International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 3 May-June 2024, pp: 2242-2250 www.ijprajournal.com ISSN: 2456-4494

"Development and evaluation of sustained release Tramadol Matrix tablet based on carboxymethyloglucan"

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Date of Submission: 10-06-2024 Date of Acceptance: 20-06-2024

ABSTRACT: The basic goal of therapy is to achieve a steady state blood level that is therapeutically effective and non-toxic for an extended period of time. A sustained release system includes any delivery system that achieves slow release of the drug over an extended period of time. The aim was to determine the release-modifying effect of carboxymethyl xyloglucan for oral drug delivery. Sustained release matrix tablets of tramadol HCl prepared by non-aqueous wet granulation techniques with DCP as a diluent. The dried blends were compressed with other necessary excipients. The tablets were evaluated for hardness, thickness, drug content uniformity, in vitro drug release studies for 24 hours (USP dissolution apparatus II, 100 rpm, 37±0.5ºC), swelling studies and in vivo performance of the matrix tablet. HPMC K100M was used to prevent the burst effect. While other tableting excipients used were DCP, talc, magnesium stearate and PVP K30 was used as a binder. Levels were decided from the observations of the in vitro evaluation of the trial batch formulation. Simplex lattice mixture design was used to find out the optimum formulation. Seven batches were formulated as per the coded levels of the design. In vitro evaluations were performed on the optimization batches. Correlation between independent variables and dependent variables were. Correlation between independent variables and dependent variables were determined form the 3D graphs and contour plots. The design expert software suggested optimum formulation based on the desirability and desired acceptance criteria. The dissolution the polymer carboxymethyl xyloglucan and HPMC K100M had significant effect on drug release from the tablet. Polynomial mathematical models, generated for various response variables using multiple regression analysis, were found to be statistically Significant, the statistical models developed for optimization were found to be valid

Keywords – Xyloglucan , matrix tablet , HPMC,sustained release ,tramadol HCL,

I. INTRODUCTION

Oral administration of drugs has been the most common and preferred route for delivery of most therapeutic agents. The popularity of oral route is attributed to patient acceptance, ease of administration, accurate dosing, cost effective manufacturing methods. An ideal drug delivery system should deliver the drug at the rate dictated by the needs of the body over the period of treatment i.e. it should provide the desired therapeutic concentration of drug in the plasma and maintain it constant for the entire duration of treatment. Many years, considerable attention has been focused on development of sustained release drug delivery systems. The rationale for the development of sustain release drug delivery system of a drug is to enhance its therapeutic benefits, minimizing its side effects while improving the management of the diseased condition [1].

Sustained release (SR) dosage forms continue to draw attention in the search for improved compliance and decrease the incidence of adverse drug reactions [2]. A sustained release system includes any delivery system that achieves slow release of the drug over an extended period of time. Figure 1 gives the co-relation of immediate, sustained and control release formulations[3].

This is achieved by better control of plasma drug levels and less frequent dosing. Pharmacokinetic theory suggests that the ultimate method for reducing the plasma maximum concentration (C_{max}) to plasma minimum concentration (C_{min}) ratio is to have zero- order absorption. Once steady state is achieved under these conditions, drug concentration in plasma is constant as long as absorption persists. Successful commercialization of an extended release formulation is usually challenging and involves consideration of many factors such as physiochemical properties of the drug, physiological factors, and manufacturing variables [1].

