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Calculation of predominant drug release mechanism using Peppas-Sahlin model (substitution method): A linear regression approach

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ABSTRACT

The objective of this study was to develop NCRD controlled release floating tablets using combination of hydrophilic and hydrophobic polymers by melt granulation technique. The *in vitro* drug release characteristics were determined using USP XXII type 2 (paddle type) apparatus, in a medium of 0.1N HCl. The dissolution profile of all the batches were extended up to 24 hrs. To study and model the drug delivery from polymeric floating tablets, the dissolution data was fitted to a pioneered method Korsmeyer-Peppas equation. The results indicate that, all the formulations followed super Case-II release mechanism, except MCS4 which followed non-Fickian or anomalous release mechanism. In order to determine the predominant mechanism (diffusion/ relaxation model), drug release data was incorporated into Peppas-Sahlin model. The results revealed that, Fickian release contribution was preponderance than corresponding Case-II relaxational contribution in all the formulations. In addition to this, the relaxational contribution was observed with negative sign in all the formulations but, only at specific time intervals. Relaxational contribution with negative values indicates the Fickian release mechanism was more pronounced than relaxation i.e. almost the relaxational mechanism was absent.

Key words: Controlled release, NCRD, Diffusion, Relaxation, Fickian diffusion.

INTRODUCTION

The quantitative analysis of data and study of drug release kinetics calculated from dissolution data was easier when mathematical formulae/ models were used to describe the process[1]. The kinetic release study was very important, since it allows constant calculations and provide a useful quantitative value to compare the behaviour of these systems in terms of its strength and ultimately help to predict the effect of device design parameters on the release kinetic of the formulation optimize and also useful to design a therapeutic device to yield information on the efficacy of various release models. The drug release phenomenon in relation to specific mathematical formulae revealed the information related to surface properties, liquid uptake behaviour, swelling and erosion of matrix tablets and drug release mechanisms[2,3,4]. However, a special attention has to pay in the selection of best mathematical model/ appropriate model depends on the desired or required predictive ability to obtain a good fit to the geometry as well as characteristics of the matrix and the drug released[5]. The study of drug release mechanism was pre-requisite step for improvement of the safety of the formulation and for effective trouble shouting during production. The objective of the present study was to develop gastroretentive floating tablets of NCRD (hereafter, NCRD) as model drug prepared by melt granulation method and evaluate the drug release mechanism using Korsmeyer-Peppas model and Peppas-Sahlin model. As the drug is freely soluble in water[6], combination of hydrophilic, swellable and retarding polymer like almond gum (hereafter, AG) and hydrophobic retarding

polymer/wax/lipid like cetosteryl alcohol (hereafter, CSA) are used to prepare NCRD floating tablets.

MATERIALS AND METHODS

NCRD was obtained as a gift sample from Torrent Pharmaceuticals (P) Ltd., Gujarat, India; CSA obtained from Loba Chemical, Mumbai, India; Sodium bicarbonate, Citric acid and Lactose were purchased from SD fine chemicals, Mumbai, India. All other chemicals and reagents used were analytical grade.

Preparation of effervescent floating tablets by melt granulation technique

NCRD effervescent floating tablets were prepared by direct compression technique using combination of AG and lipid/ wax polymer (Table 1). All the ingredients except wax were passed through sieve 60(#). As per each formulation of batch code, required quantity of wax was weighed and melted separately in a large china dish on hot plate and drug was added to it with stirring. To this mixture, other sieved ingredients except talc were added and stirred well to mix. Then mass was removed from the hot plate and subjected to scrapping until it attained room temperature. The coherent mass was passed through 22 mesh (#), and the resulting granules were resifted over 44 mesh(#) to separate granules and fines. The granules were lubricated by adding talc and compressed into a tablet using 10 mm flat-face punch on tabletting machine.

In vitro release studies[7]

In vitro drug release studies of all prepared floating matrix tablets were conducted for a period of 24 hrs using an eight station USP XXII type 2 (paddle type) apparatus. The dissolution medium consisted of 0.1N HCl (900 ml), equilibrate the dissolution medium to 37 ± 0.5°C, and rotating the paddle at 50 rpm. At specified time interval, samples of 5 ml of sample was withdrawn and filtered. The absorbance of sample preparations was measured using UV spectrophotometer at 262 nm using 0.1N HCl as blank.

