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Preparation and Evaluation of Theophyllinepress Coated Tablet

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Abstract: The present research work focuses on the development and evaluation of theophylline press coated tablet, showing controlled release pattern consigned with chronotherapeutics aspects. Provided HPMC K100LV and HPMC K4M were used in the different formulation as coating polymer for development of press coated tablet for controlled release. The formulation powder mixtures were evaluated for pre-compression parameters such as angle of the repose, bulk density, tapped bulk density, Carr's index and Hausner's ratio. Batches containing combination of HPMC K100LV and K4M controlled the drug release better at low concentration of high viscosity grade and it was used to optimize the formulation for pulsatile release. The core tablet and final press coated tablets were characterized, in which tablet (F4) gives satisfactory results as it released the drug with predetermined lag time of 6 h but lag time get increases with increase in amount of polymer HPMC K100 LV and HPMC K4M. By using low viscosity grades of HPMC it was possible to obtain a drug plasma peak at 6 to 7 h after administrating to achieve the main aim of the study. From accelerated stability study it was concluded that there was no much effect of the temperature and moisture on the hardness, drug content, and in-vitro drug release from pulsatile press coated tablet.

Key words: Theophylline; Pulsatile press coated tablet; Chronotherapeutics; HPMC (K100LV and K4M); FT-IR.

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I. INTRODUCTION

In recent years, a major goal for the drug delivery research is turned towards the development of efficacious drug delivery systems with already existing active ingredients in case of new drug discovery. Oral drug delivery system is more favored on popular controlled drug delivery system in pharmaceutical research and development business due to increase in awareness of medical and pharmaceutical community, about the importance of safe and effective use of drug. This system aims to maintain plasma drug concentration within the therapeutic window for long period of time. Oral route is the most extensively used routes of the drug administration because of its obvious advantages of drug administration; improve patient compliance, and convenience. But conventional preparation is usually administered two or three times a day, which can lead to large fluctuation in drug plasma concentration and side effects on human body [1,2]. It is becoming increasingly more evident with the specific time that patients have to take their medication may be even more significant than was recognized in the past. The tradition of prescribing medication at evenly spaced time intervals throughout the day, in an attempt to maintain constant drug levels throughout a 24-h period, may be changing as researcher's report that some medications may work better if their administration is coordinated with day-night patterns and biological rhythms. A reduction in dose, dosage frequency and patient efficacy and compliance by this delivery system also expected [3].

A release pattern of drug is not suitable in certain disease condition, at that time release profile of a delivery system characterized by lag time. In other words, the drug should not release during its initial period of administration, followed by a rapid and complete release (pulse release) of drug that is called pulsatile drug delivery system [4]. The effectiveness and toxicity of many drugs vary depending on the relationship between the dosing schedule and the 24 h rhythms of biochemical, physiological and behavioral processes, the alteration of biological rhythm is a new concept of adverse effects. It has been demonstrated that the latter can be minimized by optimizing the dosing schedule **[5, 6, 7, 8,9,10,11,12]**. Coating techniques mostly used in pharmaceutical industry are aqueous or organic coatings, it is the absolute dry coating without solvent and heat use. Also it is a time and rate-controlled drug delivery device which consists of a core tablet of drug and an outer layer, composed of single or different polymers, that is considerably thicker than typical tablet coats and which completely surrounds the inner core of tablet. Lag times can be varied by changing the barrier formulation or the coating thickness. Press coating has no limitation for the cores and hence overcomes the adhesion problem found in spraying methods **[13,14,15,16]**. If we use erodible polymer (low mol. wt. HPMC) then delayed release (after

complete erosion of coat) can be obtained. Swellable polymer (high mol. wt. HPMC) can provide modified as well as pulsatile release. Bacterial digestible polymers help to achieve site specific release while combination of waxy polymers can give zero, first, second order release. Smaller molecular weight of gellable coat (HPMC 2208) would provide a faster release rate after lag time than higher molecular weight. A press coated tablet requires a coating which is about twice the weight of the core or, more while the core must be exactly at centre so that release must be equal from all sides. Drug in press coated tablets diffuses through the swollen coat. This process might enhance some possible interaction between the drug and coat**[13, 14, 15]**

II. MATERIALS AND METHOD

Materials

Theophylline anhydrous (API) was procured as a gift sample from cipla ltd. satara, India. While hydroxypropyl methyl cellulose (HPMC K 100 LV) and hydroxypropyl methyl cellulose (HPMC K4M) polymers were gifted by wockhardt research center, aurangabad, India. Ac-di-sol (cross carmalose sodium), avicel PH102, starch and magnesium stearate samples were provided by Loba chemicals, mumbai, India.

