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Research **Article**

FORMULATION AND INVITRO EVALUATION OF LURASIDONE PULSATILE DRUG DELIVERY

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ABSTRACT

The development of site-specific, pulsatile drug delivery systems (DDS) aims to optimize therapeutic efficacy and minimize side effects by ensuring drug release at a predetermined time and site within the gastrointestinal tract. This study explores the formulation and evaluation of an oral pulsatile drug delivery system utilizing Lurasidone, an atypical antipsychotic agent, as a model drug. Lurasidone is primarily used in the treatment of schizophrenia and bipolar disorder, conditions requiring precise and timely drug release to align with the body's circadian rhythms and symptom fluctuations. The proposed system integrates time-controlled release mechanisms to target drug release at specific segments of the gastrointestinal tract, particularly the colon. This is achieved through the use of a combination of pH-sensitive polymers, enzymatically degradable materials, and chronotherapeutic approaches. The formulation involves a core tablet containing Lurasidone, coated with a series of layers designed to delay drug release until reaching the desired site of action. In vitro dissolution studies and in vivo pharmacokinetic evaluations are conducted to assess the lag time, release profile, and bioavailability of Lurasidone from the pulsatile DDS. The results demonstrate a significant improvement in the synchronization of drug release with the targeted site, achieving a pulsatile release pattern conducive to the management of psychiatric conditions. An insoluble hard gelatin capsule body, filled with a powder blend, and sealed with a hydrogel plug make up the fundamental design. The powder mix including talc, MCC, crospovidone, Lycoat, and Ludiflash as disintegrants, and Lurasidone as the medication was made and tested for flow characteristics using FTIR analysis. The F12 powder mix formulation was chosen for additional pulsatile capsule production based on the findings obtained. To maintain an appropriate lag duration, a hydrogel plug was produced in a 1:1, 1:2, and 2:1 ratio combining hydrophobic polymers such lactose with hydrophilic

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polymers like HPMC. It was discovered that the percentage of polymers utilized influenced the drug release. The produced formulations were assessed for In vitro release studies, drug content, and weight variance. Lurasidone was found to be released from the pulsincap after a predefined lag time of six hours, according to in vitro release experiments of the pulsatile device. FTIR measurements verified that there was no interaction between the medication and polymers. It was discovered that PC5F12 was an optimal formulation based on conducted in vitro investigations.

Key words: Pulsatile system; time dependent delivery; Lurasidone; Chrono pharmaceutics; In vitro release studies.

INTRODUCTION

Controlled drug delivery systems have taken center stage in the pharmaceutical research and development business. Such methods provide temporal and/or spatial control over drug release and provide a therapeutic molecule a new lease of life in terms of controlled drug delivery systems, which have the obvious benefits of oral drug administration. These dosage forms have several benefits, including a practically constant drug level at the site of action, prevention of peak-valley fluctuation, a lower dose of medication, a lower dosing frequency, the avoidance of adverse effects, and enhanced patient compliance. In such systems, drug release begins as soon as the dosage form is delivered, just as it does in traditional dosage forms. However, there are specific circumstances that need the release of drugs after there is a lag period. This release pattern, known as "pulsatile" release, synchronizes medication concentrations with disease activity cycles.[1]

Pulsatile medication delivery method: The most fascinating and time-specific system based on the pathophysiology of the disease. Pulsatile drug delivery systems are distinguished by a period of no release (lag time), followed by quick and full drug release. The drug release was impacted by the sort of pulsatile delivery mechanism used in the formulation. The lag time was minimized by switching between swelling and dissolving agents. By lowering the lag time, the medicine was released prior to the actual time of release.[2]

Pulsatile drug delivery systems (PDDS) are essentially timed medication delivery devices. These systems are meant to correspond to the body's circadian cycle. According to Latin literature, circa indicates day and dian means night. These situations need medication release after a lag period, i.e. chrono pharmacology of illnesses that exhibit circadian cycles in their pathophysiology. In other words, the medication must not be released at all during the early period of dosage form administration.

This type of release pattern is known as pulsatile release. This situation requires the medication to be released as a pulse after a time lag, and the system must be constructed so that complete and fast drug release occurs after the lag period. These systems are referred to as pulsatile drug delivery systems, time-controlled systems, or sigmoidal release systems. Lag time is defined as the period between when a dosage form is placed in an aqueous environment and when the active component begins to be released from it. CDDS are categorized into three categories based on the pulse-regulation of drug release: time-controlled pulsatile release (single or multiple unit system), internal stimuli-induced release, and external stimuli-induced pulsatile release systems. PDDS may also be categorized into three categories based on their dose form: capsules, pellets, and tablets, with the core being the cup tablet system. The core-in-cup tablet system is made up of three separate parts: a core tablet holding the active component, an impermeable outer shell, and a top cover plug layer of a soluble polymer. An inquiry was done to develop and test Lurasidone pulsincaps to optimize the medication release after a particular lag time to fulfill the therapeutic demands of schizophrenia and bipolar depression.[3]

Schizophrenia is a severe mental condition in which people see reality incorrectly. Schizophrenia can include hallucinations, delusions, and profoundly disorganized thought and behavior, which can hinder everyday functioning and be debilitating.[4,5].