MATHEMATICAL ANALYSIS OF DRUG TRANSPORT MECHANISM:

Calculation of drug release mechanism by Korsmeyer-Peppas equation:[8,9]

The dissolution data was fitted to semi-empirical equation Korsmeyer-Peppas model to the first 60% of drug release ($Mt/M\infty \leq 0.6$; $\log(Mt/M\infty) \leq -0.22$).

$$\frac{M_t}{M_\infty} = k_{KP} t^n - - - - Eq.(1)$$

Where, $\mathbf{M_t}$ = absolute cumulative amount of drug released at time **t**, $\mathbf{M_\infty}$ = absolute cumulative amount of drug release after infinite time, $\mathbf{M_t}$ /$\mathbf{M_\infty}$ = fraction of drug released at time **t**, $\mathbf{k_{KP}}$ = release rate constant at the elapsed time **t** ($time^{-n}$), and **n** = time exponent or diffusional exponent characteristic of the release mechanism of the system. According to Korsmeyer-Peppas equation, mechanism of drug release from various swellable controlled release systems, a value of diffusional exponent (**n**) may be distinguished in several classes based on solvent diffusion rate (R_{diff}) and polymer chain relaxation rate (R_{relax}). For a planar geometry, the value of **n** = 0.45 indicated Case-I diffusion (Fickian diffusion controlled drug release) in which the rate of solvent penetration was much smaller than the rate of polymer chain relaxation and the system controlled by diffusion ($R_{diff} << R_{relax}$). If the value of n lies in a range of 0.45 to 0.89 (i.e. 0.45 < **n** < 0.89) indicates anomalous (non- Fickian) diffusion mechanism where the diffusion and relaxation rates were comparable to each other ($R_{diff} \approx R_{relax}$). Otherwise, the value of **n** = 0.89 indicated Case-II transport/ zero order (swelling controlled drug release) which describes the diffusion process was much faster than the relaxation process and the system controlled by relaxation ($R_{diff} >> R_{relax}$,). Occasionally, the values of **n** > 0.89 have been observed, describes super Case-II transport of drug release mechanism and indicated that the drug release by both diffusion (R_{diff}) and relaxation of polymer chain (R_{relax}). Sometimes, the solvent diffusion rate was much below the polymer chain relaxation rate, where the **n** value can be observed below 0.5. This situation was also classified as Fickian diffusion, specially called as 'Less Fickian' behaviour.

Calculation of drug release contribution by Peppas-Sahlin equation[10]

Calculation of the approximate contribution and coupled effect of the Fickian diffusion and polymer relaxation mechanism to an anomalous release process based on logic concepts was carried out by fitting the data to the heuristic approach proposed by Peppas and Sahlin (1989) for quantify and materialize the amount of drug released by the two phenomena controlling the drug release from swellable matrix.

$$\frac{M_t}{M_\infty} = k_1 t^m + k_2 t^{2m} - - - - Eq.(2)$$

Where, $\mathbf{k_1}$ = kinetic constant for Fickian contribution of drug release, $\mathbf{k_2}$ = kinetic constant for Case-II contribution and **m** = diffusional exponent. The first term of right hand-side was Fickian contribution and the second term being the Case-II relaxational

contribution i.e. this equation accounts for the coupled effects of Fickian diffusion and Case- II transport.

The percentage of drug release due to Fickian mechanism (**F**) was calculated by,

$$F = \frac{k_1}{k_1 + k_2 t^m} - - - - Eq.(3)$$

Ratio of relaxational over Fickian contribution calculated by,

$$\frac{R}{F} = \frac{k_2}{k_1} t^m - - - - Eq.(4)$$

Calculation of kinetic constants using substitution method:

In order to determine the kinetic constants in Peppas-Sahlin model (k_1 and k_2), at first diffusional exponent (m) value has to be fixed. According to the literature[10] with comparison of Korsmeyer-Peppas and Peppas-Sahlin equations, it was concluded that m = n when the relaxational mechanism was negligible. Based on this assumption m value was fixed which was equivalent to n value from Korsmeyer-Peppas equation. After that the kinetic constants (k_1 and k_2) has to be determined. There were several methods available to calculate the constants from a system of linear or nonlinear equations namely graphical method, elimination method, substitution method and matrix method. Systems of two equations in two variables could be solved graphically since their solutions were the points at which the graphs of the equations intersect. However, the graphical method tends to give inaccurate results. Therefore, graphing was not an acceptable solution method. Another method was elimination method which involved to remove the variables until only a single last variable was left, i.e. until there was one equation with one unknown. This equation was then solved for this unknown there by the other unknown can also be deduced. But this method was practically difficult. Instead, it was possible to calculate the kinetic constants using substitution method and matrix method. In this work substitution method was used in order to describe the predominant drug release mechanism.

