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Formulation and Evaluation of Tramadol HCL Pulsatile Drug Delivery by Using Press Coating Technique

Sriharitha B[1]*, Preethi J[2] and Rishpa K[3]

[1]*Depertment of Pharmaceutics, ASN Pharmacy College, Acharya Nagarjuna University, India*

[2]*Department of Chemistry, Acharya Nagarjuna University, India*

[3]*Department of Industrial Pharmacy, St. Peter's College of Pharmacy, Kakatiya University, India*

***Corresponding author**: Sriharitha B, Department of Pharmaceutics, ASN Pharmacy College, Acharya Nagarjuna University, Tenali, India, Tel: +91-9492029026; E-mail: ballasriharitha@gmail.com

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Abstract

The main aim of the present work is to develop and evaluate pulsatile press coated tablets which release total amount of drug at early morning. Here core tablet (180 mg) containing Tramadol hydrochloride 50 mg with excipients crospovidone, sodium starch glycolate and croscarmellose sodium was prepared by direct compression. The core tablet was then coated by coating material composed of combination of polymers hydroxy propyl methyl cellulose (HPMC-K100M) and ethyl cellulose (EC) by press coating technique. Prepared Press Coated tablet was evaluated for all physical tests. *In-vitro* dissolution test was carried out in 0.1 N HCl for first two hrs and 6.8 pH phosphate buffer for remaining period. From that formulations PCF3 containing polymer ratio of (3:1) i.e. HPMC:EC was selected as optimized formulation as it retarded drug release in stomach and shows a drug release with significant lag time. Initially compatibility study was carried out by FTIR showing that all the excipients and polymers were compatible with drug.

Keywords: Pulsatile drug delivery; Press coated tablets; Tramadol hydrochloride; Lag time

Introduction

Controlled drug delivery systems exhibits a major role within the field of pharmaceutical analysis and development sector. Such systems contains temporal control over the release of drug and provides a time period to a drug molecule in terms of controlled drug delivery systems for it advantages of oral route of drug administration. In such systems the drug release starts after its administration similarly occurs in oral administered dosage forms. But due to many chronological conditions there is an urge for time lag in the release of drug (pulse release) that release pattern of the drug is known as pulsatile drug delivery [1-5].

Chronobiology and Chronopharmacotherapy of Disease

Chronotherapy is a medical treatment according to the biological rhythms, in these type of therapeutics delivery of drugs depend on the inherent properties of the drug. The Tradition of prescribing medication at regular time intervals to maintain constant drug levels, in some diseases like Asthama experience symptoms at night, in such conditions administration is coordinated with daylight patterns and biological Rhythms e.g. hydrocortisone and adrenalin secretion [6-10].

Pulsatile Drug Delivery System

Pulsatile drug delivery system shows a rapid release of a few amounts of drug molecules at certain intervals and a little amount at once then, off-release period, i.e., lag time. It aims to release of drug on programmed pattern i.e., release of drug at proper time and at proper site of action. In this pulsatile drug release system the on single dosage form the initial dose of drug get release followed by one release free interval second dose of drug get release and which is followed by another free interval and pulse of drug release, this kind of release of drug is called as pulse effect and release of drug after a lag time has to be designed [10-15].

Advantages

- Pulsatile delivery shows no side effects
- Extended day and night time activity
- Drug gets adapt to suit circadian rhythms of body functions or diseases, protection from mucosa from effecting drugs, by first pass metabolism drug loss is prevented.

Disadvantages

- No manufacturing reproducibility and efficacy
- Many number of process variables
- Multiple formulation steps
- High cost production
- Need of advanced technology.

Types of Pulsatile Release Systems

Single unit pulsatile systems

Capsular systems: In this capsular systems the capsule is housing a drug with plug and it is enclosed at one end, the plug is made off swellable hydrogel, thus the capsule when contacts with the dissolution media the plug swells pushing itself out of the capsule after a time lag,

followed by spontaneous release of the drug. The plug material consists of polymethacrylates [16,17].

