WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 6.805
Volume 5, Issue 12, 562-575. Research Article ISSN 2277– 7105

FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF TAPENTADOL HCL

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Article Received on
30 Sept. 2016,

Revised on 20 Oct. 2016,
Accepted on 10 Nov. 2016

DOI: 10.20959/wjpr201612-7368

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ABSTRACT

The aim of the present work is to prepare sustained release tablets of tapentadol HCl using a combination of hydrophilic and hydrophobic polymers. Tapentadol is a centrally-acting opioid analgesic indicated for the management of moderate to severe chronic pain and neuropathic pain associated with diabetic peripheral neuropathy in adults. For the treatment of chronic and moderate pain a steady blood concentration is essentially required as it is freely soluble BCS I drug. Matrix tablets were prepared using hydrophilic and hydrophobic polymers like hydroxy propyl methylcellulose (HPMC) K100M, xanthan gum and Eudragits either alone or in combinations by direct compression method and evaluated for various physical and chemical parameters. Hydrophilic matrix tablets failed to prolong the drug release, whereas hydrophobic based matrix tablets showed lesser release of drug. The combination of hydrophilic and hydrophobic polymers matrix tablets showed zero order kinetics and release mechanism was non-fickian diffusion controlled. The release has shown that the tablets can be alternative for conventional Tapentadol tablets.

KEYWORDS: Sustained release, Tapentadol Hydrochloride, HPMC K100M, Xanthan gum Eudragits and zero order release.

INTRODUCTION

Matrix tablets composed of drug and polymer as release retarding material offer the simplest approach in developing an extended-release drug delivery system. Matrix systems are the most popular method among innumerable methods used in the development of extended

release formulations. Hydrophilic and hydrophobic polymeric matrix systems are widely used in extended drug delivery as they cost effective and have broad FDA acceptance[1], since they make it easier to achieve a desirable drug release profile. Extended oral drug delivery systems are highly recognized today for their benefits improving the disadvantages of conventional drug delivery systems. To be a successful extended release product the drug must be released from the dosage form at a predetermined rate in gastrointestinal fluids, maintain sufficient gastrointestinal residence time and be absorbed at a rate that will replace the amount of drug being metabolized and excreted.[2,3] Extended drug delivery systems are used in the treatment of chronic rather than the acute condition and they process a good margin of safety.[4]

Tapentadol is a centrally-acting opioid analgesic, having potency between morphine and Tramadol.[5] Tapentadol has been approved as immediate release tablets in 50 mg, 75 mg and 100 mg formulations, every 6 hours with a maximum dosage 600 mg/day by the USFDA. After oral administration 32% of the drug is absorbed. It is widely distributed in the body. The plasma protein binding is low (approximately 20%). The activity of Tapentadol is independent of metabolic activation and resides in a single enantiomer which readily crosses the blood-brain barrier; hence, tapentadol displays a rapid onset of action after administration. The half life is 4 h and peak effect is attained after 1 h and duration of action is 4-6 h. The drug undergoes extensive first pass hepatic metabolism i.e. 97% and its metabolites shown no analgesic activity.[6-8] To reduce the frequency of administration and to improve patient compliance especially for chronic pain, an extended-release formulation of tapentadol hydrochloride is desirable. The drug is freely soluble in water and hence selection of release retarding polymers is necessary to achieve a constant *in-vivo* input rate of the drug. The most commonly used method of modulating the drug release is to include it in an extended release matrix system, which allows a reduction in dosing frequency and control absorption rate to achieve desired plasma profiles with reduced fluctuations to an extended period of time.[9,10]
In the present work an attempt was made to use a combination of (various ratios) hydrophilic and hydrophobic polymers to control the release of highly water soluble drug Tapentadol.

MATERIALS AND METHODS

Drugs and Excipients

Tapentadol HCl obtained from MSN Laboratories ltd., Hyderabad, India as a gift sample. HPMC K100M, Xanthan gum and Eudragit RSPO and Eudragit RLOP were obtained from

Cipro Pharmaceuticals Ltd., Hyderabad, India as a gift samples. All other reagents used were of analytical grade.

Pre-formulation studies

Identification of the drug (Tapentadol) by organoleptic evaluation, melting point determination, solubility profile were carried out as per literature methods and Indian Pharmacopoeia, 2007.[11,12] The standard calibration curve of Tapentadol for UV spectrophotometric study was carried out in Phosphate buffer media (pH 6.8) at 225 nm as per standard methodology.[13,14] The percentage purity of Tapentadol was calculated from calibration curve.

