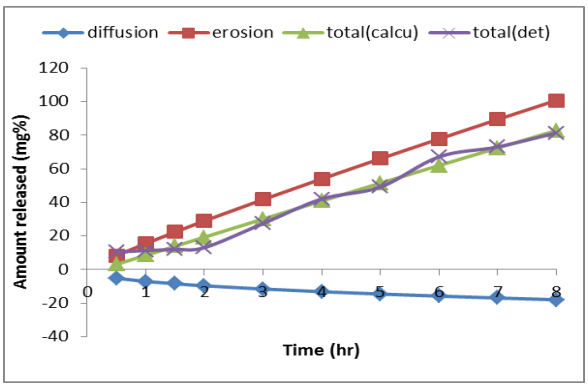


(C)

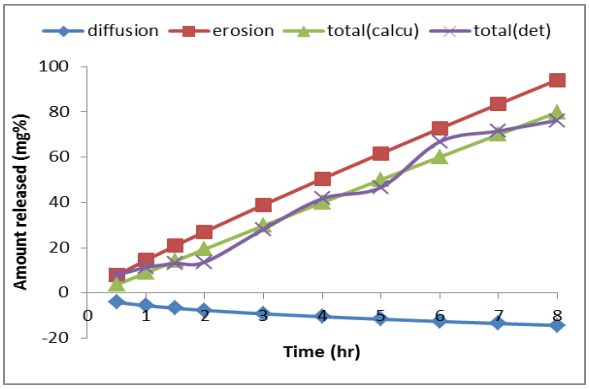
Figure (2): Drug release by different mechanisms calculated using matrix method and fixed m value from microcapsules prepared by using 33% TDC and:

(D) 800-500 µm microcapsules
(E) 500-400 µm microcapsules
(F) 315-80 µm microcapsules

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



(A)



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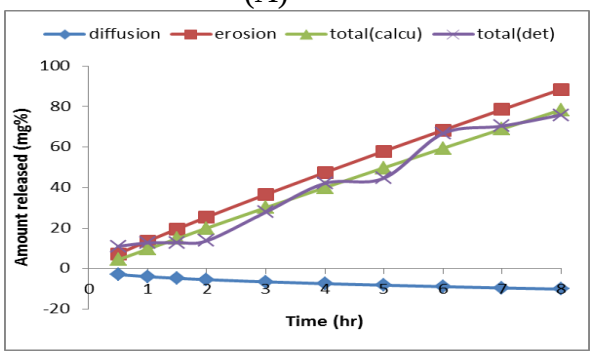
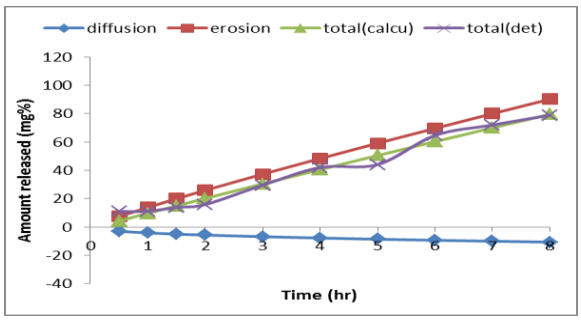


(C)

Figure (3): Drug release by different mechanisms calculated using matrix method and fixed m value from microcapsules prepared by using 50 % TDC and:

(A) 800-500 µm microcapsules
(B) 500-400 µm microcapsules
(C) 315-80 µm microcapsules

Figure 3: Drug release by different mechanisms calculated using matrix method from table 4.



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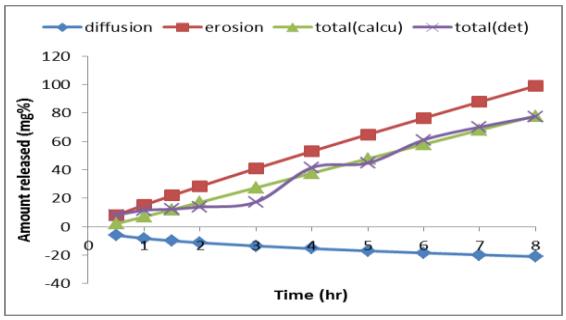
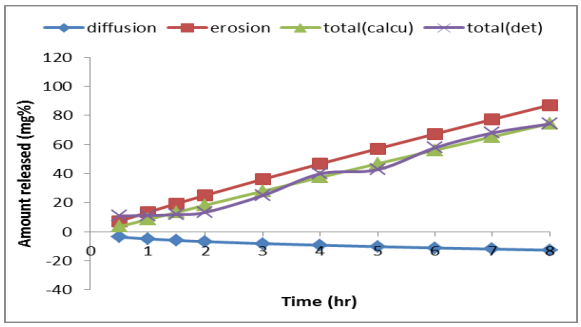


(B)

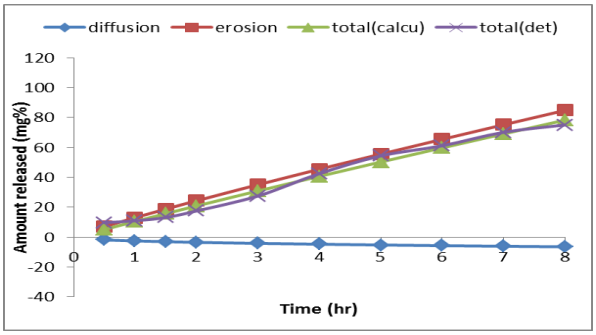


(C)

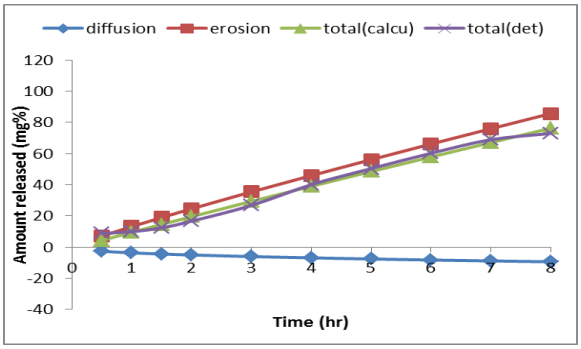
Figure (4): Drug release by different mechanisms calculated using matrix method and fixed m value from microcapsules prepared by using 66 % TDC and:

(D) 800-500 µm microcapsules
(E) 500-400 µm microcapsules
(F) 315-80 µm microcapsules

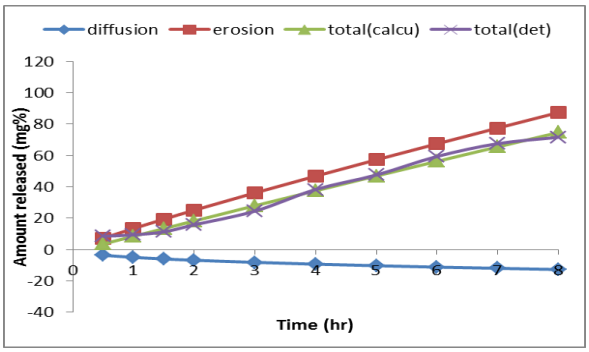
Figure 4: Drug release by different mechanisms calculated using matrix method from table 5.



(A)



(B)



(C)

Figure (5): Drug release by different mechanisms calculated using matrix method and fixed m value from microcapsules prepared by using 80 % TDC and.

(A) 800-500 µm microcapsules
(B) 500-400 µm microcapsules
(C) 315-80 µm microcapsules

Figure 5: Drug release by different mechanisms calculated using matrix method from table 6.

The second trial is calculation of the values of Peppes-Sahlin model constants ($\mathbf{k_1}$&$\mathbf{k_2}$) and the exponent **m** using DDSolver software. The results are represented in table (7). From the table it can be noticed that the values of the correlation coefficient ($\mathbf{r^2}$ ›0.97) are high enough to evaluate the drug dissolution behaviors according to Peppes-Sahlin model. From the table (7), it can be noticed that, the value of $\mathbf{k_1}$ is very low comparing with that of $\mathbf{k_2}$ and is also negative for drug release from microcapsules prepared on using 20% TDC (500-400 & 400-315 µm) 33% TDC (800-500 & 315-80 µm), 50% (500-400 µm) and 80% TDC (800-500 & 500-400 µm). This interpretable data indicates that there is no contribution for the Fickian diffusion drug release mechanism from that microcapsules prepared with the same or different TDC but it is a polymer chain relaxation one as an overall drug release mechanism. Concerning the values of the exponent (**n**) of Krosmeyer-Peppas equation it can be concluded that the drug release mechanism from the above microcapsules prepared with the same or different TDC is Super Case II transport. These results are in agreement with what stated by the author about the drug release mechanism from the above stated microcapsules (zero order kinetics). On contrary these results are not in agreement with the obeying of the release data to Higuchi models since there is no Fickian diffusion role[23].

Table (7): Calculated values of Peppes-Sahlin constants using DDSolver software

TDC	20%			33%			50%		
Microcp. PS	**500-400**	**400-315**	**315-80**	**800-500**	**500-400**	**315-80**	**800-500**	**500-400**	**315-80**
k_1	-3.642	-1.658	3.226	-3.940	4.118	-5.260	3.400	-0.211	4.980
k_2	12.243	10.509	3.651	13.598	3.090	13.498	6.040	9.568	5.402
m	0.490	0.496	0.680	0.436	0.738	0.469	0.598	0.514	0.590
r^2	0.984	0.984	0.965	0.989	0.986	0.987	0.982	0.980	0.970
n*	0.956	0.910	0.810	0.891	1.013	1.026	0.872	0.912	0.813
TDC	66%			80%					
Microcp. PS	**800-500**	**500-400**	**315-80**	**800-500**	**500-400**	**315-80**			
k_1	6.809	4.682	6.154	-0.908	-0.814	0.382			
k_2	3.779	3.592	3.166	11.540	10.547	8.552			
m	0.645	0.682	0.671	0.468	0.484	0.520			
r^2	0.982	0.973	0.982	0.986	0.989	0.988			
n*	0.823	0.886	0.814	0.854	0.881	0.894			

n* is the exponent value of Krosmeyer-Peppas model from reference[23].

On the other side and also from table (7), the contribution of the effects of Fickian diffusion and polymer chain relaxation on the overall drug release mechanism can be noticed from the constants values (**k_1&k_2**) of drug release from microcapsules prepared on using 20% TDC (315-80 µm), 33% TDC (500-400 µm), 50% TDC (800-500 & 315-80 µm), 66% TDC (all particle size ranges) and 80% TDC (315-80 µm). At the same time and based on the limit value of the exponent (**n** = 0.85 for Case II transport) of drug release mechanism from spheres, it can be noticed that the drug release mechanism from microcapsules prepared on using 20% TDC (315-80 µm), 50% TDC (315-80 µm) and 66% (800-500 & 315-80 µm) is anomalous which is in agreement with the calculated values of the drug release constants (**k_1&k_2**). As a trial to explain the above findings, it was found that it is important to correlate these results with both zero order constant (**K_0**) and Higuchi constant (**K_H**) of the drug release. These data are represented in tables (8 A-C). In addition to the image of microcapsule structure suggested by the author as a result of instrumental analysis [21, 26].

Table (8A): Calculated Zero order rate constant (k_0) and Higuchi model constant (k_H) for drug release data which has anomalous drug release mechanism according to (n)* values.

TDC %	PS (µm)	K_0	K_H	T_{lag}	F_H
20%	315-80	9.336	32.635	2.198	-26.769
50%	315-80	9.731	34.410	1.292	-24.950
66%	800-500	9.888	34.945	1.323	-25.410
	315-80	9.301	32.738	1.358	-24.273

(*) Data in the above table is from[23]

From table (8A), it is clear the similarity of the Zero order rate constant of the drug release from the microcapsules have different particle size and also containing different actual drug content [19]. This indicats the contribution of the polymer chain relaxation since the rate of

drug release is independent on the drug concentration in the formulation and the drug release rate is constant over a period of time (Zero-order release kinetics)[26]. Also the closed Higuchi rate constants indiacte the contribution of the Fickian diffusion on the overall drug release mechanism since the polymer used is insoluble but swellable one in the dissolution media (Phosphate buffer 7.4). The above results is also in aggreement with the image of the microcapsule structure since both forms of drug entrapment mechansims are reported[21]. One of them is solid solution form which normally explained by Higuchi drug release model and reservoir type which explained by Zero order kinetics[27]. The results indicate the interpertable data in relation to different drug release mechansims which is also related to the microcapsule structure.As a deep explanation, Zero order drug release rate constant and also Higuchi constant rate are similar for drug dissolution rate from microcapsules which have the same particle size (315-80 µm) and prepared on using 20% and 66% TDC where the drug content in the second microcapsules is nearly double to that in the first one[19]. Mady O.,[21], reported that the microcapsule prepared on using 20% TDC, the smaller particle size ranges contains higher drug content than that larger one and that is due to the presence of minute drug crystal beside amorphous form. At the same time increasing the TDC in the product prepared on using 66% led to increasing the drug crystal form in the bigger microcapsules and solid solution form in the smallest one which is the reflection of the effect of division mechanism. Accordingly it can be expected the similarity in the physic-chemical structure of both microcapsules which have the same size range but prepared with different TDC. Also the microcapsules prepared on using 66% TDC contain more drug crystal form which it has to be logic and this reflect on the value of T_{lag} specially the retarding polymer used is insoluble but swellable in the dissolution media. These two forms of drug entrapment mechanisms look completely logic and are also in agreement with suggested drug release mechanisms. On contrary and also based on the limit value of the exponent (**n** = 0.85 for Case II transport) of drug release mechanism from spheres, the drug release mechanism from microcapsules prepared on using 33% TDC (500-400 µm), 50% TDC (800-500 µm), 66% TDC (500-400 µm) and 80% TDC (315-80) is Super Case II as an overall drug release mechanisms (Table 7). These results are not in agreement with the calculated values of the drug release constants ($\mathbf{k_1}$&$\mathbf{k_2}$) which indicating the contribution of Fickian diffusion and non Fickian on the drug release mechanism (table 7). Mady O[15] discussed this phenomena and 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**). At the same time and as a deep explanation may be as the following: it was reported that in the anomalous process of drug release, Fickian diffusion through the hydrated layers of the matrix and polymer chain relaxation-erosion are both involved[28, 29]. Peppes et al documented that the contribution of these two mechanisms to the overall release are considered to be additive[11].