Port systems: In these pore system consist of gelatin capsule coated with semi permeable membrane housing an lipidic plug and an osmotically active agent with drug formulation, when it get contact with aqueous medium, water diffuses across the semi permeable membrane resulting in increased inner pressure that ejects the plug after a time lag.

Reservoir systems: In these reservoir systems reservoir devices coated with a barrier layer and drug is subsequently released rapidly.

Multi-unit pulsatile systems

Reservoir system with rupturable coating: This system consists of small beads, each small bead further comprised of many layers some contain drug substances and some other contains rate controlling polymers, the explosion of formulation can also be achieved through use of swelling agents.

Systems with changed membrane permeability: These systems depends on physio chemical properties of drug and its interaction with the membrane. Eudragit RS or RL and is influenced by the presence of different counter-ions in the release medium [18].

Objective of the Study

To design and characterize an oral, drug delivery system of Tramadol HCl. Tramadol, its O-desmethyl metabolite (M1) are selective, weak OP3-receptor agonists [19].

Based on the concept of press coated technique, time dependent pulsatile controlled drug delivery system was designed.

The drug is contained within the core and separated from the polymers.

The entire core tablet is coated with polymers to prevent the immediate drug release in stomach region.

The press coating prevents disintegration of the soluble core in the gastric fluid.

On reaching the small intestine the tablet will lose its press coat i.e. polymer coat swells to create a lag phase which is required to treat early morning stiffness.

This polymer erodes on swelling and releases the drug from the tablet in the small intestine.

Materials and Methods

Materials

The materials used are Tramadol hydrochloride; Micro crystalline cellulose; Cross povidone; Sodium starch glycolate; Croscarmellose sodium; Mg. stearate; Hydroxy propyl methyl cellulose; Ethyl cellulose; Potassium dihydrogen phosphate; Sodium hydroxide [20-35].

Identification of Tramadol hydrochloride

Examined by infrared spectrum where the spectrum obtained is compared with the standard.

Melting point 171°C and below Figures 1 and 2 are the FTIR results.

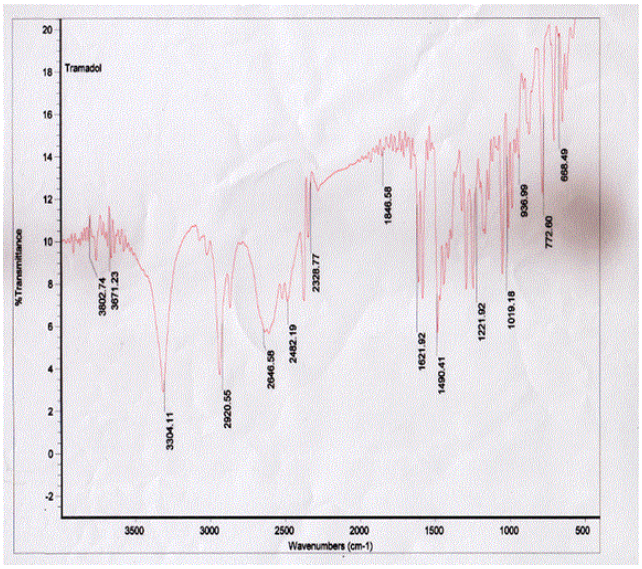

Figure 1: IR spectrum of pure drug (Tramadol hydrochloride).

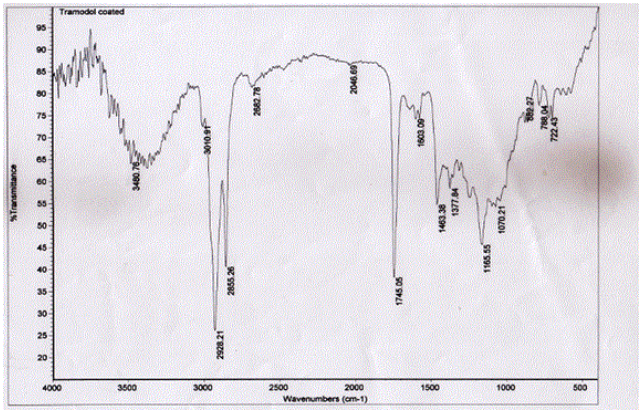

Figure 2: IR spectrum of Tramadol hydrochloride with polymers.