Drug-polymers compatibility study by FTIR

An IR spectrum of pure drug (Tapentadol) and properly blended mixtures of Tapentadol with the polymers used were recorded in FTIR spectrophotometer in the scanning range of 500 to 4000 cm^{-1} with a resolution of 4 cm^{-1}. The basic purpose of FTIR was to observe any changes in the spectrum pattern of the drug due to polymers and thus identify the chances of any chemical interactions.[15-17]

Evaluations of micromeritic properties of powder blend

The powder blends were evaluated for flow properties by measuring Angle of Repose (fixed funnel method); Bulk Density (BD) and Tapped Bulk Density (TBD) by Cylinder method; Carr's Compressibility Index using the equations (Equations 1-4)are given below:

$$\text{Bulk density}\,(D_O) = \frac{\text{Weight of powder}}{\text{Volume of powder}} \quad \textbf{(1)}$$

$$\text{Tappeddensity}\,(D_F) = \frac{\text{Weight of powder}}{\text{Volume of powder after tapping}} \quad \textbf{(2)}$$

$$\text{Compressibility}\,\% = \frac{D_F - D_O}{D_F} \times 100 \quad \textbf{(3)}$$

$$\text{Hausner's ratio} = \frac{D_F}{D_O} \quad \textbf{(4)}$$

Where 'D_F' is tapped density; 'D_O' is loose bulk density.

Preparation of sustained release tablets

The sustained release tablets were prepared by direct compression method using (8mm diameter, round flat faced punches) single punch tablet compression machine. Each tablet

contained 116.47 mg of Tapentadol HCl. Compositions of different formulations were given in the Table 1&2.

Table 1. Formulations (1-8) of Tapentadol Sustain Release Tablets.

S.No.	Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
1	Tapentadol HCl	116.47	116.47	116.47	116.47	116.47	116.47	116.47	116.47
2	HPMC K100M	50	75	100	125	-	-	-	-
3	Xanthan gum	-	-	-	-	50	75	100	125
4	Eudragit RSPO	-	-	-	--	-	-	-	-
5	Eudragit RLOS	-	-	-	-	-	-	-	-
6	MCC	100	75	50	25	100	75	50	25
7	Lactose	27.53	27.53	27.53	27.53	27.53	27.53	27.53	27.53
8	Aerosil	3	3	3	3	3	3	3	3
9	Magnesium stearate	3	3	3	3	3	3	3	3
Total weight (mg)		**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**

Table 2. Formulations (9-16) of Tapentadol Sustain Release Tablets.

S.No.	Ingredients (mg)	F9	F10	F11	F12	F13	F14	F15	F16
1	Tapentadol	116.47	116.47	116.47	116.47	116.47	116.47	116.47	116.47
2	HPMC K100M	100	100	50	50	75	75	75	75
3	Xanthan gum	-	-	-	-	-	-	-	-
4	Eudragit RSPO	50	-	-	100	75	-	50	-
5	Eudragit RLOS	-	50	100	-	-	75	-	50
6	Microcrystalline cellulose	100	75	50	25	100	75	50	25
7	Lactose	27.53	27.53	27.53	27.53	27.53	27.53	27.53	27.53
8	Aerosil	3	3	3	3	3	3	3	3
9	Magnesium stearate	3	3	3	3	3	3	3	3
Total weight (mg)		**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**

Evaluation of tablets

The prepared Tapentadol-SR tablets were evaluated for hardness using Monsanto hardness tester; friability was determined using Roche Friabilator; the thickness and diameter of the tablets were determined using Vernier calipers; weight variation test was carried out as per official methods with the specification limit that not more than two of the individual weight deviates from the average weight by 10% and none should deviate by more than twice that percentage.[21,22]

Drug content estimation

The drug content in each formulation was determined by triturating 10 tablets and powder equivalent to 10 mg was added in 100ml of pH 6.8 phosphate buffer followed by stirring for 10 minutes. The solution was filtered through a 0.45µ membrane filter, diluted suitably and the absorbance of resultant solution was measured by HPLC.[23,24]

HPLC analysis of the Tapentadol-SR tablets

HPLC analysis of the formulated Tapentadol-SR tablets was carried out using C18 column (4.6 x 150mm, 3.5 µm ID) and the HPLC Chromatogram was depicted in fig.1.

Tapentadol hydrochloride analysis:

Mobile phase was prepared by a mixture of water:methanol:acetonitrile (60:10:30 v/v) and pH was adjusted to 3.5 by using acetic acid. The chromatographic column is agilent, C18 (150×4.6 mm; 3.5 to 5 µm particle size), the flow rate was 0.9 mL/min, the column temperature was 29°C, injection volume was 20 µL, retention time was 3.01 min and at the wavelength of 272 nm.