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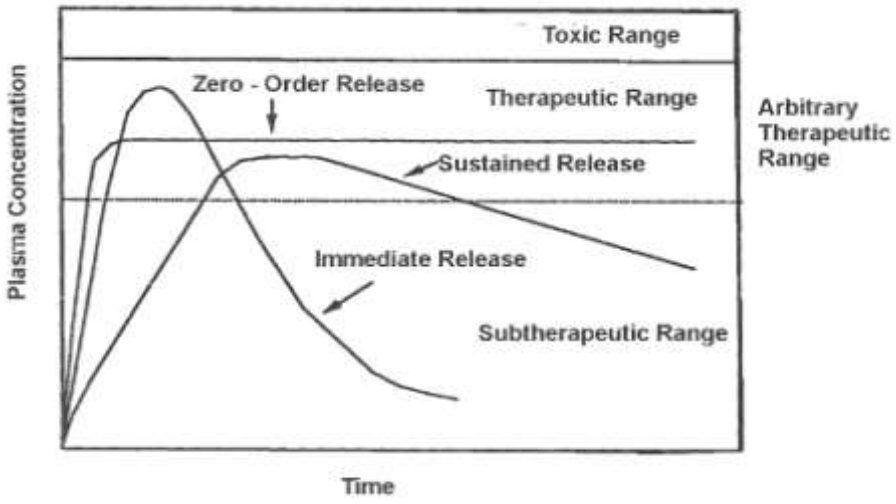

Fig. 1: Plasma drug concentration profiles for conventional tablet formulation, a sustained release formulation and a zero order controlled release formulation**.**

The United States Pharmacopoeia (USP) defines the modified-release (MR) dosage form as "the one for which the drug release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments, or promptly dissolving dosage forms" [4]. One class of MR dosage form is an extended-release (ER) dosage form and is defined as the one that allows at least a 2-fold reduction in dosing frequency or significant increase in patient or therapeutic performance when compared with that presented as a conventional dosage form (a solution or a prompt drug-releasing dosage form). The terms "controlled release (CR)", "prolonged release", "sustained or slow release (SR)" and "long-acting (LA)" have been used synonymously with "extended release". The commercial branded products in this category are often designated by suffixes such as CR, CD (controlled delivery), ER, LA, PD (programmed or prolonged delivery), Retard, SA (slow-acting), SR, TD (timed delivery), TR (timed release), XL and XR (extended release).

Mechanism and Site of absorption:

Drugs absorbed by carrier-mediated transport process and those absorbed through a window are poor candidates for controlled release system e.g. several B vitamins

Molecular size and Diffusivity:

The lower the molecular weight, the faster and more complete the absorption. In addition to biological membrane the molecule has to diffuse through a polymeric matrix in most of sustained release dosage forms. This diffusion is function of diffusivity of the drug. Diffusivity is defined as the ability of drug to diffuse through the membranes and it is inversely proportional to molecular size.

1.1. Pharmacokinetic Characteristics of the drug:

Absorption:

For a drug to be administered as controlled release formulation, its absorption rate (Ka) must be efficient since the desired rate – limiting step is rate of drug release Kr. i.e. Kr<<Ka. A drug with slow absorption is a poor candidate for such dosage forms since continuous release will result in a pool of unabsorbed drug.

Elimination Half Life:

Smaller the $t_{1/2}$, larger the amount of drug to be incorporated in the sustained release dosage form. Drugs with half life in the range of 2 to 8 hours make good candidates for such a system.

Rate of Metabolism:

A drug, which is extensively metabolized, is suitable for controlled release system as long as the rate of metabolism is not too rapid. A drug capable of inducing or inhibiting metabolism is a poor candidate for such a product since steady-state blood level would be difficult to maintain.

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Dosage form index:

It is defined as the ratio of max steady state conc.($C_{ss.max}$) to min. steady state conc.(C_{ssmin}). Since the goal of sustained release formulation is to improve therapy by reducing the dosage form index while maintaining the plasma drug levels within the therapeutic window, ideally its value should be as close to one as possible.

Protein Binding:

It is well known that many drugs bind to plasma proteins with a concomitant influence on the duration of drug action. Since blood proteins are for the most part recirculated and not eliminated, drug protein binding can serve as a depot for drug producing a prolonged release profile, especially if a high degree of drug binding occurs. Levine has shown that quaternary ammonium compounds bind to mucin in the GIT. Drug bound to mucin may act as depot and act as a sustained release product.

1.2. Pharmacodynamic Characteristics of the Drug:

Plasma concentration-Response Relationship:

Drugs whose pharmacological activity is independent of its concentration are poor candidates for sustained release systems.

