International Journal of Farmacia

Journal Home page: www.ijfjournal.com

Formulation and evaluation of tramadol using pulsincap technology

***Ch. Vijayalaxmi, Sirisha**

CMR College of Pharmcy, Kandlakoya, Medchal Road, Hyderabad-501401

Corresponding Author: Ch. Vijayalaxmi

***Email: vijaya2556@gmail.com**

ABSTRACT

The purpose of this research was to design and evaluate an oral pulsatile colon specific to achieve time and or site specific release of tramadol based on chronopharmaceutical approach tramadol a centrally acting analgesic and synthetic analog of codeine, it has asignificantly lower affinity for opiod receptors than codeine .indicated in the treatment of moderate to severe pain tramadol is used to treat postoperative dental ,cancer and as an adjuvant to nsiad therapy in patients with osteoarthritis. Tramadol was prepared by using pulisin cap technology with different polymervariation .and formulation parameter were optimized .all the formulation were evaluated for flow properties and in vitro drug release was carried out in ph 7.2 buffer using USPXXIV dissolution rate test apparatus at 100 rpm 37^0 C ± 5^0 C capsule are subjected to formaldehyde treatment. It is concluded these pulsincaps are the potential system for oral pulstaile colon specific for treatment of osteoarthritis.

Keywords: Tramadol, Pulsincaps, Colon specific.

INTRODUCTION

Controlled drug delivery systems have acquired a centre stage in the area of pharmaceutical R &D sector [1]. Such systems offer temporal &/or spatial control over the release of drug and grant a new lease of life to a drug molecule in terms of controlled drug delivery systems for obvious advantages of oral route of drug administration [2]. These dosage forms offer many advantages, such as nearly constant drug level at the site of action, prevention of peak-valley fluctuation, reduction in dose of drug, reduced dosage frequency, avoidance of side effects and improved patient compliance. In such systems the drug release commences as soon as the dosage form is administered as in the case of conventional dosage forms. However, there are certain conditions, which demand release of drug after a lag time. Such a release pattern is known as pulsatile release [3].

Methods for delayed drug delivery systems [4]

1. pH-dependent delivery
2. Time dependent delivery
3. Pressure dependent delivery
4. Bacteria- dependent delivery

Therefore, the possibility of exploiting delayed release to perform chronotherapyis quite appealing for those diseases, the symptoms of which recur mainly at night time or in the early morning, such as bronchial asthma, angina pectoris and rheumatoid arthritis [5-7]. The delay in the onset of release has so far mainly been achieved through osmotic mechanisms, hydrophilic or hydrophobic layers, coating a drug-loaded core and swellable or erodible plugs sealing a drug containing insoluble capsule body. Delivery systems with a pulsatile release pattern are receiving increasing interest for the development of dosage forms, because conventional systems with acontinuous release are not ideal [8]. Most

conventional oral controlled release drug delivery systems release the drug with constant or variable release rates [9, 10]. A pulsatile release profile is characterized by a time period of no release rates (lag time) followed by a rapid and complete release [11].

MATERIALS AND METHODS

Formulation of tramadol granules

The granules were prepared by blending tramadol with different polymers. As shown in Table no4.7 powder mixtures of Tramadol, microcrystalline cellulose (MCC, Avicel PH- 102), HPMCK4M, Ethylcellulose, guargum, PVP-K ingredients were dry blended for 20 min, followed by addition of Magnesium Stearate. The mixtures were then further blended for 10 min. Hydrogel plug was prepared by using 50mg HPMCK4M polymer. By directly compressing the polymer in compression machine.200 mg weighed granules equivalent to the dose 50mg of tramadol were placed in theformaldehyde treated body of the capsule and it was locked by hydrogel pluggin material of Gum HPMCK4M. Finally non-treated cap of the capsule was placed on it.

Insolubilisation of gelatin capsules by formaldehyde treatment

Hard gelatin capsules were taken and the bodies were separated from caps of the capsule. Formaldehyde was taken in a petri dish and placed in an dessicator , this bodies of the capsules are dipped in the formaldehyde and then the lid of dessicator is closed and kept aside for 24hrs.

