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FORMULATION AND *IN-VITRO* EVALUATION OF SUSTAINED RELEASE TABLETS OF TRAMADOL HYDROCHLORIDE

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ABSTRACT

Sustained release provides the most desirable dosing regimens with effective pharmacokinetic profile and pharmacodynamic response. This is potentially useful to overcome problems associated with conventional dose and has advantage of patient compliance. In present investigation, the study was aimed to formulate and *in- vitro* evaluation of sustained release tablets of Tramadol hydrochloride using polymeric matrix system. The matrix system adopted in this study had Hydroxy Propyl Methyl Cellulose K100M and Ethyl cellulose as rate retarding polymers individually as well as in combinations and in varying concentration of polymers in order to investigate the effect on drug release. Matrix tablets of Tramadol HCl were prepared by direct compression method. Various formulation with different concentration of polymers were tried to optimize the process and release of the drug. The pre-compression parameters were characterized for flow properties, compressibility index and other physical proprieties. The prepared tablets were evaluated for different parameter such as weight variation, diameter, hardness, friability, disintegration, swelling index and drug content. The in-vitro drug release profiles were studied in two media (0.1N HCl and Phosphate buffer pH 6.8). All the tablets prepared possess a weight variation below ±5%, hardness of (6.77 to 8.05) kg/cm^2, percentage friability of (0.33 to 0.94%), diameter (10.10 to 10.19 mm. The drug content was in between 98.01% to 105.74%. Among all the formulations, sustained release tablets (F7) were considered to be the successful formulation which showed drug release upto 95.32%, and showed very close to release profile of the marketed sample which suggests the release the mechanism of drug from diffusion coupled with erosion. Increased concentration of polymers revealed the decreased release rate due to increase in diffusional path length and decreased

concentration showed increase in release rate due to insufficient concentration of the polymer. Similarly the swelling index of higher concentration of polymer was found high and also the swelling index increased with increase in concentration of polymer. Dissolution data are fitted to Zero order Model, First order model and Krosmeyer- Peppas Model and Higuchi model.

KEYWORDS: Tramadol hydrochloride, Sustained Release, Matrix Tablet, Hydroxypropyl Methyl Cellulose (HPMC K100M), Ethyl cellulose.

INTRODUCTION

Oral route is by far the most convenient route of drug administration. Among the several types of drugs that can be used to deliver drug through per oral route are: immediate release and, slow or sustained release products. The former include the conventional oral solid dosage forms which are designed to release their medicament immediately to the body for rapid and complete absorption, where as the latter are designed to release the drug slowly for more prolonged drug release and sustained drug action.

Tablets represent unit dosage forms in which one usual dose of the drug has been accurately placed and it may consist of one or more active ingredients as well as a series of other substances. They also vary in hardness, thickness and disintegration and dissolution characteristic and in other aspects depending upon their intended use and method of manufacture. The different categories of tablet that exist include soluble tablets, effervescent tablets, and Sublingual and buckle tablets, Modified-release tablets; (sustained-release tablets i.e.extended/prolonged-release tablets and delayed-release tablets i.e. gastro- resistant/enteric-coated tablets.[1]

Sustained release dosage form is designed to achieve a prolonged therapeutic effect by the continuously releasing of medication over an extended period of time with minimum side effects after administration of single dose. Sustained release dosage form are commonly taken only once or twice daily, compared with counterpart conventional forms that may have to be taken three or four times daily to achieve the same therapeutic effect. The basic rationale of a sustained drug delivery system is to optimize the Biopharmaceutics, Pharmacokinetic and Pharmacodynamics properties of a drug in such a way that its utility is maximized through reduction in side effects and cure or control of condition in the shortest possible time by using smallest quantity of drug, administered by the most suitable route. The

novel system of drug delivery offer a means of improving the therapeutic effectiveness of incorporated drugs by providing sustained, controlled delivery and / or targeting the drug to desired site. The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and then maintain the desired drug concentration. There is a continuously growing interest in the pharmaceutical industry for sustained release oral drug delivery systems. There is also a high interest for design a dosage formulation that allows high drug loading, particularly for actives with high water solubility. Oral route has been the most popular and successfully used for sustained delivery of drugs because of convenience and ease of administration, greater flexibility in dosage form design and ease of production and low cost of such a system. The sustained release systems for oral use are mostly solid and based on dissolution, diffusion or a combination of both mechanisms in the control of release of drugs.[2]

The objective of this study was to prepare sustained release tablets of Tramadol HCl by direct compression using different concentration of HPMC and Ethyl cellulose on the drug release, comparison of the swelling index for the formulated tablets and finally comparison of dissolution profile with formulated drug formulation and market product.

MATERIALS AND METHODS

MATERIALS

The drug molecule Tramadol HCl along with excipients like HPMC K100M, Ethyl cellulose, Dibasic calcium phosphate dihydrate, Microcrystalline cellulose, Magnesium stearate, purified Talc were received as gift sample from Lomus pharmaceuticals Pvt. Ltd., Gothatar, Bhaktapur, Bagmati, Nepal. Tramadol HCl standard was obtained from National Medicine Laboratory (NML) as gift sample. Other chemicals used in this study- Hydrochloric acid, Sodium hydroxide, Potassium dihydrogen phosphate were obtained from Research Laboratory of National Model College for Advanced Learning.

METHODS

Analytical method development

A 100mg of Tramadol HCl was weighed accurately and dissolved in 0.1N HCl solution to make 100ml. A filtered aliquot of this solution was further diluted to get a solution of 50µg/ml concentration. The spectrum of this solution was run from 200-400nm range UV-visible spectrophotometer.

Analytical Method Validation

Analytical method was validated for Accuracy, Precision, Specificity, Limit of detection, Limit of quantitation, Linearity and Range.[3]

Preparation of Sustained Release tablets

Sustained Release tablets were prepared by using direct compression method. First set of the batches (F1 to F7) were prepared using HMPC K100M. Second set of the batches (F8 to F14) were prepared using Ethyl cellulose. Similarly, third set of the batches (F15 and F16) were prepared by using combination HPMC K100M and Ethyl cellulose.