Methodology

To confirm the identity, purity, suitability and micromeritic characterization for formulation and to establish a drug profile, preformulation studies of theophylline anhydrous was done [17, 18]**.** While spectroscopic analysis of *theophylline*was performed by UV-1700 double beamspectrophotometer (Shimadzu 1700, Japan) and FT-IR (Shimadzu FTIR 84005). The physical mixture of formulation ingredient and API was studied for compatibility using FT-IR [19,20]. *Theophylline* anhydrous was analyzed using UV spectrophotometer, using solution prepared in 0.1 N HCl and 7.2 pH phosphate buffer at 271.0 nm and 272.0 nm respectively [20].

Core tablet formulation by direct compression

Formulation mixture

The inner core tablets were prepared by using direct compression method. Table 01shows the composition of each core tablet formulation. All the powders were passed through sieve no.30 separately. Mixing of powders was carried out using a pestle and mortar for 10 min., magnesium stearate was then added to the powder mixture. Mixing was continued for another 3 min. finally, 150 mg of powder mixture were weighed and fed manually into the die (8 mm diameter) of a single punch tablet machine (Cadmach, Ahmadabad, India), equipped with 8 mm round concave punch to produce the desired core tablets. The hardness of the tablets was adjusted at 3-4 Kg/cm^2 using a Monsanto hardness tester (Monsanto Chemical, St. Louis, MO). The compressed tablets of each formulation batch were then evaluated for tablet characteristics such as thickness, hardness, weight variation, friability and drug content [21].

Table 01. Formulation of core tablet mixture

Sr. No.	Name of ingredient	Quantity (mg/tablet)
1	*Theophylline* anhydrous	100
2	Micro crystalline cellulose	030
3	Crosscarmellose sodium	007
4	Starch	012
5	Magnesium stearate	001
6	Total	150

The prepared powder mixture was evaluated for bulk density, tap density, Carr's index, Hausner Ratio and angle of repose

Formulation of final press coated tablets

Components of the coat which are shown in table 02 were mixed for 10 min. Half of the powder mass for one tablet coat was weighed into a die (9 mm diameter). A lower coating layer was consolidated and the core centered on an even bed. The remaining powder was then added to the die and the final compression is done by respective size round concave punches on a single punch tablet machine (Cadmach, Ahmadabad, India) to produce press coated tablets. The hardness of the tablets was adjusted at 8-9 Kg/cm^2 using a Monsanto hardness tester (Monsanto Chemical, St. Louis, MO). The press coated tablets of each formulation batch were then evaluated for tablet characteristics such as thickness, hardness, weight variation, friability, drug content and *in vitro* drug release. [22]

Table 02. Formulation of final press coated tablets

Batch code	HPMC K 100LV (mg/tablet coat)	HPMC K4M (mg/tablet coat)	total weight (mg) (core + coat)
F1	0	100	250
F2	0	120	270
F3	0	140	290
F4	100	0	250
F5	120	0	270
F6	140	0	290
F7	160	0	310
F8	250	0	400
F9	95	05	250
F10	90	10	250

Later on accelerated stability studies of *theophylline* anhydrous press coated tablets was performed [23,24].

III. RESULTS

Micromeritic characterization of drug

The micromeritic characterization of *theophylline*was observed as;

Table 03. Micromeritic characterization of*theophylline*

Sr.No.	Parameters	Result
1	Loose bulk density	0.35 ± 0.02 g/cm^3
2	Tapped density	0.39 ± 0.02 g/cm^3
3	Carr's Index	14 ± 0.036 %
4	Hausner's ratio	1.15 ± 0.016
5	Angle of repose	29.6 ± 0.16^0

All the values are expressed as mean ± SD (n = 03)

UV Spectroscopy (Determination of λ_{max})