Procedure

The selected size '0' of hard gelatin capsules (blue cap with orange body) were taken, that capsules bodies and caps were separated. The bodies were placed on a wire mesh spread as a single layer. They were placed in a desiccator containing formaldehyde liquid at the bottom in equilibrium with its vapour. The bodies of capsule were exposed for varying periods of time viz., 6, 12 and 24 hrs. The capsule bodies were removed from the desiccators after the required exposure time and air-dried for 4 hrs. Later they were dried in a desiccators for 12 hrs and stored in an air tight container.

Test for the solubility of capsules

Disintegration test was performed on both untreated and treated capsules. The formaldehyde treated body joined with untreated cap and was tested for disintegration. Disintegration test was carried out by using disintegration test apparatus. Purified water was used as medium and was maintained at 370C through the experiment.

Preparation of blend for filling in to capsules

Different blend formulations were prepared for filling into capsules are given in Tables 4.7In each formulation accurately weighed quantity of drug, polymer along with other ingredients the used in were passed through mesh No. 60. All the ingredients were mixed together in a mortar to obtain a homogeneous mixture by using geometric dilution technique. HPMC K4M and ethyl cellulose were selected as two polymers for controlling the release of drug. The polymer was used at weight of 10, 20, 30, 40 and 50 mg per unit in different formulations and studied the effect of polymer concentration. In these formulations polymer was used in two different methods. In one case (Formulation F1 to F8) the polymer was blended with other excipients and filled in to capsules

Preparation of modified pulsincaps

Bodies of the gelatin capsules of size '0' hardened with formaldehyde for 12 hours were taken for preparing the modified pulsincaps. In case of formulation F1 to F8, drug excipient blend equivalent to 200 mg tramadol was weighed and filled into the hardened capsule body. Then hydrogel plug of HPMCK4M was placed on the body. Then the solublecap was locked into the body to form the modified pulsincap.

Uniformity of weight

From each batch 20 pulsincaps were selected at random, weighed together and individually. The mean and standard deviation were determined.

Estimation of drug content

From each batch of the prepared pulsincaps of tramadol ten pulsincaps were randomly selected and the contents were removed and powdered. From this sample 100 mg powder was accurately transferred into a 100 ml volumetric flask. Added 10 ml of methanol to dissolve tramadol. The solution is made up to volume with pH 7.2 phosphate buffer. The resulted solution was filtered through 0.45 μm filter

paper and suitably diluted and the drug content was estimated spectrophotometrically by measuring the absorbance at 272 nm.

In vitro dissolution studies

In vitro drug dissolution studies were conducted by using the dissolution rate test apparatus (M/s. Electro Lab Dissolution Tester USP). For in vitro dissolution studies of tramadol pulsincaps, phosphate buffer of pH 7.2 was used as the dissolution medium. The in vitro dissolution studies were carried out by using USP XXIV Type-I dissolution rate test apparatus (basket system). The stirring rate was 100 rpm. 900 ml of the dissolution medium was used and was maintained at 37ºC ± 0.5ºC throughout the experiment. 5 ml samples of dissolution fluid were withdrawn at predetermined time intervals with a pipette fitted with a filter. The volume withdrawn at each timeBinterval was replaced with 5ml of fresh dissolution medium maintained at the same temperature. The filtered samples were suitably diluted whenever necessary and assayed for tramadol by measuring absorbance at 272 nm. All the dissolution experiments were conducted in triplicate and the mean values are reported.

Analysis of Dissolution data

The analysis of drug release mechanism from a pharmaceutical dosage form is an important but complicated problem and is practically evident in case of modified release dosage form. The dissolution data obtained was fitted to zero order [13], first order [14, 15], Higuchi [16] and erosion [17] to understand the order and mechanism of drug release from the Pulsincaps.

Stability Studies

The stability study of the formulations was carried out according to ICH guidelines at 40 ± 2o C/75 ± 5 % RH for three months by storing the samples in stability chamber (Labcare, Mumbai). The purpose of stability testing is to provide evidence of the quality of the drug substance or drug product, and how it varies with time under the influence of a variety of environmental conditions (heat, humidity, light, air etc). The final formulation was packed in suitable packing like blister and strip packs and then they will be kept at different temperature, humidity conditions and the samples will be analyzed for their physical and chemical properties.