The kinetic constants of the systems of two equations in two variables can be calculate using substitution method or addition method. The substitution method works extremely well for finding solutions of systems containing at least one non-linear equation. The addition method was often used for linear systems, but cannot always be used for systems containing non-linear equations. In order to calculate the constants from Peppas-Sahlin equation, it was essential to use the fraction of drug release say f_1 and f_2 at two measured time points say t_1 and t_2. The fraction of drug released (f_1) at t_1 can be written as the following:

$$f_1 = k_1 t_1^m + k_2 t_1^{2m} - - - - Eq.(5)$$

And the fraction of drug released ($\mathbf{f_2}$) at $\mathbf{t_2}$ can be written as the following:

$$f_2 = k_1 t_2^m + k_2 t_2^{2m} - - - - Eq.(6)$$

Rearrangement of Eq.(5) to calculate $\mathbf{k_1}$ as follows,

$$k_1 = \frac{f_1 - k_2 t_1^{2m}}{t_1^m} - - - - Eq.(7)$$

Substitution of k_1 value in Eq.(5) or Eq.(6) to get the value of k_2 as follows,

$$k_2 = \frac{f_2 t_1^m - f_1 t_2^m}{t_1^m t_2^{2m} - t_1^{2m} t_2^m} - - - - Eq.(8)$$

Substitution of f_1 and f_2 values in Eq.(7) and Eq.(8) at different time intervals one can get the values of k_1 and k_2, thereby it was possible to calculate the Fickian and relaxational contribution.

RESULTS AND DISCUSSION

Drug release profile of all the batches were extended up to 24 hrs by the use of combination of hydrophilic and hydrophobic polymers but showed a variation in drug release along with AG and CSA concentration (Fig. 1A and 1B). Based on the drug release profile it can be observed that, as the concentration of hydrophobic wax polymer was increased, greater retardation of both rate and extent of drug release was observed. The fact can be reasoned in the way that, an increase in the hydrophobic polymer content results in decrease the drug release rate due to decrease in the total porosity (initial porosity plus porosity due to the dissolution of the drug) of the matrices. Also increases the tortuosity of the matrix along with drug diffusion path-length which in turn slows down diffusion and erosion from/of the matrix. These behaviour can be explained in terms of release mechanism suggested that, because of the high hydrophobicity of lipid materials, penetration of dissolution fluid was hindered through the matrix and can progress in the dosage form by dissolving the grains of drug in contact with polymer and leading to diminished drug release over an extended period. Further, the dissolution of the drug particles on the surface of the matrix allows the formation of channels, from which the drug was slowly released followed by formation of a denser gel and slower erosion.

For Korsmeyer-Peppas model of all the formulations, square of correlation coefficient (R^2), adjusted R^2, k and n- values calculated by Microsoft Excel-2007 showed ranged from 0.9720 to 0.9975, 0.9680 to 0.9971, 3.2774 to 5.1041 and 0.8720 to 0.9989,

respectively. The highest values of R^2 and adjusted R^2 were indicates that the drug release data was good linearity with Korsmeyer-Peppas equation. The drug release mechanism from tablet matrices containing swellable polymers was complex and not completely understood. Some polymeric systems may be classified as either purely diffusion or erosion controlled, while most of the systems exhibits a combination of these systems. All the formulations showed good linearity with slope (n) values greater than 0.89, except for MCS4 (n=0.87). This indicated that, all the formulations followed super Case-II transport of drug release mechanism, in which the formulation MCS4 exploited by non-Fickian or anomalous release mechanism. The formulations which showed the n value >0.89 indicated that the drug release by both diffusion (R_{diff}) and relaxation of polymer chain (R_{relax}) and revealed the fact that, possibly owing to chain distanglement and swelling of hydrophilic polymer. Whereas the formulation MCS4 showed the n value of 0.87, indicated Case-II transport/ zero order (swelling controlled drug release) which describes the solvent diffusion process was much faster than the polymer chain relaxation process and the system controlled (rate controlling step) by relaxation (R_{diff} » R_{relax}).