Schizophrenia patients require lifelong therapy. Early therapy may help to reduce symptoms before major issues emerge, perhaps improving the long-term outlook[6].

Lurasidone is a novel second-generation antipsychotic from the chemical family of benzisothiazol derivatives used to treat acute schizophrenia in adults. The FDA authorized this medicine in October 2010. Lurasidone's action profile differs from that of other second-generation antipsychotics at key receptors. In vitro investigations have demonstrated that lurasidone is the second-generation antipsychotic with the strongest affinity for 5HT7 receptors and a high affinity for 5HT1A receptors. 5HT7 receptors [7,8] are numerous in the thalamic and hypothalamic regions involved in sleep control, as well as in cortical areas, hippocampus, and raphe nuclei implicated in memory and mood regulation [9]. Therefore, via these two receptors, lurasidone should have positive effects on memory and cognitive functioning, as well as an antidepressive and anxiolytic action [10].

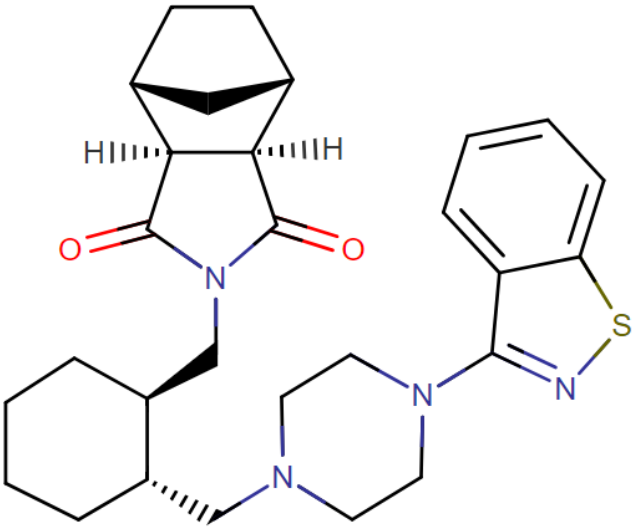

Figure No:1 Structure of lurasidone[11]

Lurasidone is a BCS Class II molecule with weak water solubility and high permeability. Its bioavailability ranges from 9 to 19%, indicating that only a little quantity of the medication is accessible for commencement of action.

MATERIALS & METHODS USED:

Lurasidone API was a gift sample and Crospovidone, Ludiflash, Lycoat, Hydrochloric acid were procured from S.D Fine Chemicals, Microcrystalline cellulose, Talc were procured from Loba chemie pvt.ltd, Lactose, HPMC K15M were procured from Otto Chemicals, Mumbai, Formaldehyde, Sodium hydroxide pellets, Potassium permanganate were procured from Qualigens fine chemicals, Mumbai.

Pulsincap Desingning:

Designing or preparation of pulsincap capsules involves 3 steps:

1. **Making the gelatin capsule with cross-linked gelatin.**
2. **Preparation of powder mixes for filling into cases.**
3. **Lurasidone's pulse capsule formulation**

Preparation of Cross-Linked Gelatin Capsule:

Formaldehyde treatment:

Approximately 100 firm gelatin capsules, size '0', were taken. Their bodies were removed from their caps and put on a wire mesh. The corpses put on a wire mesh were spread out in a single layer. 25 ml of 15% v/v formaldehyde solution was produced and put in a desiccator. To this, 5 g of potassium permanganate was added. The wire mesh containing the capsule bodies was placed on top of desiccators containing formaldehyde liquid at the bottom, in equilibrium with its vapor, and the desiccators were quickly closed and sealed. The capsule bodies were exposed to formaldehyde fumes for varied durations of time, namely 2, 4, 6, 8, and 10 hours. Then the capsules were removed and placed on filter paper before being dried for 24 hours to guarantee that the reaction between gelatin and formaldehyde vapors was complete. The capsules were then stored in an open atmosphere to assist the elimination of leftover formaldehyde. The capsule bodies were closed with an untreated cap and kept in a polythene bag.

Preparation of Lurasidone Tablet for Filling into Capsules:

All the ingredients were passed through # 60 mesh sieve separately. The drug & MCC were mixed by adding small portion of each at a time and blending it to get a uniform mixture and kept aside. Then the other ingredients were mixed in geometrical order and passed through coarse sieve (#44 mesh) and the tablets were compressed using hydraulic press. Compression force of the machine was adjusted to obtain the hardness in the range of 3-4 kg/cm2 for all batches. The weight of the tablets was kept constant for all formulations F1 to F12 (150 mg).