Table 1: Stability studies storage conditions

Study	Storage conditions	Minimum time period covered by data at submission.
Long term	25 ± 2°c / 60 ± 5% RH or 30 ± 2°c / 75 ± 5% RH	12 months
Intermediate	30 ± 2°c / 65 ± 5% RH	6 months
Accelerated	40 ± 2°c / 75 ± 5% RH	6 months

RESULTS AND DISCUSSIOIN

Pre formulation study

Organoleptic properties: the organoleptic properties i.e. color, taste and odor test were performed as per procedures

Table 2: Oraganoleptic Evaluation

Properties	results
Description	powder
Taste	Tasteless
Odor	Odorless
color	Critine

Discussion

The organoleptic properties of tramadol was found to be citrine color, unpleasant, odor less were as per the specification.

Solubility

It was determined as per procedures .the results are given table 3.

Table 3: Solubilty

Solvent	Solubility property of drug
DMSO	Soluble
Choloroform	Not soluble
Water	Partly soluble
Methanol	Soluble

Discussion

Tramadol were found to be soluble in DMSO and ethanol, partly soluble in water, not soluble in chloroform.

Table 4: Pre compression parameters for granules

Formulations	Angle of Repose (θ)	Loose Bulk Density (g/ml)	Tapped Bulk Density (g/ml)	%Compressibility	Hausner's ratio
F1	24.3	0.35	0.41	14.63	1.17
F2	26.7	0.39	0.45	13.33	1.15
F3	23.9	0.42	0.50	16.00	1.19
F4	28.4	0.38	0.44	13.64	1.16
F5	24.5	0.36	0.42	14.29	1.17
F6	26.9	0.33	0.39	15.38	1.18
F7	28.1	0.38	0.43	11.63	1.13
F8	24.9	0.33	0.38	13.16	1.15

Standard calibration curve for tramadol

The standard calibration of tramadol was developed in 0.1N Hcl. The buffer was selected in order to mimic the in vivo conditions of the git. Discussion /; standard graph of tramadol in 0.1 NHCL Show linearty range in the Concentration range 2-10ug correlation of 0.997

Table 5: Calibration curve data of tramadol In 0.1 NHCL

S. No	Concentration	Absorbance
1	0	0
2	2	0.019
3	4	0.033
4	6	0.05
5	8	0.065
6	10	0.086

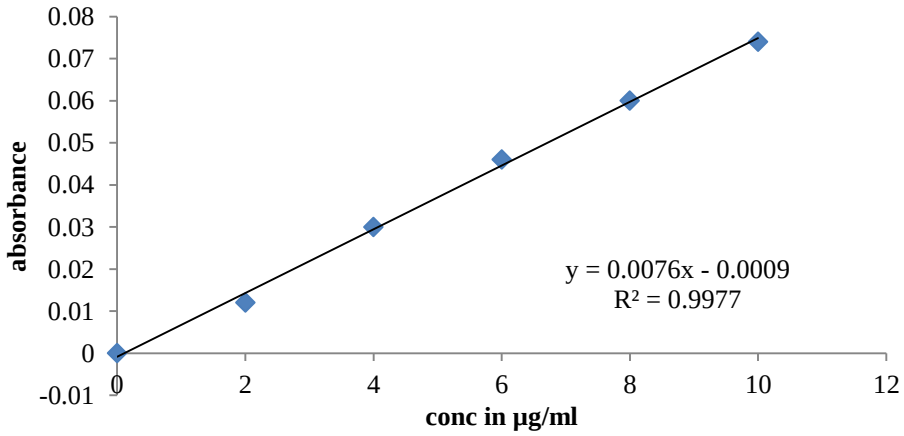

Fig 1: Calibration curve of tramadol in 0.1NHCL

Table 6: Calibration curve data of tramadol in PH 6.8 phosphate buffer

Concentration	Absorbance
0	0
2	0.012
4	0.030
6	0.046
8	0.060
10	0.074

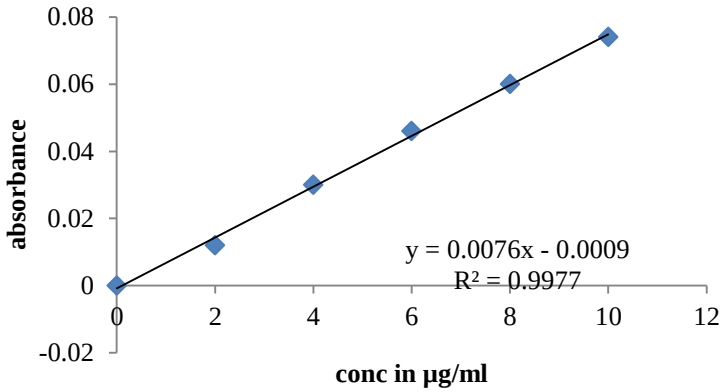

Fig no 2. Calibration curve data of phosphate PH 6.8 buffer

Discussion

Standard graph of tramadol in 6.8 ph phosphate buffer shows linearity in the concentration range of 2-10ug with correlation coefficients of 0.997

