Formulation of bi-layer matrix tablets of tramadol hydrochloride: Comparison of rate retarding ability of the incorporated hydrophilic polymers

Hasanul Arif[1], Abdullah Al Masum[2], Florida Sharmin[1], Selim Reza[3] and SM Ashraful Islam[1]*

[1]Department of Pharmacy, University of Asia Pacific, Dhanmondi, Dhaka, Bangladesh
[2]Research & Development Formulation Department, Incepta Pharmaceuticals Ltd., Savar, Dhaka, Bangladesh
[3]Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Dhaka, Dhaka, Bangladesh

Abstract: Bi-layer tablets of tramadol hydrochloride were prepared by direct compression technique. Each tablet contains an instant release layer with a sustained release layer. The instant release layer was found to release the initial dose immediately within minutes. The instant release layer was combined with sustained release matrix made of varying quantity of Methocel K4M, Methocel K15MCR and Carbomer 974P. Bi-layer tablets were evaluated for various physical tests including weight variation, thickness and diameter, hardness and percent friability. Drug release from bi-layer tablet was studied in acidic medium and buffer medium for two and six hours respectively. Sustained release of tramadol hydrochloride was observed with a controlled fashion that was characteristic to the type and extent of polymer used. % Drug release from eight-hour dissolution study was fitted with several kinetic models. Mean dissolution time (MDT) and fractional dissolution values ($T_{25\%}$, $T_{50\%}$ and $T_{80\%}$) were also calculated as well, to compare the retarding ability of the polymers. Methocel K15MCR was found to be the most effective in rate retardation of freely water-soluble tramadol hydrochloride compared to Methocel K4M and Capbomer 974P, when incorporated at equal ratio in the formulation.

Keywords: layered tablet, instant release, controlled release, kinetic model, release exponents, Fickian diffusion and MDT.

INTRODUCTION

Extended release tablets have been proven successful in attaining greater patient compliance and improved therapeutic effectiveness in the last few decades. The use of polymeric matrix devices to control the release of a variety of therapeutic agents has become increasingly important in the development of extended release dosage forms. A matrix device is a drug delivery system in which the drug is dispersed either molecularly or in particulate form within a polymeric network. The device may be a swellable, hydrophilic monolithic system, erosion controlled monolithic system or a non-erodible system. Further studies to develop the features of prolonged release dosage forms are now significant areas of interest for scientists around the world. Bi-layer tablet technology is an excellent extension to the conventional controlled drug delivery scheme that opens a new era for the successful development of controlled release formulations along with various features to provide a way of successful drug delivery system (Divya *et al*., 2011).

Bi-layer tablets have got some key advantages over the conventional controlled or sustained release dosage forms. It is one of the best ways to incorporate two drugs of different pharmacologic group in single matrix, though they are incompatible physically or chemically. It also allows formulating supportive layers for achieving site-specific drug delivery by incorporating pH dependent polymers. Rate retarding polymers can also be used in layers at different ratios for designing a sequential release profile.

Tramadol, a synthetic non-steroidal anti-inflammatory drug, has opioid-like effects. Tramadol has high oral bioavailability but it is extensively metabolized (Raffa *et al*., 1995). The mean elimination half-life is approximately 6 hours and requires dosing at every 6 hours in order to maintain optimal plasma concentration to get desired therapeutic effect (Gendle *et al*., 2010). Conventional single layer controlled release formulations of tramadol are not suitable to improve patient compliance by proper pain management. Thus tramadol hydrochloride becomes an excellent candidate for bi-layer tablet containing an instant release layer and a retarding polymer based sustained release layer.

To optimize the therapeutic profile of tramadol hydrochloride, various research works have been reported and a verity of dosage forms are available in the market like capsule, immediate release tablet, soluble tablet, oro-dispersible tablet, injection, sustained release tablets and the combination products. Various rate retarding agents have been reported to be used in the sustain release matrix of conventional tablets such hydroxy propyl methyl cellulose K100 M, ethyl cellulose (Chander *et al*., 2010), carrageenan gum, karaya gum (Raghavendra *et al*., 2009), guar gum and xanthan gum (Mishra *et al*., 2006).