Therapeutic index:

The release rate of the drug with narrow therapeutic index should be such that the plasma concentration achieved is within the therapeutically safe and effective range.

2. Various Technologies of sustained release dosage form: [3]

Technologies for designing of sustained release oral dosage forms can be classified according to two characteristics i.e. delivery mechanism and structure of the system. The "Delivery Mechanism" refers to physical and chemical principles involved i.e. dissolution, diffusion, erosion, ion exchange and osmosis. An ideal structure of a controlled release oral dosage form is that which allows the mechanism to yield the desired drug delivery rate.

Depending upon the manner of drug release from the oral sustained release systems, these are classified as,

A. Continuous release systems
B. Delayed transit and continuous release system
C. Delayed release system

A. Continuous release systems [3]

These systems release the drug for a prolonged period of time along the entire length of gastro-intestinal tract with normal transit of the dosage form. It includes dissolution-controlled release, diffusion-controlled release, ion exchange, pH dependent and osmotic pressure controlled system.

II. MATERIAL AND METHODS

Table 3: List of equipments used

Sr. No.	Instrument Name	Model	Make
1.	Tablet Compression Machine	Mini Press-II MT	Rimek
2.	USP Tablet Dissolution Apparatus Type II	DA 6D	Veego
3.	UV-Visible double beam Spectrophotometer	V-530	Jasco
4.	FTIR	460 plus	Jasco
5.	Electronic Balance Model	AY-120	Shimadzu
6.	Monsanto Hardness Tester	MH-53	Nevtex
7.	pH Meter	101	VHS Electronics
8.	Differential Scanning Calorimeter	DSC 821	Mettler
9.	XRPD Apparatus	BV (PW 1710)	Phillips
10.	Environmental Test Chamber	CHM 6 S	Remi Instruments
11.	Vacuum Oven	DTC-96	Biotechnics
12.	Bulk Density Apparatus	BDA 001	Lab. Hosp.
13.	Friabilator	RF 112	VHS Electronics
14.	Vernier Caliper	EL-50	Equip Tronics
15.	HPLC	Agilent 1120	Agilent

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Table 4: List of chemicals used

Sr. No.	Chemicals	Suppliers
1.	Cacboxymethyl xyloglucan Powder	Encore Natural Polymer, private limited
2.	HPMC K100M	SD Fine Chemicals Ltd
3.	Tramadol HCl	Rantus Pharma Ltd
4.	Magnesium Stearate	Loba Chemicals Pvt. Ltd
5.	Di-Calcium Phosphate	Loba Chemicals Pvt. Ltd
6.	PVP K- 30	SD Fine Chemicals Ltd
7.	HPLC grade Acetonitrile	Merck, Mumbai
8.	Methanol	Merck, Mumbai
9.	Potassium Dihydrogen Phosphate	Ideal Cures Ltd., Mumbai
10.	Di-Calcium Phosphate	Loba Chemicals Pvt. Ltd.

Table 5: List of softwares used

Sr. No.	Software	Make
1.	PCP Disso V3.0	Poona College Of Pharmacy.
2.	Design Expert V7.1.4.3	Micromath Inc., USA
3.	GraphPad Prism version 4.03.354	Graphpad software, Inc.