Method of Estimation of Tramadol Hydrochloride

UV spectrophotometric method

The method used in the present study was a UV Spectrophotometric method and is based on the measurement of absorbance at 271 nm in phosphate buffer of 6.8 pH.

Procedure for estimation of Tramadol hydrochloride

25 mg of Tramadol hydrochloride was weighed accurately and dissolved into a small quantity of buffer; finally make up to 25 ml with pH 6.8 phosphate buffer to give a concentration of 1 mg/ml (1000 µg/ml).

From standard solution 5 ml of solution was taken into 50 ml of 6.8 pH phosphate buffer solution to produce 100 µg/ml concentration.

From the above solution 2, 4, 6, 8, 10, 12 ml of the samples were pipette out into 10 ml volumetric flask.

The volume was made up to mark with 6.8 pH buffer solutions to produce concentration as 20, 40, 60, 80, 100 and 120 µg/ml of Tramadol respectively.

The absorbance of prepared solution of Tramadol hydrochloride was measured at 271 nm in Shimadzu UV/Visible 1700 spectrophotometer against blank.

The absorbance data for standard calibration curve are given in Table 1 and plotted graphically. The standard calibration curve yields a straight line, which shows that the drug obeys Beer's law in the concentration range of 20-120 mcg/ml (Figure 3).

Concentration (µg/ml)	Absorbance
20	0.126
40	0.227
60	0.359
80	0.467
100	0.572
120	0.689

Table 1: Absorbance of Tramadol hydrochloride in pH 6.8 phosphate buffer.

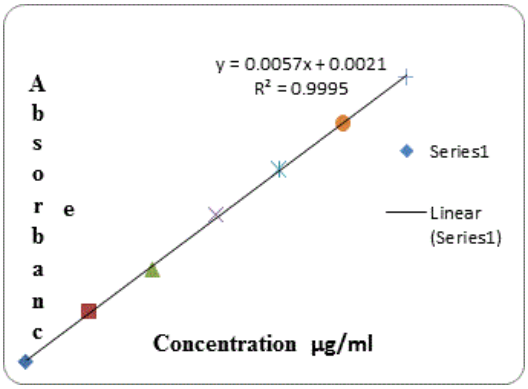

Figure 3: Calibration curve.

Formulation Procedure

Formulation for Tramadol core tablet

The inner core tablets were prepared by using direct compression method and the formulation is shown in Table 2. Powder mixtures of Tramadol, microcrystalline cellulose, cross-carmellose, sodium starch glycolate (SSG), and crospovidone were weighed accurately and dry blended for 20 min.

This is followed by the addition of accurately weighed quantity of Magnesium Stearate. This mixture is now further blended for 10 min. 180 mg of resultant powder blend was manually compressed using hydraulic press at a pressure of 1 ton to obtain the core tablet [35-40].

Ingredients	mg/tab (Formulation) (CF-----Core Formulation)								
	CF 1	CF2	CF 3	CF 4	CF5	CF6	CF7	CF8	CF9
Tramadol	50	50	50	50	50	50	50	50	50
Mcc	122.6	120.8	119	122.6	120.8	119	122.6	120.8	119
Crospovidone	5.4	7.2	9						
CCS				5.4	7.2	9			
SSG							5.4	7.2	9
Mg. stearate	2	2	2	2	2	2	2	2	2
Total wt	180 mg	180 mg	180 mg	180 mg	180 mg	180 mg	180 mg	180 mg	180 mg

Table 2: Formula of Tramadol core tablet with different excipients.