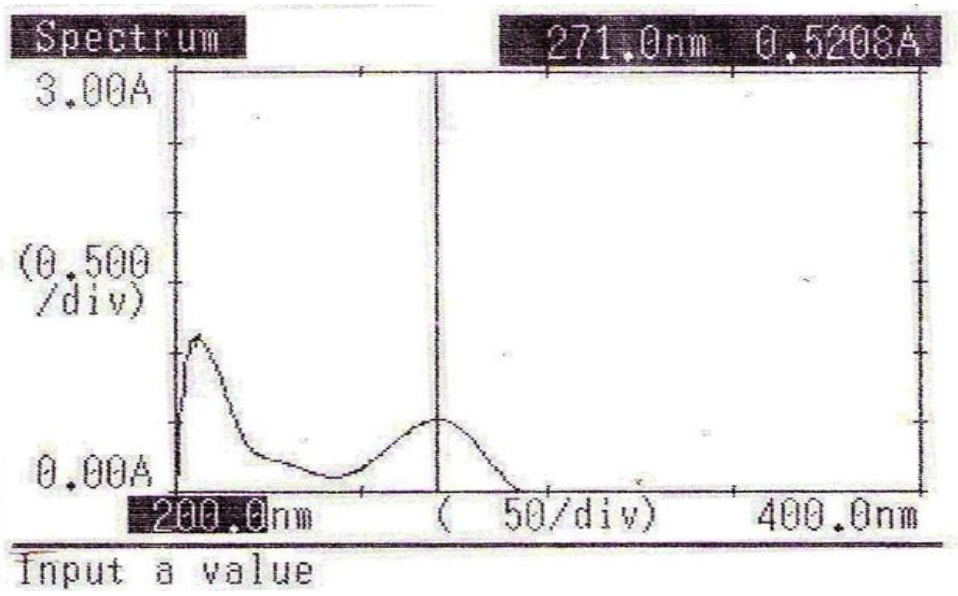

Figure 01. UV light absorption spectrum of *theophylline*in 0.1 N HCl

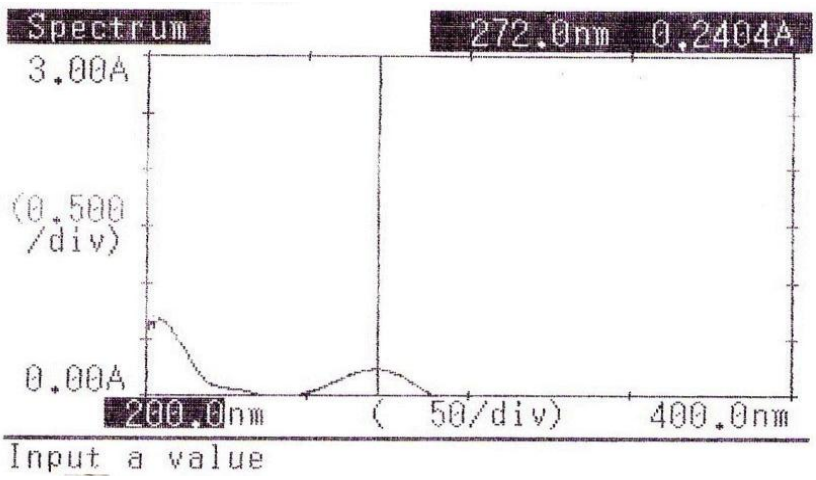

Figure 02. UV light absorption spectrum of *theophylline* in 7.2 pH phosphate buffer

FT-IR Spectra of drug

Dry sample of drug and potassium bromide was mixed uniformly and filled into the die cavity of sample holder and an IR spectrum was recorded using diffuse reflectance FTIR spectrophotometer (Shimadzu FTIR 84005). The results of IR spectra obtained were revealed by figures 03-06. The results depicted that all characteristic peaks of *theophylline* with HPMC K100, HPMC K4M and physical mixture of formulation within the range of pure *theophylline* revealing lack of significant interaction between drug and selected polymers for formulation of press coated tablets.