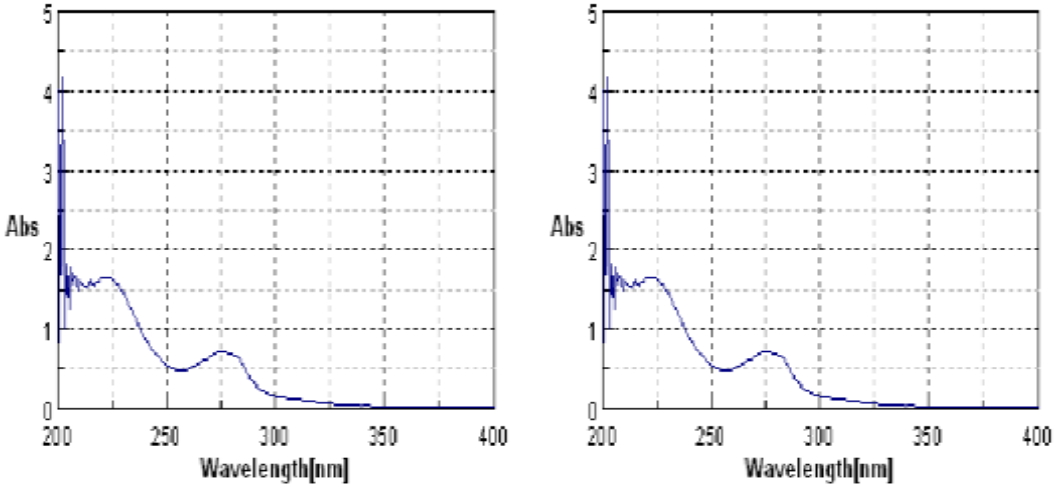
III. RESULT AND DISCUSSION

3.1 PRELIMINARY STUDIES

3.1.1 Characterization of drug

3.1.1.1 UV Spectroscopy (Determination of λmax)

The UV spectrum obtained after the proper dilution of drug in different solutions, 0.1 N HCl and phosphate buffer pH 6.8 respectively is shown in Figure 7.The spectrum showed maximum absorption at 220 nm which is nearly at the edge of the UV range, it also showed a peak at 271 nm. Hence all the further analysis was done by using 271 nm.



(a)(b)

Figure 7: The spectra of pure drug **(a)** in 0.1N HCl and **(b)** in buffer pH 6.8

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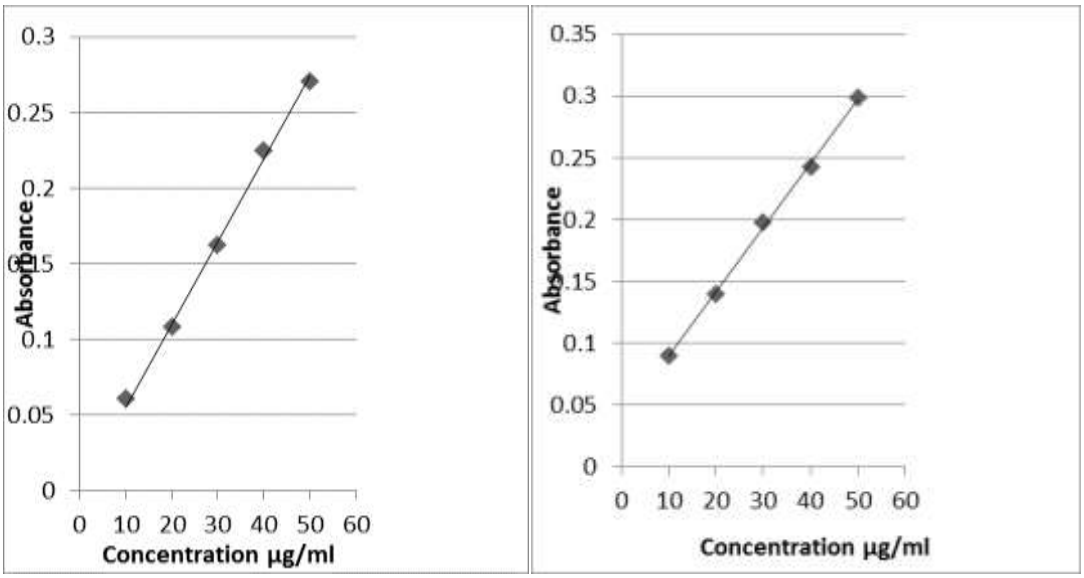
3.1.1.2 Calibration curve by UV analytical method

Calibration curves were constructed in 0.1 N HCl and phosphate buffer of pH 6.8. Beer's law at 271 nm was obeyed in the concentration range of 10-50 µg/ml. The high values of regression coefficients 0.997 and 0.999 respectively estimated the linearity of relationship between concentration and absorbance (as shown in figure 10). The equations obtained in 0.1N HCl and buffer pH 6.8 was found to be y=0.005x + 0.004 and y=0.005x+0.037 respectively.



