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TO DESIGN AND EVALUATE A CHRONOMODULATED PRESS COATED TABLET OF A PRO DRUG

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ABSTRACT

The aim of the present study was to formulate and evaluate pulsatile drug delivery system of Albuterol based on chrono pharmaceutical approach for the treatment of asthma. Pulsatile drug delivery systems were prepared by the press coated method. The pre-compression parameters of all formulations showed good flow properties and these can be used for tablet manufacture. The post-compression parameters of all formulations were determined and the values were found to be satisfactory. So Finally Based on All Parameters P3F8 was optimized from the press coated technique based upon its lag time and the cumulative percentage drug release. The press coated techniques showed the delayed release pattern in a very customized manner. As further into the study formulations showed satisfactory result in the DSC study. From DSC graphs it is evident that the polymorphic nature of the drug is intact. Pharmacokinetic study was performed to understand the bioaviability of the drug and to understand the lag time in optimized formulations. From the animal studies performed in the rabbits, formulations have shown phenomenal increase in the AUC when compared to that of the Marketed Formulation (Asthalin) i.e 5940.99 ng.mg/ml and 11119.05 ng.mg/ml for marketed formulation and press coated formulation.

KEYWORDS: Pulsatile drug delivery, Albuterol, presscoated.

INTRODUCTION

Controlled drug delivery systems have acquired a centre stage in the area of pharmaceutical R &D sector. 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. 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.[1]

Traditionally, drug delivery has meant getting a simple chemical absorbed predictably from the gut or from site of injection. A second-generation drug delivery goal has been the perfection of continuous, constant rate (zero order) delivery of bioactive agents. However, living organisms are not zero order in their requirement or response to drugs. They are predictable resonating dynamic systems, which require different amounts of drug at predictably different times within the circadian cycle in order to maximize desired and minimize undesired drug effects. Due to advances in chronobiology, chronopharmacology and global market constraints, the traditional goal of pharmaceutics (e.g. design drug delivery system with a constant drug release rate) is becoming obsolete. However, the major bottleneck in the development of drug delivery systems that match circadian rhythms (chronopharmaceutical drug delivery system: ChrDDS) may be the availability of appropriate technology. The diseases currently targeted for chronopharmaceutical formulations are those for which there are enough scientific backgrounds to justify ChrDDS compared to the conventional drug administration approach. These include asthma, arthritis, duodenal ulcer, cancer, diabetes, cardiovascular diseases, hypercholesterolemia, ulcer and neurological diseases.[2]

If the organization in time of living system including man is borne in mind, it is easy to conceive that not only

must the right amount of the right substance be at right place but also this must occur at the right time. In the last decade numerous studies in animals as well as clinical studies have provided convincing evidence, that the pharmacokinetics &/or the drug's effects -side effects can be modified by the circadian time &/or the timing of drug application within 24 hrs of a day.[3]

Circadian variation in pain, stiffness and manual and manual dexterity in patients with osteo and rheumatoid arthritis have been studied and has implication for timing anti rheumatoid drug treatment.[4] Morning stiffness associated with pain at the time of awakening is a diagnostic criterion of the rheumatoid arthritis and these clinical circadian symptoms are supposed to be outcome of altered functioning of hypothalamic pituitary adrenocortical axis.

Chronopharmacotherapy for rheumatoid arthritis has been recommended to ensure that the highest blood levels of the drug coincide with peak pain and stiffness.[5] A pulsatile drug delivery system that can be administered at night (before sleep) but that release drug in early morning would be a promising chronopharmaceutic system.[5,6]

Drug targeting to colon would prove useful where intentional delayed drug absorption is desired from therapeutic point of view in the treatment of disease that have peak symptoms in the early morning such as nocturnal asthma, angina, arthritis.[1,4,7,8]

Some orally administered drugs (E.g. Diclofenac, Theophyllin, IbuprofenIsosorbide) may exhibit poor uptake in the upper regions of GIT or degrade in the presence of GIT enzymes. Better bioavailability can be achieved through colon- specific drug delivery. Colonic targeting is also advantageous where delay in systemic absorption is therapeutically desirable.[4,7]

Pulsatile drug delivery systems

New global trends in drug discovery and development

In this century, the pharmaceutical industry is caught between pressure to keep prices down and the increasing cost of successful drug discovery and development. The average cost and time for the development of a new chemical entity are much higher (app $500 million and 10-12 years) than those required to develop a novel drug delivery system (NDDS or ChrDSS) ($20-$50 million and 3 to 4 years). In the form of an NDDS or ChrDDs, an existing drug molecule can get a new life thereby increasing its market value and competitiveness and extending patent life.[2,9]

Among modified-release oral dosage forms, increasing interest has currently turned to systems designed to achieve time specific (delayed, pulsatile) and site-specific delivery of drugs. In particular, systems for delayed release are meant to deliver the active principle after a programmed time period following administration. These systems constitute a relatively new class of device the importance of which is especially connected with the recent advances in chronopharmacology. It is by now well-known that the symptomatology of a large number of pathologies as well as the pharmacokinetics and pharmacodynamics of several drugs follow temporal rhythms, often resulting in circadian variations. Therefore, the possibility of exploiting delayed release to perform chronotherapharmaceutics 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. 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.[10]

Delivery systems with a pulsatile release pattern are receiving increasing interest for the development of dosage forms, because conventional systems with a continuous release are not ideal. Most conventional oral controlled release drug delivery systems release the drug with constant or variable release rates. A pulsatile release profile is characterized by a time period of no release rates (lag time) followed by a rapid and complete release.

These dosage forms offer many advantages such as

- Nearly constant drug levels at the site of action.
- Avoidance of undesirable side effects.
- Reduced dose and Improved patient compliance.
- Used for drugs with chronopharmacological behaviour, a high first pass effect, the requirement.

The conditions that demand pulsatile release include:

- Many body functions that follow circadian rhythm i.e. their waxes and wanes with time. Ex: hormonal secretions.