Table (8B): Calculated Zero order rate constant (k_0) and Higuchi model constant (k_H) for drug release which has Super Case II drug release mechanism according to (n) values.

TDC %	PS	K_0	K_H	T_{lag}	F_H
33%	500-400	10.793	37.897	2.314	-32.887
50%	800-500	10.493	37.037	1.371	-28.853
66%	500-400	9.982	35.081	1.433	-28.132
80%	315-80	9.409	33.426	1.316	-25.571

Abhijit Gokhale[26], as a trial to Achieving Zero-Order Release Kinetics, He used Multi-Step Diffusion-Based Drug Delivery. He prepared two core tablets contain a water-soluble excipient (lactose anhydrous) and gelling polymer (hypromellose). The cores contains release-controlling polymers Eudragit RS and Eudragit RL along with TEC as a plasticizer. The author reported the combination of release mechanisms, the drug released from the core tablets via multi-step diffusion-erosion of the core tablets (due to water-soluble filler) and diffusion through the network of gelled hypromellose and Eudragit. This diffusion was also explained using the Korsemeyer-Peppas model which was found to fit the drug-release profile after examining cores. The results indicated the combined effect of diffusion and erosion mechanisms. Because the dissolution profiles of the core tablets showed pseudo zero-order release, the core tablets in both formulations were further coated to 5% w/w using a combination of Eudragit RS and Eudragit RL. Due to this coating, the drug was released via ternary diffusion mechanism. This release was explained using the Sahlin-Peppas model, as it accounts for the combination of drug release through the hydrated matrix core and polymer-chain relaxation of the Eudragit coating. By optimizing these release-controlling polymers, reduction of the diffusional exponent of the tablet core to the Fickian diffusion was achieved (n = 0.45), and hence zero-order release was obtained. Accordingly and as a result of what is found that the overall drug release mechanism is Super Case II as the value of drug release exponent (**n**) indicated but that is not in agreement with the calculated values of the drug

release constants (**k_1&k_2**) which normally used to indicate the contribution of Fickian and polymer relaxation mechanisms. Then it can be suggested the additive effect of Fickian diffusion and polymer chain relaxation mechanisms which may be responsible about the determined Super Case II mechanism. These results are completely in agreement with the image of the microcapsule structure suggested by the author[21]. Also based on the fact that the diffusion-based drug release can be either Fickian or non-Fickian and in Fickian diffusion, the rate of release is independent of the drug concentration in the tablets[26]. From table (8B), it can be noticed that, the similarity of Zero order drug release constant and also Higuchi rate constant of drug release from microcapsules prepared on using 33% and 50% TDC. Since both microcapsules contain different actual drug content[19] accordingly it can be concluded the role of Fickian diffusion mechanism. Also the difference between both concerning to the drug release rate is only the Tlag. That is may be due to the method of drug entrapment (33% TDC is solid solution and vey minute drug crystal but 50% more drug crystal form than solid solution form). These results can be also noticed in case of microcapsules prepared on using 66% and 80% TDC with no difference in Tlag (table 8B). That is may be due the drug entrapment mechanism which is mainly solid dispersion one[21].

Table (8C): Calculated Zero order rate constant (k_0) and Higuchi model constant (k_H) for drug release which has Super Case II mechanism according to (k_1&k_2) values.

TDC %	PS	K0	KH	Tlag	FH
20%	500-400 400-315	10.694 9.810	38.006 34.877	1.346 1.311	-30.615 -27.088
33%	800-500 315-80	9.169 10.353	32.812 36.924	1.217 1.351	-23.970 -29.954
50%	500-400	10.087	35.853	1.318	-27.691
80%	800-500 500-400	9.690 9.526	34.582 33.951	1.219 1.264	-24.841 -25.198

An interesting finding from table (7) can be also noticed that on studying the overall drug release mechanism from microcapsules prepared on using 20% TDC (500-400 & 400-315 µm) 33% TDC (800-500 & 315-80 µm), 50% (500-400 µm) and 80% TDC (800-500 & 500-400 µm) which is Super Case II transport concerning the values of the exponent (**n**) for the Korsmeyer-Peppas equation. At the same time on applying Peppas-Sahlin model the interpretable data indicate that there is no contribution for the Fickian diffusion drug release mechanism. Studying the Zero order rate constants table (8C) shows the release rate constants of microcapsules prepared on using 20% TDC (500-400 µm), 33% TDC (315-80 µm) and

that of 50% TDC (500-400 µm) have the same values indicating polymer chain relaxation mechanism which is in agreement with Super case drug release mechanism. Decreasing the Higuchi rate constants from that microcapsules indicating decreasing the solid solution form of the drug and increasing solid dispersion one which is in agreement with the image suggested by the author[21]. At the same time the neglection of the effect of Fickian diffusion mechanism in the drug release in the above cases although the microcapsule structure and also the agreement of the drug release with Higuchi model lead to concluded the disagreement between the different models which normally explain each other's.

As a summary, the objections from the using the values of (**k_1, k_2 & m**) calculated by DDSolver soft wares are two things: first is, sometimes disagreement between exponent value of drug release mechanism (**n**) of Krosmeyer-Peppas equation and the coefficient constant values of Peppas-Sahlin model (**k_1, k_2**). Also the disagreements with the fixed applicable models for drug release presentations like Zero order kinetics and Higuchi model. Second is, the result also sometimes is not in agreement with the physic-chemical structure of the product.

On trying to estimate the percent of drug release by different mechanisms at each time intervals, the amount of drug release % could be calculated using the values of coefficient constants (**k_1**, **k_2** &**m**) which calculated by using DDSolver software and then substitution in Peppes-Sahlin equation[15]. The results of this substitution are summarized in tables (9-13).

Table 9: Calculation the % of drug released by different mechanisms from Eudragit RS100 microcapsules prepared by using 20% TDC & the calculated (K_1,K_2&m) by DDSolver.

PS µm	500-400				400-315			
Time	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**
0.5	-2.59	6.21	3.61	8.49	-1.18	5.28	4.11	8.4
1	-3.64	12.24	8.60	9.01	-1.66	10.51	8.85	10.01
1.5	-4.44	18.22	13.77	10.26	-2.02	15.64	13.61	11.68
2	-5.12	24.15	19.03	17.11	-2.33	20.73	18.40	13.39
3	-6.24	35.93	29.69	25.59	-2.84	30.84	28.00	26.79
4	-7.18	47.63	40.45	41	-3.27	40.89	37.61	38.09
5	-8.01	59.28	51.26	56.68	-3.65	50.88	47.23	53.06
6	-8.76	70.87	62.11	63.64	-3.99	60.83	56.84	60.44
7	-9.45	82.43	72.98	75.99	-4.30	70.75	66.45	68.95
8	-10.09	93.95	83.86	79.24	-4.59	80.64	76.05	74.39

PS µm	315-80			
Time	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**
0.5	2.01	1.42	3.44	9.39
1	3.23	3.65	6.88	9.51
1.5	4.25	6.34	10.59	9.81
2	5.17	9.37	14.54	12.59
3	6.81	16.27	23.08	16.55
4	8.28	24.06	32.34	28.75
5	9.64	32.59	42.22	45.35
6	10.91	41.75	52.66	59.8
7	12.12	51.49	63.61	66.08
8	13.27	61.75	75.02	69.68

From the tables, it can be noticed that, the amount of drug release % by diffusion mechanism for all drug release time of different particle size ranges microcapsules prepared by using the same or different TDC is depend on the sign of the value of diffusion constant (**k_1**). Also the determined amount of drug release % after half an hour, which represents the initial drug release and indicates if there is burst effect or not, in every case is markedly higher than that calculated one. In addition, it can be noticed that the calculated total % of drug release which is the summation of the amount % of drug released by diffusion and dissolution is not completely similar to the experimental determined total percent of drug release even that till 6 hours release time which represent the time for 60% drug release[15]. All of these finding was also reported on using fixed (**m**) value which may be the reason by which the model suggested researchers (Peppas-Sahlin) were not using the constant values of (**k_1&k_2**) for further calculation of the amount of drug released by each mechanism at each unit time and used instead what they called fractional contribution of each drug release mechanism.

Table 10: Calculation the % of drug released by different mechanisms from Eudragit RS100 microcapsules prepared by using 33% TDC & the calculated (k_1, k_2 &m) by DDSolver.

PS µm	800-500				500-400			
Time	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**
0.5	-2.91	7.43	4.52	7.99	2.47	1.11	3.58	6.48
1	-3.94	13.60	9.66	10.28	4.12	3.09	7.21	7.83
1.5	-4.70	19.37	14.66	11.9	5.55	5.62	11.18	10.93
2	-5.33	24.89	19.56	15.54	6.87	8.60	15.46	14.07
3	-6.36	35.44	29.08	28.41	9.26	15.64	24.90	24.65
4	-7.21	45.55	38.34	40.7	11.46	23.91	35.37	35.78
5	-7.95	55.33	47.38	49.05	13.51	33.24	46.74	41.6
6	-8.60	64.87	56.26	59.28	15.45	43.50	58.95	61.55
7	-9.20	74.20	65.00	64	17.31	54.61	71.93	78.28
8	-9.75	83.36	73.61	71.53	19.11	66.51	85.62	81.13
PS µm	315-80							
Time	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**				
0.5	-3.80	7.05	3.25	5.98				
1	-5.26	13.50	8.24	7.79				
1.5	-6.36	19.74	13.38	11.11				
2	-7.28	25.86	18.58	18.41				
3	-8.81	37.83	29.02	26.94				
4	-10.08	49.55	39.47	42.41				
5	-11.19	61.08	49.89	45.7				
6	-12.19	72.47	60.29	66.19				
7	-13.10	83.75	70.65	71.5				
8	-13.95	94.92	80.98	77.85				

Table 11: Calculation the % of drug released by different mechanisms from Eudragit RS100 microcapsules prepared by using 50% TDC & the calculated (k_1, k_2 &m) by DDSolver.

PS µm	800-500				500-400			
Time	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**
0.5	2.25	2.64	4.88	10.39	-0.15	4.69	4.54	7.86
1	3.40	6.04	9.44	11.36	-0.21	9.57	9.36	11.28
1.5	4.33	9.81	14.14	11.99	-0.26	14.52	14.26	12.99
2	5.15	13.84	18.98	13.06	-0.30	19.51	19.21	13.61
3	6.56	22.47	29.03	27.4	-0.37	29.60	29.23	28.14
4	7.79	31.70	39.49	42.01	-0.43	39.79	39.35	41.71
5	8.90	41.40	50.30	49.16	-0.48	50.04	49.56	46.7
6	9.93	51.49	61.41	67.15	-0.53	60.36	59.83	66.85
7	10.88	61.91	72.79	73.04	-0.57	70.72	70.15	71.58
8	11.79	72.63	84.42	81.39	-0.62	81.13	80.52	76.26
PS µm	315-80							
Time	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**				
0.5	3.31	2.38	5.69	11.03				
1	4.98	5.40	10.38	12.7				
1.5	6.33	8.72	15.04	12.88				
2	7.50	12.24	19.74	13.73				
3	9.52	19.75	29.27	27.88				
4	11.28	27.73	39.02	42.11				
5	12.87	36.09	48.96	44.69				
6	14.33	44.75	59.08	66.74				
7	15.70	53.68	69.38	70.41				
8	16.99	62.84	79.82	75.88				

An exploratory data analysis was also done for the calculated % of drug release by different mechanisms from Eudragit RS100 microcapsules prepared by using different or similar TDC & the calculated (**k_1,k_2 & m**) using DDSolver from tables (9-13) which will be figures (6-10). The figures indicate the amount of drug release by each mechanism and the relation between the calculated and determined total drug release % at each time interval. From the figure it can be notice the effect of the sign of constants value (**k_1&k_2**) on the amount of drug released by each mechanism i.e. the amount of drug released by Fickian is negative when the value of **k_1** is negative.