Initially drug (Tramadol HCL) and other additives (polymer and diluents) except magnesium stearate and talc were passed through 60mesh sieve and thoroughly mixed in polybag for 10 minutes. Then magnesium stearate and talc was added and further mixed for 5 minutes. The resulting mixture was fed into the die of 10 station tablet machine to produce matrix tablet using round punches of 10mm diameter.

Table 1: Composition of Sustained release Tramadol Hydrochloride tablets (Each Quantity is measured in mg)

Composition/ Formulation No.	Tramadol HCl	HPMC K100M	EC	DCP	MCC	Magnesium stearate	Talc	Total weight
F1	100	30 (7%)	–	284	30	3	3	450
F2	100	45 (10%)	–	269	30	3	3	450
F3	100	60 (13%)	–	254	30	3	3	450
F4	100	75 (16%)	–	239	30	3	3	450
F5	100	100 (22%)	–	214	30	3	3	450
F6	100	125 (27%)	–	189	30	3	3	450
F7	100	150 (33%)	–	164	30	3	3	450
F8	100	–	30 (7%)	284	30	3	3	450
F9	100	–	45 (10%)	269	30	3	3	450
F10	100	–	60 (13%)	254	30	3	3	450
F11	100	–	75 (16%)	239	30	3	3	450
F12	100	–	100 (22%)	214	30	3	3	450
F13	100	–	125 (27%)	189	30	3	3	450
F14	100	–	150 (33%)	164	30	3	3	450
F15	100	150 (33%)	30 (7%)	134	30	3	3	450
F16	100	30 (7%)	150 (33%)	134	30	3	3	450

Evaluation of pre-compression parameters of powder blend

The flow properties of powder blend were characterized in terms of Angle of repose, Bulk density, Tapped density, Carr's index and Hausner's ratio.[4]

Investigation of post compression parameters of prepared formulations

The post compression parameters will be characterized in terms of Weight Variation test, Hardness, Thickness, Friability and Swelling Index.[5, 4, 6]

Drug content

Twenty tablets were crushed to a fine powder and quantity equivalent to 100mg of Tramadol HCl was dissolved in 0.1N HCl solution to make 100ml. A filtered aliquot of this solution was further diluted to get a solution of 50µg/ml concentration. The absorbance at wavelength 271nm of this solution and the same concentration of the standard Tramadol HCl solution were compared to calculate the percentage content of the drug.

$$\text{Assay}=\frac{Spl\ Abs}{Std\ Abs}\times\frac{Std\ wt}{Spl\ wt}\times\frac{Spl\ dil}{Std\ dil}\times\frac{Std\ potency}{100}\times Avg.\ tab\ wt \quad \text{.....1}$$

***In- vitro* drug release**

USP apparatus II was used to test the dissolution profiles of the reference products and the formulated products in 900ml medium at 37±0.5˚C with paddle speed 75rpm.

Formulated tablets were in dissolution jar and 10ml of aliquots were withdrawn at 1h, 2h, 4h, 6h, 8h, 10h and 12 hours respectively and filtered with Whatman no. 1filter paper and the filtrate was suitably diluted to produce final solution of 50µg/ml concentrations with dissolution medium i.e. 0.1 HCl and analyzed for Tramadol HCl content at 271nm by using UV spectrophotometer.

$$\text{Drug release per tablet} = \frac{Spl\ Abs}{\text{Std Abs}}\times\frac{\text{Std dilution}}{\text{Spl dilution}}\times \text{potency} \quad \text{.....2}$$

The marketed product was tested in two dissolution media: 0.1N HCl and Phosphate buffer p^H 6.8. Similarly the formulated product (F7) was tested in two media. The *in vitro* release of marketed product was carried out in the similar manner and the results were compared.

Swelling Index

The swelling behavior of the dosage unit was studied by measuring its weight gain at different time intervals. The swelling index of the tablets were determined by placing the tablets in the Petri dish using dissolution medium 0.1N HCl. After 1, 2, 4, 6, 8, 10 and 12 hours, tablets were withdrawn and bottled with tissue paper to remove excess water and weighed on analytical balance.[7]

$$\text{Swelling index} = \frac{(\text{Wet weight of tablet} - \text{Dry weight of tablet})}{\text{Dry weight of tablet}}\ X\ 100 \quad \text{.....3}$$

RESULTS AND DISCUSSION

Determination of analytical wavelength

The λ max of Tramadol HCL in 0.1 HCL and phosphate Buffer $P^{H\,6}$6.8 was found to be 271nm.

Analytical Method Validation

The method was identifying accurate with % recovery of 98.73%, 99.05%, and 100.74% respectively for three different concentrations. Precision was calculated statistically and the value of mean RSD calculated was 0.253% which was less than 2% so the method was found to be precise. The method was specific to Tramadol HCl. The limit of detection (LOD) was calculated to be 1.118 µg/ml. The Limit of Quantitation (LOQ) was calculated to be 3.389 µg/ml.