Drug excipient compatibility studies

The FTIR spectra of the drug (alone), polymer (alone) and the drug-polymer (mixture) were recorded by the potassium bromide pellet method. From the infrared spectra it is clearly evident that there were no drug-polymer interactions of the drug

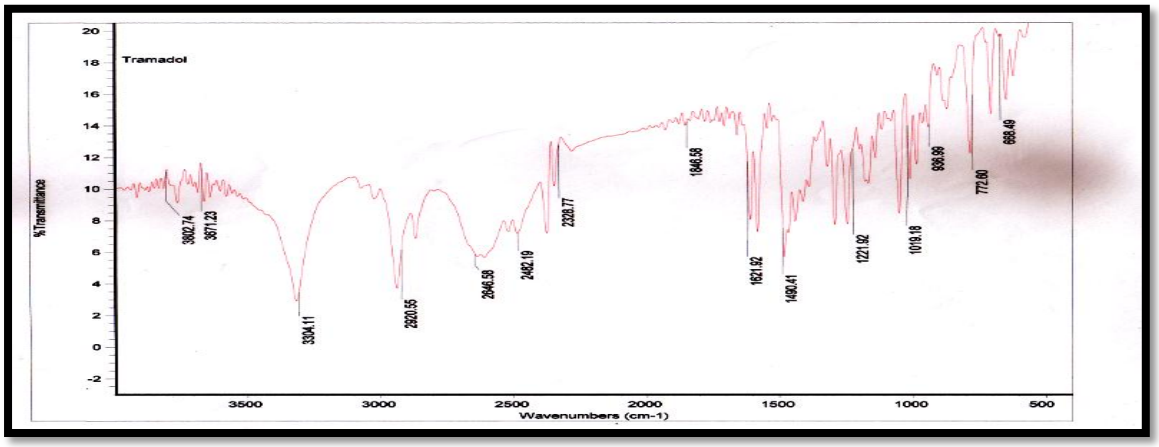

Fig no .3 FTIR SPECTRA of pure drug

Discussion

Drug –excipent computability study indicate that all used exciepents in the optimized formulation are comptabile with drug based on ftir spectra.

