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Modulating the Release Behavior and Kinetic Evaluation of Diclofenac Sodium from Natural Polymers

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Abstract: The objective of the present study was to modulate the release rate by varying concentration of rate controlling materials and by restricting the surface area available for drug release. Matrix core was prepared by wet granulation method using cationic Karaya gum (K.G), anionic Xanthan gum (X.G) and in combination of KG: XG in 1:1 ratio. Anionic Sodium carboxy methyl cellulose (SCMC) was compressed on both the surfaces of matrix core as release retardant layers. The tablets were evaluated for weight variation, hardness, thickness, friability, drug content uniformity and *in vitro* drug release studies. All the physical parameters were within the limits as per IP for the formulations. *In-vitro* dissolution study revealed that the drug release from matrix tablet F1, F2 and F3 was more than 90%,where as drug release from three layer matrix tablets decreased depends on the quantity of SCMC used in retardant layers. Different dissolution models were applied to drug release data in order to evaluate release mechanisms and kinetics. Mathematical analysis of the release kinetics indicated that the nature of drug release from the matrix tablets and three layer matrix tablets followed non-Fickian diffusion and super case II mechanism respectively. Mean dissolution time (MDT) for the formulation F3 and F3L3 were found to be 4.64h and 9.70h, while Dissolution Efficiency (DE_8%) decreases, indicating that the release of drug is slower in the three layer matrix tablets. FT-IR study showed that there is no drug–excipeints interaction. No change either in physical appearance, drug content or in dissolution pattern after storage at 40 ±2°C/RH 75 ±5% for 6 months.

Key Words: Three- layer matrix tablets, Diclofenac sodium, Karaya gum, Xanthan gum

Introduction

Oral ingestion has long been the most convenient and commonly employed route of drug delivery due to its ease of administration and flexibility in the design of the dosage form. There are many ways to design modified release dosage forms for oral administration, and one of them is a three-layer matrix tablet. It consists of a hydrophilic matrix core, containing the active ingredient, and one or two impermeable or semi-permeable polymeric coatings applied on one or both sides of the core[1]. Modulating layers incorporated during tabletting process, these partial coatings provide a modulation of the drug dissolution profile: they reduce the release rate from the device and shift the typical time-dependent release rate towards constant drug release[2]. Three layer matrix tablet concept is based on the idea that the restriction of the matrix area exposed to the dissolution medium may lead to double control in the system release performance:1) Matrix hydration rate and consequent swelling and diffusion rate are lowered 2)The surface through which the drug can be delivered (by diffusion or erosion) is reduced. These effects, possibly more effective in the initial phase of the dissolution process and less pronounced as swelling proceeds, leads to a linearization of release profile.[3]

The use of naturally occurring biocompatible polymeric materials has been the focus of recent

research activity in the design of dosage forms for oral controlled release administration, and hydrophilic polymer matrix systems are widely used because of their flexibility to provide a desirable drug release profile, cost effectiveness, and broad regulatory acceptance[4]. When solutions of polysaccharides (hydrophilic gums) are mixed, they interact with each other; this can result in an increase in viscosity, which becomes greater than the viscosity of each solution individually[5]. Under certain conditions, they may even form a gel. Such a phenomena is often called as rheology synergism. A classical example of this phenomenon is one that, observed between the Karaya gum and the Xanthan gum. Such macromolecular reactions are highly selective and strongly dependent upon molecular size and conformation. Such synergistic interactions that often lead to gelling of even those gums which otherwise are non-gelling, can be put to varied uses, more specifically in the design of controlled drug delivery systems while employing a significantly low gum concentration (in combination) as compared to when the gums are used alone. The hydrophilic polymer Xanthan gum is a high molecular weight hetero polysaccharide gum. Xanthan gum proved to have higher drug-retarding ability than the well known hydroxypropylmethyl cellulose., which not only retards the drug release but also provide the time dependent release kinetics with advantages of biocompatibility and inertnes.[6] Gum Karaya is a complex acetylated polysaccharide consisting mainly of D-galacturonic acid, D-galactose and L-rhamnose., It has been investigated as sustained release carrier and regarded as non –toxic and non –irritant.[7] The objective of this study was to evaluate the influence of coating barrier, on the matrix core of hydrophilic polymers, and cellulose derivative as layers to develop a constant rate delivery formulation of a model non steroidal anti –inflammatory drug, Diclofenac sodium.