Formulation of mixed blend for barrier layer

The various formulation compositions containing HPMC and EC. Different compositions were weighed dry blended at about 10 min.

It is used as press-coating material to prepare press-coated pulsatile tablets respectively by direct compression method.

Total weight of Tramadol hydrochloride core tablet=180 mg.

Weight of coating material=400 mg

Total weight of Tramadol hydrochloride press coat tablet=580 mg.

Individual ratios of each ingredient for the formulation of 580 mg of tramodol hydrochloride press coat tablets using different concentrations of excipients are given in the Table 3.

The core tablets were press-coated with 400 mg of mixed blend as given in Table 3. 200 mg of barrier layer material was weighed and transferred into die then the core tablet was placed manually at the center.

Sl. No	Ingredients	PCF1	PCF2	PCF3	PCF4	PCF5
1	HPMC	400	300	200	100	0
2	EC	0	100	200	300	400
3	Total Wt	400 mg	400 mg	400 mg	400 mg	400 mg
Note: PCF-Press Coated Formulation						

Table 3: Ratios of each ingredient for the formulation of of tramodol hydrochloride press coat tablets.

The remaining 200 mg of the barrier layer material was added into the die and compressed at a pressure of 5 tons for 3 m in using hydraulic press. Thus formed Tramadol hydrochloride press coated tablets are ready for further tests and *in-vitro* drug release.

Results and Discussion

Weight variation

For tablets weighing 120 mg-300 mg it should be ±7.5% and for tablets weighing more than 300 mg it should be ±5%.

The formulated Tramadol hydrochloride press coated tablets was found to be in the prescribed limits and passes the weight variation test and are shown in Tables 4 and 5.

Formulation	Wt. variation	Hardness (kg)	Friability (%)	Thickness (mm)	Disintegration time (min)
F1	179 ± 2	4 ± 0.9	0.5 ± 0.2	2.9 ± 0.3	3 min 20 sec
F2	181 ± 3	4.2 ± 1.3	0.6 ± 0.1	2.9 ± 0.4	3 min 22 sec
F3	183 ± 1	5.7 ± 0.3	0.4 ± 0.3	3.2 ± 0.2	1.10 secmin
F4	183 ± 2	4.1 ± 1.1	0.6 ± 0.1	2.7 ± 0.3	2 min 35 sec
F5	179 ± 3	4.3 ± 1.3	0.7 ± 0.2	2.4 ± 0.6	2 min 28 sec
F6	184 ± 1	4.4 ± 0.9	0.6 ± 0.1	2.5 ± 0.5	1 min 25 sec
F7	181 ± 2	4.2 ± 1.5	0.5 ± 0.3	2.3 ± 0.5	2 min 45 sec
F8	181 ± 3	4.3 ± 1	0.5 ± 0.2	2.4 ± 0.7	1 min 40 sec
F9	184 ± 1	4.4 ± 1.5	0.5 ± 0.1	2.6 ± 0.9	1 min 36 sec

Table 4: Limits of the core Tramadol hydrochloride tablets.

Formulation	Wt. variation	Hardness (kg)	Friability (%)	Thickness (mm)	Swelling index (%)
PCF1	584 ± 3	6.6 ± 1.1	0.62 ± 0.1	6.4 ± 0.3	280
PCF2	584 ± 2	5.9 ± 1	0.42 ± 0.2	5.7 ± 0.6	150
PCF3	581 ± 1	7.5 ± 0.3	0.69 ± 0.1	6.7 ± 0.1	250
PCF4	582 ± 2	6.3 ± 1.4	0.49 ± 0.3	6 ± 0.7	120
PCF5	581 ± 2	6.1 ± 1.5	0.45 ± 0.3	5.8 ± 0.8	100

Table 5: Limits of the Tramadol hydrochloride press coated tablets.

Thickness

The thickness variation limits allowed are ±5% of the size of the tablet.

