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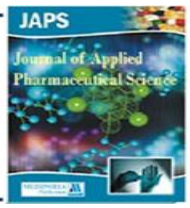

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Formulation and Evaluation of Bi-layered Sustained Release Matrix Tablets of Tramadol Hydrochloride

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ABSTRACT

Bi-layer tablets of tramadol hydrochloride were prepared by direct compression technique incorporating an immediate release layer and a sustained release layer. An immediate release layer was successfully designed to release the bolus dose instantaneously. Water soluble Xanthan gum, water insoluble Kollidon SR and Eudragit L 100 were used as carriers in the sustained release layer of the matrix tablet. All the tablets were evaluated for thickness, diameter, weight variation, hardness and friability. The *in vitro* drug release was studied for eight hour, first two hours dissolution in acidic medium followed by six hour dissolution in buffer medium. Matrix tablet showed a sustained release rate with a controlled fashion as a function of the quantity of polymer used. The *in vitro* drug release data were fitted with several mathematical models and mean dissolution time along with fractional dissolution time values ($T_{25\%}$, $T_{50\%}$ and $T_{80\%}$) were calculated. Xanthan gum was found to be the most effective rate retarding agent compared to Kollidon SR and Eudragit L 100, when used at same ratio in the formulations.

Keywords: Bi-layer tablet, Matrix tablet, immediate release layer, sustained release layer, release exponents and MDT.

INTRODUCTION

Conventional dosage forms are accused of repetitive dosing and unpredictable absorption window that cause wide ranging fluctuation in drug concentration in the blood stream and tissues with consequent undesirable toxicity and poor therapeutic efficiency (Divya *et al*., 2011). To avoid these unwanted happenings, the idea of controlled drug delivery system had arrived with profound advantages over conventional dosage forms like predictable and reproducible release rates, extended duration of activity particularly for short half life drugs, decreased toxicity, increased effectiveness of the drug by localization at the site of action, reduction in required dose that finally provide better patient compliance. But often this controlled drug delivery system fails to achieve the above stated advantages due to the lack of releasing the initial bolus dose, keeping the equilibrium of maintenance dose on patients having varying physical condition, dose dumping and failure to achieve site specific drug delivery.

These factors led to the concept of bi-layer tablet manufacturing technology in order to optimize the therapy by boosting up the advantages of controlled drug delivery system. Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose (Shiyani *et al*., 2008).

Tramadol is a centrally acting analgesic having the aminocyclohexanol group, which has a strong analgesic action similar to opioid profile (Chander *et al*., 2010). It has been in clinical use in Europe since the late 1970s and has been proved to be effective in pain conditions without causing serious cardiovascular or respiratory side effects (Lehmann, 1997). Tramadol has high oral bioavailability but it is extensively metabolized (Raffa *et al*., 1995). The half-life of the drug is about 5.5 hours and the usual oral dosage regimen is 50 to 100 mg every 4 to 6 hours with a maximum oral dosage of 400 mg/day (Alderman, 1984). To reduce the frequency of administration and to improve patient compliance, a conventional sustained release formulation of tramadol hydrochloride is not still adequate. Whereas a bi-layer tablet of tramadol hydrochloride containing an immediate and sustained release layer would be more advantageous for effective drug therapy and pain management.

Various researchers have been trying to optimize the therapeutic profile by formulating sustained release dosage forms of tramadol hydrochloride using hydrophilic matrix system (Mishra *et al*., 2006), water insoluble matrix system (Chander *et al*., 2010) and natural gums (Raghavendra *et al*., 2009). But works on bi-layer sustain release tablet of tramadol hydrochloride has not been reported yet. The target of the present study is to achieve suitable tramadol hydrochloride therapeutic profile by formulating bi-layer tablet consisting of an immediate and a sustained release layer using Eudragit L 100, Kollidone SR and Xanthun Gum.

MATERIALS AND METHODS

Materials

Tramadol hydrochloride and Eudragit L 100 were received from ACI limited, Bangladesh as gift sample. Kollidone SR was obtained from Renata limited, Bangladesh. Other ingredients were of analytical grade and purchased from local market.