(a) **(b)**

Figure 8: Calibration curve of tramadol hydrochloride in (a) 0.1N HCl and (b) phosphate buffer pH 6.8

3.1.1.3 FTIR spectroscopy

The IR spectrum of the drug was recorded and the functional groups were interpreted as per the structure and were found to be appropriate or matching the structure of the drug. Figure 8 shows the IR spectra of the pure drug.

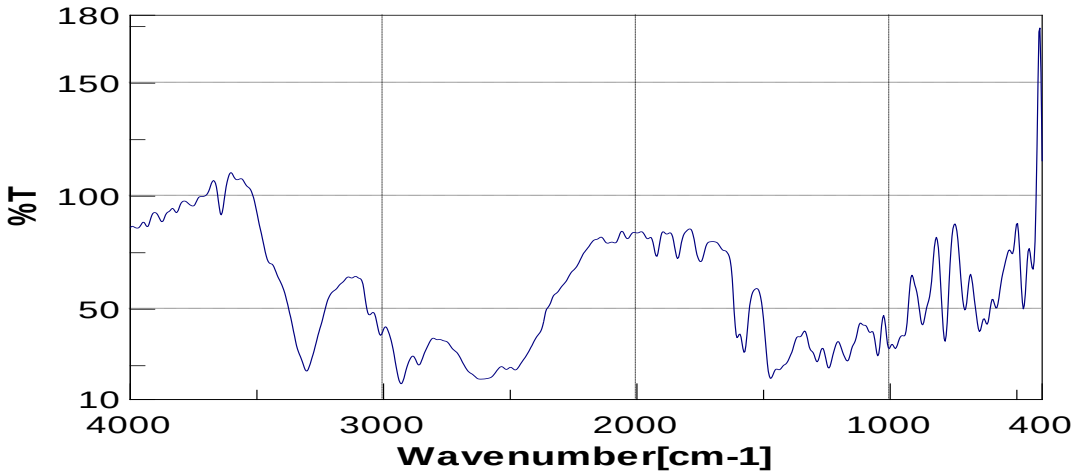


Figure 9: The FTIR spectra of pure drug

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Table 13: Interpretation of the peaks obtained in the IR spectra along with their corresponding functional groups

Functional Groups	Wavenumber (cm^{-1})
3250 cm^{-1}	C-N stretch
2950 cm^{-1}	C-H
1380 cm^{-1}	-OH stretching
1257 cm^{-1}	C-O stretching
1680 cm^{-1}	representing HCl

3.1.2 Drug-Excipient compatibility study:

Compatibility of Tramadol HCl with potential formulation excipients using FTIR spectrums are shown in Figure 9. The characteristic peaks of the drug are maintained with only minor changes in % transmittance. Thus, no evidence of any significant interaction between drug and studied excipients is seen.