Also from the figures it can be concluded the same results noticed stated before about the constant variable which is the time. This indicates the same objections on using of drug mechanisms constants of Peppes-Sahlin model (**k_1&k_2**) for comparison or for determination the mechanism of drug release[15].

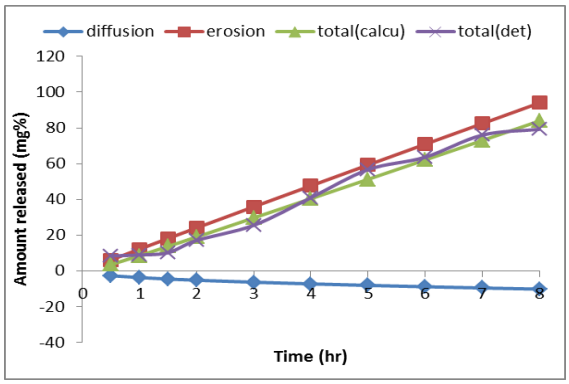
Table 12: Calculation the % of drug released by different mechanisms from Eudragit RS100 microcapsules prepared by using 66% TDC & the calculated (K_1,K_2&m) by DDSolver.

PS µm	800-500				500-400			
Time	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**
0.5	4.35	1.55	5.90	11	2.92	1.40	4.31	8.21
1	6.81	3.78	10.59	11.16	4.68	3.59	8.27	11.54
1.5	8.84	6.38	15.22	13.84	6.17	6.25	12.42	12.34
2	10.64	9.25	19.89	15.88	7.51	9.25	16.76	13.85
3	13.82	15.60	29.43	29.55	9.91	16.08	25.98	17.35
4	16.64	22.61	39.25	42.02	12.05	23.80	35.85	41.6
5	19.22	30.15	49.37	44.09	14.03	32.27	46.30	44.79
6	21.62	38.15	59.77	64.65	15.89	41.38	57.27	61.05
7	23.88	46.54	70.42	72.03	17.65	51.06	68.71	70.15
8	26.03	55.29	81.31	78.95	19.34	61.26	80.60	77.53
PS µm	315-80							
Time	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**				
0.5	3.87	1.25	5.11	10.86				
1	6.15	3.17	9.32	11.11				
1.5	8.08	5.46	13.53	11.76				
2	9.80	8.03	17.82	13.31				
3	12.86	13.83	26.69	24.85				
4	15.60	20.35	35.95	39.86				
5	18.12	27.45	45.57	42.68				
6	20.48	35.06	55.54	57.73				
7	22.71	43.12	65.83	67.99				
8	24.84	51.58	76.42	74.2				

From above it can be concluded that the exponent coefficient value (**n**) which used as an indication for the drug release mechanism[11] is an overall additive value which can be divided into two values, one for drug release by Fickian diffusion and second for non-Fickian diffusion.

Table 13: Calculation the % of drug released by different mechanisms from Eudragit RS100 microcapsules prepared by using 80% TDC & the calculated (K_1.K_2&m) by DDSolver.

PS µm	800-500				500-400			
Time	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**
0.5	-0.66	6.03	5.38	9.74	-0.58	5.39	4.81	8.81
1	-0.91	11.54	10.63	10.94	-0.81	10.55	9.73	9.89
1.5	-1.10	16.87	15.77	13.15	-0.99	15.62	14.63	12.35
2	-1.26	22.08	20.82	17.55	-1.14	20.63	19.49	16.68
3	-1.52	32.27	30.75	27.54	-1.39	30.55	29.16	26.8
4	-1.74	42.24	40.50	42.51	-1.59	40.36	38.76	40.1
5	-1.93	52.05	50.12	54.41	-1.77	50.09	48.31	50.41
6	-2.10	61.74	59.64	61.17	-1.94	59.75	57.82	60.24
7	-2.26	71.32	69.06	70.18	-2.09	69.37	67.28	68.95
8	-2.40	80.82	78.41	75.1	-2.23	78.94	76.71	72.98
PS µm	315-80							
Time	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**				
0.5	0.266	4.159	4.426	8.49				
1	0.382	8.552	8.934	9.34				
1.5	0.472	13.038	13.510	11.29				
2	0.548	17.586	18.134	15.79				
3	0.676	26.810	27.486	24.53				
*4	0.785	36.161	36.946	38.3				
5	0.882	45.606	46.488	47.59				
6	0.970	55.128	56.097	59.38				
7	1.051	64.713	65.764	67.55				
8	1.126	74.354	75.481	71.65				



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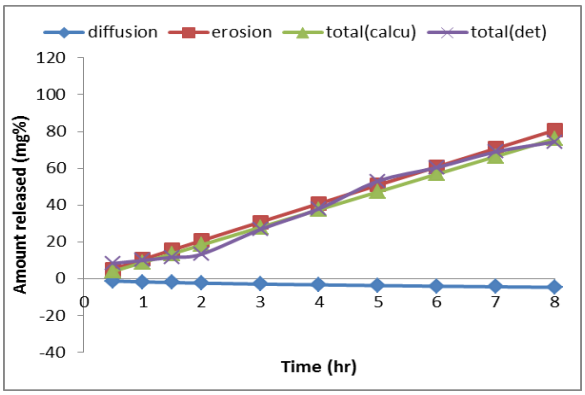

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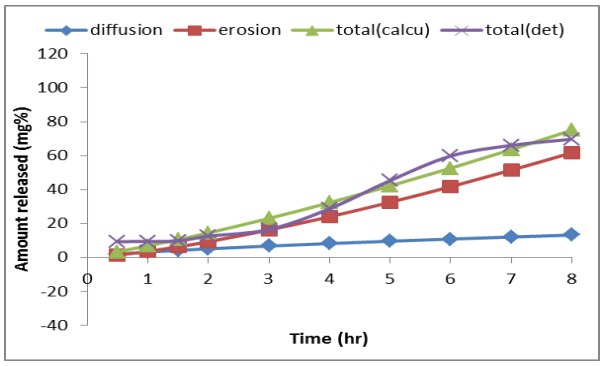
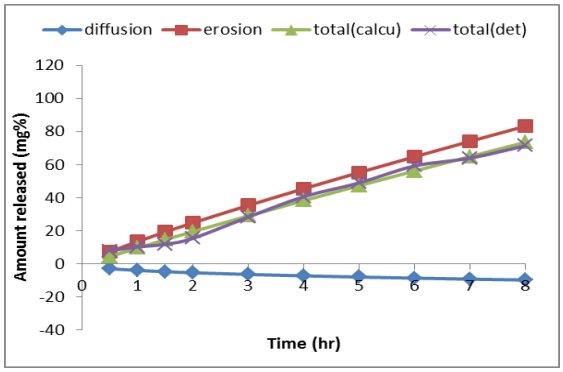


(C)

Figure (6): Drug release by different mechanisms calculated using DDSolver from microcapsules prepared by using 20% TDC and:
(A) 500-400 µm microcapsules
(B) 400-315 µm microcapsules
(C) 315-80 µm microcapsules

Figure 6: Drug release by different mechanisms calculated using matrix method from table 9.



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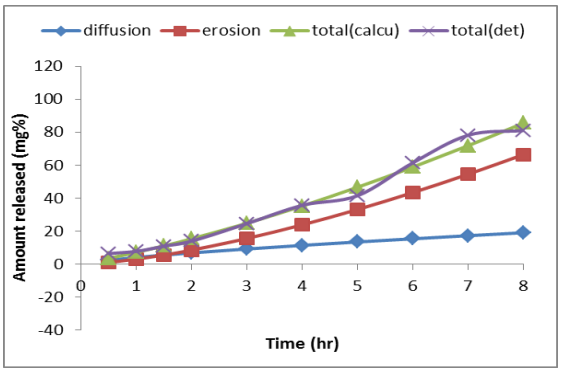

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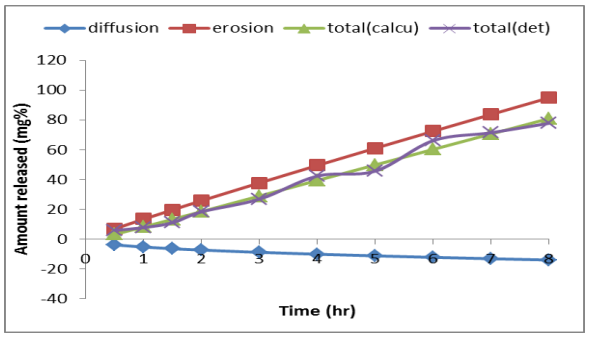
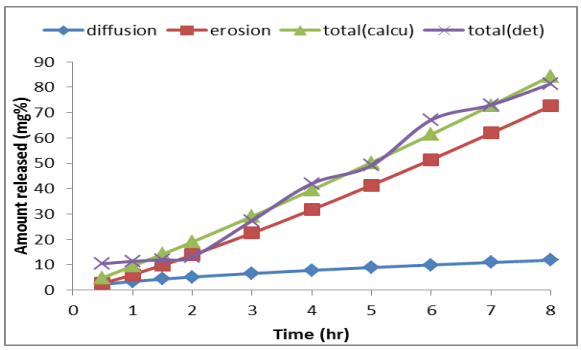


(C)

Figure (7): Drug release by different mechanisms calculated using DDSolver from microcapsules prepared by using 33% TDC and:

(A) 800-500 µm microcapsules
(B) 500-400 µm microcapsules
(C) 315-80 µm microcapsules

Figure 7: Drug release by different mechanisms calculated using matrix method from table 10.



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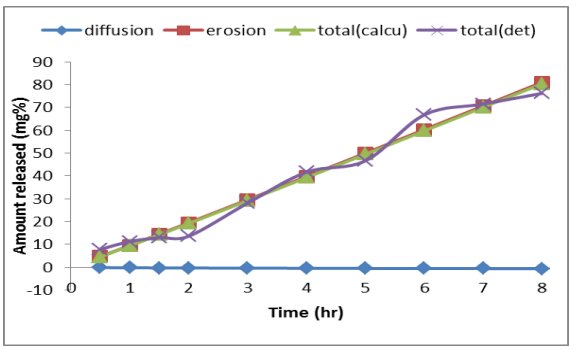

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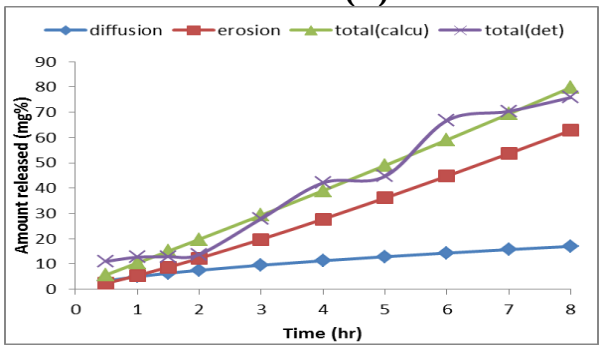
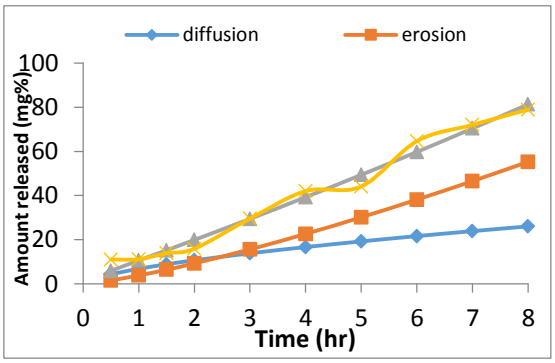


(C)

Figure (8): Drug release by different mechanisms calculated using DDSolver from microcapsules prepared by using 50% TDC and:

(A) 800-500 µm microcapsules
(B) 500-400 µm microcapsules
(C) 315-80 µm microcapsules

Figure 8: Drug release by different mechanisms calculated using matrix method from table 11.