According to the literature[11], Case-II transport (zero order) of swellable cylinder was defined by n = 0.89±0.02 (i.e. ranged from 0.87 to 0.91). From the above statement, the drug release mechanism for the formulation MCS4 (n = 0.87) also critically appears to indicate a coupling of diffusion and erosion mechanisms -so called Case-II transport which lie either in or very close to the theoretical value. Analogously, Case-II (relaxational) transport mechanism was associated with initial linear time dependence of the fractional release from all geometries and followed zero order release from dosage form in which the release was independent of time regardless of the geometry and the drug transport mechanism associated with stress and state-transition in hydrophilic glassy polymers which swell in water or biological fluids. This transport mechanism indicating combined effect of chain disentanglement, erosion and swelling of hydrophilic polymer for drug release. Case-II transport/ zero order (swelling controlled drug release) also describes the diffusion process was much faster than the relaxation process and the system controlled by relaxation (R_{diff} » R_{relax}). From the aforementioned possible phenomena it was obvious that the drug release patterns of both anomalous diffusion and Case-II transport were associated for drug release from the formulation MCS4. These two release mechanisms were demonstrated to be valid due to the good agreement between experimental data and the equation. The value of 'n' from MCS4 were the characteristic of anomalous kinetics (non-Fickian) and Case-II transport, suggesting that more than one mechanism may be involved in release kinetics, referring to combination of polymer relaxation, swelling, diffusion or erosion based drug release mechanism[12]. In case of formulation MCS4, immediate synchronization of the movement of swelling and erosion (constant gel layer thickness) was observed. It was very interesting to observed that the release profiles was not only linear, but also that the linear part of the curve showed the identical slope at different time intervals.

In order to determine the predominant mechanism among drug diffusion and polymer relaxation, the drug release profile of all the formulation were fitted to Peppas-Sahlin equation using the concept[10] of m = n, where n was obtained from Korsmeyer-Peppas equations. Here substitution method was used to calculated k_1 and k_2. Accordingly, Peppas-Sahlin model constants (k_1 and k_2) were calculated followed by respective contribution of release mechanisms (diffusion/ relaxation model) was also calculated by incorporating in respective equation. An Excel (Microsoft Corporation, Redmond, WA,USA) worksheet was used to calculate all the data in which the nonlinear data were first transformed to create a linear relationship and then were analysed with linear regression. The higher value of k_1 than k_2, indicates that Fickian diffusion was predominant mechanism of drug release from the matrices than polymer relaxation and swelling in such matrix. Otherwise, when the values of k_2 was found to be higher than k_1 indicates some level of polymer relaxation and swelling in such matrix and supports its tendency to release drug by Non-Fickian kinetics. The extreme negative values of k_1 indicates that there was an insignificant effect of Fickian diffusion mechanism in the drug release process but it was only a pure polymer chain relaxation predominant mechanism. In general, for water soluble drugs diffusional mechanism was predominant than polymer relaxation.

Substitution method of a system for linear or nonlinear equations involves expressing one variable in terms of another until there was a single equation in one unknown and this equation was used to solve second unknown. According to the equations (1) and (2), it was possible to calculate the k_1 and k_2 at all time intervals and further used to calculate the release mechanism contributions and related parameters. Several parameters (Table 2a, 2b and 2c) were calculated using substitution method by Microsoft

Office Excel like fraction of drug release with time in hr (f), kinetic constant for Fickian contribution of drug release (k_1), kinetic constant for Case-II contribution (k_2), Fickian contribution (F), Case-II relaxational contribution (R), ratio of relaxational over Fickian contribution (R/F) and percentage fraction of drug release due to Fickian mechanism (%f(F)). From the Table 2A, 2B and 2C, it was observed that, diffusional kinetic constant (k_1) was far greater than relaxational kinetic constant (k_2) with all the formulations except for formulation MCS5 only at 5^{th} hour. The average values of kinetic constants (k_1, k_2) were found to be (0.0334, -0.0011), (0.0383, -0.0009), (0.0436, -0.0017), (0.0539, -0.0006), (0.0479, -0.000033) and (0.0376, -0.0007) for MCS1, MCS2, MCS3, MCS4, MCS5 and MCS6, respectively. Whereas the average values of (k_1, k_2) were found to be (0.0453, -0.0003), (0.0407, 0.0004), (0.0317, -0.001), (0.0496, 0.0003), (0.0465, 0.0005) and (0.0332, -0.0009) for MCS7, MCS8, MCS9, MCS10, MCS11 and MCS12, respectively. The average values of release contribution (Fickian release contribution, Case-II relaxational contribution) were found to be (0.19, 0.053), (0.2098, 0.0532), (0.2199, 0.008), (0.2787, 0.016), (0.3067, -0.0105) and (0.2228, 0.0264) for MCS1, MCS2, MCS3, MCS4, MCS5 and MCS6, respectively. Whereas the average values of release contribution (Fickian release contribution, Case-II relaxational contribution) were found to be (0.2728, 0.0118), (0.2493, 0.0223), (0.1952, 0.0388), (0.2798, -0.0065), (0.2927, 0.0071) and (0.2086, 0.0397) for MCS7, MCS8, MCS9, MCS10, MCS11 and MCS12, respectively.