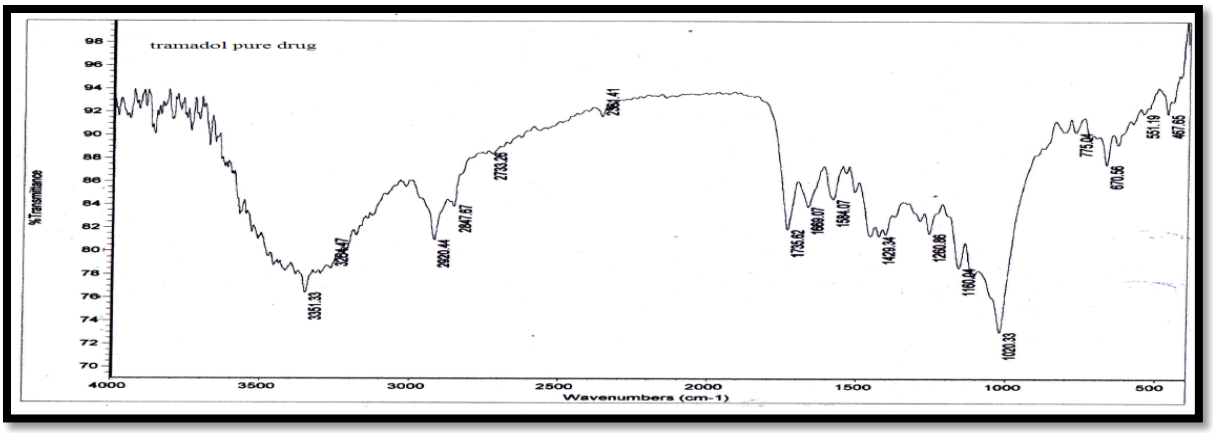

Fig no .4 FTIR SPECTRA

Time in mins	F1	F2	F3	F4	F5	F6	F7	F8
30 mins	17.9	32.0	48	25	21.62	30.8	22.5	19.8
1 hr	28.6	47.43	60	34	37.4	42.83	30.82	31.8
2 hr	40.1	58.98	82	48	45.6	69.25	38.7	45.5
3 hr	72.5	78.6	96.4	60	50.3	98.33	55.5	53.4
4 hr	99.7	96.1	--	98.6	74.45	--	69.2	56.6
6 hr	--	--	--	--	99.36	--	86.4	76.8
8 hr	--	--	--	--	--	--	95.5	88.8

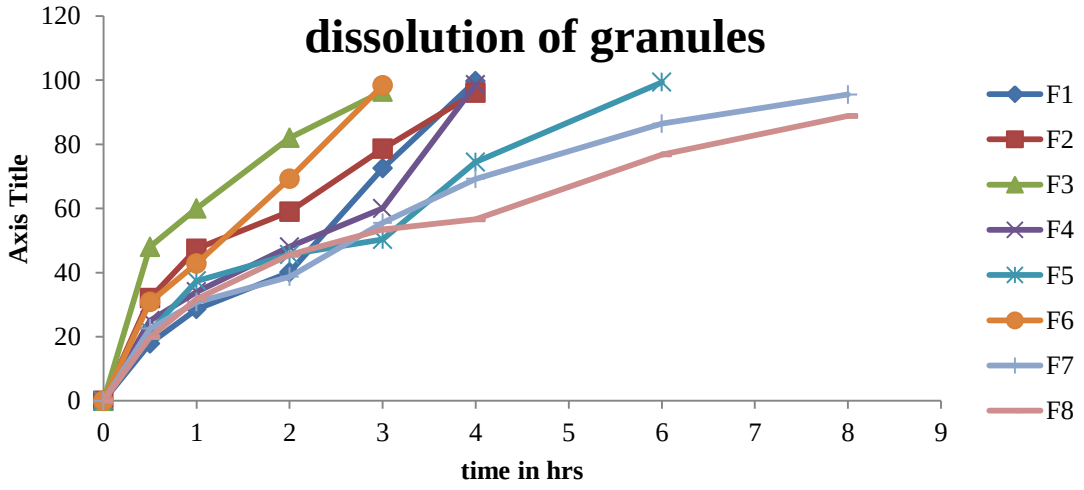

Fig no.5 dissolution graph of granules F1 to F 8

DISCUSSION

The dissolution for all f8 formulation was carried out and results are shown table 6.6. The dissolution profile graphically represented in fig no 6.d. All the f8 formulations were subjected to dissolution. studies of dissolution was carried out in USP XXIV type -1 apparatus at 100 rpm in the volume of 900ml of dissolution medium was used and maintained at $37^{o}c\pm0.5^{0}c$. in f1 formulation the polymer was HPMCK4M used and in 4 hours result found too be 99.7%. in f2 formulation the polymer was ethylcellulose used and in 4 hours results found to be 96.1%.like that it was carried for remaining formulation .in f7 and f8 combination polymers used .in f7 results found to be 95.5%in 8 hrs and by increasing polymer concentration in f8 results found be 88.8%.. Based on the drug release with in time period f7 was optimized and further formulated as pulsincaps

Table no .8 dissolution data for tramadol pulsing cap

Time in Hrs	P H 1	P H 2	P H 3	P H 4	P H 5	P H 6
0	**0**	**0**	**0**	**0**	**0**	**0**
0.5	0	0	0	0	0	0
1	0	0	0	0	0	0
2	4.8	4.8	6.9	0.9	2.2	0.59
3	11.2	9.2	9.8	1.3	3.1	1.8
4	13.8	12.2	12.3	1.5	5.2	4.1
5	99.1	14.8	14.2	1.7	7.6	6.0
6	99.3	68.3	78.9	2.0	8.3	7.5
7	--	96.9	88.9	3.1	10.8	8.9
8	--	--	99.8	3.9	11.3	9.6
9	--	--	--	98	12.7	10.8
10	--	--	--	--	101.5	12.0
11	--	--	--	--	101.4	15.9