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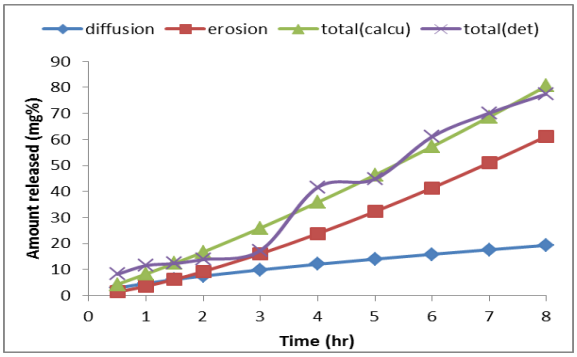

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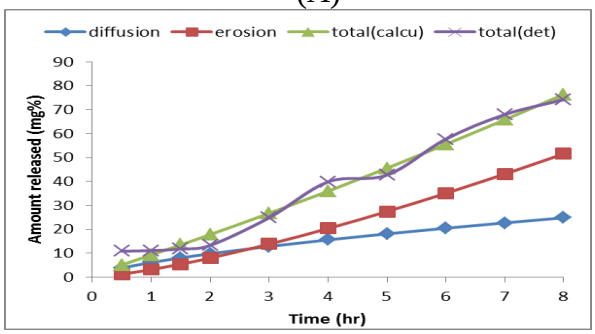
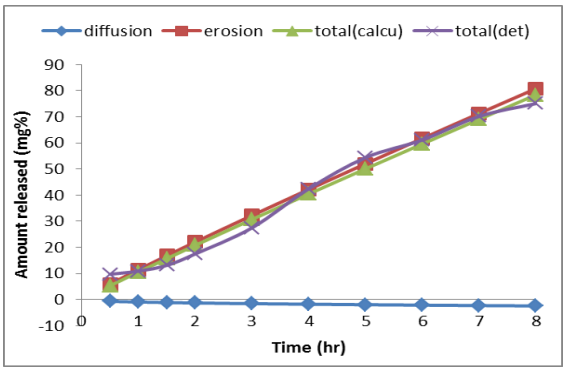


(C)

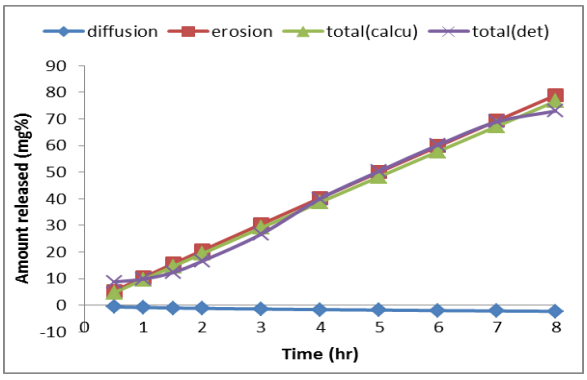
Figure (9): Drug release by different mechanisms calculated using DDSolver from microcapsules prepared by using 66% TDC and:

(A) 800-500 µm microcapsules
(B) 500-400 µm microcapsules
(C) 315-80 µm microcapsules

Figure 9: Drug release by different mechanisms calculated using matrix method from table 12.



(A)



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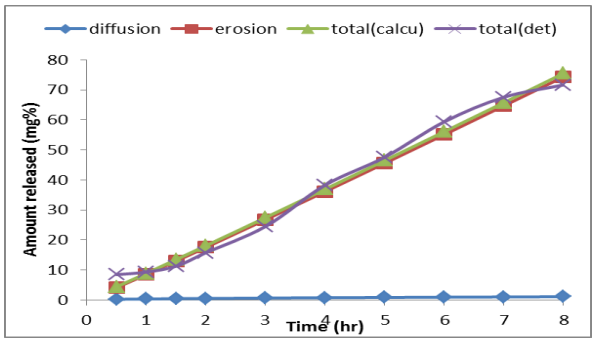


(C)

Figure (10): Drug release by different mechanisms calculated using DDSolver from microcapsules prepared by using 80% TDC and:

(A) 800-500 µm microcapsules
(B) 500-400 µm microcapsules
(C) 315-80 µm microcapsules

Figure 10: Drug release by different mechanisms calculated using matrix method from table 13.

It was reported that Peppas-Sahlin's equation is valid for the first 60% of drug released. In this equation $\mathbf{k_1}$ is the kinetic constant for Fickian contribution of drug release and $\mathbf{k_2}$ is the kinetic constant for Case II contribution, and **m** is the diffusional exponent. **m** is equal to **n** when the case II mechanism is negligible in the semi- empirical model for the analysis of release data of Ritger-Peppas equation. As in the example of a thin polymer film, **m** would be 0.50 for a pure diffusional release mechanism and in this situation **2m** would equal 1[30]. Fassihi et al, on studying the in vitro release modulation from crosslinked pellets for site-specific drug delivery to the gastrointestinal tract used **n** value of Korsmeyer-Peppas to be used in Peppas-Sahlin model[31]. Mady[15], in a new mathematic approach for determination of the mechanisms and percent of drug release of each used the exponent **n** value of Korsmeyer-Peppas equation to be equal the **m** value of Peppas-Sahlin model. Accordingly, the third trial is to calculate the values of Peppes-Sahlin model constants ($\mathbf{k_1}$&$\mathbf{k_2}$) using the exponent **n** value of Korsmeyer-Peppas equation equal to **m** in Peppas-Sahlin model and matrix method. The results are represented in table (14). From the table it can be noticed that the values of the correlation coefficient ($\mathbf{r^2}$ ›0.97) are high enough to evaluate the drug dissolution behaviors according to Peppes-Sahlin model. Also the results shows the contribution of the effects of Fickian diffusion and polymer chain relaxation on the overall drug release mechanism which can be noticed from the constants values ($\mathbf{k_1}$& $\mathbf{k_2}$) of drug release from microcapsules prepared using different or the same theoretical drug content and different particle size. Based on the two facts that, first, in case of the homogenous distribution of the drug in the matrix (solid solution or dispersion) then the drug release can be describe by Higuchi model and that reservoir type the drug release can be describe by Zero order kinetics. Second, Mady O., proved by using instrumental analysis that these two forms of drug entrapment mechanisms were found in different products depending on the TDC used in the preparation of the microcapsules and also the microcapsule particle size[21].

Table 14: Calculated values of Peppes-Sahlin constants using matrix method and n = m.

TDC		20%			33%			50%	
Microcp. PS	**500-400**	**400-315**	**315-80**	**800-500**	**500-400**	**315-80**	**800-500**	**500-400**	**315-80**
K_1	6.697	9.582	5.696	10.506	6.917	9.350	9.175	9.845	9.701
K_2	0.495	0.335	1.540	0.168	0.428	0.029	0.761	0.343	0.932
n	0.956	0.910	0.810	0.891	1.013	1.026	0.872	0.912	0.813
r^2	0.991	0.992	0.978	0.994	0.988	0.993	0.990	0.990	0.985
TDC		66%			80%				
Microcp. PS	**800-500**	**500-400**	**315-80**	**800-500**	**500-400**	**315-80**			
K_1	9.660	7.658	8.282	11.102	10.226	9.273			
K_2	0.914	0.815	1.070	0.378	0.333	0.393			
N	0.823	0.886	0.814	0.854	0.881	0.894			
r^2	0.990	0.984	0.989	0.993	0.994	0.994			

Accordingly, it can be concluded the logic correlation between the microcapsule structure and the contribution of the Fickian and Case II transport on the drug release process in each case. This conclusion can be supported with the results reported in table (8 A-C) which indicate that the overall drug release follows both Zero order kinetics and Higuchi model. Also from table (14) it can be noticed the alternative effect strength between Fickian diffusion and polymer chain relaxation i.e. increasing the value of $\mathbf{k_1}$ led to decreasing the value of $\mathbf{k_2}$ in all cases except both values ($\mathbf{k_1}$&$\mathbf{k_2}$) increased in case of products prepared on using 50% (315-80 µm), 66% TDC (315-80 µm) and decreased in 66% (500-400 µm). At the same time the products prepared on using 80% TDC it can be noticed the slight decreasing in the values of $\mathbf{k_1}$ with nearly constant values of $\mathbf{k_2}$ on decreasing the particle size ranges. These results can be explained as the following:

Mady O.,reported that the products prepared on using 20% TDC, decreasing the particle size led increasing the ADC.[19] Since the drug present in solid solution form[21], accordingly it can be expected the increasing of the Fickian diffusion mechanism in the drug release process with increasing ADC and decreasing the particle size. Also the presence of special chemical interacted form between the drug and the polymer in the microcapsules structure which has particle size range 315-80 µm may be responsible of increasing the value of $\mathbf{k_2}$[21] and decreasing the value of $\mathbf{k_1}$ since the polymer used is Eudragit RS100. That is due to the presence of quaternary amino group by which swelling occurs and any interaction between the drug and the polymer will lead to increase the polarity and the polymer relaxation. The same results can be also noticed in case of products prepared on using 33% TDC except increasing the value of $\mathbf{k_1}$ and decreasing the value of $\mathbf{k_2}$ in case of particle size range 315-80 µm. That is may be due to the appearance of very minute drug crystal form dispersed in the microcapsule structure[21].

The similarity of the values of $\mathbf{k_1}$ of the product prepared on using 50% TDC (where real drug crystal appeared in microcapsules structure), $\mathbf{k_2}$ of product prepared on using 80% TDC (where the product mainly drug crystal form), decreasing the value of $\mathbf{k_1}$ with decreasing the particle size of the product prepared on using 80% TDC and the irregular values in the other cases may be due to the ratio of the drug entrapment forms in the microcapsule structure.[21] These ratios could be expected to be controlled by the division process of the emulsified droplet which controlled by factors discussed before[19].

The drug release kinetics of either Zero order kinetic or Higuchi model or both will controlled by the presence of the drug in solid solution form, solid dispersion form, special interacted form between the drug and the polymer and crystals dispersed form. This would be reflected on the values of $\mathbf{k_1}$ **&** $\mathbf{k_2}$ i.e. the violent effect of Fickian diffusion and polymer relaxation mechanism of drug release.

These explanation would be supported with a very interested finding which is, there is a constant correlation value between Higuchi dissolution rate constant (k_H) and Zero order rate constant (k_O) which is equal to 3.5 for the drug release from different particles size microcapsules prepared by using the same or different TDC (Table 15).

Table (15): The correlation between Higuchi and Zero order rate constant of drug release from the same or different particle size range microcapsules prepared using different or the same TDC.

TDC %	PS range	K_0	K_H	k_H/k_O Ratio
20%	500-400	10.694	38.006	3.554
	400-315	9.810	34.877	3.555
	315-80	9.336	32.635	3.496
33%	800-500	9.169	32.812	3.579
	500-400	10.793	37.897	3.511
	315-80	10.353	36.924	3.567
50%	800-500	10.493	37.037	3.530
	500-400	10.087	35.853	3.554
	315-80	9.731	34.410	3.536
66%	800-500	9.888	34.945	3.534
	500-400	9.982	35.081	3.514
	315-80	9.301	32.738	3.520
80%	800-500	9.690	34.582	3.569
	500-400	9.526	33.951	3.564
	315-80	9.409	33.426	3.553

From table 14, it can be noticed the disagreement between (**n** values) which indicate that the overall drug release mechanism is either anomalous, Case II or Super Case II and the Peppas-Sahlin constant values ($\mathbf{k_1}$**&**$\mathbf{k_2}$) which indicate the drug release mechanism is anomalous one. The disagreement was consider as failure in case using fixed value of **m** on using Peppas-Sahlin model or that calculated by using DDSolver software. But this disagreement should be considered as an advantage in case of using **n** value of the power low equal to **m** for Peppas-Sahlin model for the following.

1. The value of **n** indicates the overall drug release mechanism which is an additive one for different mechanisms of drug release process[11] (this fact can be also considered in the other cases of using **m** values) and it was found the complete agreements between the drug release mechanism determined according the exponent **n** value and both Higuchi model and Zero order release kinetics.
2. According to table (14), it can be notice that in every case there is a contribution of Fickian diffusion mechanism and polymer relaxation one in the overall drug release from all microcapsules prepared on using different TDC and having different particle size.
3. This theoretical data are completely in agreement with the microcapsule structure image which is concluded as a result of instrumental analysis which indicated the different method of drug entrapment.

Table 16: Calculation the % of drug released by different mechanisms from Eudragit RS100 microcapsules prepared by using 20% TDC & the calculated (K_1&K_2) at m = n value by matrix method.

PS µm	500-400				400-315			
Time	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**
0.5	3.45	0.13	3.58	8.49	5.10	0.09	5.19	8.4
1	6.70	0.50	7.19	9.01	9.58	0.34	9.92	10.01
1.5	9.87	1.08	10.94	10.26	13.86	0.70	14.56	11.68
2	12.99	1.86	14.86	17.11	18.00	1.18	19.19	13.39
3	19.14	4.05	23.19	25.59	26.04	2.47	28.51	26.79
4	25.20	7.02	32.22	41	33.83	4.18	38.01	38.09
5	31.20	10.75	41.94	56.68	41.45	6.27	47.72	53.06
6	37.14	15.23	52.37	63.64	48.93	8.74	57.66	60.44
7	43.03	20.45	63.48	75.99	56.30	11.56	67.86	68.95
8	48.89	26.40	75.29	79.24	63.57	14.75	78.32	74.39

PS µm	315-80			
Time	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**
0.5	3.25	0.50	3.75	9.39
1	5.70	1.54	7.24	9.51
1.5	7.91	2.97	10.88	9.81
2	9.99	4.73	14.72	12.59
3	13.87	9.13	23.00	16.55
4	17.51	14.55	32.06	28.75
5	20.98	20.89	41.87	45.35
6	24.32	28.06	52.38	59.8
7	27.55	36.03	63.58	66.08
8	30.70	44.73	75.43	69.68

Table 17: Calculation the % of drug released by different mechanisms from Eudragit RS100 microcapsules prepared by using 33% TDC & the calculated (K_1&K_2) at m = n value by matrix method.