The formulated Tramadol hydrochloride press coated tablets was found to be in the prescribed limits and passes thickness test and are shown in Tables 4 and 5.

Hardness

The acceptable limits of hardness ranges from 4-8 kg/cm^2.

The formulated Tramadol hydrochloride press coated tablets was found to be in the prescribed limits and are shown in Tables 4 and 5.

Friability

The acceptance limits of weight loss should not be more than 1%.

The formulated Tramadol hydrochloride press coated tablets was found to be in the prescribed limits and are shown in Tables 4 and 5.

Disintegration time for core tablets

Generally the disintegration time for uncoated tablets is 15 minutes.

The formulated Tramadol hydrochloride press coated tablets was found to be in the prescribed limits and are shown in Table 4.

Swelling index for coated tablets

From the results of swelling study it was concluded that swelling increases as the time passes because the polymer gradually absorbed water due to hydrophilic nature and swell. In PCF1 and PCF3 higher swelling index was found.

In PCF1 hydroxy propyl methyl cellulose alone is the polymer and had high swelling index without significant lag time.

But in case of PCF3 HPMC: EC having a ratio of 3:1 shows better swelling index with significant lag time are shown in Table 5.

In-vitro release studies for core tablets

In-vitro results are shown in Tables 6-9 and Figures 4-7.

The results of *In-vitro* dissolution rate studies indicated high dissolution of the drug from all the formulations when compared with pure drug.

Among the formulations prepared formulation with crospovidone (5%) as disintegrant shows highest dissolution rate of 97% at 60 minutes when compared with the other formulations as well as pure drug.

The reason for increase in the dissolution is may be due to high concentration of disintegrants (CP).

Based on the above observations, CP with (5%) was selected for formulation of Tramadol hydrochloride press coated tablets.

Pulsatile drug delivery of Tramadol hydrochloride was developed using different ratios of HPMC and EC as polymers for press coating.

Formulated tablets were subjected to physic chemical evaluation like weight variation, hardness, thickness, friability, swelling index and *in-vitro* drug release.

Time (min)	F1 (3%)	F2 (4%)	F3 (5%)
5	36	32	40
10	42	41	60
15	58	66	73
20	59	73	83
30	78	81	97
45	81	89	97
60	90	90	97
F: Formulation			

Table 6: Percentage of drug release with different concentrations of cross povidone.

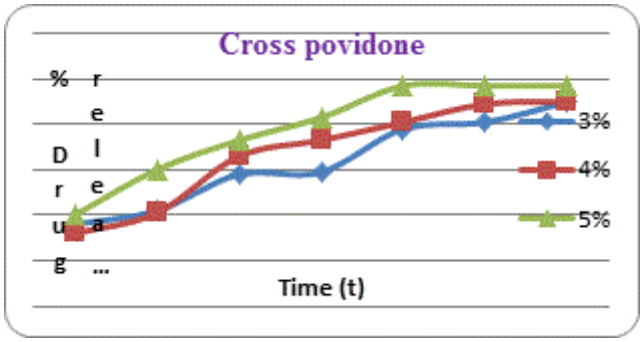

Figure 4: *In-vitro* Drug release of Cross povidone.

Time (min)	F1 (3%)	F2 (4%)	F3 (5%)
5	25	27	30
10	36	40	42
15	49	52	50
20	55	59	58
30	68	73	67
45	80	78	74
60	90	91	89
F: Formulation			

Table 7: Percentage of drug release with different concentrations of caroscarmellose sodium.