Materials

Diclofenac Sodium was obtained as a gift sample from (Amoli Organic Ltd., Mumbai, India. Karaya gum (KG), Xanthan Gum (XG) and Sodium Carboxy Methyl Cellulose (SCMC) (high viscosity grade), were gift samples from Girijan Cooperative Society, Hyderabad, India. Raj Enterprises Mumbai, India and Reliance Cellulose Product, Hyderabad. India, respectively. Di calcium phosphate was procured from M/s Loba Cheme Pvt. Ltd. Mumbai, India. All other chemicals and reagents used were of analytical grade.

Preparation of Matrix tablets:

Mathematical Consideration: The calculation for the sustained release dosage form are based on pharmacokinetics parameters (ADME) Absorption, distribution, metabolism and excretion. [(8)] The Pharmacokinetics studies showed that a dose of 25mg of Diclofenac sodium produces an effective blood level of 0.7-1.5 g/ml with in 1.5-2.5h with the half life of 1.1-4.0 h and the elimination rate constant k= 0.693/4h=0.1732h^{1}. The bioavailability rate R= K×D =0.1732h^{-1} ×25mg=4.3mg/h, where D is the usual dose of the drug. The maintenance dose Dm= R ×h = 4.3mg/h×20 h=86mg.Where h is the number of hours for which sustained action is intended. Thus total dose = D + Dm = 2 5 mg + 86 m g = 111mg.$D_{corrected}$ = D-Rt_p=25mg (4.3mg/h×2h)=16.4mg, where t_p is the time period to achieve a peak plasma level. Therefore total dose $_{corrected}$ =$D_{corrected}$ +Dm= 16.4mg+86mg=102.4mg.

Methods

Preparation of Diclofenac sodium matrix core granules: Three matrix formulations were prepared with 30% of Karaya gum, Xanthan gum and a mixture of KG: XG in 1:1 ratio and were coded as F1, F2 and F3 respectively. For the formation of the granules lactose was used as diluent, 10% starch paste was used as binding agent, the wet mass was screened through sieve No 14 and the granules were dried at 50°C for 1hr in a tray dryer. The dried granules were passed through sieve No 18 and lubricated with a mixture of talc and magnesium stearate. The composition of formulation used in the study containing 100mg of Diclofenac sodium in each case is shown in table I.

Preparation of SCMC as release retardant layer granules: The wet granulation technique was used, SCMC and 10% starch paste were mixed well and the resulting mass was passed through sieve No 14, and dried at 35° C for an hour. The dried granules were passed through sieve no 18 and lubricated with talc and magnesium stearate.

Preparation of three layer matrix tablets: The formulation of three layer matrix tablets were made using different combination of drug loaded matrix core granule and release layer granules as shown in table 1. Initially the volume of die cavity was adjusted equivalent to total weight of three layer matrix tablets (350mg, 400mg and 450 mg). Then pre weighed amount of polymer granules of SCMC equivalent to bottom layer (25mg, 50mg, and 75mg) were taken and placed in the die cavity and uniformally spreaded. The upper punch was lifted up and 300mg of matrix core granules were placed over the bottom layer of polymer granules in the die cavity and slightly compressed. The remaining volume of die cavity was filled with pre weighed amount of polymer granules equivalent to top layers (25mg, 50mg and 75mg) are coded as L1, L2 and L3 respectively. Finally compressed on a rotary compression machine (Riddhi,

Ahmedabad, India). The hardness of matrix tablet and three layer matrix tablets was adjusted to 5-6kg/cm^2.

The Evaluation of Matrix Tablets

The tablets hardness was determined using a hardness tester (Pfizer hardness tester). The tablet thickness was measured using a (Vernier caliper). The friability was determined as the percent weight loss from 20 tablets. Twenty tablets were weighed and rotated for 100 revolutions in 4 min in a friabilator (Roche friabilator. Pharama lab, Ahmedabad India).