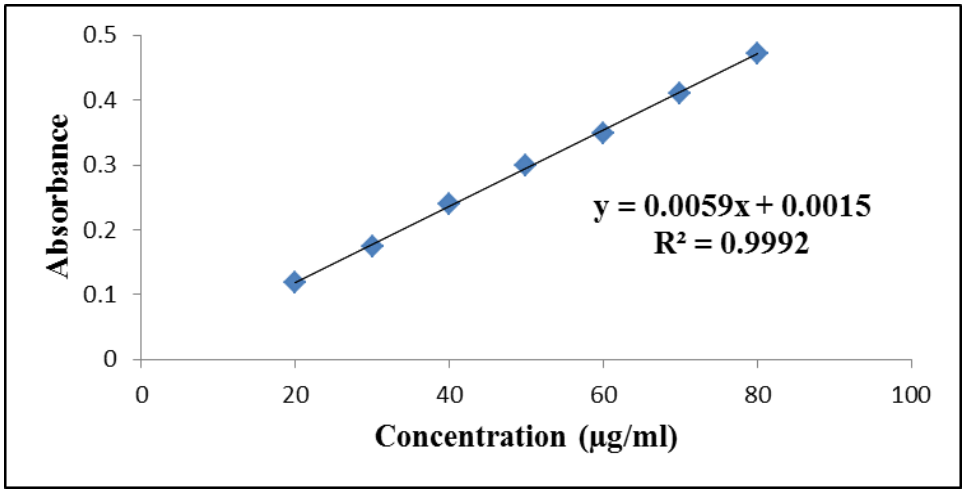

Figure 1: Calibration curve for Tramadol HCl in 0.1N HCl.

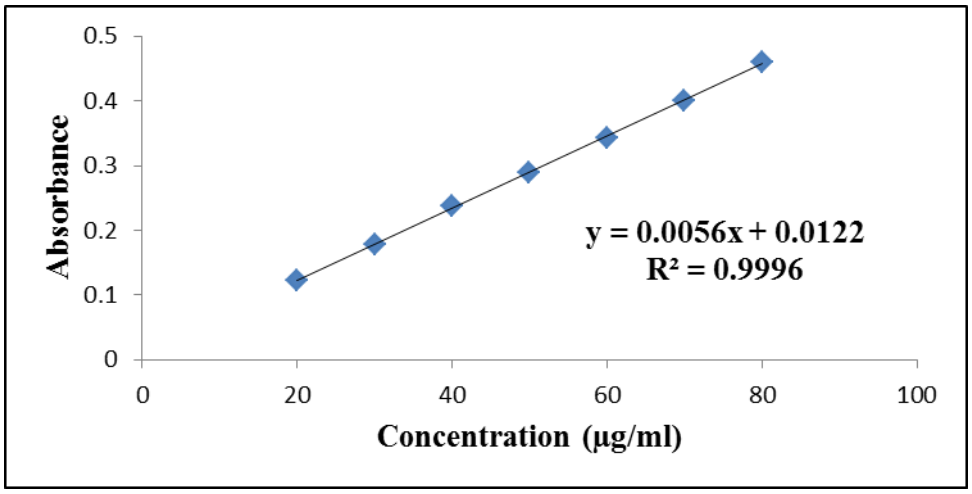

Figure 2: Calibration curve for Tramadol HCl in Phosphate Buffer p^{H} 6.8

Table 2: Pre-Compression parameters.

Formulations	Angle of Repose Degree)	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Carr's Index (%)	Hausner's ratio
F1	26.10	0.560	0.630	11.11	1.125
F2	25.50	0.561	0.631	11.09	1.124
F3	26.80	0.562	0.635	11.49	1.129
F4	27.23	0.569	0.640	11.09	1.124
F5	25.95	0.581	0.658	11.70	1.132
F6	26.68	0.575	0.650	11.53	1.130
F7	24.68	0.587	0.666	11.86	1.134
F8	26.10	0.556	0.645	13.79	1.162
F9	25.86	0.554	0.644	13.97	1.162
F10	27.79	0.598	0.698	14.32	1.167
F11	26.86	0.575	0.670	14.17	1.165
F12	25.75	0.560	0.651	13.97	1.162
F13	25.35	0.583	0.674	13.50	1.156
F14	26.01	0.581	0.673	13.67	1.158
F15	25.23	0.589	0.670	12.08	1.137
F16	26.60	0.590	0.672	12.20	1.138

Table 3: Post compression parameters

Formulations	Average Weight±sd(mg) (n=20)	Average Diameter±sd(mm) (n=10)	Average Thickness±sd(mm) (n=10)	Average Hardness±sd(kg/cm^2) (n=10)	Friability %	Assay of the drug (%Content) (n=2)
F1	451.90±2.45	10.16±0.012	4.42±0.035	7.65±0.935	0.84	98.11±0.91
F2	451.95±1.37	10.19±0.081	4.48±0.069	7.20±0.288	0.37	98.01±0.35
F3	451.34±1.39	10.18±0.021	4.44±0.085	8.01±0.382	0.94	99.45±0.86
F4	451.17±0.81	10.10±0.025	4.47±0.030	8.05±0.897	0.86	101.45±0.26
F5	452.73±2.55	10.17±0.037	4.42±0.064	7.20±0.288	0.68	105.74±0.27
F6	451.87±2.70	10.11±0.022	4.41±0.019	7.05±0.275	0.63	99.75±0.44
F7	450.87±1.89	10.10±0.017	4.49±0.097	7.10±0.208	0.33	98.15±0.52
F8	450.70±1.42	10.13±0.021	4.50±0.013	6.95±0.139	0.59	98.67±1.36
F9	451.74±1.37	10.10±0.014	4.40±0.034	6.77±0.298	0.40	98.76±0.266
F10	451.68±1.64	10.19±0.012	4.49±0.058	6.95±0.139	0.45	99.70±0.535
F11	451.18±1.00	10.15±0.023	4.42±0.089	6.93±0.256	0.54	102.93±0.44
F12	451.50±1.30	10.10±0.021	4.43±0.086	7.05±0.385	0.91	100.70±1.12
F13	450.68±1.08	10.17±0.015	4.40±0.050	7.15±0.505	0.71	103.59±0.14
F14	451.44±1.13	10.17±0.040	4.42±0.038	7.05±0.446	0.45	98.45±0.47
F15	451.17±1.38	10.15±0.026	4.40±0.019	7.21±0.673	0.72	99.390±0.37
F16	451.14±1.02	10.10±0.086	4.42±0.090	7.15±0.508	0.73	99.88±0.53