Table.No.1 Formulation table for filling the Lurasidone Pulsincap with the blend

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Lurasidone	40	40	40	40	40	40	40	40	40	40	40	40
Crospovidone	5	10	15	20	--	--	--	--	--	--	--	--
Lycoat	--	--	--	--	5	10	15	20	-	-	-	-
Ludiflash	--	--	--	--	--	--	--	--	5	10	15	20
MCC	101	96	91	86	101	96	91	86	101	96	91	86
Magnesium stearate	2	2	2	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2	2	2	2
Total	150	150	150	150	150	150	150	150	150	150	150	150

Formulation of Pulsincap of Lurasidone:

The modified release pulsincaps containing 40mg of Lurasidone were prepared by using different excipients and polymers in varying ratios. The formaldehyde treated capsule bodies which were exposed to 6 hrs was optimized and chosen for the pulsincap formulation based on disintegration time. Optimized formulation of Lurasidone tablet was filed into the capsule body. For hydrogel plug formulation, the plug was prepared by using the combination of Lactose: HPMC K15M in varying ratios. Initially the total weight of the plug was taken as 100 mg alone and the ratio of hydrophobic & hydrophilic polymer as 1:1, 1:2, and 2:1.

Method of preparation of Pulsincap dosage form:

Preparation of powder blend:

Hard gelatin capsules of 'size 0' which were hardened with formaldehyde treatment for 6hrs were chosen for the formulation. The bodies and caps separated manually. Optimized formulation F12 was fitted at the bottom of the capsule body.

Preparation of Hydrogel plug:

Plug was prepared as a compressed tablet and placed at the opening of capsule body. The capsule body was closed by a cap. Hydrogel plug was prepared by using different polymers like Lactose, HPMC at different concentrations. A combination of hydrophobic and hydrophilic polymers were used viz., Lactose: HPMC, in different ratios like 1:1, 1:2, 2:1. A tight fit between the plug and impermeable capsule shell is essential to regulate water penetration into the capsule content and the drug release prior to complete erosion of plug material. Ideally plug should erode only from the surface exposed to the release medium. Plug ejection can be done by swelling on contact with aqueous fluids (or) pushing out by increased internal pressure (or) erosion (or) by enzyme degradation.

Capsule filling

Homogeneous mixture of drug and excipients were filled into the 6th hr formaldehyde treated capsule body manually by filling method. Then, hydrogel plug in the form of a tablet is placed above the mixture i.e., at the opening of capsule body. The capsule body was closed by a cap.

Capsule sealing:

The joint of the treated capsule body and untreated cap of the capsules was sealed with a small amount of 1% lactose ethanolic solution.

RESULTS:

Drug-Excipient compatibility studies:

FT-IR:

To determine the chemical compatibility of the medication, spectroscopic techniques such as FTIR were utilized. The FTIR spectra were obtained with an IR spectrophotometer (IR-Affinity-1, Shimadzu, Japan). The IR spectra for the samples were acquired using the KBr disk technique. The samples were created by grinding the pure drug, polymer, and physical combination with KBr separately. The drug and potassium bromide pellets were made by compressing the powders on a KBr-press at 20 pressure for 10 minutes, and the spectra were scanned in the 4000-600 cm-1 region. FTIR analysis was performed on Lurasidone, a physical combination of Lurasidone, and the optimal formulation.

Pure Drug:

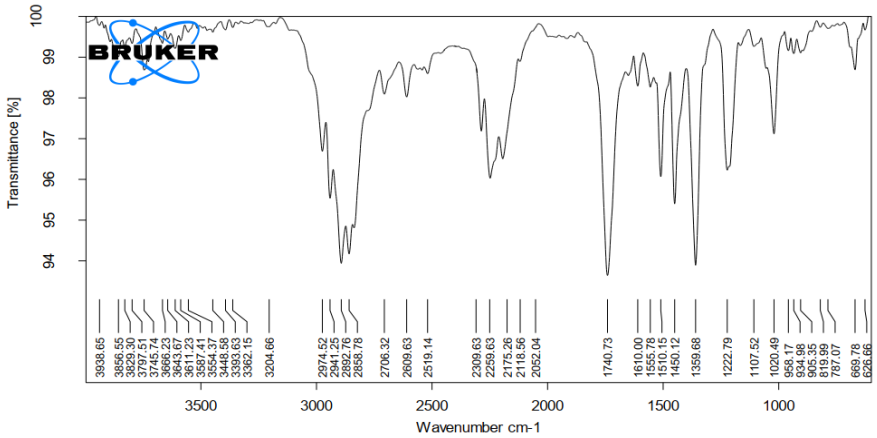

Figure No.2 FTIR spectrum of Lurasidone

Optimized Formulation:

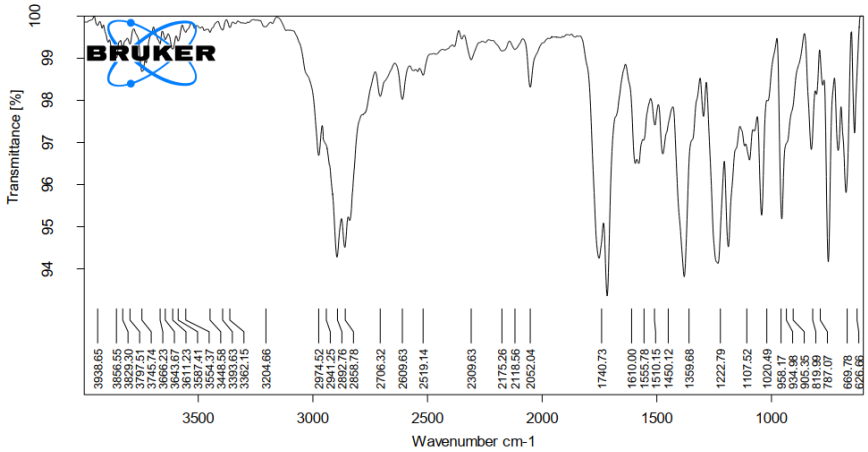

Figure No.3 FTIR Spectrum of optimized formulation

Evaluation of Powder Blend[12]

Bulk Density (Db): It is the ratio of powder's total mass to its bulk volume. It was measured by pouring the weighed powder (passed through standard sieve # 20) into a measuring cylinder and noting the original weight. This original volume was known as the bulk volume. From this, the bulk density was determined using the method below. It is represented in grams per milliliter and supplied by

$$Db=\frac{M}{Vb}$$

Where,

M=mass of powder

Vb=bulk volume of the powder respectively

Tapped Density (Dt): This is the ratio of the powder's total mass to its tapped volume. Volume was determined by tapping the powder 750 times, and the tapped volume was recorded if the difference between the two volumes was less than 2%. If it is greater than 2%, tapping is repeated 1250 times, and the tapped volume is logged. Tapping was repeated until the difference between consecutive volumes was less than 2% (in a bulk density apparatus). It is represented in grams per milliliter and supplied by

$$Dt=\frac{M}{Vt}$$

Where, M=mass of powder, **Vt=** tapped volume of the powder

Angle of Repose: The mixture was poured through the walls of a funnel, which was positioned such that the bottom tip was exactly 2.0 cm above the hard surface. The blends were poured until the higher tip of the pile surface contacted the lower tip of the funnel. The angle of repose was computed using the following equation.

$$\text{Tan } \theta=\frac{h}{r}$$

Carr's index (or) % compressibility: It indicates powder flow properties. It is expressed in percentage and is given by

$$I=\frac{Dt-Db}{Dt}x100$$

Where, Dt and Db are tapped density and bulk density respectively.

Hausner ratio: The Hausner ratio is an indirect indicator of the ease of powder flow. It was computed using the following formula.

$$\text{Hausner ratio}=\frac{Dt}{Db}$$

Where, Dt and Db are tapped density and bulk density respectively. The results were shown in the Table. No 2.

Table.No.2 flow properties of formulations

Formulation Code	Angle of Repose ±SD	Bulk Density (g/ml)±SD	Tapped Density (g/ml)±SD	Carr's Index (%) ±SD	Hausner's ratio ±SD
F1	24.18±0.27	0.329±0.008	0.446±0.005	19.20±0.06	1.19±0.02
F2	23.48±0.45	0.337±0.007	0.457±0.006	17.12±0.07	1.17±0.07
F3	24.15±0.37	0.356±0.007	0.466±0.004	15.37±0.05	1.16±0.05
F4	25.74±0.16	0.359±0.002	0.478±0.003	14.58±0.05	1.15±0.63
F5	26.24±0.38	0.337±0.006	0.456±0.005	16.24±0.03	1.16±0.42
F6	27.49±0.46	0.346±0.003	0.469±0.002	15.39±0.06	1.15±0.15
F7	25.21±0.26	0.358±0.004	0.472±0.007	14.45±0.05	1.14±0.19
F8	26.27±0.34	0.376±0.003	0.486±0.003	13.12±0.02	1.12±0.24
F9	26.48±0.45	0.346±0.007	0.454±0.004	14.05±0.04	1.14±0.15
F10	28.37±0.18	0.357±0.006	0.467±0.005	13.34±0.06	1.13±0.21
F11	26.46±0.02	0.368±0.005	0.478±0.003	12.87±0.08	1.12±0.17
F12	23.36±0.34	0.379±0.003	0.485±0.007	11.24±0.04	1.11±0.16

Discussion: The angle of repose of different formulations was ≤ 28.37±0.18, which indicates that material had good flow property. So, it was confirmed that the flow property of blends was free flowing. The bulk density of blend was found between 0.329±0.008 g/cm3 to 0.379±0.003 g/cm3.Tapped density was found between 0.446±0.005 g/cm3 to 0.485±0.007 g/cm3.These values indicate that the blends had good flow property. Carr's index for all the formulations was found to be between 11.24±0.04-19.20±0.06 and Hausner's ratio from 1.11±0.16-1.19±0.02 which reveals that the blends have good flow character**.**

Evaluation of tablets:[13]

Tablet Dimensions: Thickness was measured with a calibrated vernier caliper. Three tablets of each formulation were selected at random, and their thickness was measured separately.