Standard preparation

About 10 mg of tapentadol hydrochloride was weighed and transferred to 10 mL volumetric flask. It was dissolved in methanol and the solution was made up to volume with methanol to obtain 1000 µg/mL of stock solution. The sample solution was further diluted with mobile phase to obtain standard solutions of different concentrations containing 20-200 µL of tapentadol. The solution was filtered through 0.45 µm nylon membrane filter and 20 µL of were injected in HPLC system under the chromatographic conditions as described above. Six replicate injections were performed and the area under the curve was determined at 272 nm. The amount of drug present in the sample solutions was determined using calibration curve of standard tapentadol. The correlation coefficients, slopes and y-intercepts of the calibration curve were determined.

Sample preparation

Equivalent of 25 mg of tapentadol was transferred to a 10 mL of volumetric flask, extracted with methanol, sonicated for 30 min, diluted to volume with same solvent. It was further diluted with mobile phase. The solution was filtered through 0.45 µm nylon membrane filter and 20 µL aliquots were injected in six times in to the HPLC system under conditions explained above. The peaks were measured at 272 nm and concentrations in the samples were determined using multi level calibration curve developed on the same HPLC system under the conditions using the linear regression equation.

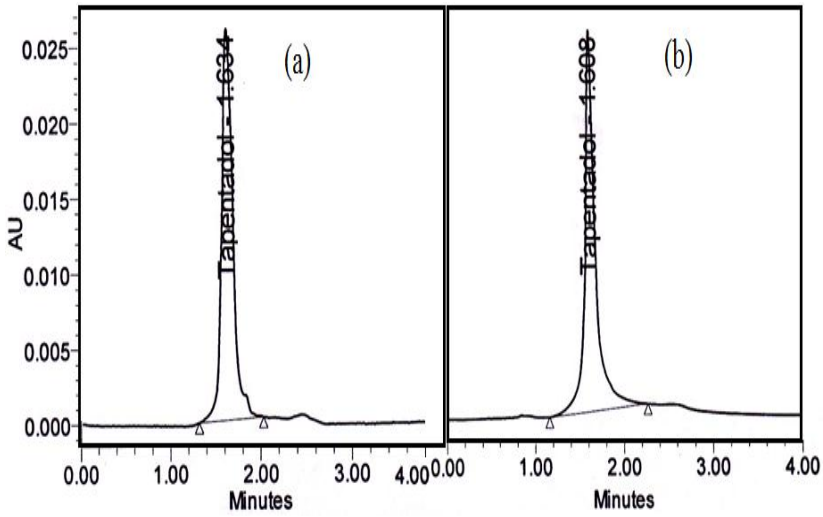

Fig. 1. HPLC analysis of (a) Tapentadol hydrochloride standard; (b) Tapentadol sustained release formulation as test sample.

In-vitro drug release study

In-vitro release rate of Tapentadol from the sustained release tablets was carried out using USP Type I rotating paddle apparatus. The dissolution medium consisted of 900 ml of phosphate buffer (pH 6.8). Experimentation was performed at 37ºC ± 0.5ºC with a rotation speed of 50 rpm. 5 mL of samples were withdrawn at one hour intervals and analyzed for Tapentadol content in spectrophotometer at 225 nm. The amount withdrawn was replaced with the same volume of the dissolution media. Experimentation was carried out up to 24 h.[25]

In order to understand the kinetics and mechanism of release of Tapentadol from the SR tablets, the results of the in vitro drug release study were fitted with various kinetic equations like zero order (cumulative percent drug release vs. time); first order (log cumulative percent drug retained vs. time); Higuchi (cumulative percent released vs. √time); Peppas (log of cumulative percent drug release vs. log time). The kinetic model that best fits the dissolution data were evaluated by comparing the regression coefficient values (r) obtained in various models. The N values (release exponent) in Peppas model were used to characterize different release mechanisms, where values of n=0.5 for Fickian diffusion and values between 0.5-1.0 for non-Fickian diffusion and n=1 for zero order.[26,27]

Zero order kinetics: $F = k_0 t_{(5)}$ **(5)**

First order kinetics: $1n(1-F) = -k_1 t$ **(6)**

To describe the drug release behavior from polymeric systems, the dissolution data were also fitted according to the well-known exponential Korsmeyer-Peppas equation (Korsmeyer et al., 1983) as. Korsmeyer-Peppas: $\frac{M_t}{M_\infty} = kt^a$ **(7)**

Where $\frac{M_t}{M_\infty}$ is the fraction of drug release at time 't' and 'k' is the kinetic constant, 'a' is the release exponent (indicating the general operating release mechanism). For tablets, depending on the aspect ratios, 'a' value between 0.43 and 0.5 indicating Fickian (case I) diffusion-mediated release, non-Fickian (Anomalous) release, coupled diffusion and polymer matrix relaxation, occurs if 0.5<n <0.89, purely matrix relaxation or erosion-mediated release occurs for n=1 (zero-order kinetics) and super case II type of release for n>0.89.