Swelling index

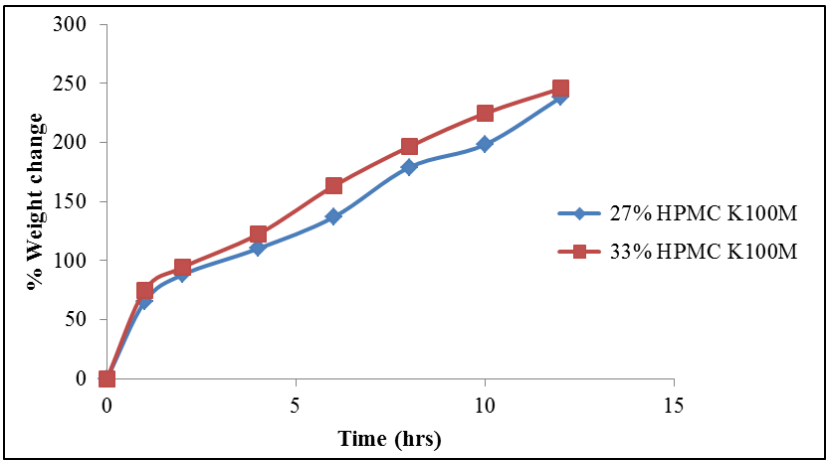

Figure 3: Swelling index of formulations containing HPMC K100M at different concentration

The swelling index for two formulations (F6 and F7) which comprised of same HPMC K100M polymer in different concentration was compared. The swelling index was calculated with respect to time. As time increase, the swelling index also increased. It may be due to proportional increase in rate of hydration upto certain limit. The result showed that with increase in HPMC K100M concentration, swelling index increased. This may be attributed to rapid hydration and gel layer formation by HPMC around the surface of the tablet. The direct relationship was observed between swelling index and polymer concentration was studied.[8]

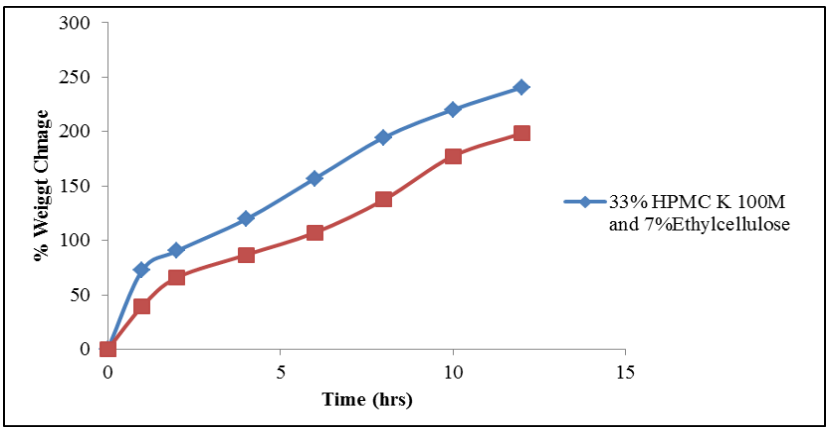

Figure 4: Swelling index of formulation containing HPMC K100M and Ethyl celulose at different concentration.

The swelling index for two formulations (F15 and F16) which comprised of HPMC K100M and Ethyl cellulose polymers in different concentration was compared. The formulation which containing high concentration of HPMC K100M, swelling index increased but the

formulation which containing low concentration of HPMC K100M, swelling index decreased. The result showed that with increase in concentration of Ethyl cellulose, swelling index did not increased. It might be due to hydrophobic nature of Ethy cellulose and non swellable matrix formation by Ethyl cellulose.[9]

Assay

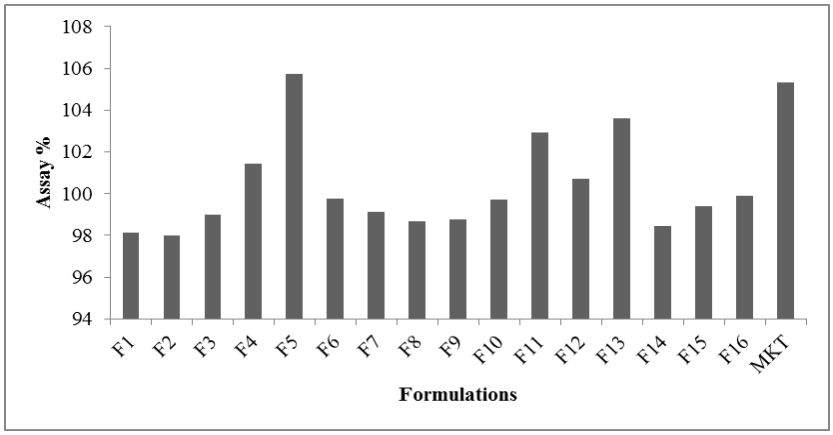

Figure 5: Assay percentage of various formulated product and marketed sample.

The assay percentages of all formulated batches were found in the range of 98.01% to 105.74% which was within the limit. Tramadol Hydrochloride Extended Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of Tramadol hydrochloride.[10]

***In Vitro* Dissolution Study**

Effect of different polymer (HPMC K100M and Ethyl cellulose) in drug release.