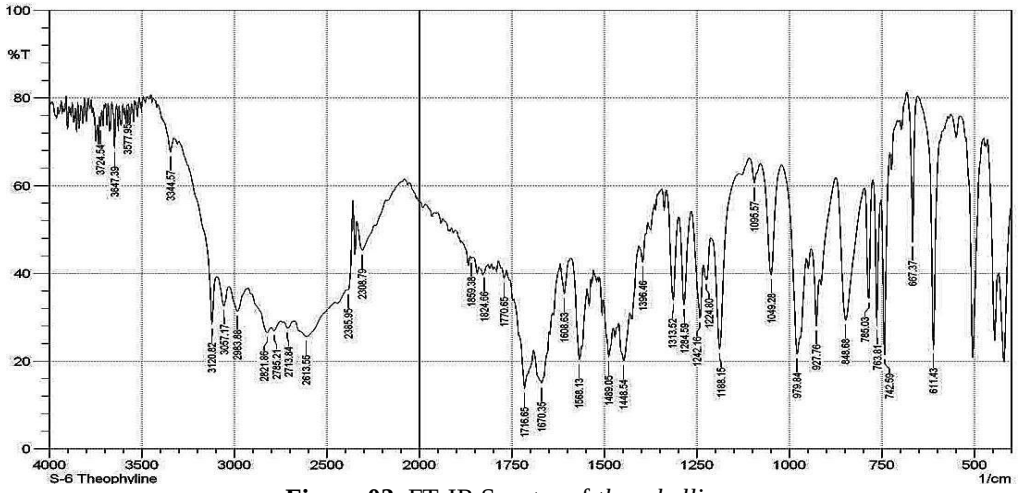

Figure 03. FT-IR Spectra of *theophylline*

Compatibility studies between drug and polymer

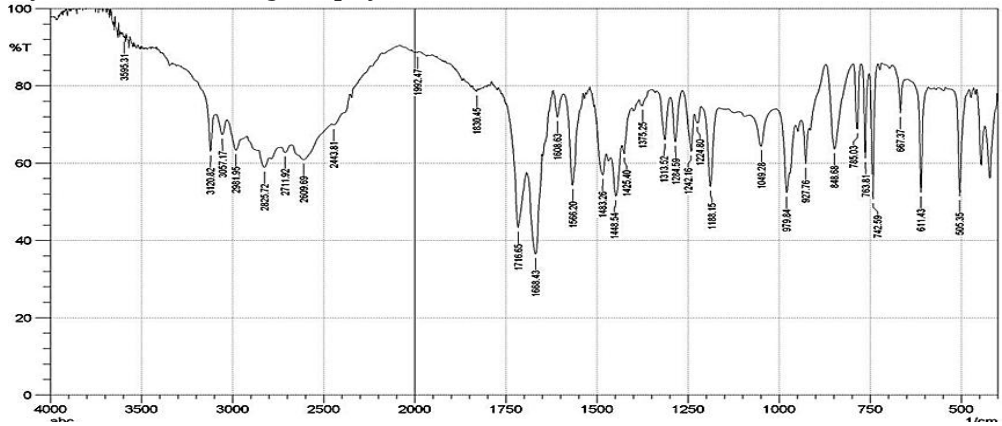

Figure 04. FT-IR spectra of combination of drug and HPMC K100LV

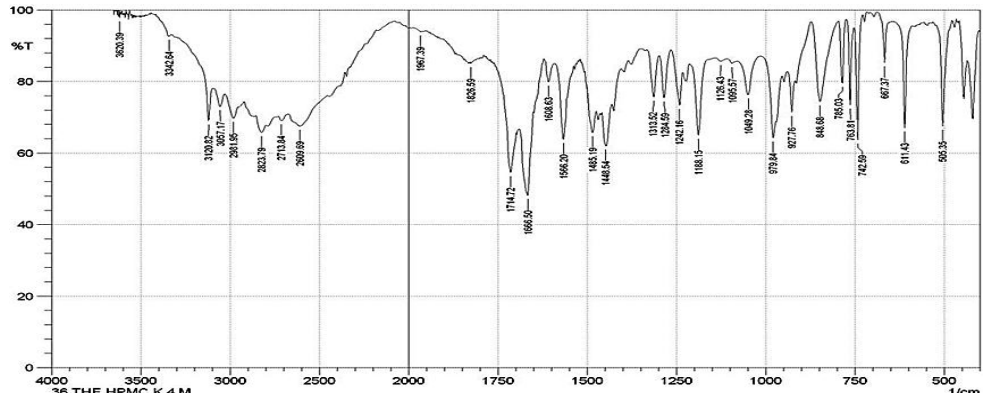

Figure 05. FT-IR spectra of combination of drug and HPMC K4M

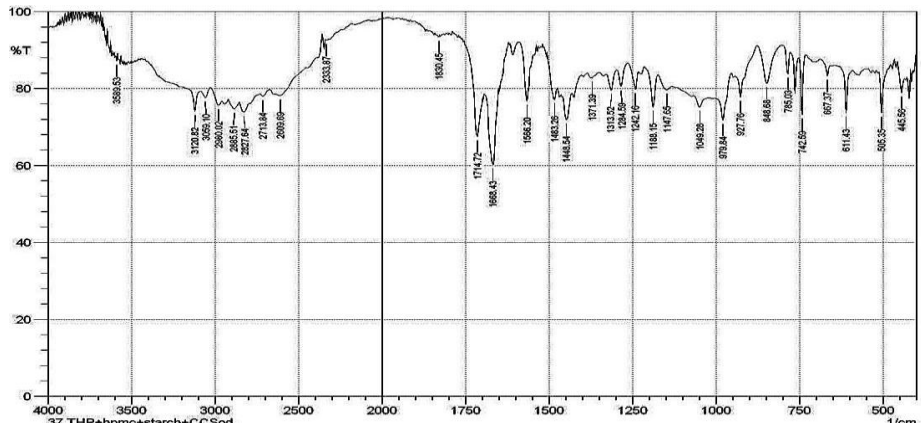

Figure 06. FT-IR spectra of physical mixture

Standard calibration curve of theophylline