RESULTS AND DISCUSSION

From the point of organoleptic evaluation, it is a white to off white powdery substance, odorless and tasteless. Melting point of Tapentadol was found to be 209.7ºC which complies with the USP specification limits where the melting point range for Tapentadol is between 209-210ºC. Tapentadol was found to be highly soluble in water and ethanol. λmax of Tapentadol in phosphate buffer (pH 6.8) was found at 520 nm. The compatibility study between drug (Tapentadol) and excipients or polymers were carried out by Fourier Transforms Infra-Red (FTIR) spectroscopy. From the Fig. 2, it was observed that, peaks due to the major functional group in the spectras of Tapentadol (fig.2a) with all the polymers remain unchanged (fig.2b) as compared with spectra of Tapentadol alone. So from the above IR interpretations it can be inferred that there was no interaction between drug and polymers used in the formulations. Fig. 3 shown the DSC theromogram in pure form (fig. 3a) and optimized dosage form (fig. 3b), revealed that the no interaction was occurred after formulation of sustained release tablets with hydrophobic and hydrophilic polymer combination. Further FTIR and DSC studies concluding that there is no possible negative interaction was noted with the above composition of sustained release tablet dosage forms.

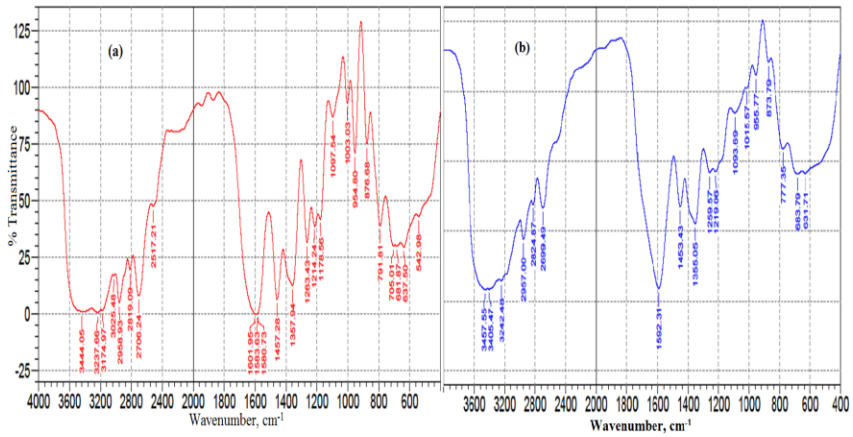

Fig. 2. FTIR Spectral comparison of (a) Tapentadol hydrochloride (b) Tapentadol sustained release formulation.

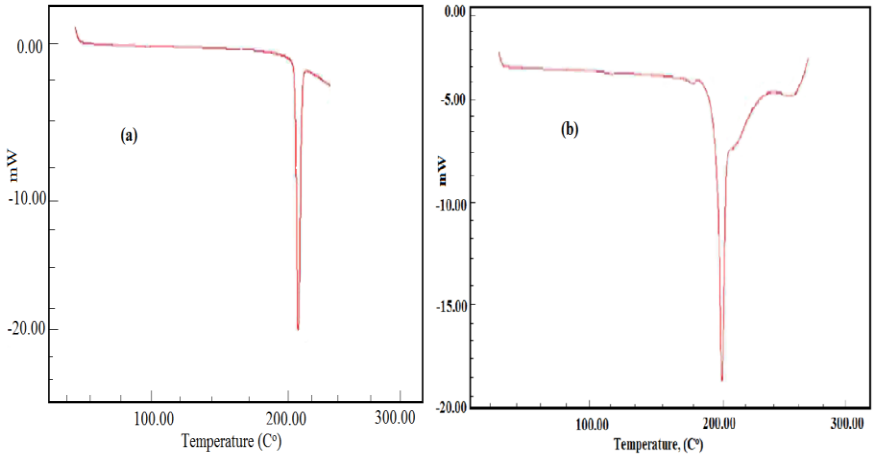

Fig. 3. DSC thermogram of (a) Tapentadol hydrochloride (b) Tapentadol sustained release formulation.