At 7% concentration of polymers

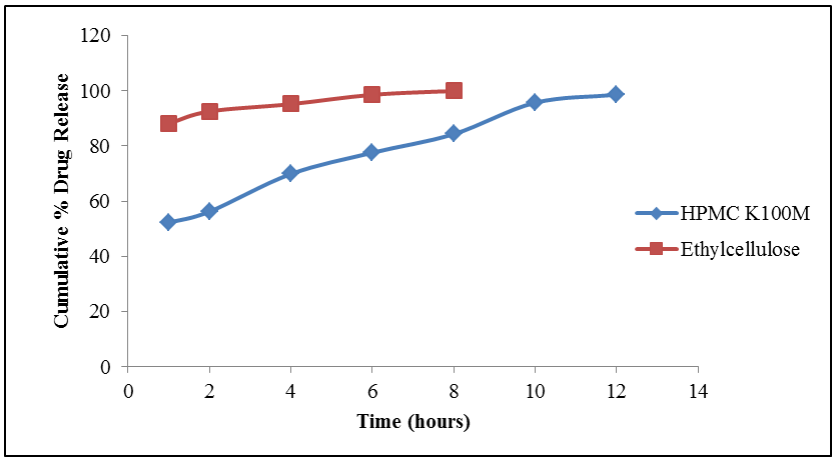

Figure 6: Cumulative % drug release from formulations containing 7% of HPMC K100M, Ethyl cellulose respectively

At 10% concentration of polymers

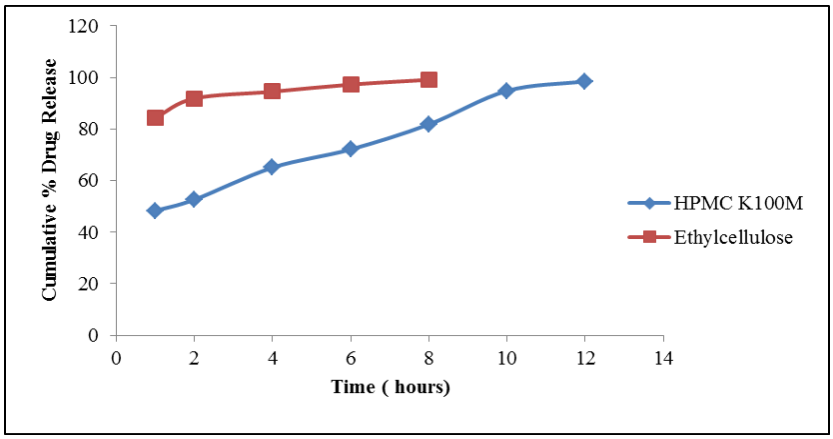

Figure 7: Cumulative % drug release from formulations containing 10% of HPMC K100M, Ethyl cellulose respectively.

At 13% concentration of polymers

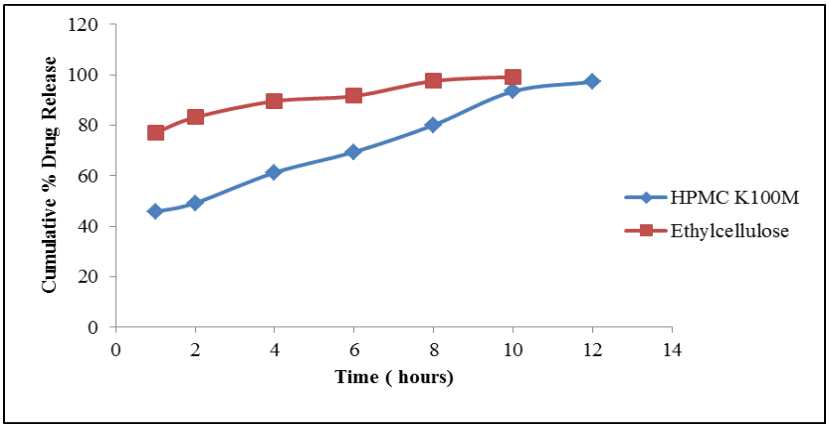

Figure 8: Cumulative % drug release from formulations containing 13% of HPMC K100M, Ethyl cellulose respectively.

At 16% concentration of polymers

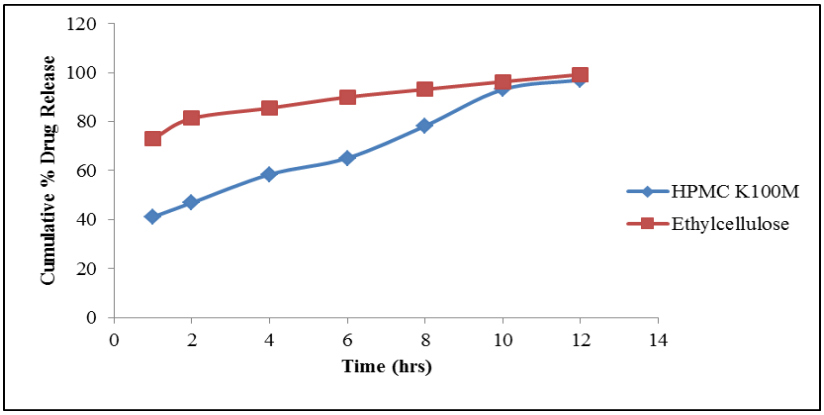

Figure 9: Cumulative % drug release from formulations containing 16% of HPMC K100M, Ethyl cellulose respectively.

At 22% concentration of polymers

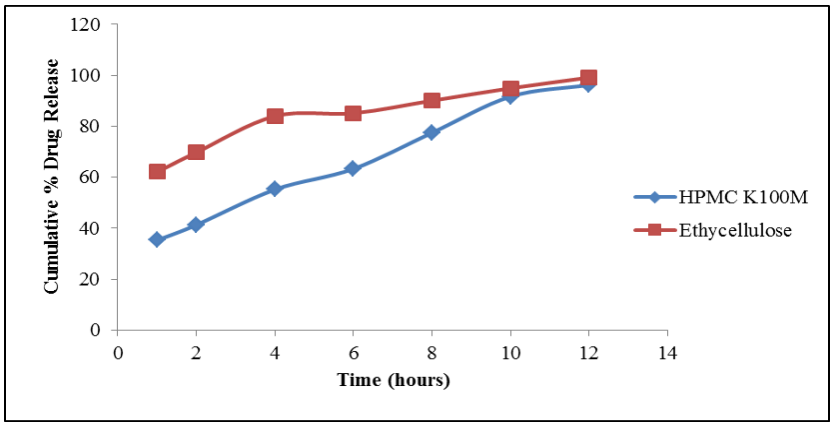

Figure 10: Cumulative % drug release from formulations containing 22% of HPMC K100M, Ethyl cellulose respectively.