Preparation of tablets

Bi-layer tablets were prepared by direct compression technique according to the formula given in table 1 for immediate release layer and table 2 for sustained release layer. The active and excipients were accurately weighed for 100 tablets and placed in a small blending container and blended in a laboratory designed small drum blender for 15 minutes separately for each layer. First, appropriate amounts of the sustain release part mixture were accurately weighed in an electronic balance compressed lightly using a KBR hydraulic press, UK and then the immediate release part was incorporated into the die cavity and finally pressed (Five ton) to produce bi-layer tablet. The tablets were packed in an air tight container and stored in a desiccator until further study.

Table. 1: Formulation of immediate release layer (mg/tab).

Ingredients	Amount (mg)
Tramadol HCl	36.50
Sodium Starch Glycolate	9.50
Avicel PH 102	99.00
Talc	3.00
Aerosil- 200	1.50
Sicopharm- Red-30	0.50
Total weight	150.00

Table. 2: Formulation of sustained release layer (mg/tab).

Formulation	Tramadol HCl	Eudragit L 100	Kollidone SR	Xanthun Gum	Avicel PH 102	Talc	Aerosil-200
F-1	163.5	95.0	-	-	81.0	7.0	3.5
F-2	163.5	110.0	-	-	66.0	7.0	3.5
F-3	163.5	125.0	-	-	51.0	7.0	3.5
F-4	163.5	140.0	-	-	36.0	7.0	3.5
F-5	163.5	155.0	-	-	21.0	7.0	3.5
F-6	163.5	170.0	-	-	6.0	7.0	3.5
F-7	163.5	-	95.0	-	81.0	7.0	3.5
F-8	163.5	-	110.0	-	66.0	7.0	3.5
F-9	163.5	-	125.0	-	51.0	7.0	3.5
F-10	163.5	-	140.0	-	36.0	7.0	3.5
F-11	163.5	-	155.0	-	21.0	7.0	3.5
F-12	163.5	-	170.0	-	6.0	7.0	3.5
F-13	163.5	-	-	95.0	81.0	7.0	3.5
F-14	163.5	-	-	110.0	66.0	7.0	3.5
F-15	163.5	-	-	125.0	51.0	7.0	3.5
F-16	163.5	-	-	140.0	36.0	7.0	3.5
F-17	163.5	-	-	155.0	21.0	7.0	3.5
F-18	163.5	-	-	170.0	6.0	7.0	3.5
Total weight of sustained release layer							350

Evaluation of tablets

The tablets of each batch were evaluated for thickness, diameter, weight variation, hardness and friability. Randomly collected 20 tablets of each batch were evaluated for thickness and diameter by digital slide calipers. For weight variation test 20 tablets were weighed individually. The average weight and deviation from the average weight of 20 tablets was calculated. Automatic Tablet Hardness Tester (8M, Dr Schleuniger, Switzerland) was used to determine hardness. 6 tablets were randomly selected from each formulation and the pressure at which each tablet crushed was recorded. 20 tablets of each formulation were weighed and subjected to abrasion by employing a Veego friabilator (VFT-2, India) at 25 rev/min for 4 min. The tablets were then weighed and compared with their initial weight and percentage friability was obtained using the formula,

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

Where, %F= friability in percentage

W = Initial weight of tablet

W_t = weight of tablet after revolution

***In vitro* drug release studies**

The *in vitro* drug release from the bi-layer tablets was studied by using tablet dissolution tester (Electrolab, India) USP XXIII, apparatus II. The dissolution test was performed using 750 ml 0.1N HCl at 37°C± 0.5°C and at 75 rpm for the first 2 hours. After that, 250 ml of 0.2M tribasic sodium phosphate was added to the dissolution media to adjust the pH to 6.8. At 10, 20, 30, 45 & 60 minutes and then every 1 hour interval, aliquots of 10 ml were withdrawn from the dissolution medium and the amount was replaced with fresh medium to maintain the volume constant. The samples were filtered through a Whatman filter paper and diluted to a suitable concentration with 0.1N HCl for the first 2 hours and then with pH 6.8 phosphate buffer. The absorbance of the solutions was measured at 271 nm for drug tramadol hydrochloride (Mishra *et al.* 2006) by using a Shimadzu UV-1201 UV/Visible double beam spectrophotometer (Shimadzu, Japan). Percentage of drug release was calculated using an equation obtained from the standard curve.