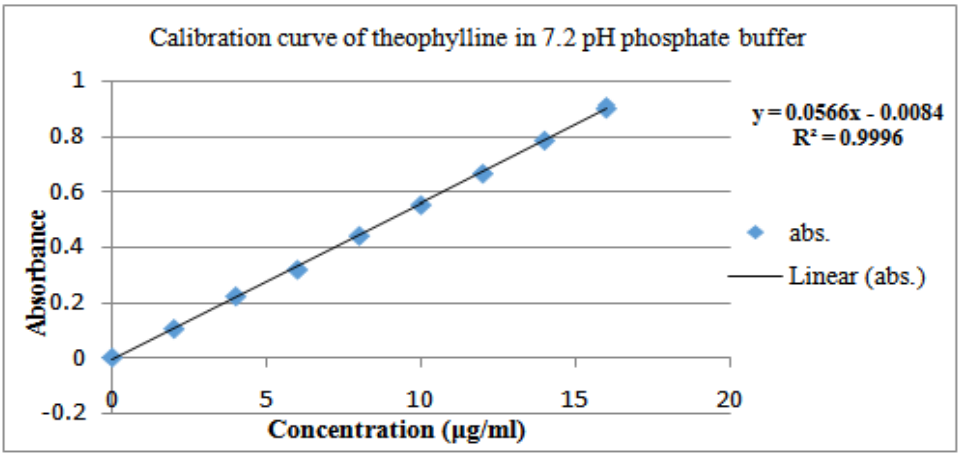

Figure 07. Calibration curve of *Theophylline*in 0.1 N HCl

UV light absorption spectrum in the range 200 nm to 400 nm of 0.0025% w/v solution of drug in 0.1 N $HCl_{(aq.)}$ exhibits a maximum peak at about 271.0 nm. The solution obeyed Beer-Lambert's law for concentration range of 02 µg/mlto 16 µg/ml with regression coefficient of 0.9988. Standard curve of *Theophylline*prepared in 0.1N HCl is shown in figure07.