Diseases like bronchial asthma, myocardial infarction, angina pectoris, rheumatoid diseases, ulcer and hypertension display time dependence.

- Drugs that produce biological tolerance demand for a system that will prevent continuous present at the biophase as this tend to reduce their therapeutic effect.
- The lag time is essential for the drugs that undergo degradation in gastric acidic medium (ex: peptide drugs) irritate the gastric mucosa or induce nausea and vomiting.
- Targeting to distal organs of GIT like the colon requires that the drug release is prevented in the upper two-third portion of the GIT.

All of these conditions demand for a time-programmed therapeutic scheme releasing the right amount of drug at the right time. This requirement is fulfilled by pulsatile drug delivery system, which is characterized by a lag time that is an interval of no drug release followed by

rapid drug release.[1]

Pulsatile systems are basically time-controlled drug delivery systems in which the system controls the lag time independent of environmental factors like pH, enzymes, gastrointestinal motility, etc. these time-controlled systems can be classified as single unit (tablet or capsule) or multiple unit (e.g., pellets) systems.[1,11]

1. Single Unit Systems

i. Drug delivery systems with eroding or soluble barrier coatings

Most pulsatile delivery systems are reservoir devices coated with a barrier layer. The barrier dissolves or erodes after a specify lag period, after which the drug is released rapidly from the reservoir core. In general, the lag time prior to drug release from a reservoir type device can be controlled by the thickness of the coating layer. E.g. The Time Clock® system and chronotropic® system consists of a drug containing core coated by hydrophilic swellable hydroxypropylmethyl cellulose (HPMC), which is responsible for a lag phase in the onset of release.

ii) Drug delivery systems with rupturable coatings

In this the drug is released from a core (tablet or capsule) after rupturing the surrounding polymeric layer, caused by inbuilt pressure within the system. The pressure necessary to rupture the coating can be achieved with gas-producing effervescent excipients, osmotic pressure or swelling agents.

iii) Capsular shaped systems

Several single unit pulsatile dosage forms with a capsular design have been developed. Most of them consist of an insoluble capsule body, containing the drug and a plug, which gets removed after a predetermined lag time because of swelling, erosion or dissolution. E.g., Pulsincap® system and Port® system.

The **Pulsincap®** system consists of a water-insoluble capsule body (exposing the body to formaldehyde vapor which may be produced by the addition of trioxymethylene tablets or potassium permanganate to formalin or any other method), filled with the drug formulation and plugged with a swellable hydrogel at the open end. Upon contact with dissolution media or gastrointestinal fluid, the plug swells and comes out of the capsule after a lag time, followed by a rapid release of the contents. The lag time prior to the drug release can be controlled by the dimension and the position of the drug. In order to assure a rapid release of the drug content, effervescent agents or disintegrants were added to the drug formulation, especially with water-insoluble drug. Studies in animals and healthy volunteers proved the tolerability of the formulation (e.g., absence of gastrointestinal irritation). In order to overcome the potential problem of variable gastric residence time of a single unit dosage forms, the Pulsincap® system was coated with an enteric layer, which dissolved upon reaching the higher pH regions of the small intestine.[12]

The plug consists of

- Swellable materials coated with insoluble, but permeable polymers (e.g., polymethacrylates)
- Erodible compressed materials (e.g., HPMC, polyvinyl alcohol, polyethylene oxide)
- Congealed melted polymers (e.g., saturated poly glycoated glycerides or glyceryl mono oleate).

ASTHMA and CHRONOTHERAPY

The number of people with asthma in the UK is among the highest in the world. More than 5 million people are affected.[1] Asthma exacerbations lead to more than 60,000 hospital admissions with an annual expenditure of £800 million on pharmaceutical costs alone. In addition, it is estimated that asthma leads to a direct cost to the National Health Service (NHS) of £1 billion and an indirect cost to society, as a result of time off work, and loss of productivity of £6 billion.[2]

Asthma is a heterogeneous disease that results in recurrent, reversible bronchial obstruction.[3] Symptoms of asthma include wheeze, cough, and breathlessness. Asthma is associated with airway hyperresponsiveness and chronic inflammation. Remarkably, there is still no consensus as to how to define asthma; however, in the last 10 years our understanding of the heterogeneity of the condition has increased immensely.

Asthma and the circadian rhythm

It is characteristic of asthma that symptoms worsen overnight, particularly in the early hours of the morning. Nocturnal symptoms in asthma are common and are an important indicator for escalation of treatment. An extensive body of research has demonstrated that nocturnal symptoms of cough and dyspnea are accompanied by circadian variations in airway inflammation and physiologic variables, including airflow limitation and airways hyperresponsiveness.

Chronotherapy in asthma

Chronotherapy may be accomplished by synchronizing drug concentrations to rhythms in disease activity, thus increasing efficacy as well as reducing adverse effects. The effectiveness of chronotherapy for asthma is most frequently determined by its effects on the morning dip in the lung function measurements of PEFR or FEV_1. When there is poor management of asthma, the morning PEFR is markedly lower than the evening PEFR. Most of the drugs that are currently used chronotherapeutically are administered once at night with the goal of preventing chronic airway inflammation or the onset of airflow limitation. Once-daily dosing also has the added benefit of improving patient adherence and promoting self-management of asthma. However, both PEFR and FEV_1 reflect airway symptoms at a particular point in time. The inflammatory process that leads to this symptomology will have been triggered many hours earlier, with the transcription of pro-inflammatory genes

and the subsequent stimulation of the immune system. Knowledge of the circadian rhythm of inflammatory biomarkers in the blood or sputum might allow us to narrow the chronotherapeutic window even further in the future.