Kinetic study

The dissolution study was continued for 8 hours to get a simulated picture of the drug release in the *in vivo* condition and drug dissolved at specified time periods was plotted as percent release versus time curve. This drug release profiles were fitted with several mathematical models, namely zero order, first order, higuchi (Higuchi, 1963) and korsmeyer-Peppas (Korsmeyer *et al*., 1983, Peppas, 1985) in order to determine the release patterns and to get an idea of *in vivo* release mechanism of Tramadol from the bilayer tablet. Besides, mean dissolution time (MDT) and fractional dissolution values ($T_{25\%}$, $T_{50\%}$ and $T_{80\%}$) were also calculated to compare the release pattern of different formulations.

RESULTS AND DISCUSSION

Bi-layer tablets of tramadol hydrochloride were prepared by direct compression method. The tablets were evaluated for weight variation, friability, hardness, diameter and thickness for all the formulations (F-1 to F-18). No significant difference was observed in the weight of individual tablets from the average weight (Table 3). The hardness of tablets of all formulations was in acceptable limits (6 kg/cm^2 to 9 kg/cm^2). % friability was less than 1.0%, which indicates ability of tablets to withstand shocks. Thickness and diameter were also found uniform.

In vitro dissolution studies on bi-layer tablets of tramadol hydrochloride using Eudragit L 100 showed an immediate release of the bolus dose of the drug and successive delayed release of remaining portions of the drug (figure 1). The immediate release layer was able to release the drug within minutes. The sustain matrix layer of Eudragit L 100 released the drug slowly over 8 hours for all the formulations.

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

Formulation	Diameter (mm)	Thickness (mm)	Hardness (Kg/cm^2)	Weight variation (mg)	Friability (%)
F-1	12.702±0.0023	3.357±0.0151	7.417±0.2787	500±0.87	0.057
F-2	12.703±0.0025	3.067±0.0258	7.058±0.2905	500±1.06	0.154
F-3	12.702±0.0025	3.550±0.0306	8.692±0.3955	500±0.45	0.043
F-4	12.705±0.0008	4.192±0.0204	6.608±0.2478	500±0.58	0.198
F-5	12.705±0.0023	3.117±0.0258	7.508±0.3904	500±0.88	0.130
F-6	12.704±0.0018	3.608±0.0204	7.667±0.2582	500±0.89	0.039
F-7	12.704±0.0016	4.275±0.0274	6.783±0.4008	500±0.27	0.035
F-8	12.703±0.0020	2.325±0.0274	6.533±0.1966	500±0.59	0.016
F-9	12.703±0.0020	3.083±0.0258	9.23±0.2563	500±0.67	0.052
F-10	12.704±0.0016	3.533±0.0258	7.567±0.3830	500±0.49	0.020
F-11	12.704±0.0018	4.278±0.0248	6.633±0.2823	500±0.55	0.031
F-12	12.704±0.0018	3.125±0.0274	7.317±0.2563	500±1.02	0.194
F-13	12.703±0.0016	3.608±0.0204	7.825±0.4022	500±1.05	0.069
F-14	12.704±0.0019	4.283±0.0258	6.567±0.3531	500±0.96	0.052
F-15	12.704±0.0019	4.283±0.0258	6.567±0.3531	500±0.58	0.082
F-16	12.705±0.0019	4.283±0.0258	6.567±0.3531	500±0.76	0.018
F-17	12.704±0.0019	4.283±0.0258	6.567±0.3531	500±0.44	0.082
F-18	12.703±0.0016	2.335±0.0288	6.633±0.2041	500±0.29	0.177

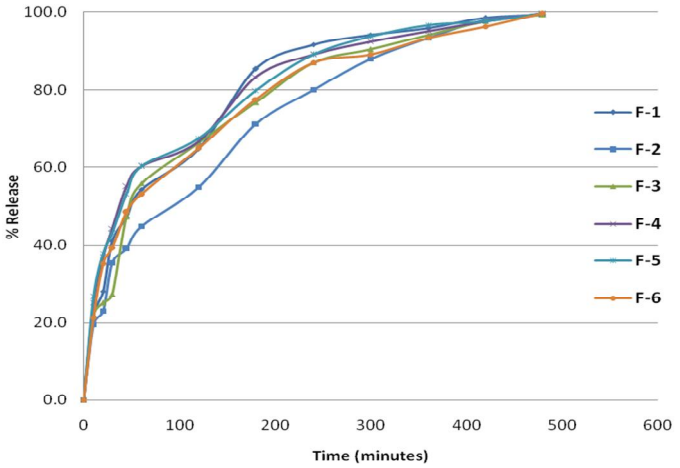

Fig. 1; Release profiles of bi-layer tablets of tramadol hydrochloride based on Eudragit L 100.