***In Vitro* Drug Release Study**

Drug release was studied using a dissolution apparatus type 2 (Lab India, DISSO 2000, Mumbai, India) with a shaft at a speed of 50 rpm. To study the effect of dissolution medium, drug release was studied in 900-mL HCl of pH 1.2 for 2 hours and then the pH of medium was raised to 6.8 by adding 4.6g Sodium hydroxide, 3.06g mono basic potassium phosphate and 4.005g dibasic sodium phosphate at 37±1°C for 12h. Samples were collected at specific time intervals and assayed by a UV spectrophotometer (Elico, Model SL-150, Mumbai, India.) at a wavelength of 276 nm. During the drug release studies, the tablets were observed for physical integrity. The experiments were repeated three times and the results were taken as average of three test readings with standard deviations. The accuracy and precision of the standard curve was sufficiently accurate, with a validated linearity for determination of drug in dissolution media.

Swelling and Erosion study

To understand the influence of swelling and erosion behavior on drug release and also to determine the effect of polymer viscosity on the swelling and erosion, matrix tablets were introduced into the dissolution apparatus under the standard set of conditions as specified for release rate studies. The tablets were removed using a small basket and swollen weight of each tablet was determined. To determine matrix erosion, swollen tablets were dried in a vacuum oven at 45°C to a constant weight. Swelling (%) and erosion (%) were calculated according to the following formula: % swelling = S/R×100, % erosion = (T-R)/T × 100; Where, S is the weight of the matrix after swelling; R is the weight of the eroded matrix; and T is the initial weight of the matrix. [9]

Analysis of release data

The description of dissolution profiles has been attempted using different release models. The data were evaluated according to the following equations.

Zero order: $M_t = M_o + K_o t$

First order: $\ln M_t = \ln M_o + K_1 t$

Higuchi model: $M_t = K_H \sqrt{t}$

Korsmeyer –Peppas model: $M_t/M_o = K_k t^n$

Where M_t is the amount of drug dissolved in time t, M_o the initial amount of drug, K_1 is the first order release constant, K_0 the zero order release constant, K_H the Higuchi rate constant, K_k the release constant and *n* is the diffusional release exponent indicative of the operating release mechanism. The correlation coefficient r was used as an indicator of the best fitting, for each of the models considered.

The other dissolution parameter used for comparing the formulations was mean dissolution time (MDT). This is calculated from the amount of drug released to the total cumulative drug. MDT is a measure of the rate of the dissolution process: the higher the MDT, the slower the release rate. The following equation was used to calculate the MDT from the mean dissolution data: [11]

$$MDT = \frac{\sum_{i=1}^{i=n} t_{mid} \times \Delta M}{\sum_{i=1}^{i=n} \Delta M} \qquad \text{eq.[1]}$$

Where i is the dissolution sample number, n is the number of dissolution sample time, t mid is the time at the midpoint between i and i-1 and ΔM is the additional amount of drug dissolved between i and i-1. To compare the results of dissolution tests of different formulations: [12] Dissolution efficiency (D.E) (Banakar, 1992) after 8hr of release test was used.

$$DE_8\% = \frac{\int_0^t y\, dt}{y_{100}\, t} \times 100 \qquad \text{eq [2]}$$

FT-IR study Infrared spectrum was taken (FT-IR, Spectrum RX1, Perkin Elmer Ltd, Switzerland) by scanning the sample in Potassium bromide discs. The samples of pure drug and formulated tablets were scanned individually.

Stability Studies [(12)] The optimized formulation was kept in the humidity chamber (Lab top, India) subjected to stability at 40 ± 2°C and 75 ± 5 % RH for a period of six months. After six months tablet sample was analyzed for physical characteristics and drug release profile.