**Corresponding author:* e-mail: ashraf@uap-bd.edu

The objective of the current study was to formulate a bi-layer oral sustained release matrix tablet of tramadol hydrochloride comprising of an instant release layer and a sustained release layer by using Methocel K4M, Methocel K15MCR and Carbomer and to evaluate the impact of polymer on the release profile of the drug. Methocel offers the advantages of being non-toxic and relatively inexpensive; it can be compressed directly into matrices and is available in different viscosity grades. Methocel tablets hydrate upon contact with water and a rate controlling gel layer forms around the solid inner core. The drug release in soluble drugs is controlled by the rate of diffusion through such a gel and in poorly water-soluble drugs, by a combination of diffusion and gel erosion. On the other hand, tablet formulations using carbomer polymers have demonstrated zero-order and near zero-order release kinetics. The polymer is effective at low concentrations and shows extremely rapid and efficient swelling characteristics in both simulated gastric fluid (SGF) and simulated intestinal fluid (SIF). The carbomer polymers produce tablets of excellent hardness and low friability.

MATERIALS AND METHODS

Materials

Tramadol hydrochloride was received from ACI limited, Bangladesh as gift sample. Carbomer 974P and Methocel K15MCR were obtained from Incepta Phatmaceuticals Ltd, Bangladesh. Methocel K4M was received from Colorcon Limited as a gift sample. All other ingredients were procured from local market.

Formulation and preparation of tablets

Bi-layer tablets of tramadol hydrochloride were prepared by direct compression method as per formula given in Table 1 and 2 that correspond to instant release layer and sustained release layer respectively. For immediate release layer Avicel PH 102 (93.5mg-108.5mg) was used as diluents. On the other hand amount of Sodium Starch Glycolate (used as super disintegrants) was used up to 15 mg. Higher drug release was found in case of IR-3 formulation and this composition was used as immediate release layer with the sustain release layer to prepare different bi-layer tablets. Adequate quantity of active ingredient and necessary excipients for 100 tablets were accurately weighed and blended in a laboratory scale drum blender for 15 minutes for each layer separately. At first, sustain release blended powder was weighed by an electronic balance and compressed lightly using a KBR-Press (laboratory scale hydraulic press, UK). Then the instant release part was added into the die cavity and pressed (5 ton) to produce bi-layer tablets. The tablets were kept in airtight glass container and stored in desiccator.

Evaluation of blended powder

Blended powder of active and excipients of both immediate and sustained release layer were evaluated for bulk density, angle of repose, moisture content and hausner ratio. LBD (Loose Bulk Density) and TBD (Tapped Bulk Density) were determined by tap density tester. Carr's index {(TBD-LBD) X 100]/TBD} and Hausner Ratio (Tapped Density/Bulk Density) were calculated from LBD (Loose Bulk Density) and TBD (Tapped Bulk Density). The angle of repose of granules was determined by passing blended powder through the funnel freely to surface. Angle of repose ($\theta = tan^{-1} (h/r)$) was calculated from the radius (r) and height (h) of the powder heap. Moisture content of granules was determined using Mettler Karl Fischer Titrator.

Evaluation of tablets

Each of the formulation was assessed for thickness, diameter, weight variation, hardness and percent friability. Thickness, diameter and crushing strength was determined with an Automatic Tablet Hardness Tester (8M, Dr. Schleuniger, Switzerland). For weight variation test 20 tablets from each of the 10 batch were weighed individually with an analytical weighing balance (AY-200, Shimadzu, Japan). The average weights for each brand as well as the percentage deviation from the mean value were calculated. Another twenty tablets of each batch were weighed and subjected to abrasion by employing a Electorlab Friabilator (India) at 25 rev/min for 4 min. The tablets were then weighed and compared with their initial weights and percentage friability was calculated by using the formula of Gendle *et al*., 2010,

$\% f = \{1- (W_t/W)\} \times 100$

Where, %f= percent friability

W = weight of tablet before rotation

W_t = weight of tablet after rotation

The average of diameter, thickness, hardness of 20 tablets of each formulation along with the weight variation and % friability of each batch have been provided on table 3.

Determination potency of tablets

Sufficient quantity of finely powdered tablet sample (Equivalent to 20mg of Tramadol Hydrochloride) was dissolve in 100ml water. The solution was filtered through Whatman filter paper. Again filtrate of this solution was passed through 0.2µ disk filter and diluted to suitable concentration. The samples were analyzed by a validated UV spectroscopic method. The absorbance of the solutions was measured at 271nm for tramadol hydrochloride (Raghavendra *et al.,* 2009) by using a Shimadzu UV-1201 UV/Visible double beam spectrophotometer (Shimadzu, Japan). Then potency was calculated by the equation obtained from the standard curve of Tramadol Hydrochloride in water.