From these values, for all the formulations it can be noticed that Peppas-Sahlin model showed higher values for the diffusional constant with respect to the relaxation constant, meaning that the principal mechanism for the drug release was Fickian diffusion than relaxation or erosion of the polymer chains. The dominant release mechanism was further confirmed by calculating their respective release mechanism contributions. Fickian release contribution was preponderance than corresponding Case-II relaxational contribution in all the formulations since the value of diffusional contribution was much higher than the relaxational contribution. In addition to this, the relaxational contribution was observed with negative sign in all the formulations only at specific time intervals. The situation where the negative values were observed at particular time interval indicates the Fickian release mechanism was more pronounced than relaxation i.e. almost the relaxational mechanism was absent. The above statement was further confirmed by calculating the ratios of relaxation to diffusional contributions (R/F) value, in which R/F >1 indicates that relaxational contribution was predominant than diffusional contribution.

Regarding drug release mechanism, the results obtained by Korsmeyer-Peppas model was in agreement with that obtained from the application of Peppas-Sahlin equation at fixed m value at 0.87. The release mechanism for all the formulations except for MCS4 obtained from Korsmeyer-Peppas model reveals to follow super Case-II transport mechanism in which the drug release was facilitated by both diffusion (R_{diff}) and relaxation of polymer chain (R_{relax}). And the drug release mechanism from Peppas-Sahlin model revealed that the drug release mechanism was facilitated by contribution of both Fickian diffusion and polymer chain relaxation.

CONCLUSION

Controlled drug release for 24 h attained in present study indicates that the floating matrix tablets of NCRD, prepared by combination of AG and CSA as retarding polymers. The drug release profile was well fitted to well known Korsmeyer-Pappas equation and the results revealed to follow super Case-II transportation except MCS4 which showed to follow non-Fickian drug release mechanism. In order to determine the exact release mechanism with respect to time, the release data was further fitted to the heuristic model proposed by Peppas-Sahlin equation. From the study it was revealed that, Fickian release was more prevalence than relaxation mechanism. At particular time interval the relaxational contribution mechanism was presented with negative value, which indicates that the relaxation was insignificant.

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Table 1: Composition of NCRD floating tablets using different amounts of CA and CSA

Ingre-dients	Quantity per tablet (mg)											
	MCS 1	**MCS 2**	**MCS 3**	**MCS 4**	**MCS 5**	**MCS 6**	**MCS 7**	**MCS 8**	**MCS 9**	**MCS 10**	**MCS 11**	**MCS 12**
NCRD	21	21	21	21	21	21	21	21	21	21	21	21
AG	100	90	80	70	60	50	70	70	70	80	90	100
CSA	50	60	70	80	90	100	90	100	110	80	80	80
$NaHCO_3$	30	30	30	30	30	30	30	30	30	30	30	30
CA	10	10	10	10	10	10	10	10	10	10	10	10
SA	5	5	5	5	5	5	5	5	5	5	5	5
Lactose	78	78	78	78	78	78	68	58	48	68	58	48
Talc	6	6	6	6	6	6	6	6	6	6	6	6

(NCRD is NCRD, AG is almond gum, CSA is cetosteryl alcohol, $NaHCO_3$ is sodium bicarbonate, CA is citric acid, SA is stearic acid)

Table 2a: Drug release by diffusion, relaxational contribution with time and related parameters from Peppas-Sahlin equation