Results and Discussion

Matrix and three layer matrix tablets of Diclofenac sodium were prepared using natural polymers such as Karaya gum (F1), Xanthan gum (F2) and mixture of both cationic (KG) and anionic (XG) in the ratio of 1:1(F3), and it produces a synergistic increase in viscosity. The three layer matrix tablets of Diclofenac sodium were developed to retarded the drug release from the surfaces of matrix core by compressing SCMC on both the surfaces.

The physical parameters such as hardness, thickness, friability and weight variation of the matrix tablets and three layer matrix tablets are shown in table 2. All the values were found to be with in the limits indicating that the tablets were of sufficient standards. The hardness and the thickness of the tablets were

increased as the amount of coating layer was increased. The hardness of three layer matrix tablets tended to increase and the friability decreased as the compression force was increased. Drug content uniformity was with in the range of calculated values of SR dosage form. (103.2± 2.65% to 98.3± 2.06 %.) FT-IR spectrum reveals that the principal absorption peaks at 1576cms $^{-1}$ of Diclofenac sodium, matrix tablets and three layer matrix tablets as shown in figure1. Indicating that there is compatibility between the drug and the polymer used in the study. Drug release studies were carried out in pH 0.1NHCl for 2hrs and the pH of the media was raised to pH 6.8.for remaining 10hrs. The amount of Diclofenac sodium released from the matrix tablets and three layer matrix tablets are shown in fig 2.The percentage drug release from the formulations F1, F2 and F3 ranged from 98.9±0.17%, 98.26±0.11%and 90.23±0.12%, similarly in case of formulations F1L3, F2L3 and F3L3, the drug release was upto 68.36±0.17% 64.96±0.12% and 62.68±0.21%. The results (figure 2a, b and c) indicated that the rate and extent of drug release were decreased for the three layer matrix tablets, which may be attributed to increase in the thickness of retardant layers.

The dissolution mechanism was studied using different release models. The correlation co-efficient (r^2) was used as an indicator of the best fitting for each of the models considered. The correlation co-efficient (r^2) for zero order kinetics, first order kinetics and Higuchi model was shown in (table 3).The results indicated that matrix tablets F1, F2 and F3 followed first order release rate indicated by their higher correlation co-efficient (r^2), where as three layer matrix tablets (F1L3,F2L3 and F3L3) with SCMC on both the surface of matrix core mostly provided better fit to zero order kinetics than first order and Higuchi equation due to higher (r^2) values.

At the end of 12h of dissolution testing, the three layer matrix tablets (F3L3) were found to be swollen and retained their physical integrity except that the edges of the swollen tablets were rounded off due to slight erosion of swollen SCMC layers.

On the basis of drug release data, it is evident that as thickness of the polymer layer increased the rate of drug release was found to be decreased. The release rate patterns of all formulations are given in the table 3. The results suggested that the developed three layer tablets showed zero- order or case II release. The values of kinetic constant (k) were in accordance with the values of n, the diffusional exponents, with k having lower values when the mechanism was Case II and higher values for formulations that released the drug by non-Fickian diffusion. The diffusional exponents (n) values for all formulations ranged from 0.62 to 1.30. It can be inferred that the release was dependent on both drug diffusion and polymer relaxation. The poor correlation coefficient r^2 values (F1, F2 and F3) in kinetic parameter based on zero-order model equation was mainly due to the drug release mechanism. Based on swelling and erosion studies of KG and XG matrices (F3), the matrix tablets undergo swelling during the dissolution study, tablet weight increases till the completion of release indicating that absorption of water and swelling process were taking place simultaneously. This indicates that polymer relaxation had a role in drug release mechanism. By determination and adjustment of the erosion rate and swellability of the matrix tablets, the drug release was extended for over a period of more than 12h.