In vitro dissolution studies

The dissolution test was performed in Tablet Dissolution Tester (TDT-08L, Electrolab, India) by using USP XXIII, apparatus II according to method described by Rahman *et al.* 2012. 750ml 0.1N HCl was selected as dissolution media for first two hours and then to adjust the pH to 6.8,

250 ml of 0.2M tribasic sodium phosphate solution was added to the dissolution media. The medium was maintained at 37±0.5°C at 75 rpm of paddle speed. Aliquots of 10 ml were withdrawn at 10, 20, 30, 45 & 60 minutes and then every 1hour interval from the dissolution medium. Fresh medium was added each time to maintain the volume unchanged. The aliquots were filtered and diluted to suitable concentration with appropriate solution either with 0.1N HCl or with pH 6.8 phosphate buffer based on the time point of withdrawal. The absorbance of the solutions was measured at 271 nm for tramadol hydrochloride (Raghavendra *et al.* 2009) by using a Shimadzu UV-1201 UV/Visible double beam spectrophotometer (Shimadzu, Japan) and percent drug release was calculated by the equation obtained from the standard curve.

Table 1: Formulation of instant release layer (in mg)

Ingredients	IR-1	IR-2	IR-3	IR-4
Tramadol HCl	36.5	36.5	36.5	36.5
Sodium starch glycolate	0	6	9	15
Avicel PH 102	108.5	102.5	99.5	93.5
Talc	3	3	3	3
Aerosil- 200	1.5	1.5	1.5	1.5
Sicopharm- Red-30	0.5	0.5	0.5	0.5
Total weight	150	150	150	150

Kinetic study

The release data obtained from dissolution study in acidic media followed in buffer media were fitted with zero-order, (Gibaldi and Feldman, 1967) by plotting cumulative amount of released drug with time, first-order by plotting logarithm of cumulative percentage of drug remaining against time, Higuchi, (Higuchi, 1963) by plotting cumulative percentage of drug release with square root of time, Korsmeyer-Peppas models (Korsmeyer *et al.*, 1983, Peppas, 1985) by plotting logarithm of cumulative percentage of drug release with logarithm of time and Hixon-Crowell model (Hixson and Crowell, 1931) by plotting cubic root of percent releases (cubic root of initial drug load minus cubic root of % drug remaining) against time. To categorize the drug release pattern in different experimental conditions, $T_{25\%}$, $T_{50\%}$ and $T_{80\%}$ were calculated according to the following equations:

$T_{25\%} = (0.25/k)^{1/n}$

$T_{50\%} = (0.5/k)^{1/n}$

$T_{80\%} = (0.8/k)^{1/n}$

Where *k* is the antilog of intercept & *n* is a release exponent of Korsmeyer's plot and *y* is the percentage of dissolved drug. Mean dissolution time (MDT) value has been used to predict the drug release rate from the dosage form and the retard ability of the polymer. Mean Dissolution Time (MDT) was calculated by the below equation of Mockel and Lippold, 1993.

$MDT = (n/n+1).\ K^{-1/n}$

Stability study

Stability study of the formulations was carried out in Incepta Pharmaceuticals Ltd in stability Chamber. Test condition was 40ºC; 75% RH. Tablets were filled and sealed in HDPE container before storage and samples were withdrawn after 1 month and 3 months time and were evaluated for appearance and drug content.

RESULTS

The objective of current study was to evaluate release rate of Tramadol from matrix of three widely used sustaining polymers (Methocel K4M, Methocel K15MCR and Carbomer 974P). Each tablet contains an instant release layer with a sustained release layer.

Fig. 1: Bi-layer tablets of tramadol hydrochloride using Methocel K4M as the release rate modifier.

Characterization of blended powder

The blended powders of different proposed formulations (F-1 to F-15) were evaluated for LBD, TBD, compressibility index and angle of repose. Average LBD and TBD were 0.401 and 0.496g/cm^3. The results of compressibility index (%) ranged from 10.43 to 11.43.The results of angle of repose ranged from 25^o to 29^0. The results of angle of repose (<30°) indicate good flow properties of powder, which was supported the results found from compressibility index.