	Time (hr)	**f**	**k_1 ($hr^{-0.87}$)**	**k_2 ($hr^{-1.74}$)**	**F**	**R**	**R/F**	**% f (F)**
MCS1	0	0	-	-	-	-	-	-
	1	0.0479	0	0	-	-	-	-
	2	0.0685	0.0612	-0.0133	0.1186	-0.0501	-0.4221	173.0494
	3	0.0909	0.0428	-0.0038	0.1222	-0.0313	-0.2563	134.4647
	4	0.1187	0.0326	-0.0003	0.1223	-0.0036	-0.0298	103.0686
	5	0.1546	0.0246	0.0019	0.1142	0.0404	0.3540	73.8561
	6	0.2044	0.0139	0.0042	0.0768	0.1275	1.6603	37.5904
	9	0.3055	0.0358	0.0002	0.2911	0.0144	0.0494	95.2896
	12	0.4326	0.0285	0.0011	0.3055	0.1271	0.4162	70.6137
	15	0.5746	0.0279	0.0012	0.3692	0.2054	0.5563	64.2567
	Average		0.0334	-0.0011	0.1900	0.0537	0.2910	94.0236
MCS2	0	0	-	-	-	-	-	-
	1	0.0512	0	0	-	-	-	-
	2	0.0787	0.0621	-0.0110	0.1187	-0.0401	-0.3374	150.9319
	3	0.1021	0.0511	-0.0052	0.1425	-0.0404	-0.2833	139.5356
	4	0.1379	0.0328	0.0013	0.1199	0.0179	0.1494	87.0025
	5	0.1769	0.0310	0.0019	0.1393	0.0376	0.2698	78.7523
	6	0.2215	0.0275	0.0026	0.1467	0.0748	0.5097	66.2400
	9	0.3266	0.0406	0.0002	0.3166	0.0099	0.0314	96.9538
	12	0.4537	0.0335	0.0011	0.3417	0.1120	0.3277	75.3171
	15	0.6066	0.0281	0.0016	0.3530	0.2535	0.7182	58.1996
	Average		0.0383	-0.0009	0.2098	0.0532	0.1732	94.1248
MCS3	0	0	-	-	-	-	-	-
	1	0.0536	0	0	-	-	-	-
	2	0.0827	0.0656	-0.0118	0.1275	-0.0447	-0.3509	154.0616
	3	0.1114	0.0507	-0.0041	0.1455	-0.0340	-0.2340	130.5557
	4	0.1547	0.0318	0.0024	0.1203	0.0344	0.2856	77.7867
	5	0.1954	0.0372	0.0010	0.1741	0.0213	0.1224	89.0980
	6	0.2316	0.0429	-0.0002	0.2393	-0.0078	-0.0324	103.3537

	9	0.3474	0.0399	0.0003	0.3282	0.0192	0.0586	94.4653
	12	0.4727	0.0373	0.0006	0.4045	0.0682	0.1687	85.5685
	Average		0.0436	-0.0017	0.2199	0.0081	0.0025	104.9835
MCS4	0	0	-	-	-	-	-	-
	1	0.0581	0	0	-	-	-	-
	2	0.0972	0.0641	-0.0060	0.1172	-0.0200	-0.1705	120.5502
	3	0.1399	0.0517	0.0008	0.1344	0.0055	0.0407	96.0936
	4	0.1782	0.0554	-0.0006	0.1849	-0.0067	-0.0364	103.7733
	5	0.2161	0.0537	-0.0001	0.2177	-0.0015	-0.0071	100.7166
	6	0.2502	0.0570	-0.0009	0.2711	-0.0209	-0.0769	108.3360
	9	0.3602	0.0512	0.0003	0.3463	0.0139	0.0401	96.1464
	12	0.4962	0.0396	0.0020	0.3444	0.1518	0.4408	69.4082
	15	0.6002	0.0582	-0.0001	0.6135	-0.0134	-0.0218	102.2266
	Average		0.0539	-0.0006	0.2787	0.0136	0.0261	99.6619

Table 2b: Drug release by diffusion, relaxational contribution with time and related parameters from Peppas-Sahlin equation