Hardness: Hardness denotes a tablet's capacity to absorb mechanical shocks when handling. The hardness of the tablets was measured using a Monsanto hardness tester. It is stated in kilograms per square centimeter. Three tablets were selected at random, and their hardness was assessed.

Friability test: The friability of tablets was tested using an electrolab Friabilator. It's given as a percentage (%). Ten pills were originally weighted (WI) and transferred to the Friabilator. The Friabilator was run at 25 rpm for 4 minutes, or up to 100 rotations. The pills were weighed again (WF). The percentage of friability was then computed as –

$$\%F = 100\ (1\text{-}WI/WF)$$

% Friability of tablets less than 1% was considered acceptable.

Weight Variation Test: Ten pills were chosen at random from each batch and weighed separately to check for weight variance. The weight of a tablet was allowed to vary somewhat according to the United States Pharmacopoeia. The following % variance in weight fluctuation was permitted.

Test for Content Uniformity: A tablet containing 10mg of medication was dissolved in 50ml of 7.4 pH buffer in a volumetric flask. The medication was left to dissolve in the solvent. The solution was filtered, 2ml of filtrate was placed in a 10ml volumetric flask, diluted to the mark with distilled water, and evaluated spectrophotometrically at 230 nm. The concentration of Lurasidone was determined using the drug's standard calibration curve. Drug content analyses were performed in triplicate for each formulation batch.

In vitro Disintegration Time: The tablet was introduced to 900ml of distilled water at 37±0.5oC. The time necessary to completely disperse a pill was measured.

Table.No.3 Post compression Evaluation parameters of formulations

Formulation code	%Weight variation (mg)	Thickness (mm)	Hardness	Friability (%)	Disintegration time (sec)	Drug content (%)
F1	152.48±1.48	4.21±1.21	5.78±1.67	0.76±0.07	21	95.15±1.24%
F2	151.74±1.67	4.18±1.26	5.62±1.54	0.68±0.06	18	96.24±1.74%
F3	148.54±1.35	4.26±1.98	5.74±1.20	0.53±0.07	17	97.06±1.35%
F4	150.27±1.25	4.28±1.37	5.69±1.69	0.47±0.05	15	95.76±1.27%
F5	147.26±1.74	4.37±1.54	5.45±1.45	0.89±0.03	20	96.32±1.26%
F6	149.28±1.45	4.38±1.36	5.61±1.25	0.75±0.06	17	97.35±.1.47%
F7	151.47±1.36	4.65±1.57	5.39±1.37	0.68±0.07	16	95.35±1.56%
F8	152.15±1.58	4.35±1.47	5.78±1.54	0.53±0.06	15	98.48±1.26%
F9	151.35±1.20	4.28±1.25	5.68±1.67	0.72±0.04	15	98.74±1.67%
F10	149.17±1.74	4.21±1.49	5.87±1.25	0.63±0.08	14	95.25±1.28%
F11	151.14±1.26	4.38±1.65	5.65±1.48	0.55±0.05	13	96.65±1.45%
F12	150.04±1.58	4.49±1.74	5.98±1.25	0.41±0.01	11	98.84±1.37%

Discussion: Hardness of the tablet was acceptable and uniform from batch-to-batch variation, which was found to be 5.39±1.37-5.98±1.25kg/cm2. All the formulations passed the weight variation test as the % weight variation was within the pharmacopoeia limits of the tablet weight. Friability values were found to be less than 1% in all the formulations F1 –F12 and considered to be satisfactory ensuring that all the formulations are

mechanically stable. The drug content values for all the formulations (F1-F12) were found to be in the range of 95.15±1.24%-98.84±1.37%.

In vitro Dissolution Study: [14,15]

In vitro dissolution of Lurasidone tablets was studied in USP XXII dissolution test apparatus. 900ml Phosphate buffer 7.4 (simulated fluid) was used as dissolution medium. The stirrer was adjusted to rotate at 100RPM. The temperature of dissolution medium was maintained at 37±0.5ºC throughout the experiment. One tablet was used in each test. Samples of dissolution medium (5ml) were withdrawn by means of syringe fitted with pre-filter at known intervals of time and analyzed for drug release by measuring the absorbance at 230 nm. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. Cumulative percent Lurasidone released was calculated and plotted against time.