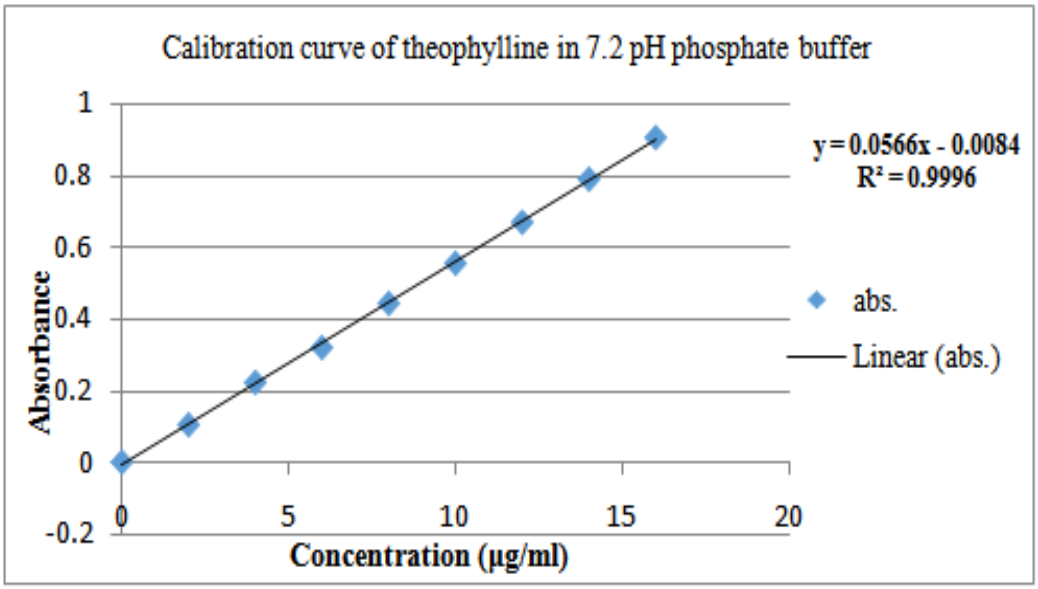

Figure 08. Calibration curve of *Theophylline*in 7.2 pH phosphate buffer

Theophylline showed maximum absorbance in phosphate buffer pH 7.2 at 272 nm. The solution obeyed Beer-Lambert's law for concentration range of 2 to 16 µg/mlwith regression coefficient of 0.9996. Standard curve of *theophylline* prepared in phosphate buffer pH 7.2 is shown in figure 08.

Evaluation of prepared powder mixtures

All the formulation powder mixtures were evaluated for pre-compression parameters such as angle of the repose, bulk density, tapped bulk density, Carr's index and Hausner's ratio and results obtained are shown in the table 04.

Table 04. Evaluation of physical properties of powder mixtures

Properties	Values
Angle of repose	27.7 ± 0.14°
Bulk density	0.33 ± 0.021 g/cm^3
Tapped density	0.37 ± 0.020 g/cm^3
Carr's index	12 ± 0.36 %
Hausner's ratio	1.13 ± 0.020

All the values are expressed as mean ± SD (n = 3)

Bulk density

It has been stated that the bulk density values less than 1.2 g/cm^3 indicate good packing & values greater than 1.5 g/cm^3 indicate poor packing. The bulk density and tapped bulk density values of powder mixture for core tablet formulation was found to be 0.33 ± 0.021 g/cm^3 and 0.37 ± 0.020 g/cm^3 respectively. The values obtained were found to be within the acceptable range.

Compressibility index

The percent compressibility of powder mixtures was determined by Carr's compressibility index. The percent compressibility (12 ± 0.36 %) was found within the range, indicates good flow property.

Hausner's ratio

Hausner's ratio was found to be 1.13 ± 0.020, which showed acceptable flow property and good packing ability.

Angle of repose

The results of angle of repose of powder mixture for core tablet formulation was found to be 27.7 ± 0.14°, indicated excellent flow property and this was further supported by lower compressibility index values concluding powder mixtures possessed good flow characteristics.

Evaluation of core tablet and final press coated tablets

Table 05. Standard physical tests for final press coated tablets

Batch code	Thickness (mm)*	Hardness (Kg/cm^2)*	Friability (% w/w) *	Content uniformity (%) *	Weight variation (mg)**
Core	3.7 ±0.073	3.4 ± 0.028	0.84 ± 0.012	99.42 ± 0.22	passes
F1	4.64 ± 0.22	8.85 ± 0.16	0.5 ± 0.014	99.32 ± 0.24	passes
F2	4.69 ± 0.18	8.72 ± 0.24	0.5 ± 0.018	98.82 ± 0.18	passes
F3	4.81 ± 0.19	9.17 ± 0.14	0.3 ± 0.011	99.72 ± 0.32	passes
F4	4.45 ± 0.28	9.12 ± 0.11	0.3 ± 0.016	99.16 ± 0.16	passes
F5	4.62 ± 0.18	8.96 ± 0.19	0.4 ± 0.019	98.62 ± 0.18	passes
F6	4.95 ± 0.20	8.92 ± 0.12	0.4 ± 0.012	99.42 ± 0.21	passes
F7	5.13 ± 0.16	9.11 ± 0.20	0.3 ± 0.019	97.96 ± 0.28	passes
F8	4.40 ± 0.24	8.84 ± 0.14	0.5 ± 0.018	99.58 ± 0.12	passes
F9	4.44 ± 0.21	9.01 ± 0.17	0.4 ± 0.024	99.34 ± 0.25	passes
F10	4.45 ± 0.17	8.91 ± 0.13	0.5 ± 0.018	98.82 ± 0.18	passes

All values are expressed as mean± SD, *n=3, **n=10

Tablet hardness

hardness was determined by using Monsanto hardness tester.Fromtable 05it was clear that hardness of tablet of the formulation F1 to F10 was found to be 8.72 ± 0.24 to 9.17 ± 0.14 $kg/cm^{2.}$ This indicated good strength of tablet. This complies with pharmacopeial standards. Each sample was analyzed in triplicate.