No significant differences were observed in the release kinetics of the formulations because, all the formulations were found to release more than 90% of the incorporated amount of drug after 6 hours. Such release patterns of all the formulations based on Eudragit L 100 are might be due to the formation of a water insoluble matrix of Avicel PH 102 and Eudragit L 100 initially. Micorcrystalline cellulose (Avicel PH 102) is practically insoluble in water (Raymond *et al*., 2006) and Eudragit L 100 is only soluble in basic pH ranges. Freely water soluble tramadol hydrochloride (USP-33) dissolves in the dissolution media from the surface of the matrix and form pores that facilitate further leaching out of the drug from the matrix. Therefore no significant control is observed in the later period when both drug and Eudragit L 100 leaches out of the matrix and dissolved in the buffer media. The mean dissolution time (MDT) values and fractional dissolution time values (table 5) showed a variable release rate of the formulations using Eudragit L 100. Similar findings were reported by Kamlesh *et al*., 2011, who found more than 90% drug release at both cases using Eudragit L 100 at 20% and 30% of the total tablet weight. They claimed the sustaining capacity of the Eudragit matrix was counterbalanced by the high solubility of the polymeric matrix at intestinal pH and the irregular erosion process of the matrix.

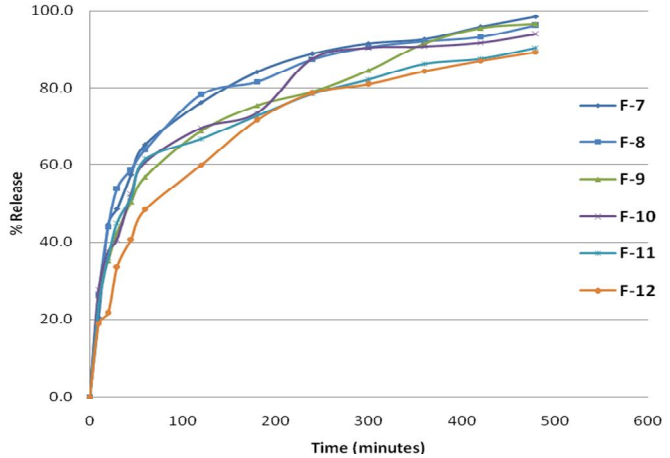

Fig. 2: Release profiles of bi-layer tablets of tramadol hydrochloride based on Kollidon SR

Drug release from bi-layer tablets of tramadol hydrochloride cantaining Kollidon SR is shown in figure 2. All six formulations (F-7 to F-12) released 18.75% to 26.44% drug within 10 minutes that was desired for the immediate release layer. Later on, the sustained release layer released the drug at a controlled fashion; as a function of the polymer content. After 8 hours of dissolution, formulation F-7 and F-12 were found to release 99.68% and 89.18% of incorporated drug respectively owing to having polymer content 27% and 47% respectively. Even though there is a little fluctuation, the gradual growing order of mean dissolution values and fractional dissolution values in response to polymer content in the matrix also indicate that drug release delepds on polymer content (table 5). The formulations containing lower amount of Kollidon SR in the matrix (F-7 and F-8), were found to best fit with first order release kinetics; but on addition of more polymer (F-9 to F-12), the release kinetics shifted to fickian diffusion.

The variable release profile might be caused by the composition and the properties of Kollidon SR. It consists of 80% polyvinyl acetate and 19% povidone that are capable of forming water insoluble matrix of polyvinyl acetate. But the water soluble povidone get dissolved from the matrix and form channels for drug diffusion and hence dissolution .Thus higher the polymer used in the formulation, tougher the water insoluble matrix and as a result, slower the drug release from the matrix.

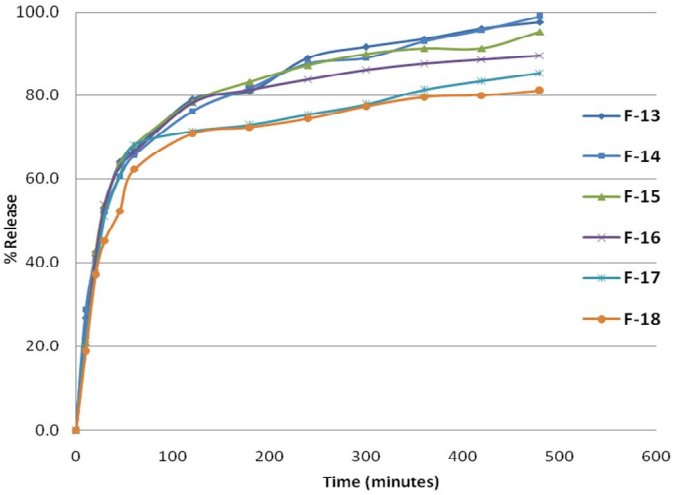

Fig. 3: Release profiles of bi-layer tablets of tramadol hydrochloride based on Xanthan gum.