At 27% concentration of polymers

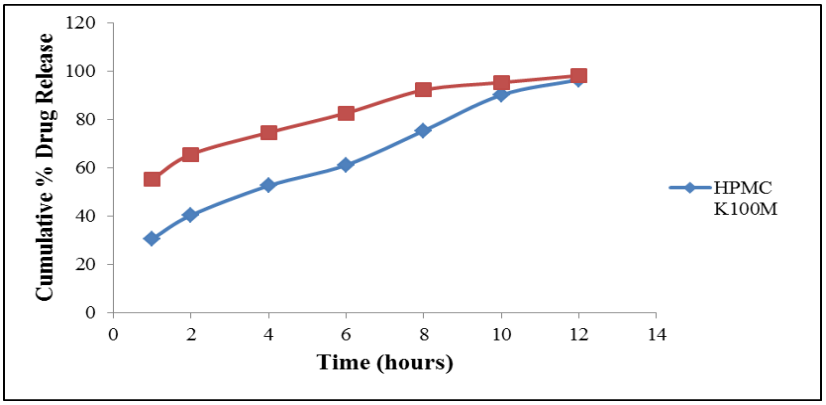

Figure 11: Cumulative % drug release from formulations containing 27% of HPMC K100M, Ethyl cellulose respectively.

At 33% concentration of polymers

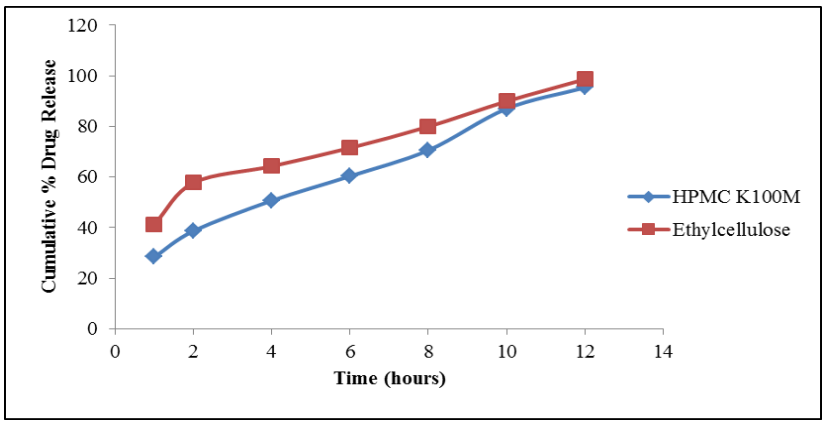

Figure 12: Cumulative % drug release from formulations containing 33% of HPMC K100M, Ethyl cellulose respectively.

While comparing the cumulative drug release from matrix tablets containing different concentration of HPMC K100M and Ethyl cellulose. The low concentration of HPMC K100M was not found to be effective to sustain the release of drugs from their matrices since medium can penetrate easily. By increasing the concentration of HPMC K100M from 7% w/w (30mg) to 33% w/w (150mg) the release rate has been reduced from 52.50% to 28.36% in 1st hour. This is because; higher concentration of HMPC K100M can strengthen the gel layer and retard the penetration of water into the dry matrix core. Also when the matrix is hydrated, diffusion path length increases which retards the drug release.[11]

The low concentration of Ethyl cellulose i.e.7% w/w (30mg) was not sufficient to sustain the release rate of drugs from their matrices. The release rate i.e. 88.14% at 1st hrs was not found to be sustained. By increasing the concentration of Ethyl cellulose i.e. 33% w/w (150mg) the release rate i.e. 41.25% at 1hour which has been found to be sustained. It concluded that the release rate decrease as the concentration of Ethyl cellulose increase. This might be because of hydrophobic nature and drug retarding property of Ethyl cellulose.

The HPMC K100M showed better sustaining action in drug release than Ethyl cellulose.

Effect of different concentrations of HPMC K100M and Ethyl cellulose in drug release

Effect of HPMC K100M in drug release

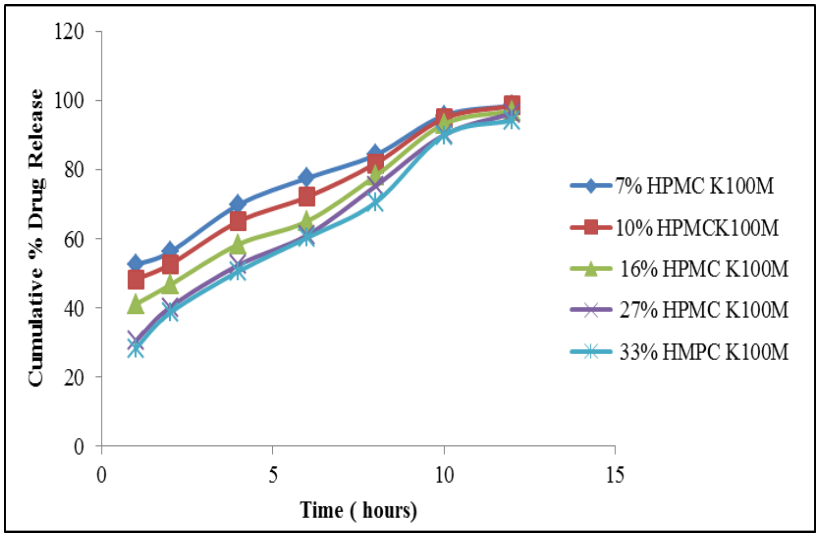

Figure 13: Cumulative % drug release from formulations containing different concentrations of HPMC K100M.