PS µm	800-500				500-400			
Time	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**
0.5	5.67	0.05	5.71	7.99	3.43	0.11	3.53	6.48
1	10.51	0.17	10.67	10.28	6.92	0.43	7.35	7.83
1.5	15.08	0.35	15.42	11.9	10.43	0.97	11.40	10.93
2	19.48	0.58	20.06	15.54	13.96	1.74	15.70	14.07
3	27.96	1.19	29.15	28.41	21.05	3.96	25.01	24.65
4	36.13	1.99	38.12	40.7	28.17	7.10	35.27	35.78
5	44.08	2.96	47.03	49.05	35.32	11.16	46.47	41.6
6	51.85	4.09	55.94	59.28	42.48	16.14	58.62	61.55
7	59.49	5.39	64.87	64	49.66	22.06	71.72	78.28
8	67.00	6.83	73.84	71.53	56.85	28.91	85.77	81.13
PS µm		315-80						
Time	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**				
0.5	4.59	0.01	4.60	5.98				
1	9.35	0.03	9.38	7.79				
1.5	14.17	0.07	14.24	11.11				
2	19.04	0.12	19.16	18.41				
3	28.86	0.28	29.14	26.94				
4	38.77	0.50	39.27	42.41				
5	48.75	0.79	49.54	45.7				
6	58.78	1.15	59.92	66.19				
7	68.85	1.57	70.42	71.5				
8	78.96	2.07	81.02	77.85				

4. The constant correlation between Higuchi constant model and Zero order constant indicate the role of both mechanisms in the drug release process which is in agreement with the image of the microcapsule structure. This agreement support the theoretical calculated finding form application of Peppas-Sahlin equation about the contribution of Fickian diffusion and polymer chain relaxation mechanisms since the polymer used is swellable one in the dissolution media used.

On trying to estimate the percent of drug release by different mechanisms at each time intervals, the amount of drug release % could be calculated using the values of coefficient constants ($\mathbf{k_1}$,$\mathbf{k_2}$) which.

Table 18: Calculation the % of drug released by different mechanisms from Eudragit RS100 microcapsules prepared by using 50% TDC & the calculated (k_1&k_2) at m = n value by matrix method.

PS µm	800-500				500-400			
Time	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**
0.5	5.01	0.23	5.24	10.39	5.23	0.10	5.33	7.86
1	9.18	0.76	9.94	11.36	9.85	0.34	10.19	11.28
1.5	13.07	1.54	14.61	11.99	14.25	0.72	14.97	12.99
2	16.79	2.55	19.34	13.06	18.52	1.21	19.74	13.61
3	23.91	5.17	29.08	27.4	26.81	2.54	29.36	28.14
4	30.73	8.54	39.27	42.01	34.86	4.30	39.16	41.71
5	37.33	12.60	49.93	49.16	42.72	6.46	49.18	46.7
6	43.77	17.32	61.09	67.15	50.45	9.01	59.46	66.85
7	50.06	22.66	72.72	73.04	58.07	11.93	70.00	71.58
8	56.25	28.60	84.85	81.39	65.59	15.22	80.81	76.26
PS µm	315-80							
Time	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**				
0.5	5.52	0.30	5.82	11.03				
1	9.70	0.93	10.63	12.7				
1.5	13.49	1.80	15.29	12.88				
2	17.04	2.88	19.92	13.73				
3	23.70	5.56	29.26	27.88				
4	29.94	8.88	38.82	42.11				
5	35.90	12.76	48.66	44.69				
6	41.63	17.17	58.80	66.74				
7	47.19	22.06	69.25	70.41				
8	52.61	27.41	80.01	75.88				

calculated by using matrix method and then substitution in Peppes-Sahlin equation [15]. The results of this substitution are summarized in tables (16-20). From the tables it can be noticed the same observations reported before concerning with the initial drug release and effect of the data with the sign of kinetic constants (**k_1&k_2**). In addition to the insimilarity between the calculated and determined total amount of drug release even that till 6 hours release time which represent the time for 60% drug release[15]. That is may be again the reason by which the model suggested researchers (Peppas-Sahlin) were not using the constant values of (**k_1**&**k_2**) for further calculation of the amount of drug released by each mechanism at each unit time and used instead what they called fractional contribution of each drug release mechanism.

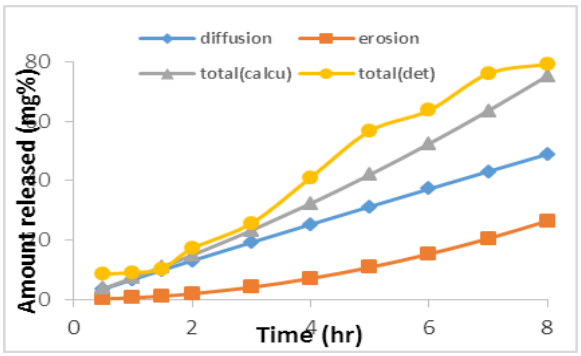
Table 19: Calculation the % of drug released by different mechanisms from Eudragit RS100 microcapsules prepared by using 66 TDC & the calculated (k_1&k_2) at m = n value by matrix method.

PS µm	800-500				500-400			
Time	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**
0.5	5.46	0.29	5.75	11	4.14	0.24	4.38	8.21
1	9.66	0.91	10.57	11.16	7.66	0.82	8.47	11.54
1.5	13.49	1.78	15.27	13.84	10.97	1.67	12.64	12.34
2	17.09	2.86	19.95	15.88	14.15	2.78	16.94	13.85
3	23.86	5.58	29.43	29.55	20.27	5.71	25.98	17.35
4	30.23	8.95	39.18	42.02	26.15	9.51	35.66	41.6
5	36.33	12.93	49.25	44.09	31.87	14.12	45.99	44.79
6	42.21	17.45	59.66	64.65	37.46	19.50	56.96	61.05
7	47.92	22.49	70.41	72.03	42.94	25.63	68.57	70.15
8	53.48	28.02	81.50	78.95	48.33	32.47	80.80	77.53
PS µm		315-80						
Time	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**				
0.5	4.48	0.35	4.83	10.86				
1	8.28	1.07	9.35	11.11				
1.5	11.86	2.07	13.93	11.76				
2	15.31	3.31	18.61	13.31				
3	21.92	6.40	28.32	24.85				
4	28.29	10.22	38.51	39.86				
5	34.47	14.70	49.17	42.68				
6	40.51	19.78	60.29	57.73				
7	46.44	25.42	71.86	67.99				
8	52.27	31.59	83.87	74.2				

An exploratory data analysis was also done for the calculated % of drug release by different mechanisms from Eudragit RS100 microcapsules prepared by using different or similar TDC & the calculated (**k_1**, **k_2**) using matrix method and **n** values equal to **m** values from tables (16-20) which will be figures (11-15). The figures indicate the amount of drug release by each mechanism and the relation between the calculated and determined total drug release % at each time interval. From the figure it can be notice the effect of the sign of constants value (**k_1**&**k_2**) on the amount of drug released by each mechanism i.e. the amount of drug released by Fickian is negative when the value of **k_1** is negative. Also from the figures it can be concluded the same results noticed stated before about the constant variable which is the time. This indicates the same objections on using of drug mechanisms constants of Peppes-Sahlin model (**k_1**&**k_2**) for comparison or for determination the mechanism of drug release[15].

Table 20: Calculation the % of drug released by different mechanisms from Eudragit RS100 microcapsules prepared by using 80 TDC & the calculated (K_1&K_2) at m = n value by matrix method.

PS µm	800-500				500-400			
Time	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**
0.5	6.14	0.12	6.26	9.74	5.55	0.10	5.65	8.81
1	11.10	0.38	11.48	10.94	10.23	0.33	10.56	9.89
1.5	15.70	0.76	16.45	13.15	14.62	0.69	15.30	12.35
2	20.07	1.23	21.30	17.55	18.83	1.15	19.98	16.68
3	28.37	2.47	30.84	27.54	26.92	2.37	29.29	26.8
4	36.27	4.03	40.31	42.51	34.68	3.97	38.65	40.1
5	43.89	5.91	49.79	54.41	42.22	5.92	48.14	50.41
6	51.28	8.06	59.34	61.17	49.57	8.20	57.77	60.24
7	58.49	10.49	68.99	70.18	56.79	10.80	67.59	68.95
8	65.56	13.18	78.74	75.1	63.87	13.71	77.59	72.98
PS µm		315-80						
Time	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**				
0.5	4.99	0.11	5.10	8.49				
1	9.27	0.39	9.67	9.34				
1.5	13.32	0.81	14.14	11.29				
2	17.23	1.36	18.59	15.79				
3	24.76	2.80	27.56	24.53				
4	32.02	4.69	36.71	38.3				
5	39.09	6.98	46.08	47.59				
6	46.01	9.68	55.69	59.38				
7	52.81	12.75	65.56	67.55				
8	59.51	16.19	75.69	71.65				



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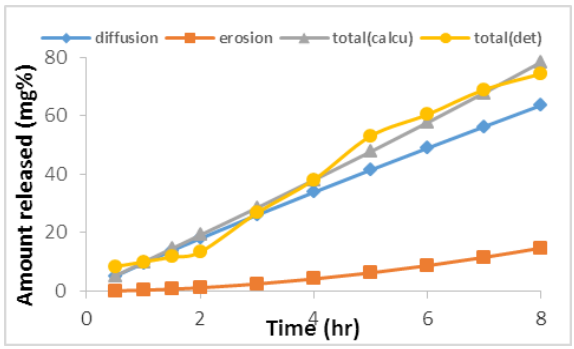
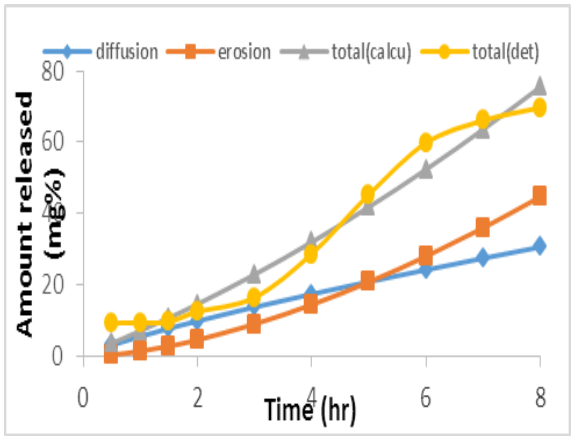


(B)

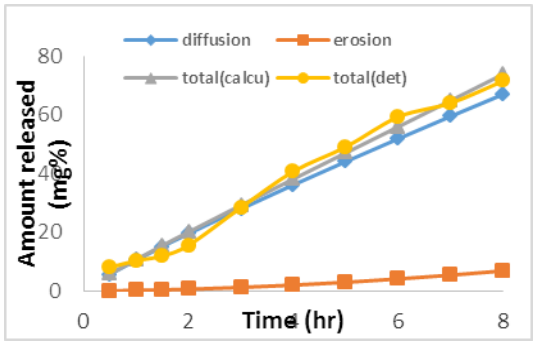


(C)

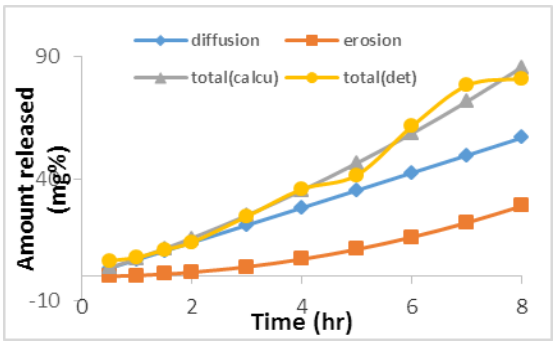
Figure (11): Drug release by different mechanisms calculated using matrix method and m=n values from microcapsules prepared by using 20% TDC and.

(A) 500-400 µm microcapsules
(B) 400-315 µm microcapsules
(C) 315-80 µm microcapsules

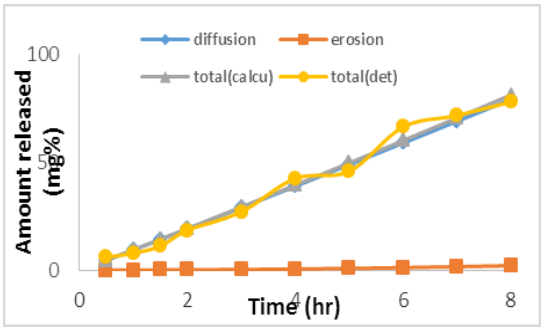
Figure 11: Drug release by different mechanisms calculated using matrix method from table 16.