Current asthma treatment guidelines

Current treatment guidelines do not reflect chronotherapy, phenotype, or endotype; rather they provide a linear treatment algorithm, based on asthma symptoms. ICSs, with or without long-acting beta agonists (LABAs), continue to be the mainstay of pharmacological treatment for mild-to-moderate asthma. Severe asthma is defined as asthma that requires treatment with high-dose ICSs plus a second controller and/or systemic corticosteroids to prevent it from becoming "uncontrolled" or that remains "uncontrolled" despite this therapy.[36] Although the majority of asthma is effectively treated with existing medications, a substantial subset exists that remains difficult to treat.

To design and characterize the pulsatile drug delivery system of Albuterol by using Press coated method to obtain optimized formulations. A major objective of chronotherapy in the treatment of several diseases is to deliver the drug in higher concentrations during the time of greatest need according to the circadian onset of the disease or syndrome.

OBJECTIVE

- To prepare the sustained release granules with different rate controlling polymers by using wet granulation method.
- To perform the evaluation studies for the prepared granules .Based on the results a formulation was considered for the next level.
- Formulation of pulsing cap drug delivery system by treating the empty capsule bodies with formaldehyde and filling the capsules with the optimized formulation granules weight equivalent to 4 mg of Albuterol and inserted a hydrogel plug to ensure lag time i.e. pulsing cap technology.
- Formulation of press coated tablets using different polymers for press coating using optimized granules as the middle layer
- Perform all the evaluation parameters for press coated tablets formulations.
- To optimize the best press coated formulation and the best polymer showing lag time based on the results of *In-vi*tro drug release.
- To perform pharmacokinetic studies on animals to understand the release pattern and the lag time.

IMPORTANCE OF THE RESEARCH WORK

Asthma is a disease with a strong circadian rhythm. Symptoms of asthma frequently show exacerbation in the early hours of the morning, at around 4 am. Sudden death in asthma also tends to occur at this time. By using chronotherapy in the treatment of several diseases by delivering the drug in higher concentrations during the time of greatest need according to the circadian onset of the disease or syndrome. Chronotherapy may be accomplished by synchronizing drug concentrations to rhythms in disease activity, thus increasing efficacy as well as reducing adverse effects. The effectiveness of chronotherapy for asthma is most frequently determined by its effects on the morning dip in the lung function measurements of PEFR or FEV_1. When there is poor management of asthma, the morning PEFR is markedly lower than the evening PEFR. Most of the drugs that are currently used chrono therapeutically are administered once at night with the goal of preventing chronic airway inflammation or the onset of airflow limitation. Although the majority of asthma is effectively treated with existing medications, a substantial subset exists that remains difficult to treat. Current treatment guidelines do not reflect chronotherapy, phenotype, or endotype; rather they provide a linear treatment algorithm, based on asthma symptoms. ICSs, with or without long-acting beta agonists (LABAs), continue to be the mainstay of pharmacological treatment for mild-to-moderate asthma. In the present study we will formulate different chrono modulated dosage forms in treatment of asthma.

MATERIALS AND METHODS

Albuterol was procured from Chandra labs, Hyderabad Pvt. Ltd., Cross povidone, sodium
Starch Glycolate, Cross caramellose sodium, was procured from MYLN CHEM Mumbai, other ingredients Magnesium stearate, Micro crystalline cellulose, HPMC, Ethyl cellulose obtained from SD Fine Chemicals Pvt Ltd, Mumbai.

Preparation of standard calibration curve of Albuterol

The standard calibration curve for Albuterol was prepared using 0.2 % of SLS.

Standard solution

10 mg of Albuterol was dissolved in few ml of methanol and make up with 0.2 % of SLS to give a concentration of 1 mg/ ml (1000 µg/ml).

Stock solution

From standard solution take 10 ml of solution in 100 ml of solution to produce the 100 µg/ml concentration and take from the 100 µg/ml of the solution, aliquots of 0.5, 1, 1.5, 2, 2.5 ml of stock solution were pipette out in 10 ml volumetric flask. The volume was made up to mark with SLS solution to produce concentration as 5, 10, 15, 20, and 25 µg/ml of Albuterol respectively.

The absorbance of prepared solution of Albuterol was measured at 242 nm in Shimadzu UV/visible 1700 spectrophotometer against 0.2 % of SLS solution as blank. The absorbance data for standard calibration curve are given in Table no- and plotted graphically as shown in the Figure. The standard calibration curve yields a straight line, which shows that drug obeys Beer's law in the concentration range of 5 to 25 mcg/ml.

Drug – Excipient Compatibility Study

Infrared spectroscopy is a useful analytical technique utilized to check the chemical interaction between the drug and excipients used in the formulation.1-2 mg of solid fine powder of drug and 200-300 mg of dry powder of KBr(IR grade) were taken in a mortar and mixed well with the help of a spatula. Spectrum measurement was carried out using KBr disk method in the wavelength region of 4000-400cm^{-1} by FTIR spectrophotometer. The IR spectrum of the physical mixture was compared with that of the pure drug to check any possible drug-excipient interaction.

Formulation of core tablets by direct compression:

- The inner core tablets were prepared by using direct compression method.
- As shown in Table powder mixtures of Albuterol, microcrystalline cellulose, cross-carmellose sodium (Ac-Di-Sol), SSG, crospovidone ingredients were dry blended for 20 min. followed by addition of Magnesium Stearate.
- The mixtures were then further blended for 10 min., 200mg of resultant powder blend was manually compressed using KBr hydraulic press at a pressure of 1 ton, with 8mm punch and die to obtain the core tablet.

FORMULATION DEVELOPMENT

Table No 1: Composition of core tablets.