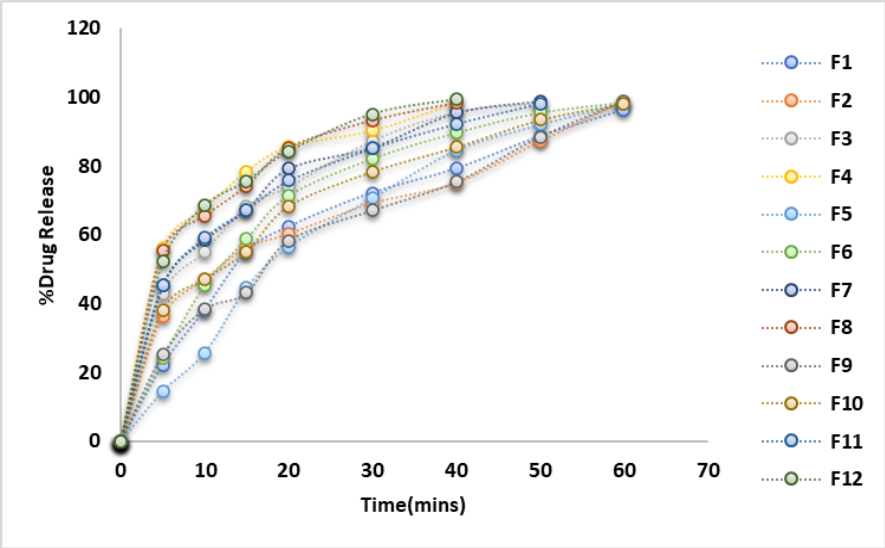

Figure No:4 In vitro drug release of formulations F1-F12

Discussion:

The formulations containing Ludiflash as a super disintegrant in different concentrations like 5,10,15 and 20 mg in weight reveals that the increased in the super disintegrant concentration decreases the drug release time and the F12 formulation containing Ludiflash with 20mg concentration shows maximum amount of drug release (99.35±1.37 mg) at the end of 40mins. So, F12 formulation containing 20mg concentration of Ludiflash shows max. release 99.35±1.37 mg % within 40mins, so that it is chosen as optimized formulation.

EVALUATION OF FORMALDEHYDE TREATED CAPSULES:

Physical tests:

Identification attributes: The size '0' capsules chosen were opaque, with white colored body and red cap. The normal capsule bodies were soft and sticky when touched with wet hand. After treating with formaldehyde, there were no significant changes in the physical appearance of the capsules except for the stickiness. The body of capsule was hard and non-sticking even when touched with wet hand due to treatment with the formaldehyde.

Visual defects: Among 100 capsules body which were treated with formaldehyde, about 15 to 20 capsule bodies showed visual defects. They were found to be shrunk and distortion into different shapes due to the complete loss of moisture.

Dimensions: Dimensional examination was done by using vernier calipers.

Average capsule length:

Before formaldehyde treatment (untreated cap and body) : 22.5 mm
After formaldehyde treatment (treated body and untreated cap): 19.5 mm

Average diameter of capsule body:

Before formaldehyde treatment : 7.8 mm
After formaldehyde treatment : 6.8 mm

Average length of capsule body:

Before formaldehyde treatment : 17.6 mm
After formaldehyde treatment : 16.6 mm

Discussion: On formaldehyde treatment, the "0" size capsules bodies showed a significant decrease in length and diameter and attained hardness.

Chemical test:

Qualitative test for free formaldehyde: The formaldehyde treated capsules were tested for the presence of free formaldehyde by comparing color of sample solution with standard solution. It was found that the sample solution was not more intensity colored than the standard solution inferring that less than 20µg/ml of free formaldehyde was present in 25 capsule bodies.

Discussion: Limit test for the presence of residual formaldehyde, indicated that the amount of formaldehyde present in treated capsules was well within limits.

Invitro release studies:

Dissolution study was carried out to measure the release rate of drug from prepared pulsincap formulation using USP I dissolution apparatus at 37^0C using 2 different dissolution media of pH 1.2, pH 7.4 phosphate buffers in order to mimic in vivo GIT conditions. Initially first 2hrs of dissolution was conducted in pH 1.2 buffer, followed by 10hrs of dissolution study in pH 7.4 phosphate buffer.

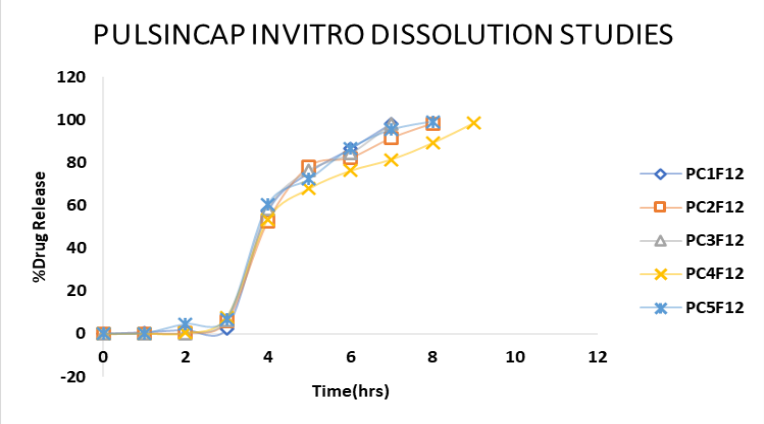

Figure No:5 Dissolution plots for formulations PC1F12 to PC5F12

Discussion:

All the 5 formulations of Lurasidone pulsincaps were subjected to dissolution studies. Formulations PC1F12, PC2F12, PC3F12, PC4F12 & PC5F12, contain the hydrogel plug with alone and combination of hydrophobic polymer and Hydrophilic polymer i.e., lactose: HPMC in single and in the ration of 1:1, 2:1, 1:2 lactose and HPMC of total 100mg weight of the plug. It was observed that a proper lag time of 6 hours was maintained with minimal upper GIT drug release for the combination of Lactose and HPMC K15M hydrogel plug in the 2:1. It was observed that as the concentration of Hydrophilic polymer was increased the release rate of drug was delayed and finally burst release of drug from the formulation occurred after lag time. So basing on these observations, of all the 5 pulsincap formulations, PC5F12 formulation containing hydrogel plug of Lactose & HPMC K15M in 2:1 ratio was selected as optimized pulsincap formulation.

RELEASE KINETICS:[16,17]

Drug release mechanisms and kinetics are the two important characteristics of a drug delivery system in describing drug dissolution profile. Mathematical models are used to evaluate the kinetics and mechanism of drug release from the tablets. The model that best fits the release data is selected based on the correlation coefficient(R) value in various models. The models with high 'R-value is considered as the best fit on the release data.

Various mathematical models are:

- **Zero order release model**
- **First order release model**
- **Higuchi release model**
- **Korsmeyer – peppas release model**