The three layer matrix tablets (F3L3) released 62.68±0.21% in simulated gastro intestinal fluid (figure 2c) upto 12hrs. It is clear that about 37.32% of the drug is still left over in the formulation after reaching the physiological environment of colon that may be available for systemic delivery through colon at a controlled rate because of low absorption area and higher solubility of Diclofenac sodium[13]. In initial phase, barriers applied to the core delayed the interaction of core with the dissolution medium by reducing the surface for drug release and by limiting the solvent penetration rate. Anionic SCMC showed rapid hydration and forms a viscous gel layer that slows down further seeping-in of dissolution fluids toward the matrix core[14]. The strength of viscous gel layer around the core of the matrix tablets generally depend on the viscosity of the polymer used. Earlier it was reported from our laboratory that, SCMC shows rapid hydration and less erosion than other cellulose derivatives[15]. Thus, in this system the burst effect is controlled and the area available for drug release is maintained relatively at constant level. Thus on the basis of drug release data, the compressed SCMC layers on both sides of matrix core could prolong Diclofenac sodium release and modify the drug release to achieve constant release rate. Zero order release could be qualitatively explored by the delayed diffusion through the two laminated faces as a result of increasing polymer hydration.

Natural polymers KG and XG were well established hydrophilic polymers, have been extensively utilized in the design of sustained /controlled diffusion process. Diclofenac release from the monolithic KG, XG and KG: XG 1:1 ratio, matrix tablets have shown to be swelling controlled diffusion process; such release modulation was controlled by the retardant layers. It is evident that the increased amount of coating layer resulted in the trend of decreasing drug release rate was shown in figure 2. MDT of three layer matrix tablets is higher than matrix tablets (table 3). It also indicated that MDT is increased, while DE_8%

decreased, while increasing the coating layer on the matrix core. MDT and DE_8% values of F3 and F3L3 formulations were found to be 4.62h, 9.70h and 84.59%, 66.70% respectively, indicating that the release of drug is slower from the three layer matrix tablets.

Release rate profiles in this study clearly demonstrated that both zero order/linear kinetics can be easily achieved using KG: XG in 1:1 ratio as matrix core, and 75mg of SCMC as retardant layers on both the surfaces. The three layer matrix tablets (F3L3), after storing at 40±2°C /75±5% RH for 6 months showed no changes both in physical appearance, drug content and in dissolution profile as shown in table 4. This study demonstrated that drug delivery from this system may reduce the side effects associated with NASIDs and provide extended therapeutic effect.

Conclusion

The hydrophilic matrix of Xanthan gum (XG) and Karaya gum (KG) alone could not prolong the Diclofenac sodium release effectively, for more than 12hrs. A combination of KG: XG and the amount of anionic SCMC as retardant layers could apparently prolong the drug release in a linear fashion approaching to zero order release. Hence it is feasible to achieve a linear release by modulating the release rate by using SCMC as release retardant layers.

Table 1: Different formulations of Diclofenac Sodium matrix tablets and three- layer matrix tablets based on natural gums and Cellulose derivatives as layer.

Formulation code	Ingredients(mg)								
	DiclofenacSodium	Karaya Gum	Xanthan Gum	SCMC	Lactose	Starch	Talc	Mg Stearate	Total weight
F1(K.G)	100	100	-		70	18	8	4	300
F1L1	100	100		50	70	18	8	4	350
F1L2	100	100	-	100	70	18	8	4	400
F1L3	100	100	-	150	70	18	8	4	450
F2(X.G)	100	-	100	-	70	18	8	4	300
F2L1	100		100	50	70	18	8	4	350
F2L2	100	-	100	100	70	18	8	4	400
F2L3	100	-	100	150	70	18	8	4	450
F3(K.G:X.G)	100	50	50	-	70	18	8	4	300
F3L1	100	50	50	50	70	18	8	4	350
F3L2	100	50	50	100	70	18	8	4	400
F3L3	100	50	50	150	70	18	8	4	450

Table 2. Physical Parameters of Diclofenac Sodium matrix tablets and three layer matrix tablets (Mean ± SD)