Uniformity of weight

In weight variation test, the pharmacopeial limit for percent of deviation for tablets weighing in range of 130 mg to 324 mg is not more than 7.5 %. The average percent deviation of all tablets was found to be within the limit and henceall formulation passed the weight variation test. This is same for final press coated tablet with variation below 7.5 % and 5 %.

Friability

Tablet friability was determined by Roche friabilator and the percentage weight loss of tablets of each formulation was found to be in the range 0.3 ± 0.011 %to 0.5 ± 0.018 %. which is less than 1%, indicates better strength of tablet.

Uniformity of content

The drug content was found to be uniform among all formulation which ranges from 97.96 ± 0.28 % to 99.72 ± 0.32 %.

Tablet thickness

Thickness of the formulation F1 to F10 found in range from 4.40 ± 0.24 to 5.13 ± 0.16 which indicates proper relation with coating amount and maintained properly.

In-vitro dissolution study of press-coated tablet

The *in-vitro* drug release characteristics were studied for press coated tablets in triplicate using an eight-station USP type Π (paddle) apparatus (Electro lab) at 37°C ± 0.5°C and 50 rpm speed in 900 ml each of

0.1 N HCl (1st fluid; simulated gastric fluid) for 2 h and pH 7.2 phosphate buffer (2nd fluid; simulated intestinal fluid) for rest of time as dissolution media.

Table 06. *In-Vitro* drug release from batch F1 to F5

Time (h)	Cumulative % drug release				
	F1	F2	F3	F4	F5
0	0	0	0	0	0
1	0	0	0	0	0
2	0	0	0	0	0
3	0.93±0.17	0.43±0.28	0.35±0.17	1.42±0.32	1.21±0.09
4	0.95±0.54	0.45±0.15	0.48±0.24	2.60±0.31	3.50±0.13
5	0.96±0.12	0.60±0.41	0.53±0.42	4.56±0.21	3.57±0.21
6	1.06±0.52	0.79±0.29	0.45±0.23	97.54±0.11	3.87±0.23
7	0.94±0.16	0.81±0.25	0.43±0.19	98.76±0.29	4.08±0.11
8	1.01±0.31	0.74±0.53	0.57±0.52	98.76±0.29	97.06±0.54
9	1.29±0.08	0.89±0.19	0.69±0.32	98.76±0.29	97.13±0.42
10	1.29±0.13	0.90±0.26	0.72±0.10	98.76±0.29	97.36±0.89
11	1.44±0.42	1.11±0.12	0.76±0.18	98.76±0.29	97.36±0.89
12	1.88±0.51	1.16±0.47	0.78±0.37	98.76±0.29	97.36±0.89

All the values are expressed as mean ± SD (*n*=3)