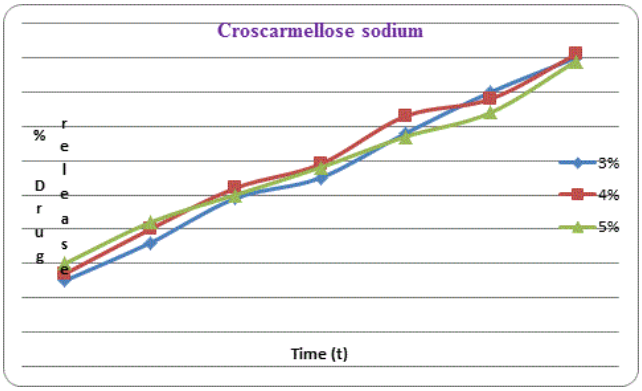

Figure 5: *In-vitro* drug release of croscarmellose sodium.

Time (min)	F1 (3%)	F2 (4%)	F3 (5%)
5	22	24	27
10	37	36	41
15	49	51	48
20	59	62	57
30	67	71	72
45	78	82	78
60	86	92	86
F: Formulation			

Table 8: Percentage of drug release with different concentrations of Sodium starch glycolate.

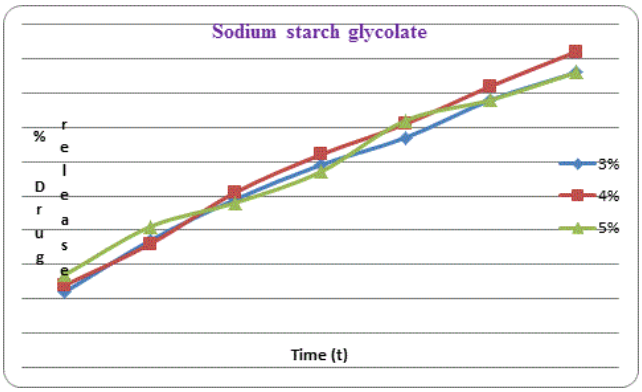

Figure 6: *In-vitro* drug release with sodium starch glycolate.

In-vitro dissolution methods for press-coated tablets

Drug release was found to be more with a significant lag time in PCF3 formulation having a ratio of HPMC: EC (3:1). The results are given in the Table 9 and Figure 7. The hydrophilic polymer ethyl

cellulose is responsible for delaying the drug release with significant lag time.

Time (hrs)	PCF1	PCF2	PCF3	PCF4	PCF5
1	0	0	0	0	0
2	0	0	0	0	0
3	19.0	16.4	0	0	0
4	28.5	24.2	12.7	17.3	8.2
5	59.2	37.4	47.3	27.7	19.4
6	73.6	51.2	65.9	48.9	31.3
7	89.7	73.4	84.6	61.0	49.5
8	95.0	88.7	98.2	73.4	65.8
PCF: Press coated formulation					

Table 9: Percentage of drug release for press coated tablets.

The decrease in drug release from tablets containing more hydrophobic polymer combination (PCF4 and PCF5) OF HPMC: EC in comparison of tablets containing more hydrophilic polymer combination (PCF1, PCF2 and PCF3) may be attributed to the relatively hydrophobic nature of polymer (EC) which have less affinity for water, this results in decreased drug release.

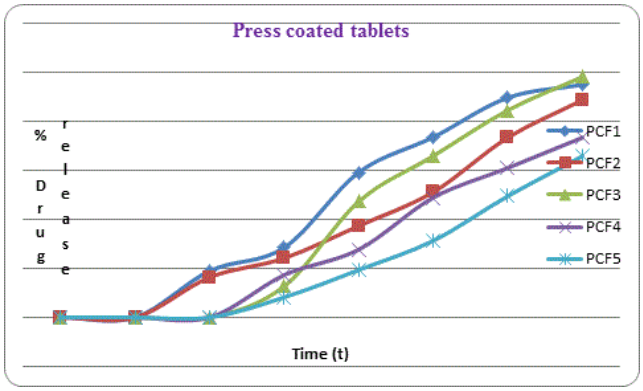

Figure 7: Drug release for press coated tablets.