(A)



(B)

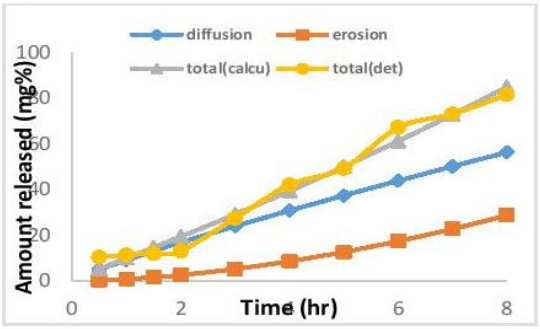


(C)

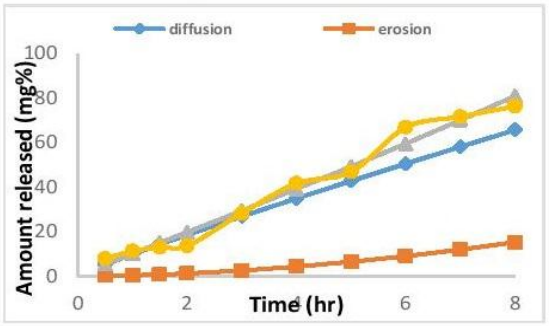
Figure (12): Drug release by different mechanisms calculated using matrix method and m=n values from microcapsules prepared by using 33% TDC and:

(A) 800-500 µm microcapsules
(B) 500-400 µm microcapsules
(C) 315-80 µm microcapsules

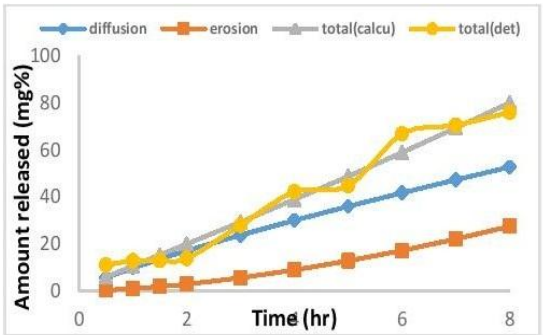
Figure 12: Drug release by different mechanisms calculated using matrix method from table 17.



(A)



(B)

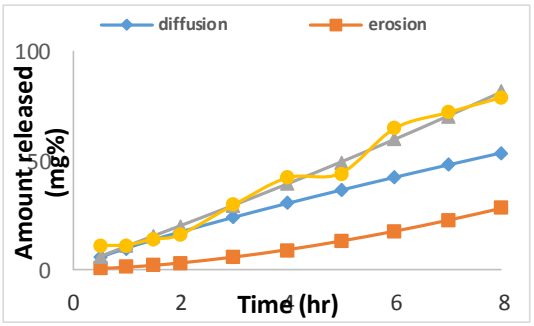


(C)

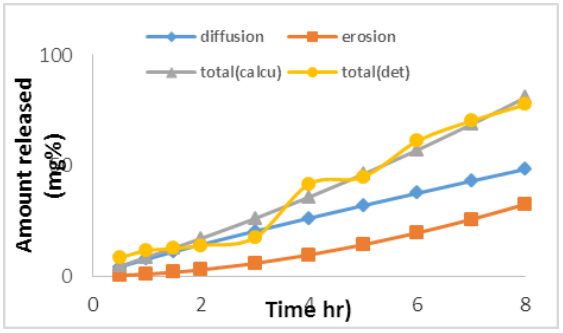
Figure (13): Drug release by different mechanisms calculated using matrix method and m=n values from microcapsules prepared by using 50% TDC and:

(A) 800-500 µm microcapsules
(B) 500-400 µm microcapsules
(C) 315-80 µm microcapsules

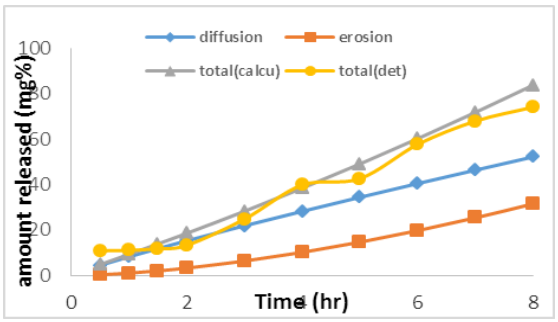
Figure 13: Drug release by different mechanisms calculated using matrix method from table 18.



(A)



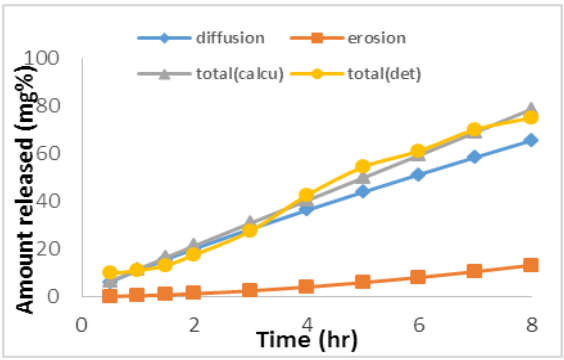
(B)



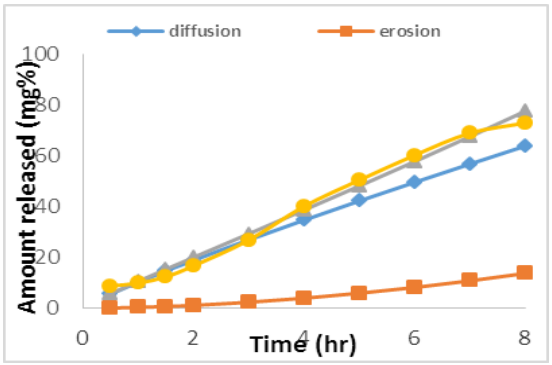
(C)

Figure (14): Drug release by different mechanisms calculated using matrix method and m=n values from microcapsules prepared by using 66% TDC and:
(A) 800-500 µm microcapsules
(B) 500-400 µm microcapsules
(C) 315-80 µm microcapsules

Figure 14: Drug release by different mechanisms calculated using matrix method from table 19.



(A)



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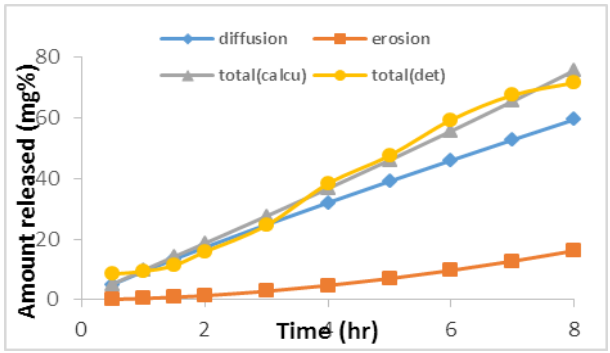


(C)

Figure (15): Drug release by different mechanisms calculated using matrix method and m=n values from microcapsules prepared by using 80% TDC and:

(A) 800-500 µm microcapsules
(B) 500-400 µm microcapsules
(C) 315-80 µm microcapsules

Figure 15: Drug release by different mechanisms calculated using matrix method from table 20.

Mady O., suggested another mathematic method for calculation of the kinetic constants (**k_1&k_2**) which is substitution method. The author enumerates the advantages of using substitution method[15]. Accordingly it will try to use the substitution method for calculation the kinetic constants (**k_1&k_2**) using the exponent coefficient (**n**) of Krosmeyer-Peppas equal the (**m**) of the Peppas-Sahlin equation. The results are summarized in table (21-25). From the tables it can be noticed that, in each cases, 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 in every case the 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. Mady O.,discussed this phenomena and found that it is due to mathematical calculation process[15].

Table 21: Calculation the % of drug released by different mechanisms from Eudragit RS100 microcapsules prepared by using 20% TDC using calculated (K_1&K_2) by substitution method and m value = n value.

PS µm	500-400				400-315			
Time	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**
0.5	132.66	-124.17	8.49	8.49	56.14	-47.74	8.40	8.40
1	-4.85	13.86	9.01	9.01	-5.64	15.65	10.01	10.01
1.5	2.81	7.45	10.26	10.26	-1.97	13.65	11.68	11.68
2	-0.03	17.14	17.11	17.11	2.76	10.63	13.39	13.39
3	1.90	23.69	25.59	25.59	0.73	26.06	26.79	26.79
4	1.20	39.80	41	41	1.35	36.74	38.09	38.09
5	-0.81	57.49	56.68	56.68	-0.67	53.73	53.06	53.06
6	0.28	63.36	63.64	63.64	-0.28	60.72	60.44	60.44
7	-1.06	77.05	75.99	75.99	-0.69	69.64	68.95	68.95

PS µm	315-80			
Time	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**
0.5	37.56	-28.17	9.39	9.39
1	-10.39	19.90	9.51	9.51
1.5	-0.56	10.37	9.81	9.81
2	-1.24	13.83	12.59	12.59
3	2.62	13.93	16.55	16.55
4	2.98	25.77	28.75	28.75
5	1.44	43.91	45.35	45.35
6	-0.85	60.65	59.80	59.80
7	-1.20	67.28	66.08	66.08

Mady O., was also suggested that Since the addition or subtraction (depending on the sign of (**k_1** & **k_2**) 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 22: Calculation the % of drug released by different mechanisms from Eudragit RS100 microcapsules prepared by using 33% TDC using calculated (K_1&K_2) by substitution method and m value = n value.

PS µm	800-500				500-400			
Time	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**
0.5	39.16	-31.17	7.99	7.99	-283.3	289.85	6.48	6.48
1	-6.29	16.57	10.28	10.28	-1.05	8.88	7.83	7.83
1.5	-0.31	12.21	11.90	11.90	-0.37	11.30	10.93	10.93
2	2.20	13.34	15.54	15.54	1.15	12.92	14.07	14.07
3	0.91	27.50	28.41	28.41	0.71	23.94	24.65	24.65
4	-0.47	41.17	40.70	40.70	-0.61	36.39	35.78	35.78
5	0.09	48.96	49.05	49.05	1.88	39.72	41.60	41.60
6	-0.97	60.25	59.28	59.28	0.90	60.65	61.55	61.55
7	-0.27	64.27	64.00	64.00	-1.01	79.29	78.28	78.28
PS µm		315-80						
Time	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**				
0.5	-114.6	120.63	5.98	5.98				
1	-0.72	8.51	7.79	7.79				
1.5	2.56	8.55	11.11	11.11				
2	-0.21	18.62	18.41	18.41				
3	1.53	25.41	26.94	26.94				
4	-1.38	43.79	42.41	42.41				
5	1.78	43.92	45.70	45.70				
6	-0.77	66.96	66.19	66.19				
7	-0.45	71.95	71.50	71.50				

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 microcapsules prepared on using the same or different TDC and have different particle size are represented in tables (26-30). From the tables, 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. This alternative and combined release mechanisms effect can be easily observed from figures (16-20) which are the exploratory representation of the data in tables (26-30).

Table 23: Calculation the % of drug released by different mechanisms from Eudragit RS100 microcapsules prepared by using 50% TDC using calculated (K_1&K_2) by substitution method and m value = n value.

PS µm	800-500				500-400			
Time	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**
0.5	55.48	-45.09	10.39	10.39	37.52	-29.66	7.86	7.86
1	-9.56	20.92	11.36	11.36	-6.60	17.88	11.28	11.28
1.5	-2.87	14.86	11.99	11.99	-3.33	16.32	12.99	12.99
2	3.53	9.53	13.06	13.06	3.16	10.45	13.61	13.61
3	1.84	25.56	27.40	27.40	1.28	26.86	28.14	28.14
4	-0.91	42.92	42.01	42.01	-1.34	43.05	41.71	41.71
5	1.86	47.30	49.16	49.16	2.23	44.47	46.70	46.70
6	-1.04	68.19	67.15	67.15	-1.14	67.99	66.85	66.85
7	-0.36	73.40	73.04	73.04	-0.87	72.45	71.58	71.58

PS µm	315-80			
Time	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**
0.5	38.50	-27.47	11.03	11.03
1	-14.24	26.94	12.70	12.70
1.5	-3.88	16.76	12.88	12.88
2	3.84	9.89	13.73	13.73
3	1.92	25.96	27.88	27.88
4	-2.49	44.60	42.11	42.11
5	3.47	41.22	44.69	44.69
6	-1.71	68.45	66.74	66.74
7	-0.94	71.35	70.41	70.41

From figures (16-20) it can be noticed that, in every case, the effect of the diffusion mechanism started higher than erosion one and increased with time to be maximum after one hour and then started to decrease. The opposite effect can be noticed in case erosion mechanism. These results are in agreement with the image of the microcapsule structure since diffusion mechanism occurred from drug entrapped in molecular stat or near to the surface of the microcapsule which does not need a long time to be released. At the same time the erosion one will be released as a result of polymer chain relaxation which need a time.

Table 24: Calculation the % of drug released by different mechanisms from Eudragit RS100 microcapsules prepared by using 66% TDC using calculated (K_1&K_2) by substitution method and m value = n value.