Characterization of tablet

Bi-layer tablets of tramadol were prepared by direct compression technique. Tablets from all the batches had similar appearance that is white to off-white color tablet with a reddish layer at the bottom. The tablets were assessed for thickness and diameter, weight variation, hardness and percent friability for all the formulations (F-1 to F-15). Thickness and diameter were found uniform for all formulations. In the weight variation test, all the tablets were found to have limited difference from the theoretical weight and also from the average weight. The hardness of tablets was found from 5kg/cm^2 to 7kg/cm^2 for all the batches. All the formulations showed percent

friability below 1.0% that refers to the adequate binding of ingredients to withstand shocks. Drug content of the formulations was also within accepted range (98.11-100.3%). Stability studies showed that tablets were stable in respect of physical appearance, hardness (4.5kg/cm^2 to 6.5kg/cm^2) and potency (97.17-99.07%).

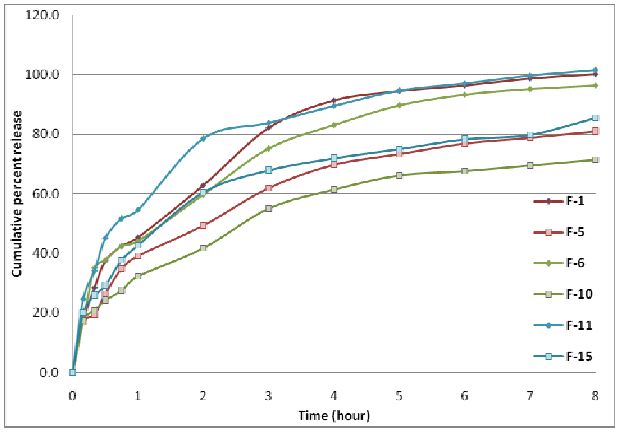

Fig. 2: Comparison in cumulative percent release profile of formulations containing highest and lowest quantity of different polymer.

Fate of instant release layer

Burst release was observed from the incorporated instant release layer of bi-layer tablets of tramadol hydrochloride and then the tablet showed a successive slow release from the sustain release layer (table 4). The instant release layer contains 22.5% drug. It released 16.13% to 18.00% Within 10 minutes when it was compressed with Methocel K4M based sustain release layer (formulation F-1 to F-5). Similarly, Methocel K15MCR based formulations (F-6 to F-10) and Carbomer 974P based formulations (F-11 to F-15) also showed a quick release of incorporated drug (17.62% to 22.25% and 20.24% to 24.75% respectively). Rapid disintegration of the instant release layer in the dissolution fluid is mainly responsible for rapid drug release from immediate release layer.

Sustainability and mechanism of drug release

The sustained release portion of the bi-layer tablets based on Methocel K4M was found to release the drug as a function of the polymer loading. After 8 hours of dissolution, 100.22% and 80.84% drug were released from the formulation F-1 and F-5 respectively containing polymer at ratio of 26% and 43% of the sustain release part. Similar rate retarding ability of Methocel K4M was reported earlier (Naimuzzaman *et al*., 2012). Mishra *et al*., 2006 claimed that higher viscosity, high molecular weight, slower rate of erosion and higher swelling ability render the polymer the ability to retard the rate of drug release. Bi-layer tablets of tramadol hydrochloride containing Methocel K15MCR (formulation F-6 to F-10) showed a rapid drug release from the instant release layer, followed by a successive slow release profile (table 4) on the basis of the amount of incorporated polymer. After 8 hours of dissolution study, 96.37%, 89.44% and 71.41% drug were released from the formulation F-6, F-8 and F-10 that contain about 26%, 34% and 43% Methocel K15MCR polymer respectively. HPMC K15M contains polymeric backbone of cellulose, which produces strongly viscous gel that plays an important role in drug release (Raghavendra *et al*., 2009). Besides higher swelling ability in presence of dissolution fluid rendered the polymer more capable in controlling the release rate.

Similarly Carbomer 974P based formulations (F-11 to F-15) showed burst release initially from the immediate release layer and slow release at a controlled manner as a function of the polymer loading (table 4). Formulation F-11(containing 26% of Carbomer) was found to release 101.46% drug after eight hours whereas formulation F-15 (containing about 46% carbomer) released 85.49% drug at same time. Such retarding ability of Carbomer 974P might be due to its composition; since it is comprised of three-dimensionally cross linked micro gels. A gelatinous layer is formed up on hydration of the tablet surface and even on further hydration, these hydro gels remain intact in water rather swells to a great extent and the drug has to diffuse through the gel layer in order to be released (Umesh *et al*., 2009).