The *in vitro* drug release data obtained from the formulations F-13 to F-18 containing different amount of Xanthan gum showed varying drug release kinetics depending on the content of gum in the tablet (figure 3). The immediate release layer of all six formulations has been proved successful once again to release the drug immediately within 10 minutes. Later on the matrix of Xanthan gum is found to release the drug at a progressive manner independent of the type of media used for the dissolution. Though the lower Xanthan gum containing formulations (F-13 and F-14) have been found to rise and fall the linearity of drug release rate and extent, high gum loading has eliminated the fluctuation;

rather released the drug clearly at a controlled manner throughout the dissolution period. Formulation F-18, F-17, F-16 and F-15 have been found to release the drug at a decreasing order at each time point of dissolution as a function of high Xanthan gum content in the formulation respectively.

The MDT values and fractional dissolution values (table 5) have also confirmed the same. Besides, the regression coefficient values of different models indicate that the mechanism of drug release in the formulations containing lower amount of Xanthan gum (F-13 to F-16) is first order. But later on adding more gum in the formulation, the mechanism shifted to fickian diffusion having *n* value 0.279 and 0.307 respectively for formulation F-17 and F-18 respectively.

Deshmukh *et al*. 2009 and Mishra *et al.* 2006 have been reported similar rate retarding capacity of Xantahan gum and also predicted that the swelling characteristics of Xanthan gum have contributed on slower rate of drug release. High degree of swelling by uptaking water and a small amount of erosion due to Polymer relaxation (Munday and Cox, 2000) might be responsible for rate controlling property of the gum.

CONCLUSION

Bi-layer tablets of tramadol hydrochloride were successfully prepared by using Eudragit L 100, Kollidon SR and Xanthan gum. The immediate release layer was found to release the incorporated drug within minutes. The sustained release layer was found to control the release behavior of the tablets. Best sustaining ability was revealed by Xanthan gum having MDT value 294 minutes; whereas Kollidon SR and Eudragit L 100 have MDT value 287 and 217 minutes respectively, when used in equal quantity in the matrix. Effective bi-layer tablet of tramadol hydrochloride is thus possible to formulate by using the polymers and gum in varying quantity.

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Table. 4: Mathematical modeling and drug release kinetics of bi-layer tablets.

Formulation	Zero Order		First Order		Highuchi		Korsmeyer	
	K_o	R^2	K_1	R^2	K_h	R^2	n	R^2
F-1	0.178	0.797	-0.004	0.986	4.557	0.946	0.397	0.969
F-2	0.185	0.888	-0.003	0.941	4.579	0.987	0.433	0.987
F-3	0.180	0.819	-0.003	0.967	4.567	0.954	0.422	0.953
F-4	0.163	0.769	-0.004	0.932	4.233	0.930	0.335	0.967
F-5	0.165	0.781	-0.004	0.948	4.249	0.939	0.330	0.979
F-6	0.170	0.815	-0.003	0.902	4.329	0.958	0.370	0.976
F-7	0.152	0.695	-0.003	0.963	4.030	0.880	0.330	0.879
F-8	0.142	0.672	-0.002	0.949	3.793	0.865	0.285	0.916
F-9	0.156	0.791	-0.002	0.975	4.001	0.942	0.323	0.983
F-10	0.151	0.746	-0.002	0.946	3.932	0.916	0.311	0.971
F-11	0.139	0.724	-0.001	0.939	3.643	0.899	0.308	0.971
F-12	0.159	0.813	-0.001	0.963	4.056	0.956	0.414	0.966
F-13	0.145	0.669	-0.003	0.968	3.868	0.861	0.288	0.910
F-14	0.146	0.697	-0.003	0.945	3.877	0.882	0.285	0.943
F-15	0.140	0.628	-0.002	0.911	3.778	0.828	0.310	0.835
F-16	0.130	0.596	-0.001	0.837	3.546	0.803	0.296	0.825
F-17	0.118	0.585	-0.001	0.805	3.221	0.786	0.279	0.817
F-18	0.120	0.614	-0.001	0.792	3.257	0.819	0.307	0.841

Table. 5: Mean dissolution time (in minutes) and fractional dissolution time values bi-layer tablets.