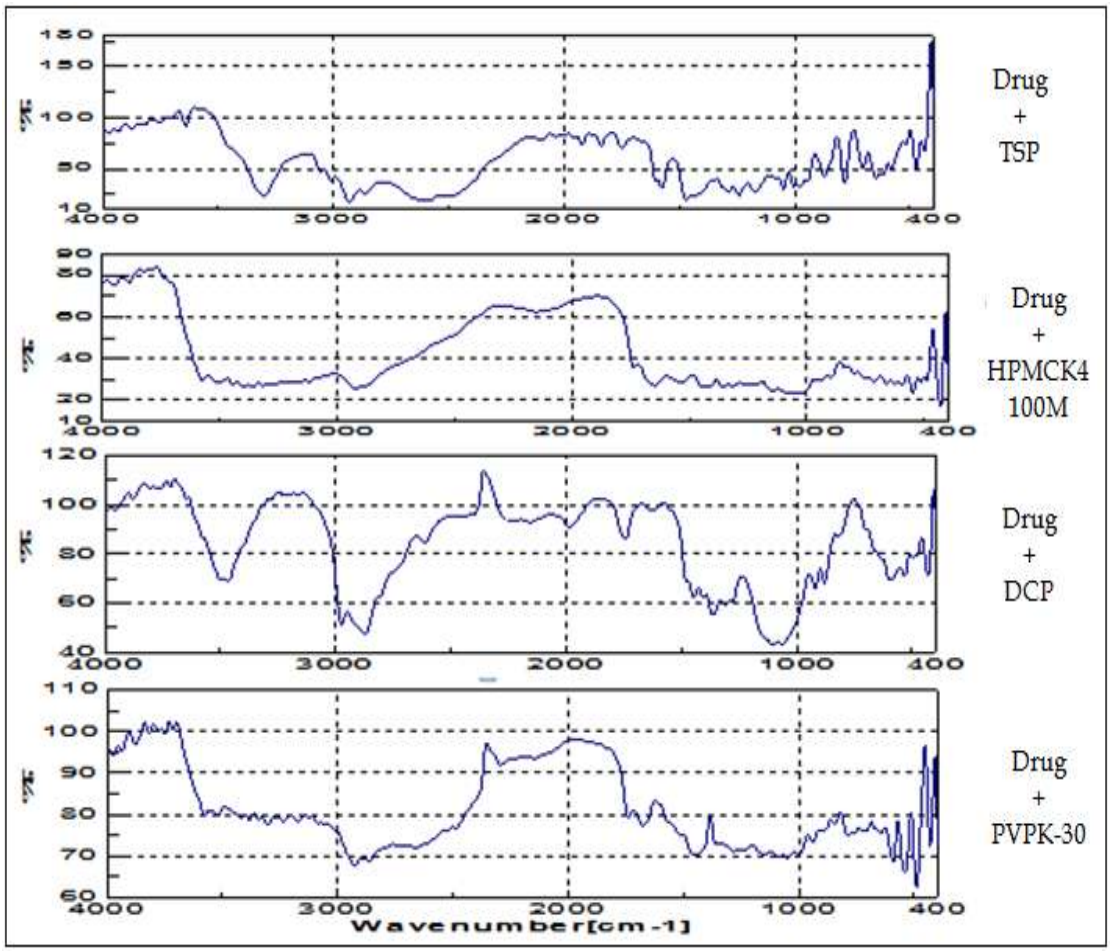

Figure 10: The IR spectra for drug excipient compatibility

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Table 14: Pre Compression properties of A1 to A5 batches

Parameters	A1	A2	A3	A4	A5
Bulk density	0.506 ± 0 .02	0.493 ± 0.03	0.512 ± 0.04	0.283 ± 0.03	0.306 ± 0.04
Tapped density	0.582 ± 0.04	0.555 ± 0.03	0.581 ± 0.02	0.325 ± 0.06	0.352 ± 0.02
Angle repose	19.24± 0.15	21.91± 0.12	19.86± 0.08	23.05± 0.19	20.18 ±0.04
Carrs index	13.08 ± 0.02	11.25 ± 0.03	11.82 ± 0.03	12.95 ± 0.03	13.08 ± 0.03
Hausners ratio	1.15 ± 0.16	1.12 ± 0.09	1.13 ± 0.09	1.14 ± 0.02	1.15 ± 0.06

The hardness, thickness, friability, weight variation and drug content of all the trial formulations (A1 to A5) were determined and the results obtained are mentioned in the tables 26. The tablets weighing above 250mg have the limit of ± 5% variation according to Pharmacopoeia of India [87]. The tablets evaluated showed the weight variation within limit, and thus passed the test. Weight of tablet is an important factor which affects the drug content of the tablet, if not within the limit. Hardness alone cannot be considered as absolute indicator of the tablet strength. Hence, another parameter measured was the friability of the tablets. The friability of the tablets was found to be less than 1% which was considered within the limit [4]. The measure of these two parameters gives the strength of the tablets during handling, packaging, shipping etc. The drug content of the all the selected matrix formulations were found to be within the limits (98 – 102%) as per Indian Pharmacopoeia.