S.no	Ingredients	AL1	AL 2	AL 3	AL 4	AL 5	AL 6	AL 7	AL 8	AL 9
1	Albuterol	4	4	4	4	4	4	4	4	4
2	HPMCK100M	20	30	40	-	-	-	-	-	-
3	EudragitL100	-	-	-	20	30	40	-	-	-
4	Ethylcellulose20CPS	-	-	-	-	-	-	20	30	40
5	Starch	12	12	12	12	12	12	12	12	12
6	Talc	2	2	2	2	2	2	2	2	2
7	Mg stearate	2	2	2	2	2	2	2	2	2
8	Mannitol	qs	qs	qs	qs	qs	qs	qs	qs	qs
9	Total wt.(mg)	120	120	120	120	120	120	120	120	120

Formulation of mixed blend for barrier layer

The various formulation compositions containing HPMC, Ethyl cellulose in Different compositions were weighed dry blended at about 10 min. and used as press-coating material to prepare press-coated pulsatile tablets respectively by direct compression method.

Preparation of press-coated tablets

The core tablets were press-coated with 300mg of mixed blend as given in Table no 2. 150mg of barrier layer material was weighed and transferred into a 12mm die then the core tablet was placed manually at the centre. The remaining 150mg of the barrier layer material was added into the die and compressed at a pressure of 5 tons for 3min using KBr hydraulic press.

Table No.2: Composition of Albuterol press-coated Tablets.

Press coat	P1 AL8 (mg)	P2 AL8 (mg)	P3 AL8 (mg)	P4 AL8 (mg)
HPMCK4M	150	100	--	300
Ethyl cellulose	150	200	300	--
Total wt(mg)	420	420	420	420

EVALUATION OF PRECOMPRESSION BLEND

Flow Properties

Angle of Repose

The flow property was determined by measuring the Angle of Repose. In order to determine the flow property, the Angle of Repose was determined. It is the maximum angle that can be obtained between the free standing surface of a powder heap and the horizontal.

$$\text{Angle of repose} = \tan^{-1}(h/r)$$

Where,

h = height of a pile (2 cm)

r = radius of pile base.

Procedure

- 20gms of the sample was taken
- The sample was passed through the funnel slowly to form a heap.
- The height of the powder heap formed was measured.
- The circumference formed was drawn with a pencil on the graph paper.
- The radius was measured and the angle of repose was determined. This was repeated three times for a sample.

Bulk density

Bulk density is ratio of given mass of powder and its bulk volume. Bulk density was determined by measuring the volume of known mass of powder sample that has been passed through the screen in to graduated cylinder or through volume measuring apparatus in to cup.

$$\text{Bulk density} = M / V_0$$

Where M= mass of the powder;

V_0=bulk volume of the powder.

Limits: It has been stated that the bulk density values having less than 1.2 g/cm3 indicates good
Packing and values greater than 1.5 g/cm3 indicates poor packing

Tapped density
A known quantity of powder was transferred to a graduated cylinder and volume V_0 was noted. The cylinder fixed to a density determination apparatus, tapped for 500 times then reading was observed. The density is achieved by mechanically tapped by a measuring cylinder containing the powder sample. After observing the initial volume the cylinder is mechanically tapped and volume reading were taken until little further volume changes is observed.

Tap density = M / Vr

Where M = mass of the powder,
Vr = final tapping volume of the powder.

Compressibility index and Hausner ratio
The compressibility index and hausner ratio may be calculated using measured values of bulk density and tapped density as follows:
Compressibility index = 100 × tapped density / bulk density
Hausner ratio = tapped density / bulk density

Flow properties and corresponding Angle of repose, Compressibility index and Hausner ratio:
Table No 3: Acceptance Criteria of Flow Properties.

S. No	Flow properties	Angle of repose(θ)	Compressibility Index (%)	Hausner ratio
1.	Excellent	25-30	<10	1.00-1.11
2.	Good	31-35	11-15	1.12-1.18
3.	Fair	36-40	16-20	1.19-1.25
4.	Passable	41-45	21-25	1.26-1.34
5.	Poor	46-55	26-31	1.35-1.45
6.	Very poor	56-65	32-37	1.46-1.59
7.	Very very poor	> 66	>38	>1.6

EVALUATION OF TABLETS
The quantitative evaluation and assessment of a tablets chemical, physical and bioavailability properties are important in the design of tablets and to monitor product quality. There are various standards that have been set in the various pharmacopoeias regarding the quality of pharmaceutical tablets. These include the diameter, size, shape, thickness, weight, hardness, Friability and invitro-dissolution characters.

Hardness
Hardness of the tablet was determined by using the Monsanto hardness tester. The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by turning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force.

Thickness
Control of physical dimensions of the tablets such as size and thickness is essential for consumer acceptance and tablet-tablet uniformity. The diameter size and punch size of tablets depends on the die and punches selected for making the tablets. The thickness of tablet is measured by Vernier Callipers scale. The thickness of the tablet related to the tablet hardness and can be used an initial control parameter. Tablet thickness should be controlled within a ±5%. In addition thickness must be controlled to facilitate packaging.

Friability
Friction and shock are the forces that most often cause tablets to chip, cap or break. The friability test is closely related to tablet hardness and designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping. It is usually measured by the use of the Roche friabilator.

Method
A number of tablets are weighed and placed in the apparatus where they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After four minutes of this treatment or 100 revolutions, the tablets are weighed and the weight compared with the initial weight. The loss due to abrasion is a measure of the tablet friability. The value is expressed as a percentage. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable and any broken or smashed tablets are not picked.

The percentage friability was determined by the formula:

% Friability = $(W_1-W_2) / W_1$ X 100

W_1 = Weight of tablets before test
W_2 = Weight of tablets after test

Disintegration time
LAB INDIA DT 1000 USP disintegration test apparatus. To test the disintegration time of tablets, one tablet was placed in each tube and the basket rack was positioned in a 1 litre beaker containing water at 37°C ± 1°C such that the tablet remains 2.5 cm below the surface of the liquid. The time taken for the complete disintegration of the tablets was noted.

***In-vitro* Dissolution methods for Core tablets**

In –vitro Dissolution studies of Pulsatile delivery systems was done with the conventional paddle method of core tablets were performed at 37 ± 0.5 °C using 0.2 % of SLS in USP II paddle method at 50 rpm. 5 ml of filtered aliquot was manually withdrawn at pre-determined time intervals and replaced with 5 ml of fresh buffer maintained at the same temperature. The samples were analysed at 242nm using a UV spectrophotometer percentage release was determined for each formulation.