Kinetic modeling

Bi-layer tablets of tramadol containing both grades of Methocel showed high linearity (R^2) with first order plot particularly when incorporated at lower amount (F-1, F-2 and F-6) in the matrix and hence the release is dependent on the initial drug loading in the matrix. But upon addition of more polymer in the matrix, tablets showed high linearity (R^2) with korsmeyer peppas model (R^2 value ranging from 0.983 to 0.996, except the formulation F-9, which best fits with Higuchi model that confirms the drug release mainly by diffusion). The *n* value of these formulations was found < 0.45; hence the drug release mechanism can be claimed as fickian diffusion (table 5). Two of the Carbomer 974P based formulations F-12 and F-13 were best fitted with first order kinetics and remaining three formulations (F-11, F-14 and F-15) showed highest linearity (R^2=0.971 to 0.984) with korsmeyer peppas model. The *n* value for these three formulations was found < 0.45, therefore the drug release mechanism can be claimed as fickian diffusion.

Effect of polymer concentration and viscosity grade

Instant release layer of all bi-layer tablets disintegrated very rapidly and released the entrapped drug within 10 minutes. Percent drug release within 10 minutes dissolution were almost similar in respect of polymer (Carbomer, Methocel K4M and Methocel K15MCR) as there was no polymer in immediate layer (table 4).

Table 2: Formulation of sustained release layer (in mg)

Formulation	Tramadol HCl	Methocel k4m	Methocel k15 mcr	Carbomer 974P	Avicel PH 102	Purified Talc	Aerosil-200
F-1	163.5	90.0	-	-	86.0	7.0	3.5
F-2	163.5	105.0	-	-	71.0	7.0	3.5
F-3	163.5	120.0	-	-	56.0	7.0	3.5
F-4	163.5	135.0	-	-	41.0	7.0	3.5
F-5	163.5	150.0	-	-	26.0	7.0	3.5
F-6	163.5	-	90.0	-	86.0	7.0	3.5
F-7	163.5	-	105.0	-	71.0	7.0	3.5
F-8	163.5	-	120.0	-	56.0	7.0	3.5
F-9	163.5	-	135.0	-	41.0	7.0	3.5
F-10	163.5	-	150.0	-	26.0	7.0	3.5
F-11	163.5	-	-	90.0	86.0	7.0	3.5
F-12	163.5	-	-	105.0	71.0	7.0	3.5
F-13	163.5	-	-	120.0	56.0	7.0	3.5
F-14	163.5	-	-	135.0	41.0	7.0	3.5
F-15	163.5	-	-	150.0	26.0	7.0	3.5
Total weight of sustained release layer							350

Table 3: Physical properties of bilayer tablet of tramadol hydrochloride.

Formulation	Diameter (mm)	Thickness (mm)	Hardness (Kg/cm^2)	Weight variation (mg)	Friability (%)	Drug content (%)
F-1	11.702±0.0023	2.357±0.0151	5.417±0.2787	500±0.78	0.257	99.21
F-2	11.703±0.0025	3.067±0.0258	5.058±0.2905	500±0.84	0.254	98.98
F-3	11.702±0.0025	3.550±0.0306	6.692±0.3955	500±0.46	0.233	99.01
F-4	11.705±0.0008	4.192±0.0204	5.608±0.2478	500±0.67	0.198	100.30
F-5	11.705±0.0023	3.117±0.0258	6.508±0.3904	500±0.79	0.130	99.47
F-6	11.704±0.0018	3.608±0.0204	6.667±0.2582	500±1.02	0.039	98.69
F-7	11.704±0.0016	4.275±0.0274	5.783±0.4008	500±0.87	0.035	99.90
F-8	11.703±0.0020	2.325±0.0274	5.533±0.1966	500±0.59	0.016	99.73
F-9	11.703±0.0020	3.083±0.0258	7.317±0.2563	500±0.63	0.052	98.93
F-10	11.704±0.0016	3.533±0.0258	6.567±0.3830	500±0.89	0.020	98.88
F-11	11.704±0.0018	4.278±0.0248	5.633±0.2823	500±0.81	0.031	99.60
F-12	11.704±0.0018	3.125±0.0274	7.317±0.2563	500±0.91	0.194	99.24
F-13	11.703±0.0016	3.608±0.0204	6.825±0.4022	500±1.05	0.069	98.98
F-14	11.704±0.0019	4.283±0.0258	5.567±0.3531	500±0.91	0.082	99.87
F-15	11.703±0.0016	2.335±0.0288	5.633±0.2041	500±0.96	0.177	98.11