The composition of Tapentadol Sustained Release Tablets is presented in Table 1. Basing on the preformulation studies, details of the micromeritic properties of the powder blend are provided in Table 3. From the results of BD, TBD, Hausner's ratio, Carr's Compressibility Index and Angle of repose it can be inferred that the powder blend exhibited good flow properties. Hausner's ratio less than 1.25 indicates good flow while greater than 1.5 indicates poor flow.[18-20] Hence all the formulations were showed good flow except F3-F7, then these were accepted for industrial purposes in future.

Table.3. Pre-compressional parameters of prepared tablets

S.No.	Angle of repose (Θ)	Bulk density (g/ml)	Tapped density (g/ml)	Hausner's ratio	Carr's index
F1	23.64±0.35	0.67±0.002	0.723±0.004	1.079	7.33
F2	24.18±0.12	0.665±0.003	0.716±0.003	1.076	7.12

F3	25.16±0.42	0.716±0.001	0.824±0.005	1.151	13.1
F4	22.39±0.26	0.698±0.004	0.788±0.006	1.128	11.4
F5	19.69±0.58	0.713±0.006	0.826±0.007	1.158	13.6
F6	20.54±0.64	0.679±0.005	0.796±0.002	1.172	14.6
F7	22.26±0.18	0.732±0.005	0.823±0.003	1.124	11.05
F8	23.89±0.34	0.754±0.007	0.852±0.006	1.129	11.50
F9	24.58±0.84	0.638±0.002	0.728±0.003	1.140	12.30
F10	21.5±0.26	0.687±0.003	0.726±0.004	1.050	5.37
F11	22.5±0.20	0.612±0.004	0.676±0.005	1.104	9.46
F12	22.8±0.75	0.638±0.003	0.698±0.002	1.094	8.59
F13	24.3±0.37	0.726±0.005	0.776±0.001	1.068	6.44
F14	23.9±0.07	0.748±0.006	0.818±0.005	1.096	8.55
F15	19.62±0.33	0.696±0.007	0.726±0.004	1.043	4.13
F16	19.56±0.75	0.728±0.008	0.816±0.005	1.121	10.78

The tapentadol-SR tablets formulated (F1-F16) didn't show any visual defects like capping, chipping and lamination after punching. The results of physico-chemical evaluations of the Tapentadol-SR tablets (Table.4) showed that tablets indicated good mechanical strength, the percentage friability of all the formulations were found to be less than 1%, percentage deviation from average tablet weight for all the formulations ranged from 0 to 1.25% which are within the Indian Pharmacopoeial specified limits. Uniform percentage of drug content among different batches of tablets was as per limits given in Indian Pharmacopoeia.

Table 4. Physicochemical parameters of prepared tablets

Formulation code	Hardness (kg/cm^2)	Weight (mg)	Friability (%)	Drug content
F1	4.08±0.2	301.16±0.28	0.39±0.03	98.21±0.76
F2	5.25±0.27	301.78±0.52	0.28±0.04	98.76±0.24
F3	4.45±0.25	302.26±0.35	0.34±0.07	99.53±0.47
F4	4.53±0.16	301.63±0.32	0.56±0.08	98.47±0.26
F5	4.61±0.06	299.05±0.46	0.72±0.09	99.26±0.75
F6	5.02±0.06	298.16±0.22	0.16±0.02	100.58±0.26
F7	4.98±0.26	299.50±0.86	0.46±0.05	98.70±0.55
F8	5.24±0.31	300.01±0.18	0.66±0.07	99.53±0.56
F9	4.96±0.12	298.96±0.57	0.37±0.03	98.24±0.48
F10	4.76±0.28	299.50±0.86	0.45±0.01	99.53±0.56
F11	5.32±0.15	298.72±0.11	0.33±0.05	100.06±0.41
F12	5.16±0.27	299.10±1.01	0.52±0.03	101.76±0.22
F13	4.80±0.19	298.76±0.32	0.48±0.04	99.89±0.22
F14	4.78±0.22	299.63±0.46	0.38±0.05	96.76±0.22
F15	4.23±0.44	301.56±0.32	0.56±0.07	97.58±0.12
F16	4.66±0.55	300.16±0.28	0.46±0.05	99.76±0.22

In-vitro drug release studies revealed that the release of drug from different formulations varies with the characteristics and composition of matrix forming polymers. The release rate of Tapentadol decreased with decreasing concentration of HPMC. On the other hand both HPMC and Xanthan gum decreases the release rate of the drug when their concentration increases. The release of drug was further sustained by a combination of hydrophilic polymers with Eudragits (Figure 3-5).