***In-vitro* Dissolution methods for press-coated tablets**

In –vitro Dissolution studies of Pulsatile delivery systems was done with the conventional paddle method of press coated tablets were performed at 37 ± 0.5 °C using 0.2 % of SLS in USP II paddle method at 50 rpm. 5 ml of filtered aliquot was manually withdrawn at pre-determined time intervals and replaced with 5 ml of fresh buffer maintained at the same temperature. The samples were analysed at 242nm using a UV spectrophotometer. The lag time and percentage release was determined for each formulation.

Stability Studies

The stability study of the formulations was carried out according to ICH guidelines at 40 ± 2°C/75 ± 5 % RH for three months by storing the samples in stability chamber (Lab-care, 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.

STABILITY STUDIES STORAGE CONDITIONS

Table No 4: 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 DISCUSSION

Preparation of standard calibration curve of Albuterol

Standard solution

Weight of Albuterol taken	100 mg
Volume made up to	100 ml
Concentration of standard solution	1000µg/ml(SSI)
Volume taken from SS-I	10 ml
Volume made up to	100 ml
Concentration of standard solution	100 µg/ml (SSII)

Table No 5: concentration and absorbances of Albuterol.

S.No	Concentration (µg/ml)	Absorbance
1	0	0
2	5	0.134
3	10	0.298
4	15	0.452
5	20	0.588
6	25	0.74

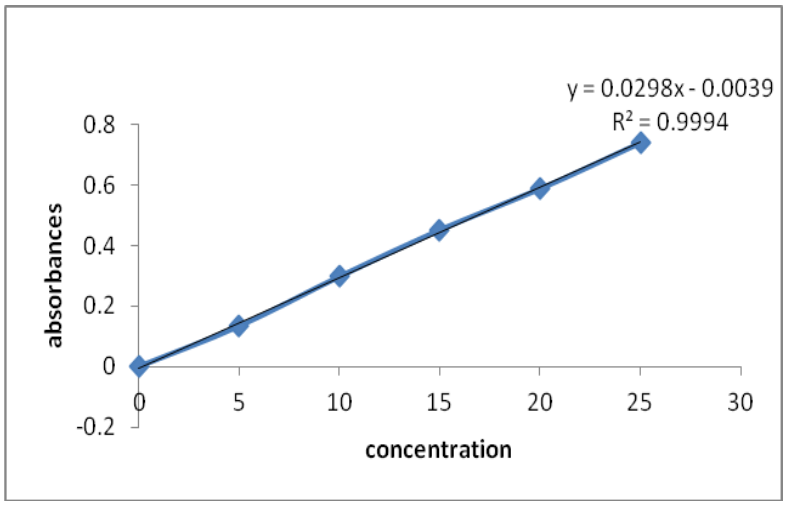

Fig No: 1 Calibration curve of Albuterol.

Drug and excipient compatibility study

Drug and excipients compatibility was studied by using FTIR studies. FTIR graphs for present research work were attached below.

From below figures it was concluded that there was no change in the position and areas of peaks presented in pure drug compared to the final best formulation. So there was no incompatibility among these ingredients.

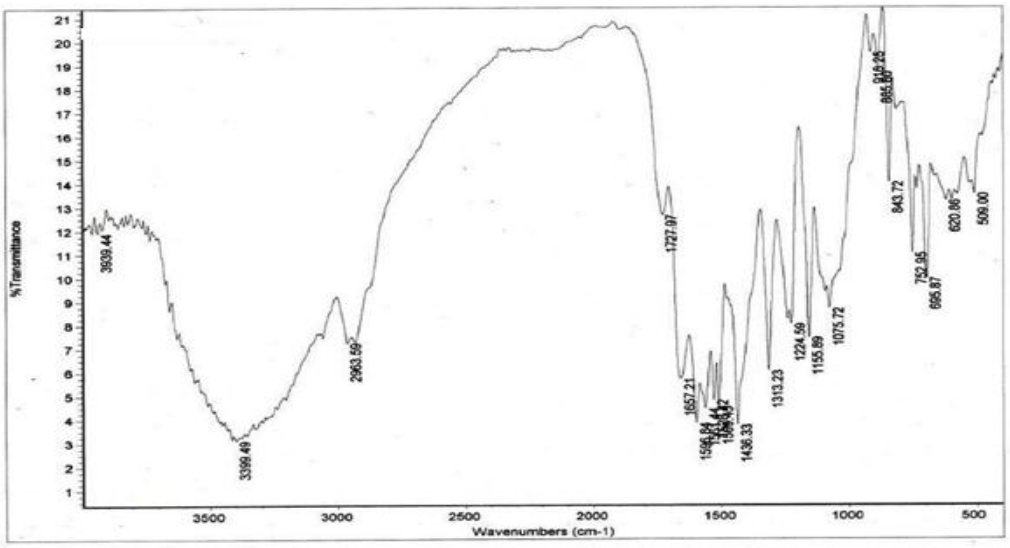

Fig no.2: FT-IR Spectra of pure Albuterol drug.