Zero Order

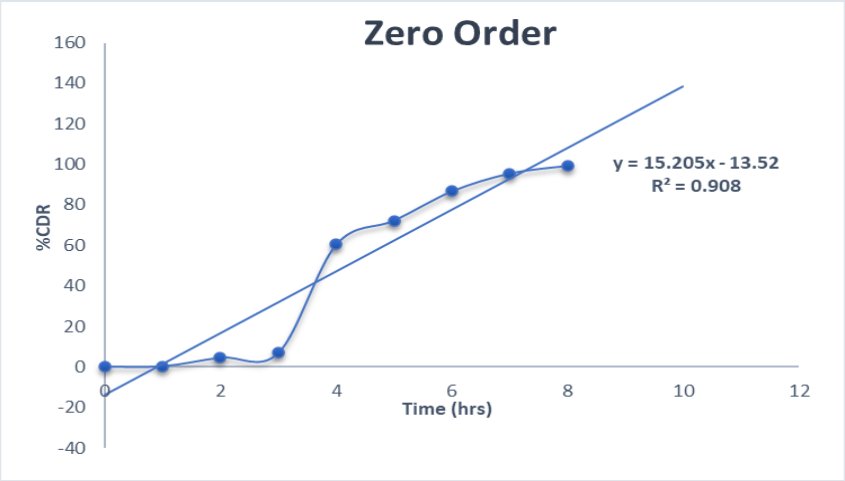

Figure No:6 Zero order plot for optimized formulation PC5F12

First Order

Figure No:7 First order plot for optimized formulation PC5F12

Higuchi Plot

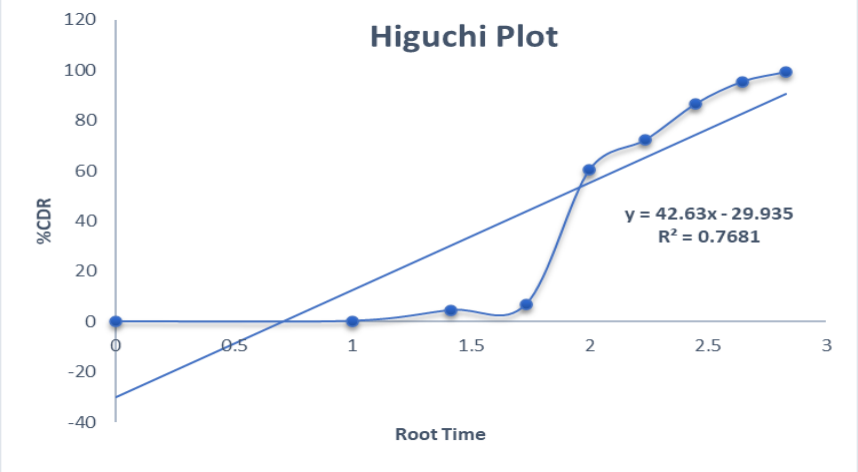

Figure No:6 Higuchi's order plot for optimized formulation PC5F12

Peppas Plot

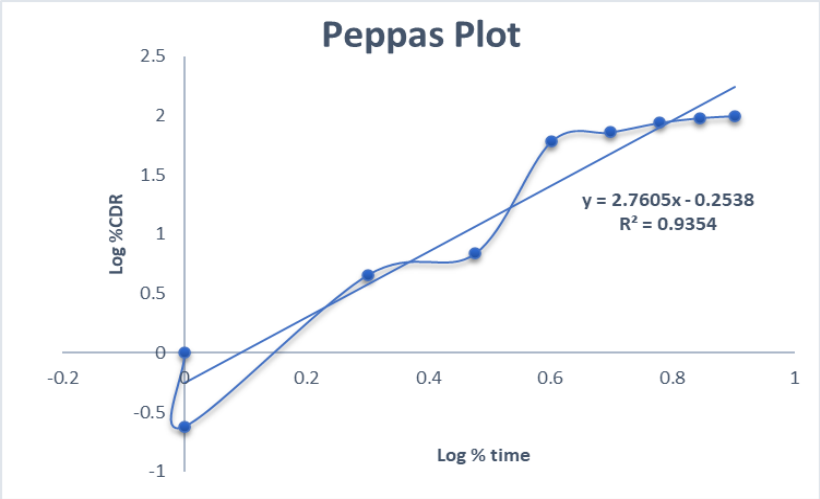

Figure No:8 Koresmayer peppas order plot for optimized formulation PC5F12

Discussion:

To analyze the mechanism of drug release from optimized PC5F12 pulsincap formulation, data obtained from the drug release studies was subjected to different kinetic treatments. The correlation coefficient (R) was used as indicator of the best fitting for each of the models considered. The drug release kinetics for the optimized formulation PC2F12 followed the zero order and follows super case II transport mechanism.

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SUMMARY & CONCLUSION

Over the past two decades there has been a growing appreciation on the importance of circadian rhythms on GIT physiology and on disease states, together with the realization of the significance of the drug administration on resultant pharmacodynamic and pharmacokinetics parameters. The significance of these day-night variations has not been over looked from the drug delivery perspective and pharmaceutical scientists have displayed considerable ingenuity in development of time delayed drug delivery systems to address emerging Chronotherapeutic formulations. Pulsincap technique helps us to deliver the drug at colon which helps to treat chronotherapeutic. The colon is a site where both the local and systemic delivery of drugs can take place; treatment could be more effective if it were possible for drugs to be targeted directly on the colon. In the present study, attempt was made to target the drug to the colon and intentionally delaying the drug absorption from the therapeutic point of view in the treatment of lowering cholesterol. Prior to formulation, Preformulation studies were carried out in order to establish compatibility between Lurasidone and excipients by FTIR spectroscopy. The results revealed that the drug and polymers were satisfactorily compatible, without any significant changes in the chemical nature of Lurasidone. The capsule bodies were made insoluble by formaldehyde treatment by exposing at various time intervals viz., 2, 4, 6, 8, 10hrs and then optimized by using disintegration studies and finally the optimized treated capsule bodies were then subjected to various physical and chemical tests such as identification attributes, visual defects, dimensional studies and qualitative test for free formaldehyde. Total 12 formulations were formulated by using super disintegrant in different ratios by direct compression method. The formulations were subjected to flow properties and FTIR study. Based on the results obtained F12 containing 30mg crospovidone was considered as the optimum powder blend for fabrication of pulsincap capsule. Different concentration of the polymers like HPMC, lactose alone and in combination were used for the preparation of hydrogel plug to maintain the suitable lag period and it was found that the drug release was controlled by the proportion of polymers used. The powder blend F12 was filled into the 6th hr formaldehyde treated capsule bodies and plugged with hydrogel polymers, 100mg hydrogel plug. The ratios of hydrophobic polymer like

lactose and HPMC were taken in alone and 1:1, 2:1, and 1:2. Finally after arranging the plug, the joint of the capsule body and cap was sealed with a small amount of 1% lactose ethanolic solution. The prepared pulsincaps were evaluated for Invitro studies. All the 5 formulations of Lurasidone pulsincaps were subjected to dissolution studies. Formulations PC1F12, PC2F12, PC3F12, PC4F12 & PC5F12, contain the hydrogel plug with alone and in combination of hydrophobic polymer and Hydrophilic polymer i.e., Lactose: HPMC in the ratio of 1:1, 2:1 & 1:2 of total 100mg weight of the plug. It was observed that a proper lag time of 6 hours was maintained with minimal upper GIT drug release for the combination of Lactose and HPMC hydrogel plug in the 2:1. It was observed that as the concentration of Hydrophilic polymer was increased the release rate of drug was delayed and finally burst release of drug from the formulation occurred after lag time. So, basing on these observations, of all the 5 pulsincap formulations, PC5F12 formulation containing hydrogel plug of lactose & HPMC K15M in 2:1 ratio was selected as optimized pulsincap formulation.

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