Table 5. Kinetics of drug release from Tapentadol SR tablets

Formulation Code	Zero order	First order	Higuchi	Korsemeyer –peppas	
				R^2	N
F1	0.986	0.76	0.86	0.931	0.785
F2	0.986	0.83	0.915	0.966	0782
F3	0.979	0.743	0.891	0.948	0.746
F4	0.961	0.863	0.964	0.994	0.703
F5	0.969	0.766	0.876	0.933	0.888
F6	0.962	0.842	0.916	0.943	0.849
F7	0.969	0.825	0.909	0.938	0.879
F8	0.974	0.877	0.912	0.94	0.869
F9	0.986	0.718	0.889	0.97	0.862
F10	0.989	0.615	0.9	0.981	0.97
F11	0.984	0.709	0.881	0.965	0.884
F12	0.987	0.768	0.894	0.975	0.928
F13	0.986	0.727	0.907	0.979	0.78
F14	0.983	0.594	0.94	0.987	0.76
F15	0.988	0.744	0.902	0.978	0.797
F16	0.985	0.678	0.934	0.986	0.776

Further to characterize the release mechanism of Tapentadol from SR tablets, the dissolution data was fitted to different models like zero order, first order, Korsemeyer peppas and Higuchi diffusion models. The optimized formulation (F-16) shown the results, zero-order (r2=0.985), first-order (r2=0.678), Higuchi equation (r2=0.934) and korsemeyer-peppas (r2=0.986 & n=0.776), which explains drug release follows zero-order, in-vitro release profile of drug from all the formulations could be best expressed by Higuchi's equation, as the plot showed high linearity (r2=0.934). To conform the diffusion mechanism, the data were fit into Korsmeyer peppa's plot with linearity. 'n' value (0.776) indicates anomalous diffusion i.e, coupling of diffusion and erosion mechanisms. Results were showed in table 5.

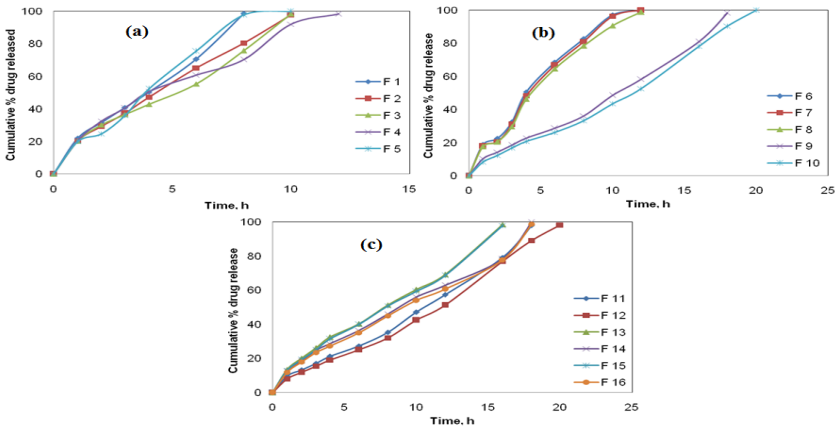

Fig. 4. Release profile of Tapentadol sustained release formulations of (a) F1 to F5, (b) F6 to F10 and (c) F11-F16.

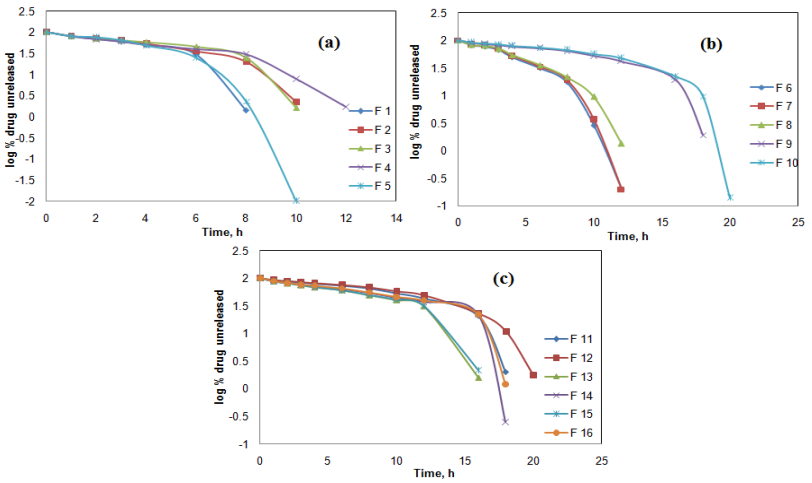

Fig. 5. First order kinetic plots of Tapentadol sustained release formulations of (a) F1 to F5, (b) F6 to F10 and (c) F11-F16.