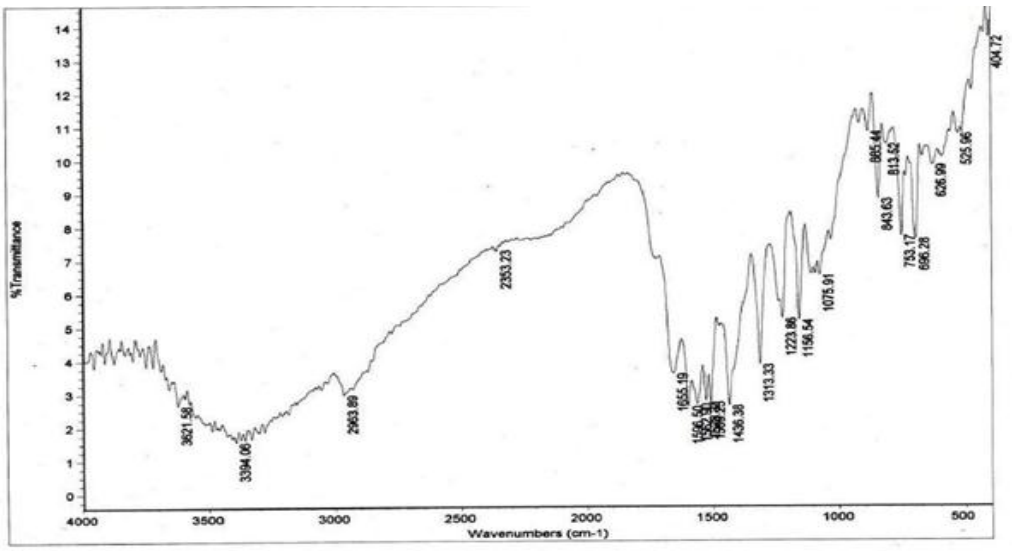

Fig no.3: FT-IR Spectra of Albuterol press coated tablet.

PRE COMPRESSION PARAMAETRS

Table No 6: precompression parameters.

Formulations	Loose Bulk Density(g/ml)	Tapped Bulk Density (g/ml)	% Compressibility	Hausner's ratio	Flow property
F1	0.5151	0.58883	12.6452	1.1514	Good
F2	0.42016	0.48682	13.8269	1.1615	Good
F3	0.42723	0.49995	14.6854	1.1817	Good
F4	0.31209	0.35653	12.5846	1.1514	Good
F5	0.30906	0.35855	13.938	1.1716	Good
F6	0.3636	0.4141	12.322	1.1514	Good
F7	0.3838	0.4444	13.7764	1.1716	Good
F8	0.3434	0.3838	10.6353	1.1312	Good
F9	0.3636	0.4141	12.322	1.1514	Good

From the above pre-compression parameters it was clear evidence that drug and excipients has good flow properties and suitable for direct compression.

POST COMPRESSION PARAMETERS
Tooling: 6mm round shape for core tablet

Evaluation of core tablets of Albuterol.

Tablet compression parameters	
Weight of the tablet	120 mg (core tablet)
Hardness	3.7 Kg/cm^2 (core tablet)
Thickness	3.7 Kg/cm^2 (core tablet)

***Invitro* dissolution studies for core tablets:-**

Dissolution Parameters	
Medium	1.2 pH Acidic buffer
Type of apparatus	USP - II (paddle type)
RPM	50
Volume	900ml

In vitro dissolution for core tablets were done in 1.2 pH Acidic buffer.

Table No 7: Evaluation for Press coated tablets

S. No	Physical parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Weight variation	121	122	121.5	121.3	119.2	121.5	120.5	120	121.6
2	Hardness(Kg/cm^2)	3.6	3.7	3.6	3.8	3.7	3.5	3.8	3.7	3.7
3	Thickness (mm)	2.55	2.6	2.6	2.62	2.65	2.45	2.55	2.60	2.45
4	Friability %	0.04	0.01	0.02	0.05	0.06	0.04	0.02	0.05	0.04

The weight variation was within the limits as per U.S.P guidelines.
Hardness was found to be 3.6-3.8 and the hardness of F8 was found to be 3.7
Thickness was found to be 2.4-2.65 and the thickness of F8 was found to be 2.16
Friability was less than 1%.

Table No 8: Dissolution for core tablets.

Time in mins	F1	F2	F3	F4	F5	F6	F7	F8	F9
10	03.03	15.51	14.34	8.06	17.44	12.4	12.34	48.2	76.82
20	16.83	29.32	35.61	19.35	38.11	**36.5**	34.61	78.3	89.95
30	19.95	34.24	46.23	33.08	51.21	54.2	56.2	99.5	99.8
40	37.42	49.91	67.48	51.79	76.82	70.1	72.6	99.5	99.4
50	44.77	51.80	81.21	63.7069	89.95	80.2	85.4	98.94	99.4
60	58.78	84.92	94.54	85.51	90.01	89.5	99.2	98.70	99.3

Among all the formulation F8was selected as optimise batch based on drug release pattern as it showed 99% drug release in 30 mins.

***In vitro* dissolution studies for press coated tablets**

Dissolution Parameters	
Medium	1.2 pH Acidic buffer & 6.8 pH phosphate buffer
Type of apparatus	USP - II (paddle type)
RPM	50
Volume	900ml
Time	2 hours &8 hours

In vitro dissolution for press coated tablets were done in 6.8 phosphate buffer.

POST COMPRESSION PARAMETERS
Tooling: 12mm round shape tooling for press coat.

Evaluation of press-coated tablets Of Albuterol

Tablet compression parameters	
Weight of the tablet	200mg (core tablet) 500mg (press coated tablet)
Hardness	7.8 Kg/cm^2(press coat tablet)
Thickness	4.5±0.3mm(press coat tablet)

Table No 9: Evaluation for Press coated tablets.

S. No	Physical parameter	P1 F8	P2 F8	P3 F8	P4 F8
1	Weight variation	500	502	505	499
2	Hardness (Kg/cm^2)	7.7	7.8	7.7	7.6
3	Thickness (mm)	4.67	4. 5	4.55	4.4
4	Friability %	0.4	0.6	0.6	0.7

The weight variation was within the limits as per U.S.P guidelines.

Hardness was found to be 7.6-7.8 and the hardness of **P3 F8** was found to be 7.7

Thickness was found to be 4.4-4.67 and the thickness of **P3 F8** was found to be 4.55

Friability was less than 1%.

Table No: 10 Dissolution for press coated tablets.