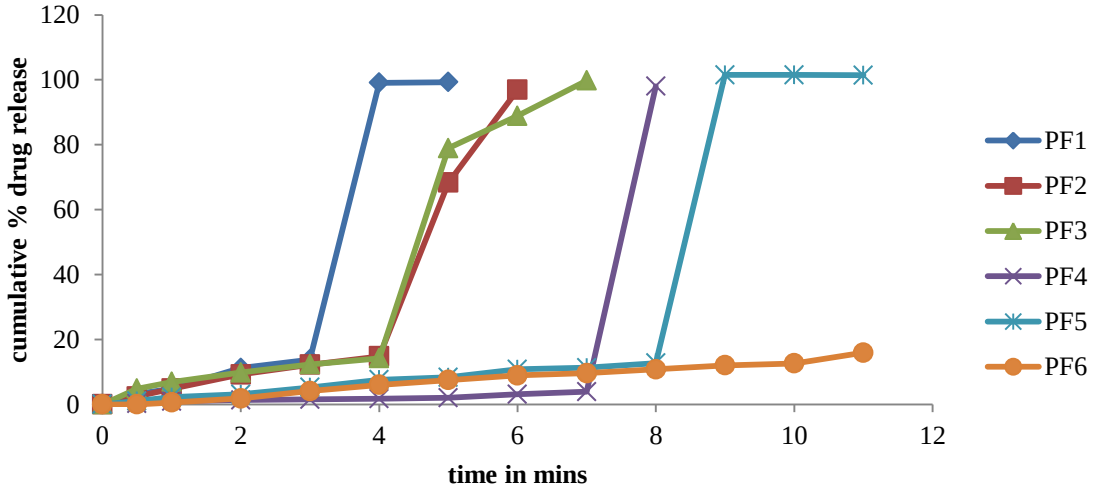

Fig 6: Dissolution graph for pulsincap formulations

Discussion

From the above formulations PH5 pulsin cap was selected as best formulation based on the lag time 0f 7 hrs which was obtained by using HPMC, Ethyl cellulose in 12.5 mg and 12.5 mg respectively.

Kinetic studies

Table 9: Dissolution data was fitted in zero order, first order, higuchi and peppas equations.

	ZERO % CDR Vs T	FIRST Log % Remain Vs T	HIGUCHI %CDR Vs √T	PEPPAS Log C Vs Log T
Slope	11.43866667	-0.28431355	28.69857353	2.258959417
Intercept	-21.8224444	2.533259955	-28.0632172	-0.13621408
Correlation	0.796128873	-0.80606941	0.655259131	0.957927363
R 2	0.633821183	0.649747908	0.429364529	0.917624833