Effect of Ethyl cellulose in drug release

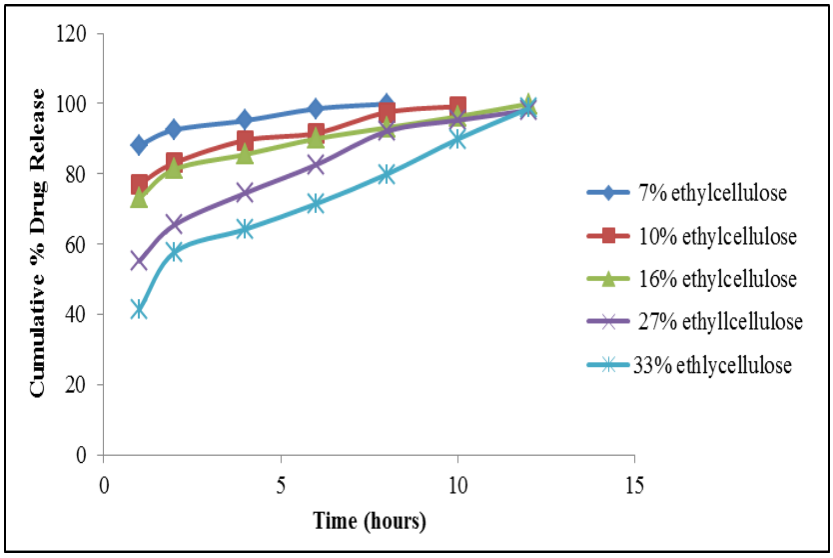

Figure 14: Cumulative % drug release from formulations containing different concentrations of Ethyl cellulose.

The drug release data obtained show that the release rate decreased as the concentration of HPMC K100M increased. With increase in concentration of HPMC polymers, the burst effect and the drug release were reduced significantly. This may be attributed to greater gel formation \resulting in increased diffusional path length for drug dissolution.[12]

When matrices are immersed in aqueous medium the polymer hydrates and swells resulting in increase in size. After some time the matrix dissolves or erodes allowing drug release. The soluble portion of the drug is released by the process of diffusion through the gel layer while the insoluble portion is released through tablet erosion. The drug release from swellable matrices is dependent on the thickness of the hydrated layer that is formed during polymer hydration. The degree of swelling determines the rate of drug release; the thicker the gel layer; the slower the rate of drug release.[12]

1. Drug release became more sustained with increasing polymer concentration or viscosity grade;
2. Different levels of methyl and hydroxypropoxy substitution results in intrinsically different hydration rates, which affected the performance of the polymer in the initial stages of tablet hydration and;
3. Different substitution level gave rise to different drug release profiles, principally as a result of differences in gel strength and susceptibility to erosion.

It have also reported that other factor that may contribute to difference in drug dissolution profile as a function of change in total polymer concentration include differences in water penetration rate, water absorption capacity and polymer swelling.[13]

Initial burst release of drug was observed with formulations containing low concentration of Ethyl cellulose. With increase in the concentration of Ethyl cellulose, this burst effect reduced and the drug released in a well controlled manner. Ethyl cellulose particles might contribute to the increased compressibility and produce more uniform matrices with uniform channels for water to diffuse and to dissolve the drug in a controlled manner.

Effect of combination HPMC K100M and Ethyl cellulose in drug release

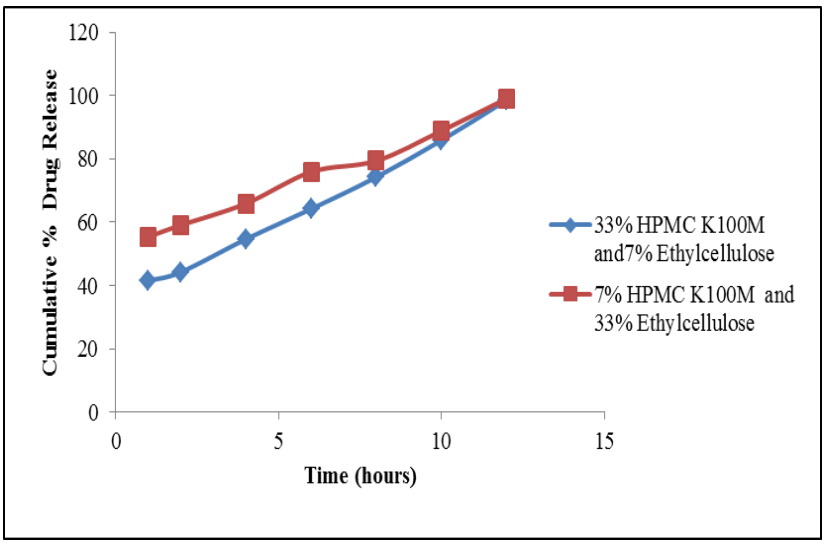

Figure 15: Cumulative % drug release from formulations containing different concentrations of combination HPMC K100 and Ethyl cellulose.

The drug release was retarded with high concentration of HPMC K100M and low concentration of Ethyl cellulose. High concentration of Ethyl cellulose and low concentration of HPMC 100M did not retard drug release sufficiently. It has been observed that the cumulative percent drug release decrease with increasing concentration of polymers. The reason attributed to this fact is slow diffusion and erosion of the gelled layer from the tablets containing higher amount of HPMC K100M or Ethyl cellulose polymer. This slow release is because of a thick gel structure that delays drug release from tablet matrix.