Formulation code	**Average wt of tablets (mg) n=3**	**Hardness kg/cm^2 n=3**	**Thickness (mm) n=3**	**Friability (%)n=3**	**Drug content (%) n=3**
F1	302.1 ± 0.01	5.02± 0.10	3.02± 0.01	0.840± 0.015	102.3 ± 3.6
F1L1	351.2 ± 0.16	5.07± 0.02	4.01± 0.02	0.781± 0.036	103.2± 2.65
F1L2	402.2 ± 1.02	5.94± 0.05	5.80± 0.01	0.561± 0.025	98.15 ±2.25
F1 L3	451.1± 0.13	6.05± 0.03	6.02± 0.02	0.369± 0.015	101.0± 0.32
F2	301.1 ± 0.01	5.14± 0.03	3.01± 0.01	0.751± 0.025	98.6± 2.06
F2 L1	352.2 ± 0.15	6.11± 0.06	4.01± 0.02	0.365± 0.042	100.3± 0.91
F2 L2	401.2 ± 1.01	6.04± 0.03	5.81± 0.02	0.302±0.001	101.0± 0.52
F2 L3	452.1± 0.14	6.05± 0.02	6.01± 0.01	0.268± 0.012	103.0± 2.5
F3	301.1 ± 0.01	5.06± 0.01	3.04± 0.01	0.820± 0.028	99.82 ±0.76
F3 L1	352.2 ± 0.14	5.01± 0.03	4.01± 0.02	0.407± 0.013	98.3± 2.06
F3 L2	402.2 ± 1.03	6.02± 0.03	5.82± 0.01	0.534± 0.001	98.5± 2.05
F3 L3	451.1± 0.12	6.10± 0.02	6.02± 0.02	0.262± 0.026	100± 1.97

Table 3. *In-vitro* dissolution kinetics, MDT and DE_8% of Diclofenac sodium released from matrix tablet and three layer matrix tablets (n=3).

Formulation code	Zero order		First order		Higuchi		Korsemeyer- peppas			MDT hrs	D.E_8 %
	R^2	K_o (mg/h^{-1})	R^2	K_1(h^{-1})	R^2	K (mg.h^{-1})	R^2	*n*	K_0		
F1	0.897	7.64	0.913	0.324	0.987	29.02	0.956	0.626	1.378	3.85	82.54
F1L1	0.937	7.63	0.968	0.206	0.971	28.06	0.972	0.775	1.188	4.83	79.49
F1L2	0.975	6.41	0.988	0.135	0.964	24.16	0.987	0.798	1.081	6.21	76.09
F1L3	0.996	5.53	0.994	0.086	0.913	19.11	0.995	1.097	0.659	8.70	71.89
F2	0.905	7.71	0.996	0.019	0.968	28.76	0.954	0.655	1.144	4.60	86.85
F2L1	0.966	7.33	0.988	0.157	0.957	26.32	0.973	1.006	0.935	5.73	76.26
F2L2	0.998	5.82	0.971	0.096	0.916	20.12	0.987	1.031	0.749	8.24	66.01
F2L3	0.995	4.94	0.959	0.072	0.878	16.73	0.988	1.309	0.383	8.47	62.35
F3	0.932	7.96	0.968	0.239	0.964	30.06	0.968	0.746	1.147	4.62	84.59
F3L1	0.958	7.01	0.943	0.162	0.968	26.15	0.977	0.796	1.112	5.76	77.57
F3L2	0.995	6.51	0.939	0.126	0.937	23.44	0.991	1.047	0.792	7.28	72.29
F3L3	0.997	5.69	0.928	0.971	0.913	20.22	0.992	1.283	0.491	9.70	66.7

Table 4: Stability study of three layer matrix tablets of Diclofenac Sodium (F3L3).

Characteristics	Before storage	After storage
Physical appearance	Off white, smooth	Off white, smooth
Hardness kg/cm^2	6.10± 0.02	6.10± 0.02
Friability (%)	0.562± 0.026	0.560± 0.023
Swelling index (%)12hrs	706.25±0.021	704.25±0.025
Drug content (mg/tablet)	100±1.97	98.56±1.25
***In vitro* release (%) 24hr.**	57.96±1.18	57.15±1.61

Figure 1. FT –IR spectra of pure Diclofenac Sodium (A) powdered samples of matrix tablet F1(B),F2(C) and powdered sample of three layer matrix tablets F3L3 (E).