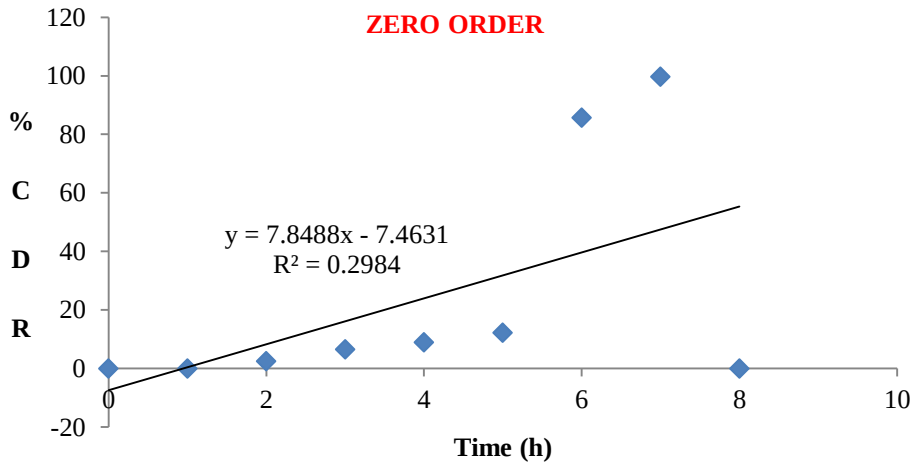

Fig 7: Zero order plot for optimized formulations

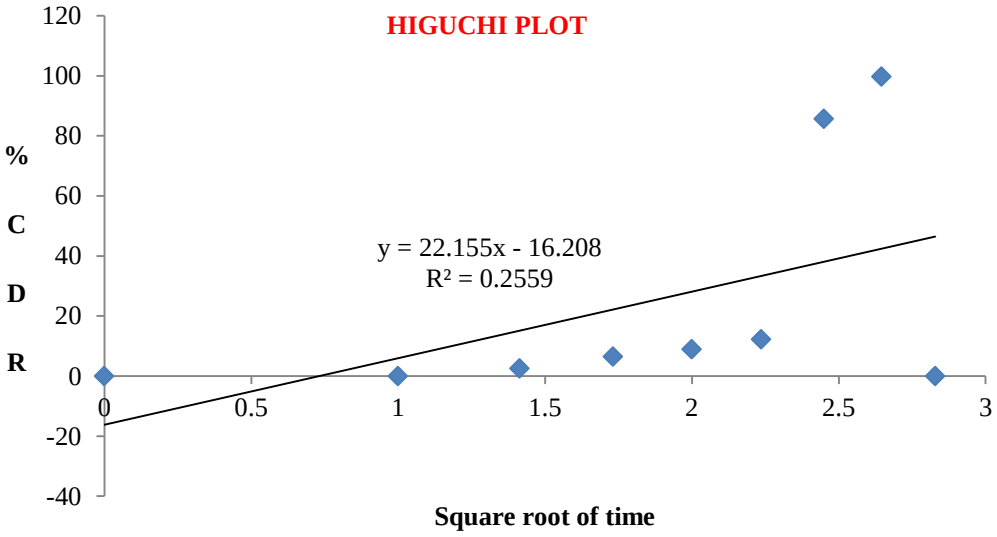

Fig 8: Higuchi plot for optimized formulations

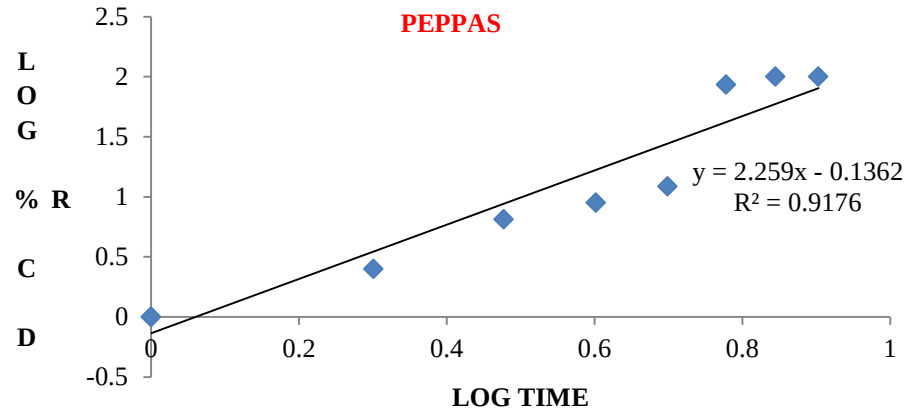

Fig no .9 peppas plot for optimized formulations

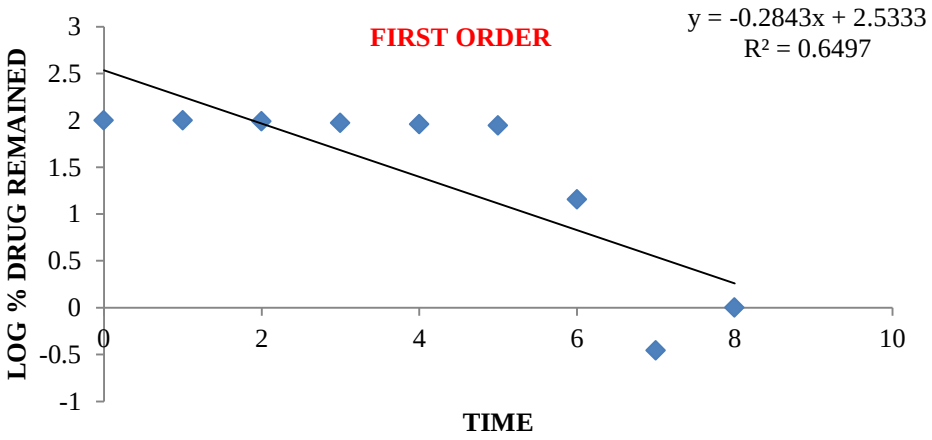

Fig no. 10 first order plot for optimized formulations

DISCUSSION

The invitro drug release was fitted to the various kinetic models. The regression coefficient R2 value for zero order, first order, higuchis and peppas were formulated for optimized formulation was found to be 0.298, 0.649, 0.255, and 0.917 respectively.