Name	MDT	$T_{25\%}$	$T_{50\%}$	$T_{80\%}$
F-1	101.80	10.91	62.50	204.20
F-2	128.36	17.29	85.70	253.73
F-3	113.59	14.33	74.06	225.58
F-4	95.21	6.05	47.92	194.90
F-5	95.39	5.76	47.06	195.52
F-6	107.52	9.39	61.15	217.81
F-7	89.59	5.41	44.19	183.62
F-8	91.20	3.17	36.12	187.93
F-9	112.25	6.29	53.77	230.41
F-10	108.22	5.29	49.12	222.62
F-11	124.73	5.88	55.80	256.67
F-12	144.47	17.34	92.49	287.84
F-13	84.98	3.09	34.25	175.13
F-14	88.30	3.07	34.97	181.96
F-15	90.10	4.35	40.70	185.37
F-16	100.13	4.05	42.16	206.30
F-17	129.70	4.13	49.57	267.21
F-18	143.18	6.67	63.75	294.68

REFERENCES

Alderman DA. A review of cellulose ethers in hydrophilic matrices for oral controlled-release dosage forms. Int. J. Pharm. Tech. Prod. Mfr. 1984; 5 :1-9.

Chander S, Shireesh K, Nagendra B. Design and evaluation of sustained release monolithic matrix tablets of tramadol hydrochloride. IJPI's J. Phar. & Cosmet. 2010; 1: 1-11

Divya A, K Kavitha, Rupesh K, Dakshayani S, Jagadeesh S. Bilayer tablet technology: An overview. J. App. Phar. Sci. 2011; 1: 43-47.

Deshmukh VN, SP Singh and DM Sakarkar. Formulation and Evaluation of Sustained Release Metoprolol Succinate Tablet using Hydrophilic gums as Release modifiers. Int. J. Pharm. Res. 2009; 1(2): 159-163.

Higuchi T. Mechanism of sustained action medication, Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J. Pharm. Sci. 1963; 52: 1145-1149.

Kamlesh JW, Rajendra BK, Milind JU. Formulation and Evaluation of Sustained Release Matrix Tablets of Metformin Hydrochloride Using pH Dependent and pH Independent Methacrylate Polymers. Br. J. Phar. Res. 2011; 1(2): 29-45.

Korsmeyer RW, Gumy R, Doelker E, Buri P, Peppas NA. Mechanism of solute release from porous hydrophilic polymer. Int. J. Pharm. 1983; 15: 25-35.

Lehmann KA. Tramadol in acute pain. Drugs. 1997; 53 (2):25-33.

Munday DL, Cox PJ. Compressed xantham and karaya gum matrices: hydration, erosion and drug release mechanisms. Int. J. Pharm. 2000; 203: 179–192.

Mishra B, Bharti VB, P N Singh, P. Kumar. Development and In-vitro Evaluation of Oral Sustained Release Formulation of Tramadol Hydrochloride. Acta Phar. Sci. 2006; 48: 153-166.

Peppas NA. Analysis of Fickian and non-Fickian drug release from polymers. Pharm. Acta. Helv. 1985; 60: 110-111.

Raffa RB, Nayak RK, Minn FL. The mechanism(s) of action and pharmacokinetics of

tramadol hydrochloride. Rev. Contemp. Pharmacother. 1995; 6:485-497.

Raghavendra RN, Gandhi S, Patel T. Formulation and evaluation of sustained release matrix tablets of tramadol hydrochloride. Int. J. Phar. & Phar. Sci. 2009; 1(1): 60-69.

Raymond CR, Paul JS, SC Owen. Handbook of Pharmaceutical Excipients. 5th ed. Pharmaceutical Press. London (2006); 131-135.

Shiyani B, Gattani S, Surana S. Formulation and evaluation of bi-layer tablet of Metoclopramide hydrochloride and Ibuprofen. AAPS Pharm. Sci. Tech. 2008; 9(3): 818-27.

United States Pharmacopeia (USP - 33), 2009.