Time in hrs	P1 F8	P2 F8	P3 F8	P4 F8
1	13.03	15.51	4.34	8.06
2	16.83	19.32	5.61	9.35
3	19.95	34.24	6.23	13.08
4	27.42	39.91	7.48	21.79
5	54.77	41.80	11.21	23.70
6	56.78	44.92	74.54	35.51
7	60.52	58.59	97.24	44.88
8	61.16	65.49	-	52.38
9	62.40	77.32	-	62.97

Among all the formulation **P3 F8** was selected as optimise batch based on drug release pattern as it was delayed for 5 hrs and then the drug released immediately with in 2hrs.

Table No: 11 STABILITY DATA FOR OPTIMISED FORMULATION P3 F8.

S.No	Time points (hr)	Initial	Cumulative % Drug Release (mean ± SD) (n=3)			
			25C/60%RH		40C/75%RH	
			1st Month	3rd Month	1stMonth	3rdMonth
1	0	0	0	0	0	0
2	1	0	0	0	0	0
3	2	0	0	0	0	0
4	3	2.5	2.0	1.8	1.3	1.1
5	4	7.3	7.1	6.7	6.2	5.8
6	5	18.9	18.5	18.1	17.8	17.4
7	6	97.8	97.1	96.8	96.1	95.7
9	Assay	99.6	99.3	99.6	98.9	98.5

Differential Scanning Colorimetry

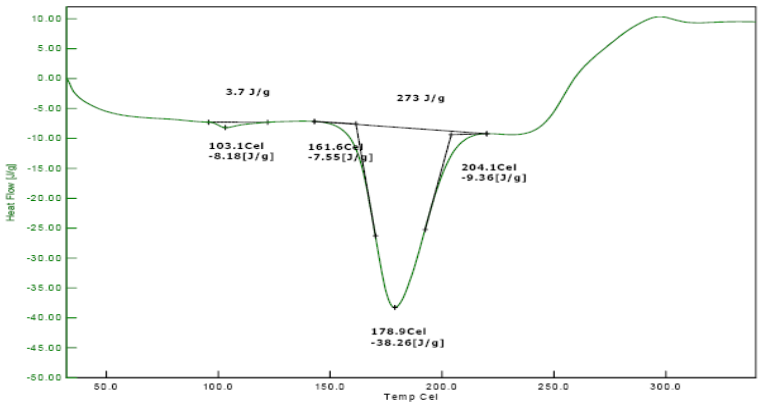

Fig no: 4 DSC of Albuterol pure drug.

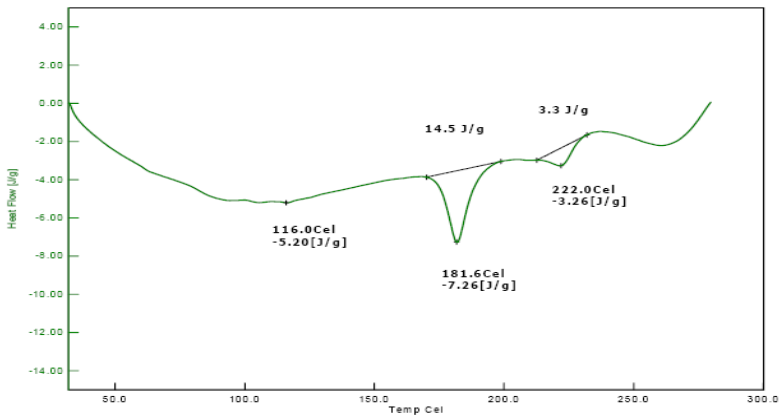

Fig no: 5 DSC of Albuterol Press coated Tablets.

From the above DSC graphs it is evident that the melting point of both pure drug and the optimized formulation are within the range which determines that there is no change in the polymorphic form of the drug.

Table No: 12 Pharmacokinetic study of Albuterol Press coated tablets.

Time	Conc.	C1 + C2	t2 - t1	AUC	AUC(0-t)	Log Conc.
0	0	0	0	0	0	0
1	0	0	1	0	0	0
2	0	0	1	0	0	0
4	65.3	65.3	2	65.3	65.3	1.814913
6	86.1	151.4	2	151.4	216.7	1.935003
8	110.6	196.7	2	196.7	413.4	2.043755
9	362.3	472.9	1	236.45	649.85	2.559068
10	578.7	941	1	470.5	1120.35	2.762453
12	1198.6	1777.3	2	1777.3	2897.65	3.078674
16	762.4	1961	4	3922	6819.65	2.882183
20	368.9	1131.3	4	2262.6	9082.25	2.566909
24	109.6	478.5	4	957	10039.25	2.039811

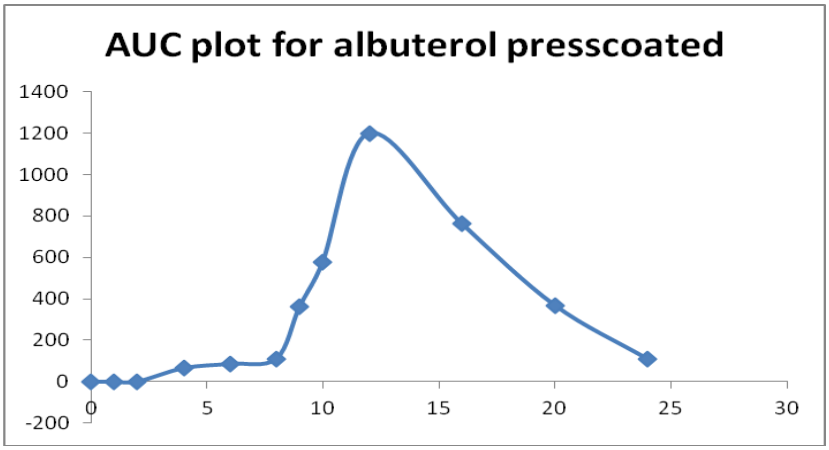

Fig no. 6: AUC plot of Albuterol Press coated tablets.