SUMMARY

A successful colon specific drug delivery system was prepared with modified release mechanism to release the drug at predetermined time after a lag time sothat drug from the formulation will be released according to the physiological need of the body for effective treatment of arthritis. The identification of drug was carried out by preformulation studies include organoleptic evaluation, solubility and flow properties .the analytical profile drug was evaluated for development of standard curve and percentage purity of drug .Formulations containg f1to f8 granules were prepared and it is composed of tramadol, HPMCK4M, ethyl cellulose, guargum, mg sterrate, talc, mcc. all formulation were evaluated for stability studies,uniform thickness and invitro dissolution studies .capsule are treated with formaldehyde .the formulation show burst release after pre determined lag time 7hrs 99.6% drug release .according to stability studies there was nosignificant change in drug and invitro dissolution of optimized formulation f7.and further formulated as pulsincap.

CONCLUSION

From the above experimental results it can be concluded that, Formulated pulsing caps gave

satisfactory results for various physicochemical parameters like lag time, drug content, thickness, weight variation. Ethyl cellulose has predominant effect on the lag time, while also shows significant effect on drug release. Pulsing cap formulations shows a delayed release pattern. Among all the granule formulations F7 was selected based on drug release within a given period of time. In-vitro release rate studies showed that the PH5 was optimized based on less amount of drug release during lag time. Formulations PH5 found to be stable at 45^{o} C and 75% RH for a period of 3 months. FT-IR studies revealed that there was no interaction between tramadol and the polymers.

REFERENCES

[1]. Gothaskar, AV, Joshi AM, Joshi, NH, 2004. Pulsatile drug delivery system a review. Drug Del. Technol. 4.

[2]. Shivkumar HG, Promod KTM, Kashappa GD. Pulsatile drug delivery systems .Indian JPharma Edu 37(3), 2003 , 125:8.

[3]. Sarasija S, Stutie P. Chronotherapeutics: emerging role of biorhythms inoptimizing drug therapy. Indian J Phrma Sci 67, 2000, 135 140.

[4]. Ross AC, Macrae RJ, Walther M, Stevens HNE. Chronopharmaceutical drug delivery from a pulsatile capsule device based on programmable erosion. J Pharm Pharmacol. 52, 2000, 903-909.

[5]. Samanta MK, Suresh NV, Suresh B. Development of Pulsincap Drug Delivery of salbutamol sulphate for drug tareting. Indian. Pharma Science. 62(2), 102-7.

[6]. Seshasayan A, Sreenivasa RB, Prasanna R, Ramana Murthy KV. Studies on release of Rifampicin from Modified Pulsincap Technique. Indian J Pharma Sci 2001, 337-9.

[7]. Sangalli ME, Maroni A, Zema L, Busetti C, et al. 2001. In vitro and in vivo evaluation of an oral system for time and/or site-specific drug delivery. J Control Rel; 73, 2001, 103 110.

[8]. Zahirul Khan MI, Zeljko P, Nevenka K. A pH-dependent colon targeted oral drug delivery system using methacrylic acid copolymers. I. Manipulation of drug release using Eudragit® L100-55 and Eudragit® S100 combinations. J Control Rel 58, 1999, 215 222.

[9]. Howard NES, Clive GW, Peter GW, Massoud B, Julei SB, Alan CP. Evaluation of PulsincapTM to provide regional delivery of dofetilide to the human GI tract. Int J Pharm 236, 2002, 27 34.

[10]. Ying-huan Li, Jia-bi Zhu. Modulation of combined release behaviours from a novel tablets -in-capsules system. J Control Rel 50, 2004, 111 -22.

[11]. Listair CR, Jonathan CDS, Walter K, Richard WB, Ross JM, Howard NES, et al. Investigating the coating-dependent release mechanism of a pulsatile capsule using NMR microscopy. J Control Rel 92, 2003, 341-7.