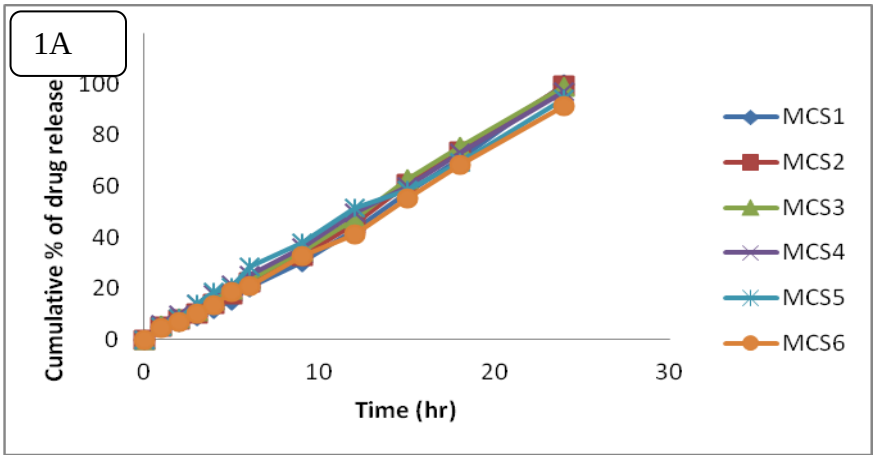
	Time (hr)	**f**	**k_1 ($hr^{-0.87}$)**	**k_2 ($hr^{-1.74}$)**	**F**	**R**	**R/F**	**% f (F)**
	0	0	-	-	-	-	-	-
	1	0.0522	0	0	-	-	-	-
	2	0.0818	0.0624	-0.0102	0.1190	-0.0372	-0.3125	145.4609
	3	0.1379	0.0284	0.0076	0.0792	0.0587	0.7411	57.4343
MCS5	4	0.1839	0.0464	0.0011	0.1690	0.0148	0.0878	91.9325
	5	0.2038	0.0722	-0.0060	0.3240	-0.1202	-0.3710	158.9729
	6	0.2863	0.0001	0.0101	0.0004	0.2859	747.5705	0.1336
	9	0.3773	0.0652	-0.0021	0.5059	-0.1286	-0.2542	134.0796
	12	0.5128	0.0424	0.0008	0.4307	0.0820	0.1905	83.9983
	15	0.5864	0.0661	-0.0015	0.8257	-0.2393	-0.2898	140.7997
	Average		0.0479	-0.000033	0.3067	-0.0105	93.4203	101.6039
	0	0	-	-	-	-	-	-
	1	0.0453	0	0	-	-	-	-
	2	0.0694	0.0553	-0.0100	0.1067	-0.0374	-0.3500	153.8505
	3	0.1028	0.0353	0.0003	0.1002	0.0026	0.0258	97.4873
	4	0.1363	0.0351	0.0004	0.1309	0.0053	0.0408	96.0830
MCS6	5	0.1853	0.0210	0.0042	0.0968	0.0885	0.9140	52.2479
	6	0.2086	0.0516	-0.0025	0.2825	-0.0739	-0.2617	135.4393
	9	0.3252	0.0331	0.0009	0.2664	0.0588	0.2208	81.9143
	12	0.4128	0.0448	-0.0005	0.4738	-0.0611	-0.1289	114.7926
	15	0.5537	0.0249	0.0013	0.3252	0.2285	0.7027	58.7301
	Average		0.0376	-0.0007	0.2228	0.0264	0.1454	98.8240
	0	0	-	-	-	-	-	-
	1	0.0543	0	0	-	-	-	-
	2	0.0865	0.0640	-0.0096	0.1208	-0.0343	-0.2842	139.7054
	3	0.1157	0.0536	-0.0042	0.1470	-0.0313	-0.2129	127.0479
	4	0.1566	0.0367	0.0020	0.1311	0.0255	0.1944	83.7220

MCS7	5	0.2087	0.0273	0.0046	0.1197	0.0890	0.7434	57.3597
	6	0.2744	0.0183	0.0067	0.0950	0.1793	1.8874	34.6330
	9	0.3653	0.0627	-0.0019	0.4707	-0.1055	-0.2240	128.8703
	12	0.4866	0.0449	0.0005	0.4395	0.0470	0.1070	90.3355
	15	0.5833	0.0548	-0.0005	0.6584	-0.0751	-0.1141	112.8764
	Average		0.0453	-0.0003	0.2728	0.0118	0.2621	96.8232
MCS8	0	0	-	-	-	-	-	-
	1	0.0486	0	0	-	-	-	-
	2	0.0797	0.0573	-0.0075	0.1094	-0.0273	-0.2495	133.2438
	3	0.1237	0.0350	0.0030	0.0975	0.0230	0.2361	80.8987
	4	0.1427	0.0652	-0.0060	0.2377	-0.0805	-0.3385	151.1765
	5	0.2286	-0.0239	0.0137	-0.1075	0.2771	-2.5785	-63.3514
	6	0.2852	0.0329	0.0031	0.1753	0.0887	0.5060	66.4001
	9	0.3525	0.0789	-0.0033	0.6131	-0.2002	-0.3266	148.4997
	12	0.4331	0.0580	-0.0011	0.5902	-0.1166	-0.1976	124.6189
	15	0.5747	0.0223	0.0014	0.2789	0.2138	0.7666	56.6072
	Average		0.0407	0.0004	0.2493	0.0223	-0.2727	87.2624

Table 2c: Drug release by diffusion, relaxational contribution with time and related parameters from Peppas-Sahlin equation