PS µm	800-500				500-400			
Time	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**
0.5	46.94	-35.94	11.00	11.00	32.11	-23.90	8.21	8.21
1	-6.46	17.62	11.16	11.16	-9.01	20.55	11.54	11.54
1.5	-2.83	16.67	13.84	13.84	-2.48	14.82	12.34	12.34
2	2.94	12.94	15.88	15.88	-1.50	15.35	13.85	13.85
3	1.00	28.55	29.55	29.55	6.01	11.34	17.35	17.35
4	-2.58	44.60	42.02	42.02	-1.89	43.49	41.60	41.60
5	3.03	41.06	44.09	44.09	1.61	43.18	44.79	44.79
6	-0.76	65.41	64.65	64.65	-0.20	61.25	61.05	61.05
7	-0.67	72.70	72.03	72.03	-0.44	70.59	70.15	70.15
PS µm	315-80							
Time	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**				
0.5	43.86	-33.00	10.86	10.86				
1	-11.28	22.39	11.11	11.11				
1.5	-2.67	14.43	11.76	11.76				
2	2.57	10.74	13.31	13.31				
3	2.61	22.24	24.85	24.85				
4	-2.24	42.10	39.86	39.86				
5	1.72	40.96	42.68	42.68				
6	0.15	57.58	57.73	57.73				
7	-0.71	68.70	67.99	67.99				

After one hour release time it can be noticed the erosion mechanism increased gradually and the diffusion effect decreased also gradually to be maximum and minimum respectively at two hours release time. Also the total amount of drug released is the summation of the two mechanisms effect till at two hours where the drug release occurred by erosion one. These results indicated the complete exhaustion of the molecular state entrapped drug and the maximum relaxation of the polymer chain at two hours release time.

Table 25: Calculation the % of drug released by different mechanisms from Eudragit RS100 microcapsules prepared by using 80% TDC using calculated (K_1&K_2) by substitution method and m value = n value.

PS µm	800-500				500-400			
Time	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**
0.5	44.36	-34.62	9.74	9.74	48.82	-40.01	8.81	8.81
1	7.61	3.33	10.94	10.94	5.80	4.09	9.89	9.89
1.5	-0.03	13.18	13.15	13.15	-0.40	12.75	12.35	12.35
2	-1.46	19.01	17.55	17.55	-2.14	18.82	16.68	16.68
3	-6.91	34.45	27.54	27.54	-5.21	32.01	26.80	26.80
4	-1.50	44.01	42.51	42.51	-0.34	40.44	40.10	40.10
5	4.81	49.60	54.41	54.41	0.29	50.12	50.41	50.41
6	1.37	59.80	61.17	61.17	1.54	58.70	60.24	60.24
7	5.85	64.33	70.18	70.18	6.67	62.28	68.95	68.95
PS µm		315-80						
Time	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**				
0.5	119.85	-111.36	8.49	8.49				
1	-24.81	34.15	9.34	9.34				
1.5	-14.07	25.36	11.29	11.29				
2	-10.14	25.93	15.79	15.79				
3	-10.44	34.97	24.53	24.53				
4	-12.29	50.59	38.30	38.30				
5	-12.31	59.90	47.59	47.59				
6	-12.90	72.28	59.38	59.38				
7	-12.68	80.23	67.55	67.55				

The similarity of the behavior of the drug release mechanisms in every cases indicate two things, first, the full agreement between the microcapsule structure image based on the instrumental analysis specially the model drug used has lower solubility in the organic phase used which lead to solid solution entrapment form. Second, the correct method used for drug release mechanism determination.

Table 26: Calculation the % of drug released by different mechanisms from Eudragit RS100 microcapsules prepared by using 20% TDC using calculated (K_1&K_2) by substitution method and m value = n value using the absolute values of each mechanism.

PS µm	500-400				400-315			
Time	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**
0.5	6.17	2.32	8.49	8.49	6.10	2.30	8.40	8.40
1	7.28	1.73	9.01	9.01	8.09	1.92	10.01	10.01
1.5	4.05	6.21	10.26	10.26	4.61	7.07	11.68	11.68
2	0.27	16.84	17.11	17.11	0.21	13.18	13.39	13.39
3	9.60	15.99	25.59	25.59	10.05	16.74	26.79	26.79
4	13.68	27.32	41.00	41.00	12.71	25.38	38.09	38.09
5	41.85	14.83	56.68	56.68	39.18	13.88	53.06	53.06
6	12.34	51.30	63.64	63.64	11.71	48.73	60.44	60.44
7	60.19	15.80	75.99	75.99	54.61	14.34	68.95	68.95
PS µm	315-80							
Time	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**				
0.5	6.82	2.57	9.39	9.39				
1	7.68	1.83	9.51	9.51				
1.5	3.87	5.94	9.81	9.81				
2	0.20	12.39	12.59	12.59				
3	6.21	10.34	16.55	16.55				
4	9.59	19.16	28.75	28.75				
5	33.49	11.86	45.35	45.35				
6	11.59	48.21	59.80	59.80				
7	52.34	13.74	66.08	66.08				

The dissolution time between 2 to 3 hours, in every case, it can notice the gradual increase of the effect of diffusion mechanism but the erosion effect dependence on the microcapsule particle size and TDC used for preparation. For example in case of all particle size products prepared on using 80% TDC, the erosion effect between 2 and 3 hours decreased. That is may be due to the high drug crystal concentration in the microcapsule structure which need a time to dissolve before release. This result supported with the finding that the erosion effect from product prepared on using 33% TDC and have particle size (800-500 & 500-400 µm) increased between 2 and 3 hour release time. That is may be due to the absence of actual drug crystal form in the microcapsules structure.

Table 27: Calculation the % of drug released by different mechanisms from Eudragit RS100 microcapsules prepared by using 33% TDC using calculated (K_1&K_2) by substitution method and m value = n value using the absolute values of each mechanism.

PS µm	800-500				500-400			
Time	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**
0.5	5.81	2.18	7.99	7.99	4.71	1.77	6.48	6.48
1	8.30	1.98	10.28	10.28	6.32	1.51	7.83	7.83
1.5	4.70	7.20	11.90	11.90	4.31	6.62	10.93	10.93
2	0.25	15.29	15.54	15.54	0.22	13.85	14.07	14.07
3	10.66	17.75	28.41	28.41	9.25	15.40	24.65	24.65
4	13.58	27.12	40.70	40.70	11.94	23.84	35.78	35.78
5	36.22	12.83	49.05	49.05	30.72	10.88	41.60	41.60
6	11.49	47.79	59.28	59.28	11.93	49.62	61.55	61.55
7	50.69	13.31	64.00	64.00	62.00	16.28	78.28	78.28

PS µm	315-80			
Time	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**
0.5	4.35	1.63	5.98	5.98
1	6.29	1.50	7.79	7.79
1.5	4.38	6.73	11.11	11.11
2	0.29	18.12	18.41	18.41
3	10.11	16.83	26.94	26.94
4	14.15	28.26	42.41	42.41
5	33.75	11.95	45.70	45.70
6	12.83	53.36	66.19	66.19
7	56.63	14.87	71.50	71.50

At the same time the presence of minute drug crystal form in case microcapsule with size range of 315-80 µm led to decrease the erosion effect[21]. Based on this finding and in addition to the image of microcapsule structure for each product prepared with the same or different TDC and also different particle size it can explain the increase or decrease the erosion effect at this release time. Also at that time the total amount of drug released in the summation of the effect of both mechanisms.

After 3 hours drug release, the effect of both mechanism increased with different strength till 4 hours. The amount of drug released by erosion mechanism is higher than that by diffusion one which may occurred as reflection of the time required for the polymer relaxation and drug solubility occurring one hour before.

Table 28: Calculation the % of drug released by different mechanisms from Eudragit RS100 microcapsules prepared by using 50% TDC using calculated (K_1&K_2) by substitution method and m value = n value using the absolute values of each mechanism.

PS µm	800-500				500-400			
Time	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**
0.5	7.55	2.84	10.39	10.39	5.71	2.15	7.86	7.86
1	9.18	2.18	11.36	11.36	9.11	2.17	11.28	11.28
1.5	4.73	7.26	11.99	11.99	5.13	7.86	12.99	12.99
2	0.21	12.85	13.06	13.06	0.22	13.39	13.61	13.61
3	10.28	17.12	27.40	27.40	10.56	17.58	28.14	28.14
4	14.02	27.99	42.01	42.01	13.92	27.79	41.71	41.71
5	36.30	12.86	49.16	49.16	34.48	12.22	46.70	46.70
6	13.02	54.13	67.15	67.15	12.96	53.89	66.85	66.85
7	57.85	15.19	73.04	73.04	56.70	14.88	71.58	71.58

PS µm	315-80			
Time	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**
0.5	8.02	3.01	11.03	11.03
1	10.26	2.44	12.70	12.70
1.5	5.08	7.80	12.88	12.88
2	0.22	13.51	13.73	13.73
3	10.46	17.42	27.88	27.88
4	14.05	28.06	42.11	42.11
5	33.00	11.69	44.69	44.69
6	12.94	53.80	66.74	66.74
7	55.77	14.64	70.41	70.41

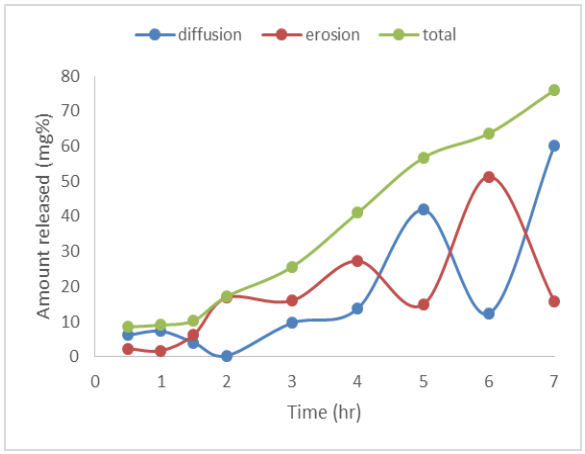
Starting from 4 hours, it can be noticed an predominated alternative effect for both drug release mechanisms (diffusion & erosion) i. e. in every case when the effect of the diffusion mechanism increased till reach to the maximum value, the effect of erosion decrease till reach to a minimum value and vice versa. That is may be represent the diffusion of the dissolved drug from the microcapsules to the dissolution media and that released as a results of Eudragit RS100 chain relaxation process. But in every case both mechanisms worked at the same time with different violent[15]. Also in every case the total amount of drug released represents the summation of both released by the two different mechanisms.

Table 29: Calculation the % of drug released by different mechanisms from Eudragit RS100 microcapsules prepared by using 66% TDC using calculated (K_1&K_2) by substitution method and m value = n value using the absolute values of each mechanism.

PS µm	800-500				500-400			
Time	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**
0.5	7.99	3.01	11.00	11.00	5.97	2.24	8.21	8.21
1	9.01	2.15	11.16	11.16	9.32	2.22	11.54	11.54
1.5	5.46	8.38	13.84	13.84	4.87	7.47	12.34	12.34
2	0.25	15.63	15.88	15.88	0.22	13.63	13.85	13.85
3	11.09	18.46	29.55	29.55	6.51	10.84	17.35	17.35
4	14.02	28.00	42.02	42.02	13.88	27.72	41.60	41.60
5	32.56	11.53	44.09	44.09	33.07	11.72	44.79	44.79
6	12.53	52.12	64.65	64.65	11.83	49.22	61.05	61.05
7	57.05	14.98	72.03	72.03	55.56	14.59	70.15	70.15
PS µm	315-80							
Time	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**				
0.5	7.89	2.97	10.86	10.86				
1	8.97	2.14	11.11	11.11				
1.5	4.64	7.12	11.76	11.76				
2	0.21	13.10	13.31	13.31				
3	9.33	15.52	24.85	24.85				
4	13.30	26.56	39.86	39.86				
5	31.52	11.16	42.68	42.68				
6	11.19	46.54	57.73	57.73				
7	53.85	14.14	67.99	67.99				

Table 30: Calculation the % of drug released by different mechanisms from Eudragit RS100 microcapsules prepared by using 80% TDC using calculated (K_1&K_2) by substitution method and m value = n value using the absolute values of each mechanism.