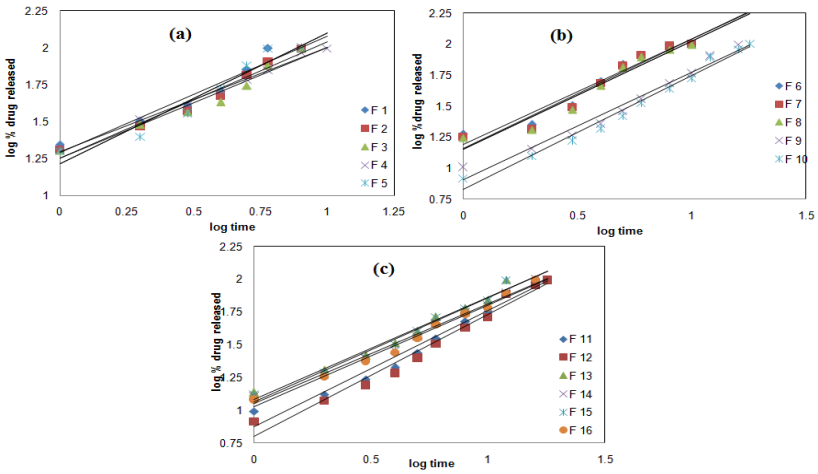

Fig. 6. Erosion plots of Tapentadol sustained release formulations of (a) F1 to F5, (b) F6 to F10 and (c) F11-F16.

CONCLUSION

The results of the study demonstrate that hydrophilic polymers like HPMC K100M and xanthan gum alone could not control the Tapentadol release effectively for 24 hours. It is evident from the results that an extended tablet prepared with combination of hydrophilic and hydrophobic polymer is a better system for 24 h extended release of a highly water soluble drug like Tapentadol. FTIR and DSC studies concluded that there is no drug-polymer interaction. The drug release was diffusion controlled on polymer concentration and followed zero order kinetics. Therefore the prepared formulation of Tapentadol containing HPMC K100M- Eudragit in combination as release retarding polymers is best formulation and could be used for industrial application.

REFERENCES

1. Wade WE, Spruill WJ. Tapentadol hydrochloride: A centrally acting oral analgesic. Clin Ther. 2009; 31: 2804-2818.
2. Dewan Roshan Singh, Kusha Nag, Akshaya N. Shetti and N. Krishnaveni. Tapentadol hydrochloride: A novel analgesic. Saudi J Anaesth. 2013; 7: 322–326.
3. Deepti Jain, Pawan Kumar Basniwal. Tapentadol, a novel analgesic: Review of recent trends in synthesis, related substances, analytical methods, pharmacodynamics and pharmacokinetics. Bulletin of Faculty of Pharmacy, Cairo University. 2013; 51: 283–289.
4. Nalini Vadivelu, Alexander Timchenko, Yili Huang and Raymond Sinatra. Tapentadol extended-release for treatment of chronic pain: a review. J Pain Res. 2011; 4: 211–218.
5. Etropolski M, Kelly K, Okamoto A, Rauschkolb C. Comparable efficacy and superior gastrointestinal tolerability (nausea, vomiting, constipation) of tapentadol compared with oxycodone hydrochloride. Adv Ther. 2011; 28(5): 401-17.
6. D Vamshidhar Reddy, Ambati Sambashiva Rao. Formulation and evaluation of extended release tablets of Tapentadol hydrochloride using hydrophilic-hydrophobic polymer combinations. J Pharma Res. 2014; 8(10): 1368-1374.
7. Nalini Vadivelu, Alice Kai, Benjamin Maslin, Gopal Kodumudi, Aron Legler and Jack M Berger. Tapentadol extended release in the management of peripheral diabetic neuropathic pain. Ther Clin Risk Manag. 2015; 11: 95–105.
8. Lange B, Kuperwasser B, Okamoto A, et al. Efficacy and safety of tapentadol prolonged release for chronic osteoarthritis pain and low back pain. Adv Ther. 2010; 27(6): 381–399.