Table 15: Post Compression properties of A1 to A5 batches

Parameters	A1	A2	A3	A4	A5
Hardness	5.4 ± 0.16	5.5 ± 0.14	5.70 ± 0.22	5.50 ± 0.91	5.4 ± 0.08
Friability	0.34 ± 0.22	0.31 ± 0.12	0.28 ± 0.31	0.35 ± 0.18	0.29± 0.27
Weight variation	208 ± 1.03	261 ± 0.83	308 ± 1.09	358 ± 0.95	409 ± 0.83
Drug content	98.34 ± 0.22	99.21 ± 0.11	100.56 ± 0.89	98.10 ± 0.18	98.31 ± 0.21
Thickness (mm)	3.154 ± 0.009	3.115 ± 0.009	2.89 ± 0.015	3.133 ± 0.014	3.03 ± 0.036

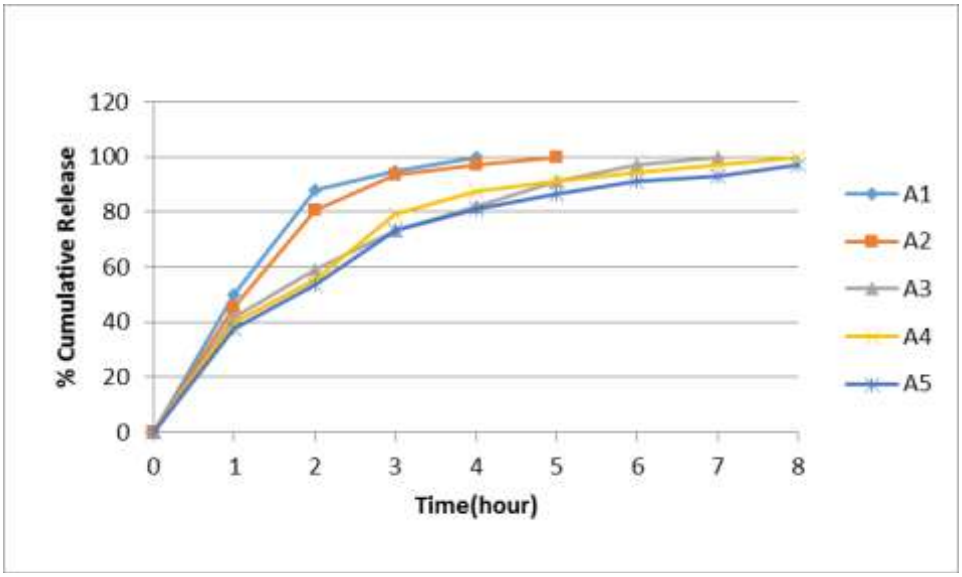

Figure 11: Dissolution profile for batches A1 to A5

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Swelling study result showed slow and gradual increase in swelling index with time, as CM xyloglucan does not swell instantaneously as soon as it comes in contact with water as shown in figure 12; this results in burst release due to improper swelling.**Figure 12**: Swelling index for A1 to A5 formulation

IV. CONCLUSION:

Sustained drug release following Higuchi kinetics attained in the current study indicates that the hydrophilic matrix tablet prepared using carboxymethyl xyloglucan and HPMC K100M, can successfully be employed to sustain the drug release up to 10 hours. Carboxymethyl xyloglucan played major role in sustaining release of tramadol at later stage of release profile, where as HPMC K100M prevented the burst effect by controlling the sudden release of drug from the dosage form at the initial stage of the release profile. It was concluded that appropriate balancing between various levels of the polymers may contribute better results. High degree of prognosis obtained using RSM corroborates that a simplex lattice design is quite efficient in optimizing drug delivery systems. A novel twice a daily product, carboxymethyl xyloglucan matrix tablet, was found to demonstrate similar AUC relative to marketed Tramadol HCl tablet given four times daily. The plasma concentration versus time profile demonstrated prolonged systemic delivery of Tramadol. This product is therefore suitable for twice a daily administration.

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