PS µm	800-500				500-400			
Time	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**
0.5	7.08	2.66	9.74	9.74	6.40	2.41	8.81	8.81
1	8.84	2.10	10.94	10.94	7.99	1.90	9.89	9.89
1.5	5.19	7.96	13.15	13.15	4.87	7.48	12.35	12.35
2	0.28	17.27	17.55	17.55	0.27	16.41	16.68	16.68
3	10.34	17.20	27.54	27.54	10.06	16.74	26.80	26.80
4	14.19	28.32	42.51	42.51	13.38	26.72	40.10	40.10
5	40.18	14.23	54.41	54.41	37.22	13.19	50.41	50.41
6	11.86	49.31	61.17	61.17	11.68	48.56	60.24	60.24
7	55.59	14.59	70.18	70.18	54.61	14.34	68.95	68.95
PS µm		315-80						
Time	**diffusion**	**erosion**	**total(calcu.)**	**total(det.)**				
0.5	6.17	2.32	8.49	8.49				
1	7.54	1.80	9.34	9.34				
1.5	4.45	6.84	11.29	11.29				
2	0.25	15.54	15.79	15.79				
3	9.21	15.32	24.53	24.53				
4	12.78	25.52	38.30	38.30				
5	35.14	12.45	47.59	47.59				
6	11.51	47.87	59.38	59.38				
7	53.50	14.05	67.55	67.55				



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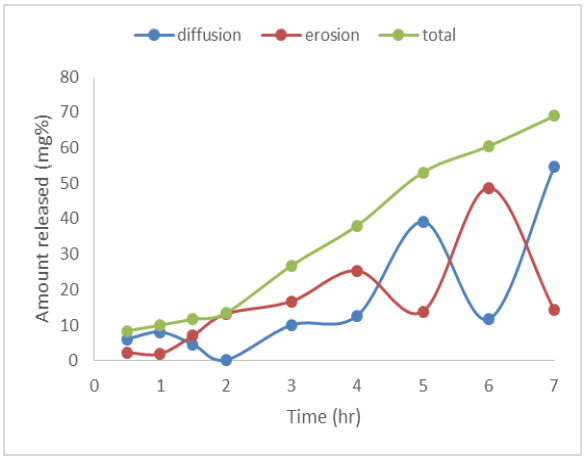
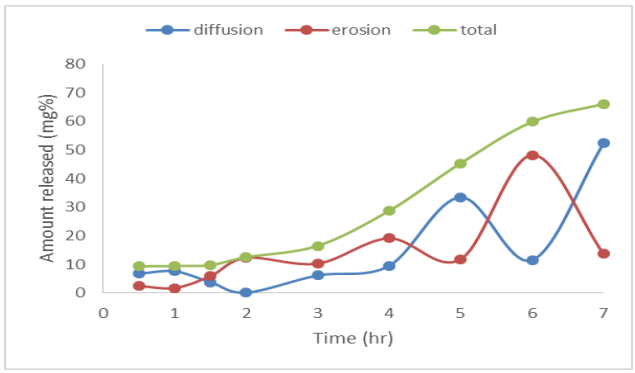


(B)

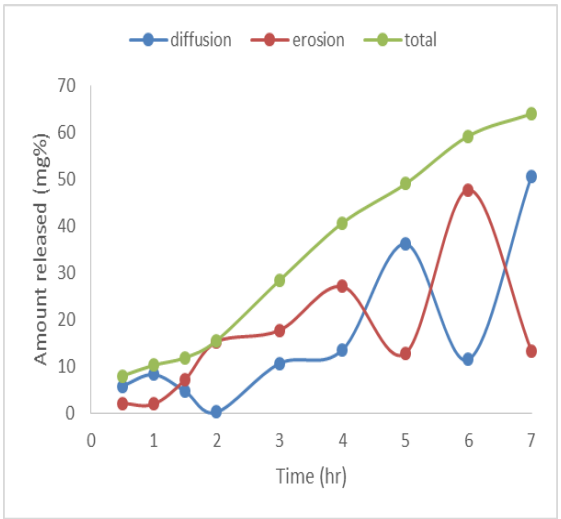


(C)

Figure (16): Drug release by different mechanisms calculated using substitution method and m=n values from microcapsules prepared by using 20% TDC and:

(A) 500-400 µm microcapsules
(B) 400-315 µm microcapsules
(C) 315-80 µm microcapsules

Figure 16: Drug release by different mechanisms calculated using matrix method from table 26.



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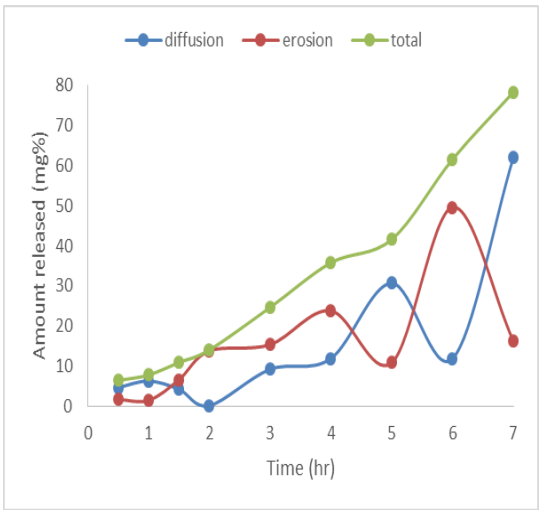


(B)

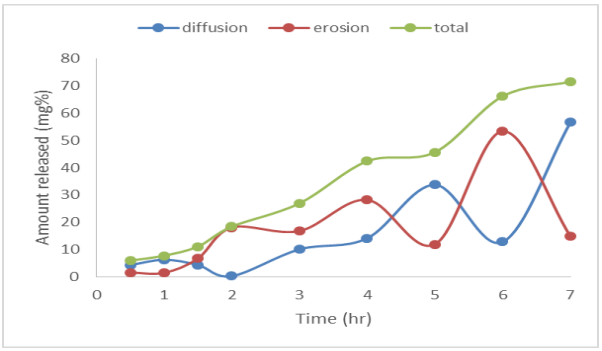
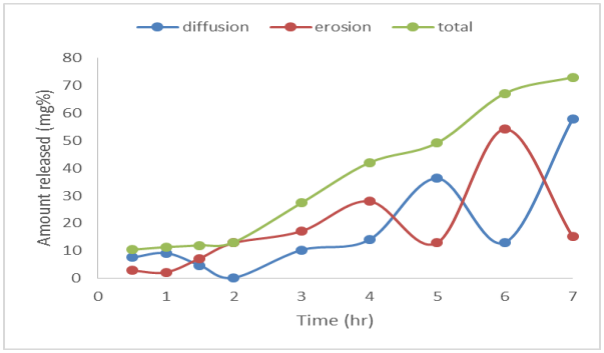


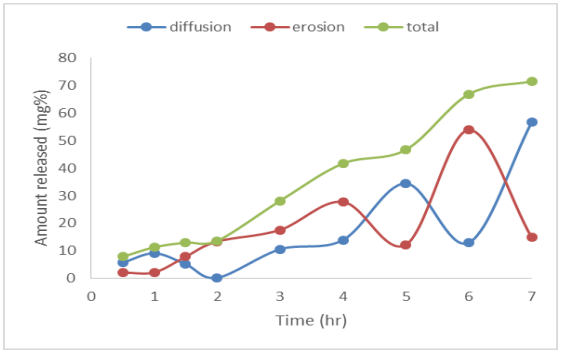
Figure (17): Drug release by different mechanisms calculated using substitution method and m=n values from microcapsules prepared by using 33% TDC and:
(A) 800-500 µm microcapsules
(B) 500-400 µm microcapsules
(D) 315-80 µm microcapsules

(C)

Figure 17: Drug release by different mechanisms calculated using matrix method from table 27.



(A)



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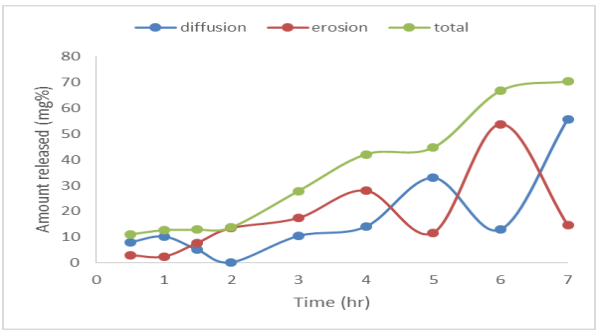
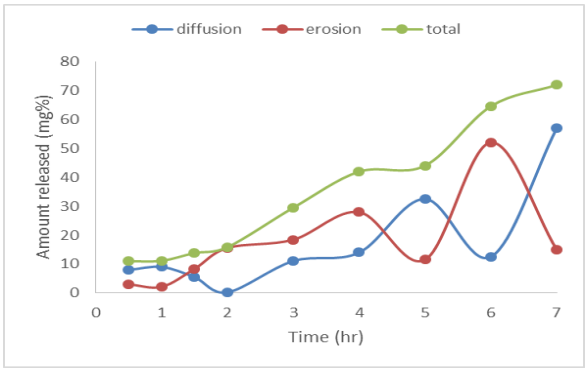


(C)

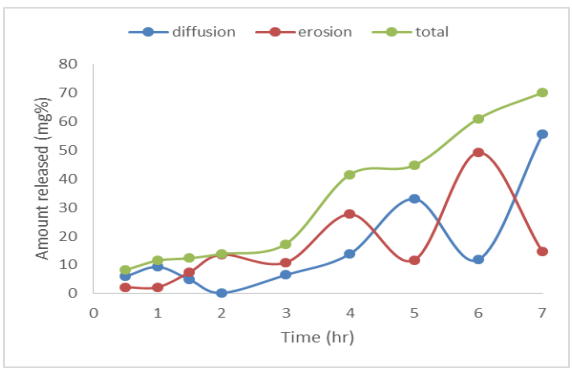
Figure (18): Drug release by different mechanisms calculated using substitution method and m=n values from microcapsules prepared by using 50% TDC and:

(C) 800-500 µm microcapsules
(D) 500-400 µm microcapsules
(E) 315-80 µm microcapsules

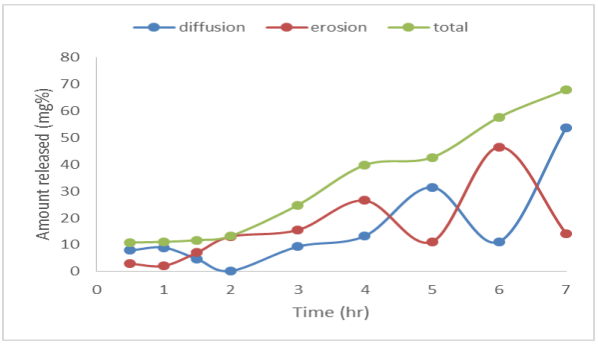
Figure 18: Drug release by different mechanisms calculated using matrix method from table 28.



(A)



(B)

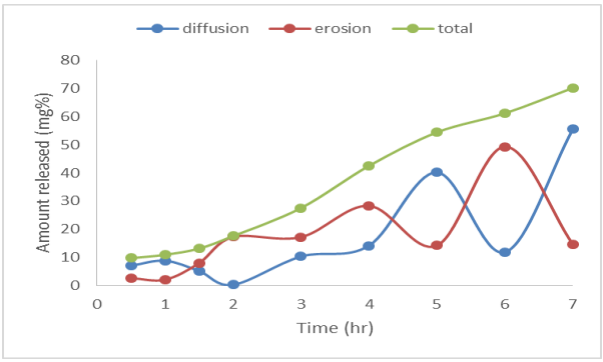


(C)

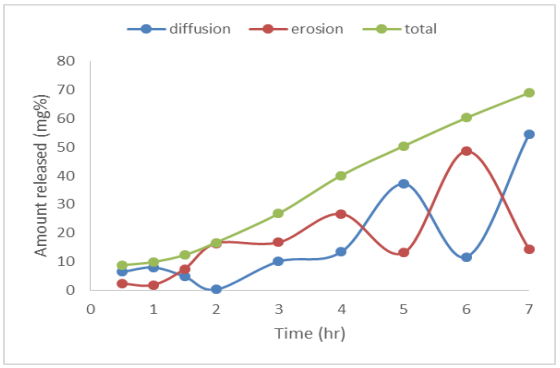
Figure (19): Drug release by different mechanisms calculated using substitution method and m=n values from microcapsules prepared by using 66% TDC and:

(E) 800-500 µm microcapsules
(F) 500-400 µm microcapsules
(F) 315-80 µm microcapsules

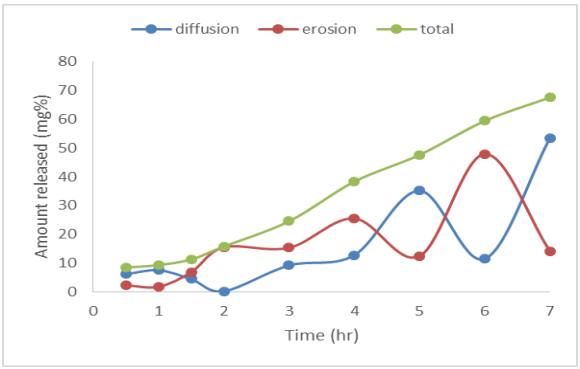
Figure 19: Drug release by different mechanisms calculated using matrix method from table 29.



(A)



(B)



(C)

Figure (20): Drug release by different mechanisms calculated using substitution method and m=n values from microcapsules prepared by using 80% TDC and:

(G) 800-500 µm microcapsules
(H) 500-400 µm microcapsules
(G) 315-80 µm microcapsules

Figure 20: Drug release by different mechanisms calculated using matrix method from table 30.

CONCLUSION

To study the contribution of Fickian and non Fickian diffusion on the drug release it is essential to apply Pappas-Sahlin model. But to achieve this goal it has to use the coefficient factor (**m**) of Peppas-Sahlin model equal to the exponent factor (**n**) of Krosmeyer-Peppas model to calculate the constants drug release mechanisms ($\mathbf{k_1}$**&**$\mathbf{k_2}$).

At the same time the use of a new mathematic method which based on mathematic substitution method for the calculation gives the chance to calculate the amount of drug released by each mechanism at each unite time. Not only that but also it shows the overlap, alternate, predominate and also combination of all drug release mechanisms at each unite time indicating the dynamic complex drug release process which is in agreement with the logic concept of the drug release.[15]

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