The significant lag time is due to hydrophobic nature of ethyl cellulose (EC). Increased drug release rate is due to higher hydrophilic nature of HPMC. Due to its high hydrophilicity it absorbs water and swells resulting in more release of drug from tablets. From the release studies it was observed that combination of high concentration of hydrophilic polymer and low concentration of hydrophobic polymer (HPMC: EC) with a ratio of (3:1) tends to increase the amount of drug release with significant lag time.

Stability studies

Tablets were evaluated for its physico-chemical properties and *in-vitro* dissolution studies after 90 days and there was no significant physico-chemical changes was observed and observed percentage drug release during 8th hour was 98%. Hence formulation PCF3 was found to be stable during the stability studies.

Drug release kinetics

Tramadol hydrochloride tablets made with hydroxy propyl methyl cellulose and ethyl cellulose were subjected to various kinetic studies like zero order (Cumulative percentage drug released vs. Time), first order (Log cumulative percentage of drug unreleased vs. Time), Higuchi equation (Cumulative percentage of drug unreleased vs. Square root of time) and Korsemeyer's (Log cumulative percentage released vs. Log time) and are reported in Figure 8.

The release kinetics profile of Tramadol hydrochloride tablets was found to obey zero order kinetics and Higuchi.

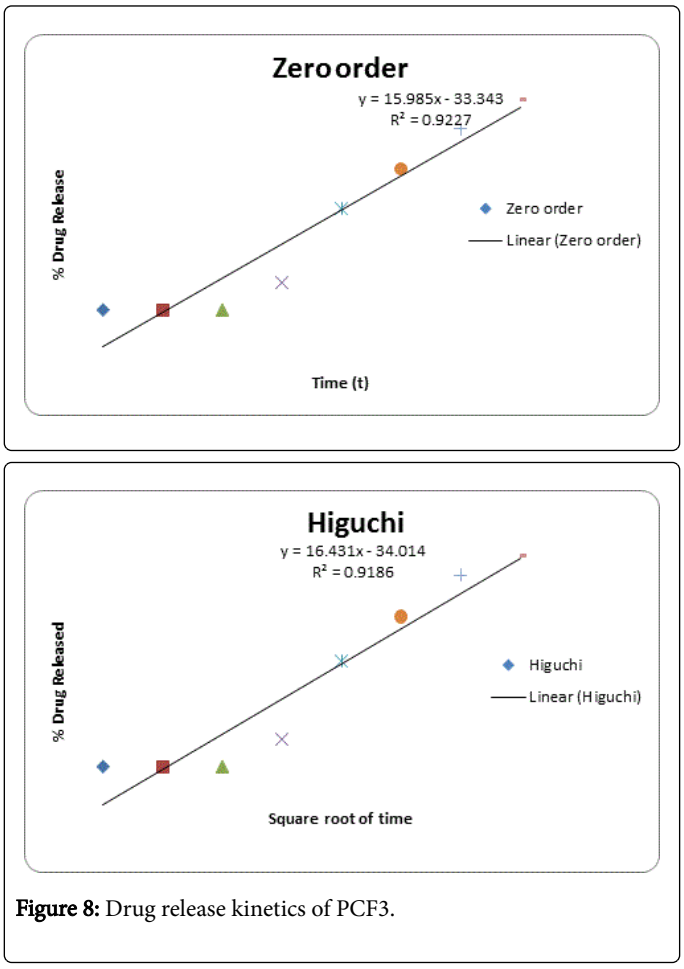

Figure 8: Drug release kinetics of PCF3.

Conclusion

Consistent lag time with immediate release of the active pharmaceutical ingredient and the requirements for developing the chronotherapeutics was achieved with the developed formulation. At the coating ratio of (3:1) HPMC: EC has been proved as the most appropriate polymer combination for pulsatile drug delivery with a significant lag time and enhanced bioavailability, reduced side effects. Thus this approach of pulsatile release where in tablet of Tramadol hydrochloride is taken at bed time, releasing drug in the morning hours when the symptoms are more prevalent can prove to be a revolution in the treatment of arthritis.

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