	Time (hr)	**f**	**k_1 ($hr^{-0.87}$)**	**k_2 ($hr^{-1.74}$)**	**FC**	**RC**	**R/F**	**% f (F)**
MCS9	0	0	-	-	-	-	-	-
	1	0.0399	0	0	-	-	-	-
	2	0.0612	0.0491	-0.0093	0.0980	-0.0368	-0.3759	160.2366
	3	0.0898	0.0319	-0.0006	0.0953	-0.0055	-0.0581	106.1725
	4	0.1265	0.0248	0.0018	0.0985	0.0280	0.2842	77.8724
	5	0.1426	0.0443	-0.0031	0.2201	-0.0775	-0.3522	154.3692
	6	0.1690	0.0304	-0.0003	0.1811	-0.0122	-0.0672	107.2036
	9	0.3346	0.0100	0.0031	0.0892	0.2454	2.7510	26.6598
	12	0.3854	0.0528	-0.0017	0.6274	-0.2421	-0.3858	162.8137
	15	0.5633	0.0103	0.0019	0.1523	0.4110	2.6992	27.0332
	Average		0.0317	-0.0010	0.1952	0.0388	0.5619	102.8015
MCS10	0	0	-	-	-	-	-	-
	1	0.0565	0	0	-	-	-	-
	2	0.0922	0.0657	-0.0091	0.1256	-0.0335	-0.2664	136.3140
	3	0.1237	0.0567	-0.0045	0.1585	-0.0348	-0.2195	128.1158
	4	0.1748	0.0328	0.0041	0.1199	0.0549	0.4578	68.5952
	5	0.2717	-0.0060	0.0147	-0.0268	0.2985	-11.1230	-9.8785
	6	0.3325	0.0499	0.0023	0.2667	0.0658	0.2465	80.2229
	9	0.4153	0.0818	-0.0037	0.6388	-0.2236	-0.3500	153.8390
	12	0.5027	0.0661	-0.0017	0.6756	-0.1729	-0.2559	134.3909
	Average		0.0496	0.0003	0.2798	-0.0065	-1.6443	98.8021
	0	0	-	-	-	-	-	-
	1	0.0512	0	0	-	-	-	-
	2	0.0843	0.0590	-0.0078	0.1128	-0.0285	-0.2527	133.8124
	3	0.1353	0.0346	0.0049	0.0967	0.0385	0.3983	71.5137

MCS11	4	0.1658	0.0584	-0.0036	0.2136	-0.0478	-0.2240	128.8640
	5	0.2535	-0.0018	0.0129	-0.0081	0.2616	-32.2683	-3.1981
	6	0.3056	0.0513	0.0011	0.2741	0.0315	0.1149	89.6981
	9	0.3762	0.0767	-0.0037	0.5989	-0.2226	-0.3717	159.1696
	12	0.4742	0.0540	-0.0007	0.5515	-0.0773	-0.1402	116.3084
	15	0.6033	0.0399	0.0006	0.5021	0.1011	0.2014	83.2393
	Average		0.0465	0.0005	0.2927	0.0071	-4.0678	98.0143
MCS12	0	0	-	-	-	-	-	-
	1	0.0416	0	0	-	-	-	-
	2	0.0647	0.0508	-0.0092	0.1015	-0.0368	-0.3626	156.8932
	3	0.0963	0.0329	-0.0003	0.0986	-0.0023	-0.0231	102.3599
	4	0.1338	0.0281	0.0014	0.1121	0.0217	0.1936	83.7834
	5	0.1574	0.0413	-0.0020	0.2061	-0.0487	-0.2364	130.9575
	6	0.1877	0.0325	-0.0002	0.1948	-0.0072	-0.0368	103.8218
	9	0.3266	0.0213	0.0017	0.1908	0.1358	0.7115	58.4274
	12	0.4283	0.0381	-0.0002	0.4565	-0.0282	-0.0619	106.5933
	15	0.5917	0.0206	0.0013	0.3087	0.2830	0.9168	52.1704
	Average		0.0332	-0.0009	0.2086	0.0397	0.1376	99.3859



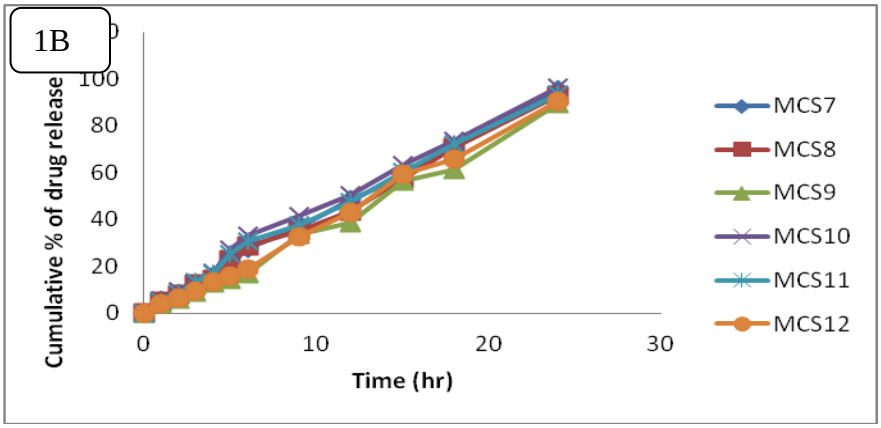


Figure 1A and 1B: *In vitro* release profiles of NCRD floating tablets

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