9. David M. Biondi, Jim Xiang, Mila Etropolski, Bruce Moskovitz. Tolerability and efficacy of Tapentadol extended release in elderly patients ≥75 years of age with chronic osteoarthritis knee or low back pain. J Opioid Manag. 2015; 11(5).
10. Ricardo Vallejo, Robert L. Barkin and Victor C. Wang. Pharmacology of Opioids in the Treatment of Chronic Pain Syndromes. Pain Physician, 2011; 14: E343-E360.
11. Etropolski MS, Okamoto A, Shapiro DY, Rauschkolb C. Dose conversion between tapentadol immediate and extended release for low back pain. Pain Physician. 2010; 13(1): 61–70.
12. Michael J Brennan. Update on prescription extended-release opioids and appropriate patient selection. J Multidiscip Healthc. 2013; 6: 265–280.
13. Owlia Mohammad Bagher, Mehrpoor Golbarg and Modares Mosadegh Moneyreh. Bedtime Single-Dose Prednisolone in Clinically Stable Rheumatoid Arthritis Patients. ISRN Pharmacology Volume 2012; Article ID 637204, 1-5.
14. Shyam Shimpi, Bhaskar Chauhan, K. R. Mahadik and Anant Paradkar. Preparation and evaluation of diltiazem hydrochloride-gelucire 43/01 floating granules prepared by melt granulation. AAPS Pharm Sci Tech. 2004 Sep; 5(3): 51–56.
15. Swapna Velivela, K. Abbulu and D.Varun. Formulation And Evaluation of Acyclovir Multiunit Floating Formulations to Increase Gastric Retention by Employing Lipoidal Carriers. PHARMANEST. 2013; 4(6): 1350-1360.
16. Ravi Teja Pusapati, MVR Kalyan Kumar, Siva Satyanandam Rapeti and TEGK Murthy. Development of co-processed excipients in the design and evaluation of atorvastatin calcium tablets by direct compression method. Int J Pharm Investig. 2014 Apr-Jun; 4(2): 102–106.
17. Sameer Nadaf, Petra Nnamani and Namdeo Jadha. Evaluation of Prosopis africana Seed Gum as an Extended Release Polymer for Tablet Formulation. AAPS Pharm Sci Tech, June 2015; 16(3): 716-29.
18. Rao K.S., Jadhav S., Patil P., Ddattatraya D.U. Development And Evaluation Of Sustained Release Tablets Of Venlafaxine Hydrochloride, International Research Journal Of Pharmacy, 2011; 2(5): 261-270.
19. Doddayya H., Patil S.S., Kaledhele A., Udupi R.H., Reddy S.R., Kumar P. Effect of gum rosin and ethyl cellulose on in vitro release of venlafaxine hydrochloride from hydrophilic matrix tablets. Int. Pharm. Biol. Archiv. 2011; 2(3): 980-988.

20. Radhika P.R., Karanam D., Sivakumar T. Fabrication of sustained release matrix tablets of venlafaxine hydrochloride using eudragits. Int. Res. Ayur. Pharm. 2011; 2(4): 1386-1389.
21. Atul A. B, Prashant Z, A.V. Chandewar, S B Jaiswal, Designing And Evaluation Of Extended Release Tablet Of Venlafaxine Hydrochloride Using Hydrophobic Matrix. Der Pharmacia Lettre. 2010; 2(1): 329-335.
22. Phoke S.V., Sakarkar D.M., Mitkare S.S. Formulation and characterization of sustain release matrix tablets of venlafaxine hydrochloride by using natural polymers. Int. Pharm. Front. Res. 2012; 2(4): 14-26.
23. Purvi T. Bhatasana and Askok R. Parmal. Development and validation of RP-HPLC methodfor estimation of Tapentadol HCl in its tablet dosage form. Pelgia Research Library. 2012, 3(4): 422-426.
24. Y. Indira Muzib., Ravi Kumar Reddy. J., Chowdary K. P. R and E. swathi. Development and validation of RP-HPLC method for estimation of Tapentadol HCl in bulk and tablet dosage forms., International journal of chemical and analytical science. 2013; 4: 67-72.
25. OmPrakash B., Sav A., Gejage S., Amin P. Formulation development of venlafaxine hydrochloride extended release tablet and in vitro characteristics. Int. J. Pharm. Tech Res. 2012; 4(4): 1777-1784.
26. Bhutani S.B. Development and optimization of venlafaxine hydrochloride sustain release triple layer tablets adopting quality by design approach. Pharmacol. Pharm. 2013; 4: 9-16.
27. Gohel M.C., Soni, C.D., Nagori S.A., Sarvaiya K.G. Modulation of Venlafaxine Hydrochloride Release from Press Coated Matrix Tablets. Indian J. Pharm. Sci. 2008; 70(3): 292-297.