However, drug release was found quite different with the passes of time. This difference in the release behavior was due to different type and different viscosity grade of polymers (fig. 2). On the other hand, formulation F-1 containing 26% Methocel K4M showed similar drug release of formulation F-11, containing same amount of Carbomer 974P. After 8 hours of dissolution formulation F-1 was found to release 100.22% of incorporated drug whereas Formulation F-11 released 101.46%. But relatively stronger retarding ability was found for the formulation of F-6 containing 26% Methocel K15M which released 96.37% drug after 8 hour. But the differences in drug release became more comprehensible after incorporating higher amount of polymer. After completion of 8 hour of dissolution, formulation F-5, F-10 and F-15 had found to release 80.84%, 71.41% and 85.49% drug respectively containing 43% Methocel K4M, Methocel K15M and Carbomer 974P respectively.

DISCUSSION

Blended powders of all formulations showed optimum angle of repose and compressibility index for good flow properties. Compressed tablets from each batch have undergone different physical and analytical tests. Satisfactory findings from the test criteria indicate the suitability of the manufacturing process and compatibility of chosen excipients. Instant disintegration of immediate release layer released incorporated drug within minutes. On the contrary, sustained release layer was found to release drug based on nature, extent and type of polymer used in the formulations. Rate of hydration and gel formation was found the main role playing mechanism in drug release. Methocel polymers were found to swell in presence of water and Carbomer was shown to form a gelatinous layer that finally contributed and governed the drug release from the matrix.

Table 4: Cumulative percent release of bi-layer tablets of tramadol hydrochloride.

Time (Min)	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9	F-10	F-11	F-12	F-13	F-14	F-15
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
10	17.50	16.13	18.00	16.88	16.88	17.62	22.25	17.75	17.63	17.63	24.75	21.75	20.25	20.25	20.24
20	28.48	26.84	24.99	20.48	19.35	35.11	26.05	25.24	19.36	20.86	34.08	29.54	28.77	27.27	25.77
30	37.36	35.45	32.82	27.12	26.36	37.83	31.39	30.32	23.74	24.14	45.03	40.43	36.65	32.88	29.11
45	42.35	39.66	38.50	34.98	34.95	42.45	34.55	32.22	30.43	27.45	51.62	49.21	45.38	40.81	37.74
60	45.40	42.05	41.50	40.68	39.16	44.12	41.50	39.38	32.70	32.31	54.54	52.85	50.47	47.34	42.73
120	62.98	54.97	52.78	50.21	49.41	59.69	57.03	50.39	45.12	41.72	78.49	70.03	67.62	64.45	60.53
180	82.21	72.38	70.49	67.06	62.00	75.16	66.93	62.54	53.86	55.05	83.75	80.93	77.41	76.36	67.81
240	91.34	78.07	73.67	70.20	69.68	82.96	72.02	69.25	67.71	61.41	89.55	87.54	84.82	82.10	71.79
300	94.43	81.32	78.81	77.13	73.27	89.59	80.76	76.30	71.28	66.16	94.57	91.71	89.79	86.21	74.98
360	96.44	92.09	84.56	81.61	76.88	93.35	86.52	82.02	78.21	67.63	97.13	95.07	93.97	87.86	78.19
420	98.74	93.80	88.41	84.88	78.85	95.07	89.84	86.41	80.62	69.51	99.70	95.96	94.86	91.19	79.75
480	100.22	95.51	90.07	87.34	80.84	96.37	93.46	89.44	82.21	71.41	101.46	98.80	96.57	92.87	85.49

Table 5: Mathematical modeling and drug release kinetics of bi-layer tablets.