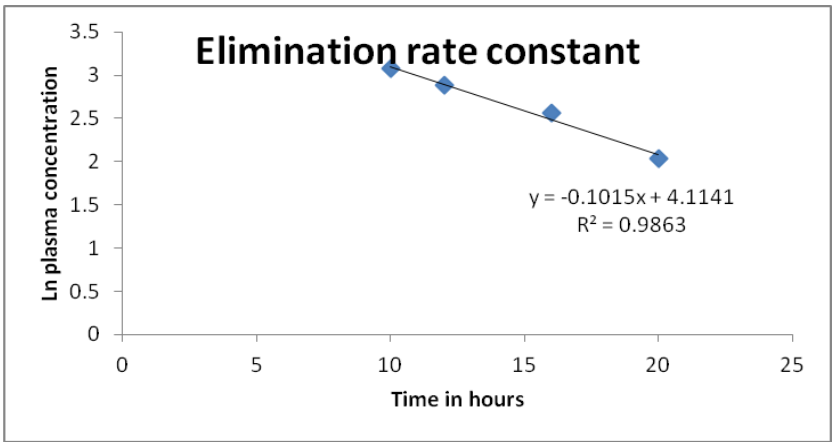

Fig no. 7: Elimination rate constant of Press coated tablets.

Pharmacokinetic Parameters

Cmax(ng/ml)	1198.6
Tmax	12 hrs
AUC(0-t)(ng.mg/ml)	10039.25
Ke	0.1015
t half	6.827586
AUC(t-inf)(ng.mg/ml)	1079.803
AUC(0-inf)(ng.mg/ml)	11119.05

Pharmacokinetic study of Asthalin (Marketed Formulation)

Time	Conc.	C1 + C2	t2 - t1	AUC	AUC(0-t)	LOG CONC.
0	0	0	0	0	0	0
1	128	128	1	64	64	0
2	231.2	359.2	1	179.6	243.6	0
4	572.4	803.6	2	803.6	1047.2	2.7577
6	982.6	1555	2	1555	2602.2	2.992377
8	705.2	1687.8	2	1687.8	4290	2.848312
9	456.4	1161.6	1	580.8	4870.8	2.659346
10	272.9	729.3	1	364.65	5235.45	2.436004
12	105.2	378.1	2	378.1	5613.55	2.022016
16	29.26	134.46	4	268.92	5882.47	1.466274
20	0	29.26	4	58.52	5940.99	#NUM!
24	0	0	4	0	5940.99	#NUM!

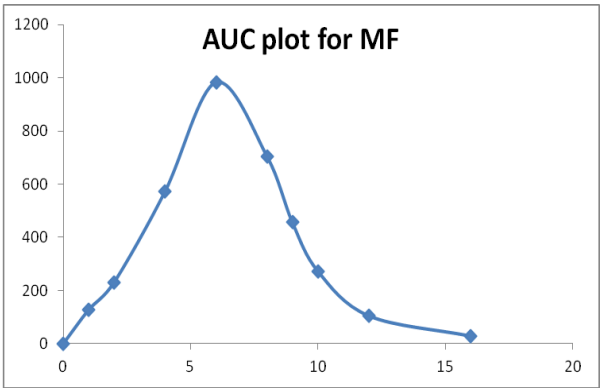

Fig no. 8: AUC plot of Asthalin Marketed Formulation.

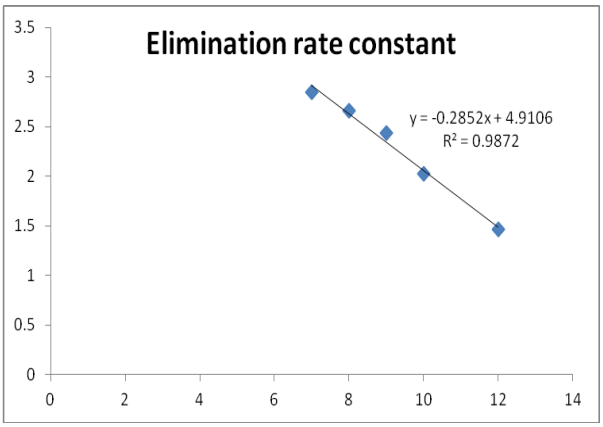

Fig no. 9: Elimination rate constant of Asthalin Marketed Formulation.

Pharmacokinetic Parameters

Cmax(ng/ml)	**982.6**
Tmax	08 hrs
AUC(0-t)(ng.mg/ml)	5940.99
Ke	0.2852
t half	2.429874
AUC(t-inf)(ng.mg/ml)	0
AUC(0-inf)(ng.mg/ml)	5940.99

SUMMARY AND CONCLUSION

- Pulsatile drug delivery systems were prepared by press coat method. The pre-compression parameters of all formulations showed good flow properties and these can be used for tablet manufacture. The post-compression parameters of all formulations were determined and the values were found to be satisfactory.
- So Finally Based on All Parameters P3F8 was optimized from the press coated technique has been optimized based upon its lag time and the cumulative percentage drug release. Both the press coated techniques showed the delayed release pattern in a very customized manner. As further into the study formulations showed satisfactory result in the DSC study. From DSC graphs it is evident that the polymorphic nature of the drug is intact.
- Pharmacokinetic study was performed to understand the bioavailibity of the drug and to understand the lag time in both the optimized formulations. From the animal studies performed in the rabbits, formulations have shown phenomenal increase in the AUC when compared to that of the Marketed Formulation (Asthalin) i.e 5940.99 ng.mg/ml, and11119.05 ng.mg/ml presscoated formulation
- The techniques meet the requisites of the pulsatile drug delivery system.

CONCLUSION

As a result of this study it may be concluded that the pulsatile drug delivery system can be used to increase the delayed action of drug release to deliver the drug in a delayed manner. The concept of formulating Pulsatile drug delivery of albuterol offers a suitable and practical approach in serving desired objectives of pulsatile drug delivery system.

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