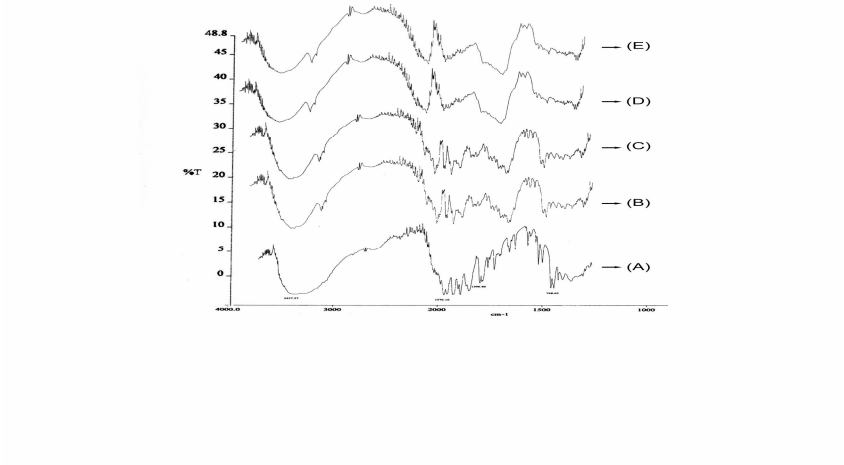
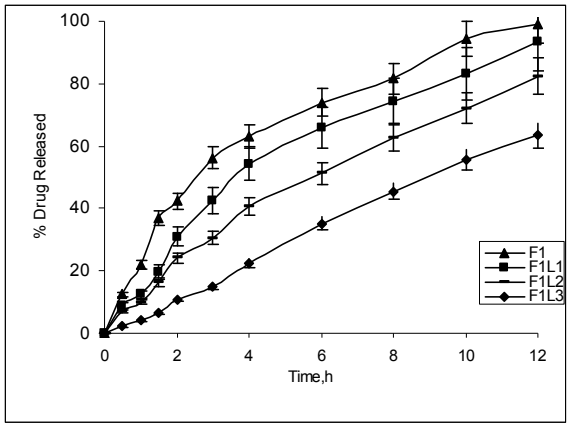
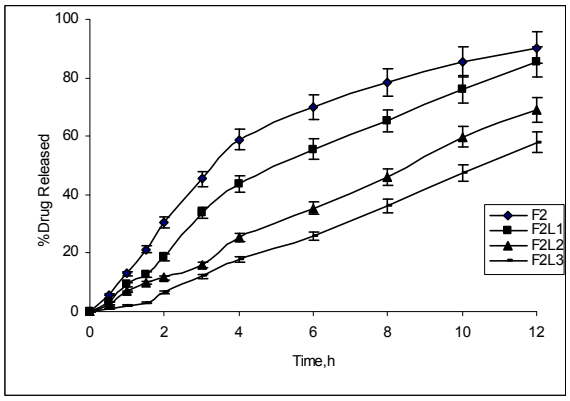


Figure 2. Dissolution profiles of Diclofenac sodium from matrix tablets and three layer matrix tablets conducted in pH 1.2 for 2 hrs and in pH 6.8 phosphate buffers remaining 10 hrs. a) F1, F1L1, F1L2 and F1L3 b) F2, F2L1, F2L2 and F2L3 c) F3, F3L1, F3L2 and F3L3. Each point represent the mean SD, (*n*=3).

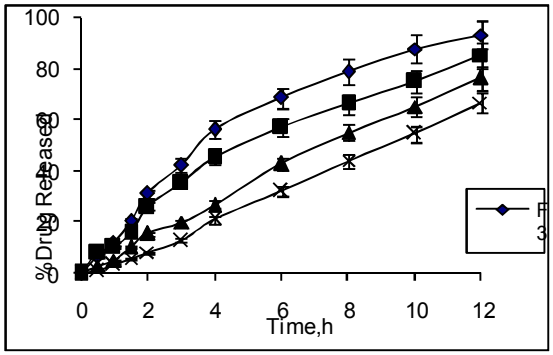
a)



b)



c)



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