Batch	Zero Order		First Order		Highuchi		Korsmeyer		Hoxon-Crowell	
	K_o	R^2	K_1	R^2	K_h	R^2	n	R^2	K_{hc}	R^2
F-1	0.187	0.833	-0.004	0.991	4.742	0.963	0.439	0.976	0.005	0.501
F-2	0.175	0.873	-0.002	0.985	4.376	0.981	0.433	0.980	0.005	0.512
F-3	0.163	0.863	-0.002	0.985	4.081	0.979	0.412	0.990	0.005	0.499
F-4	0.162	0.873	-0.001	0.983	4.040	0.982	0.443	0.988	0.005	0.524
F-5	0.149	0.854	-0.001	0.958	3.750	0.975	0.430	0.983	0.005	0.507
F-6	0.174	0.843	-0.002	0.994	4.384	0.968	0.401	0.964	0.005	0.480
F-7	0.167	0.886	-0.002	0.992	4.153	0.988	0.395	0.994	0.005	0.507
F-8	0.162	0.898	-0.001	0.993	4.008	0.991	0.416	0.996	0.005	0.522
F-9	0.156	0.910	-0.001	0.984	3.841	0.991	0.440	0.989	0.005	0.552
F-10	0.131	0.866	-0.001	0.942	3.276	0.977	0.397	0.988	0.004	0.503
F-11	0.171	0.773	-0.004	0.934	4.428	0.935	0.356	0.971	0.004	0.424
F-12	0.172	0.795	-0.003	0.984	4.412	0.948	0.385	0.972	0.005	0.448
F-13	0.172	0.814	-0.002	0.992	4.399	0.958	0.400	0.979	0.005	0.466
F-14	0.167	0.816	-0.002	0.976	4.252	0.959	0.404	0.984	0.005	0.474
F-15	0.146	0.815	-0.001	0.946	3.726	0.957	0.382	0.983	0.004	0.461

Form the cumulative release pattern of bi-layer tablets of tramadol hydrochloride (fig. 2), rate retarding ability of Methocel K15MCR was found highest, followed by Methocel K4M and Carbomer 974P. Mean dissolution time (MDT), $T_{25\%}$, $T_{50\%}$ and $T_{80\%}$ also indicated the same retarding ability (table 6). MDT value of formulation F-1, F-6 and F-11 were found 110.28, 121.66 and 92.67 minutes respectively. These formulations contained about 26% Methocel K4M, Methcel K15MCR and Carbomer 974P respectively. Again the MDT value of F-5, F-10 and F-15(containing about 43% of the above mentioned polymers) were found 191.77, 276.06 and 171.69 minutes. $T_{25\%}$, $T_{50\%}$ and $T_{80\%}$ also indicated that drug retarding ability of the polymers for tramadol hydrochloride bi-layer tablets was as follows:

Methcel K15MCR > Methocel K4M > Carbomer 974P

Table 6: Mean dissolution and fractional dissolution time values (in minutes) of bi-layer tablets.

Name	MDT	$T_{25\%}$	$T_{50\%}$	$T_{80\%}$
F-1	110.28	15.37	74.54	217.44
F-2	136.09	18.33	90.86	269.01
F-3	155.16	18.38	98.87	309.39
F-4	169.75	24.19	115.65	334.12
F-5	191.77	25.38	127.23	379.56
F-6	121.66	13.40	75.46	243.65
F-7	153.53	16.22	93.77	308.20
F-8	172.69	20.99	111.07	343.77
F-9	209.63	29.38	141.97	413.16
F-10	276.06	29.57	169.49	553.73
F-11	92.67	7.19	50.37	188.60
F-12	104.24	10.24	61.96	210.04
F-13	114.40	12.51	70.78	229.21
F-14	128.09	14.40	80.06	256.24
F-15	171.69	16.49	101.19	346.34

CONCLUSION

Bi-layer tablets containing an instant release layer and a sustained release layer of tramadol hydrochloride were prepared by direct compression method based on Methcel K4M, Methocel K15MCR and Carbopol 974P. The instant release layer was found capable of releasing the incorporated drug within 10 minutes. On the other hand, all three polymers were found effective in retarding the release of freely water-soluble tramadol hydrochloride both in acidic and basic media. Each of the polymers showed characteristic rate retardation on the basis of the quantity type and viscosity grade. Therefore successful once daily bi-layer matrix tablet of tramadol hydrochloride can be prepared using these polymers either alone or in combination.

ACKNOWLEDGEMENT

The authors are thankful to ACI Limited, Bangladesh and Incepta Pharmaceutical Ltd, Bangladesh for their generous material support.

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