Dissolution profile of formulated product (F7) and marketed sample

Dissolution profile of formulated product (F7) and marketed sample in 0.1N HCl

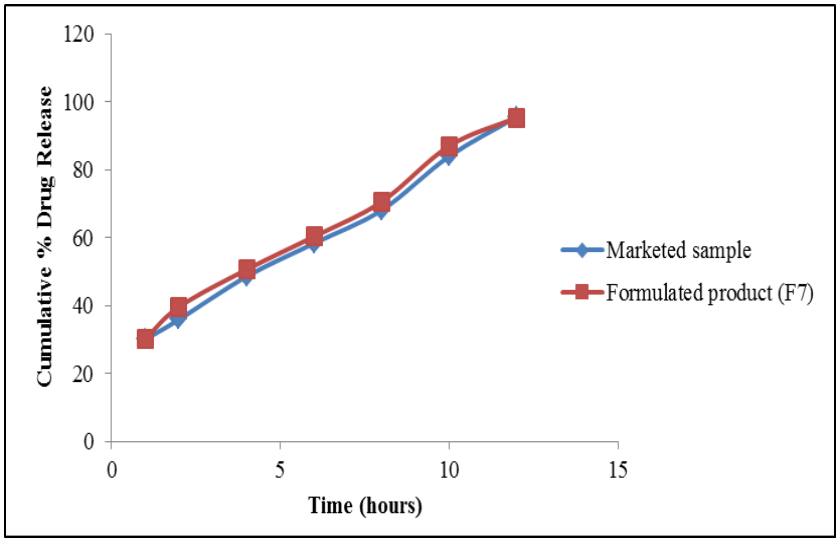

Figure 16: Cumulative % drug release from formulated product (F7) and marketed sample in 0.1N HCl.

Dissolution profile of formulated product (F7) and marketed sample in phosphate buffer pH 6.8

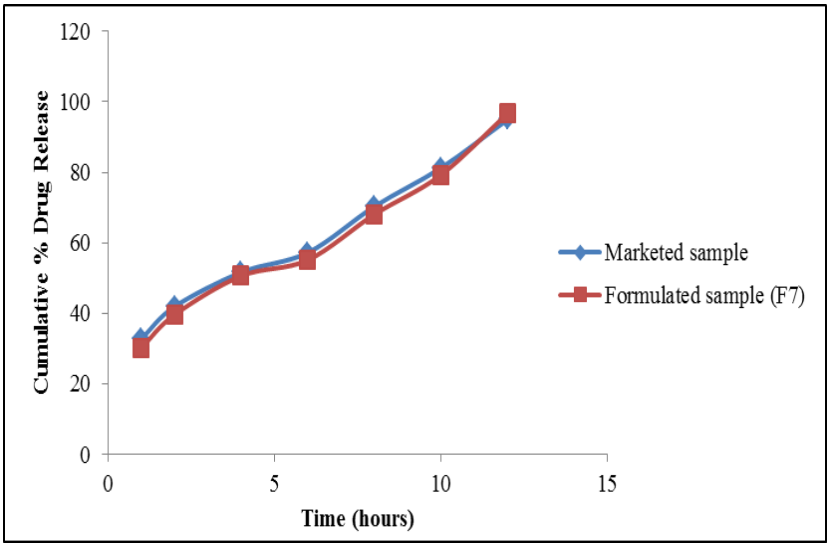

Figure 17: Cumulative % drug release from formulated product (F7) and marketed sample in phosphate buffer pH 6.8.

The formulated product (F7) which containing 33% HPMC K100M exhibited satisfactory drug release in both medium i.e. (0.1N HCl and phosphate buffer pH 6.8) was compared with the marketed formulation sample and showed very close to release profile which suggest sustained release which mechanism of drug release from was diffusion coupled with erosion.

Drug release kinetics

The data obtained from *in-vitro* dissolution studies were fitted to Zero-order, First-order, Korsymer-Peppas Model and Higuchi Model. The best fit with higher correlation coefficient (r^2 =0.99) was found with Zero order equation for F7.

Table 4: The determination of coefficients and the relevant kinetics constants.

Formulations	ZeroOrder Model		First Order Model		Korsmeyer- Peppas Model		Higuchi Model	
	R^2	K	R^2	K	R^2	n	R^2	K
F1	0.98	4.35	0.99	0.015	0.96	0.267	0.98	19.69
F2	0.99	4.74	0.99	0.015	0.95	0.298	0.97	21.28
F3	0.99	4.94	0.99	0.016	0.90	0.319	0.97	22.08
F4	0.98	5.29	0.99	0.018	0.95	0.351	0.96	23.61
F5	0.99	5.76	0.99	0.021	0.91	0.410	0.97	25.84
F6	0.99	5.96	0.97	0.023	0.97	0.419	0.98	27.73
F7	0.99	6.02	0.97	0.024	0.95	0.408	0.97	26.73
F7(buffer)	0.98	5.77	0.96	0.023	0.95	0.411	0.94	25.56
F11	0.94	2.19	0.96	0.013	0.95	0.413	0.98	10.10
F12	0.89	3.21	0.92	0.006	0.92	0.195	0.96	14.98
F13	0.94	3.83	0.99	0.012	0.95	0.195	0.98	17.70
F14	0.96	4.69	0.99	0.016	0.92	0.320	0.97	21.27
F15	0.99	5.19	0.99	0.018	0.92	0.348	0.95	22.94
F16	0.99	3.85	0.99	0.012	0.92	0.225	0.95	17.09

(The dissolution profiles of the formulated products were fitted to the Zero Order Model, First Order Model and Korsmeyer-Peppas Model and Higuchi Model. The HCl (0.1N) was the principal dissolution medium. The medium other than HCl is indicated in the parenthesis.

CONCLUSION

In the present study, attempts were made to develop sustained release tablet formulations for a highly water-soluble drug Tramadol Hydrochloride using HPMC K100M and Ethyl cellulose polymer as retarding agent. Results showed that the formulation (F7) containing sustained release tablet of Tramadol Hydrochloride containing 33% HPMC K100M have best result. At the low concentration, HPMC K100M and Ethyl cellulsoe polymers are not sufficient to show sustained release of drugs from their matrices. At the high concentration, Ethyl cellulose polymer did not retard drug release sufficiently. The HPMC K100M showed better sustaining action in drug release than Ethyl cellulose. Hence, Sustain release tablet of Tramadol Hydrochloride can be formulated using HPMC K100M.

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