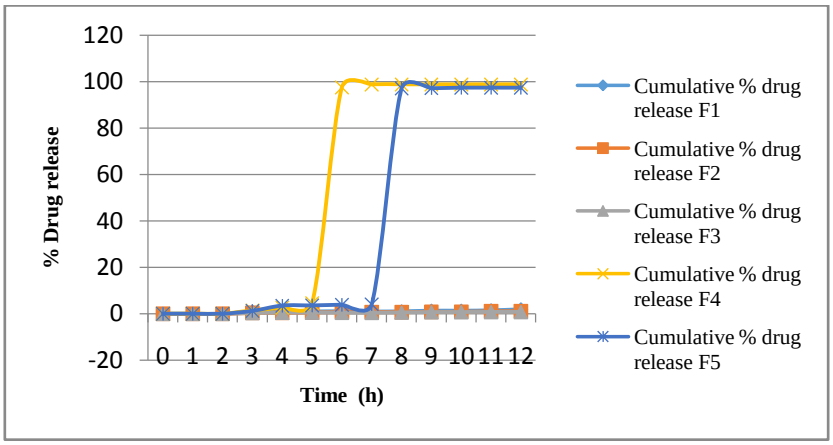

Figure 09.*In-Vitro* drug release from batch F1 to F5

Table 07.*In-Vitro* drug release from batch F6 to F10

Time (h)	Cumulative % drug release				
	F6	F7	F8	F9	F10
0	0	0	0	0	0
1	0	0	0	0	0
2	0	0	0	0	0
3	0.98±0.13	0.52±0.19	1.25±0.28	0.14±0.35	0.20±0.29
4	1.29±0.22	0.61±0.79	1.22±0.49	0.07±0.26	0.39±0.49
5	1.42±0.31	0.71±0.45	1.50±0.43	0.27±0.36	0.35±0.29
6	4.18±0.28	3.65±0.14	2.12±0.16	0.25±0.28	0.69±0.58
7	4.60±0.18	3.82±0.28	3.24±0.11	97.91±0.18	0.57±0.24
8	86.78±0.41	3.83±0.15	3.26±0.53	97.91±0.18	94.99±0.73
9	95.81±0.54	96.74±0.63	5.35±0.31	97.91±0.18	95.68±0.37
10	97.90±0.25	97.07±0.41	9.83±0.47	97.91±0.18	95.69±0.34
11	97.90±0.25	97.11±0.09	98.11±0.39	97.91±0.18	95.69±0.34
12	97.90±0.25	97.11±0.09	99.38±0.27	97.91±0.18	95.69±0.34

All the values are expressed as mean ± SD (*n*=3)

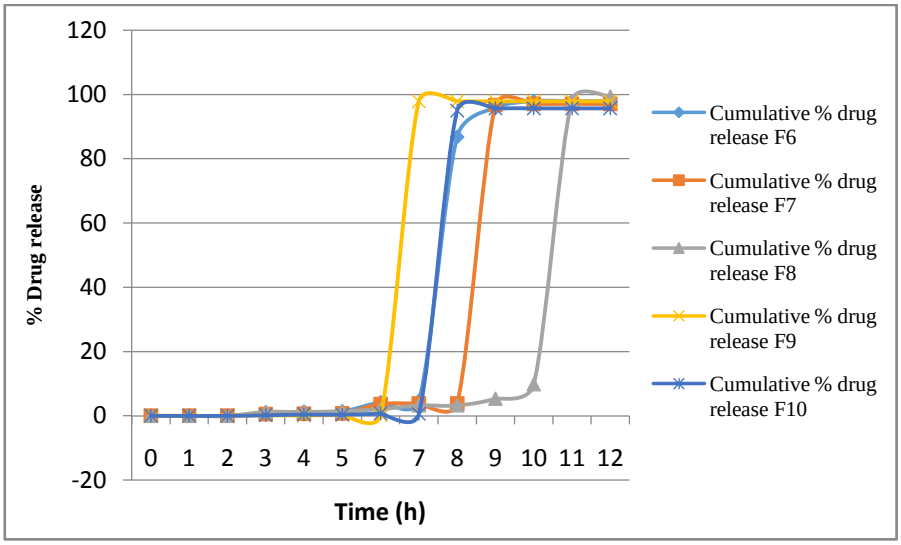

Figure 10.*In-Vitro* drug release from batch F6 to F10

The aim of the study was to release drug after 6 h from the time of administration of formulation. HPMC K100 LV was used in five quantities where batch F4 containing 100 mg of HPMC K100LV gives lag time of 6 h. But at lower amount lower lag time was obtained which was not desired. At higher quantities lag time moves up to 11 h which wasalso not preferable. Higher viscosity grade of HPMC (HPMC K4M), was used in the same concentration then lag time was found more than 12 h which was not preferable. At the same time the amount cannot be lowered without minimizing the size of core which was not possible. When the proportion of HPMC K4M in combination coat with HPMC K100LV was used then batch F9 containing 5% HPMC K4M in the constant coat amount of 100 mg, gives the lag time of 7 hr but at higher and lower proportions the lag time was not desired. At the same time the amount cannot be lowered without minimizing the size of core which was also not possible.

Accelerated stability study of theophylline press-coated tablet

The accelerated stability studies were carried out on optimized formulation(F4). The formulation was stored at 40 ± 2^0 C / 75 ± 5 % RH for three months (90 days). After 30, 60 and 90 days, samples were withdrawn and retested for thickness, hardness, drug content and *in-vitro* drug release studies.

Table 08. Parameters studied on F4 formulation before and after accelerated stability study

Parameters	At Initial	After 30 days	After 60 days	After 90 days
Thickness (mm)	4.45 ± 0.28	4.45 ± 0.27	4.45 ± 0.25	4.449 ± 0.23
Hardness (Kg/cm^2)	9.12 ± 0.11	9.10 ± 0.09	9.06 ± 0.12	9.01 ± 0.08
Drug content (%)	99.16 ± 0.16	99.08 ± 0.11	98.979 ± 0.14	98.912 ± 0.21

All the values are expressed as mean ± SD (*n*=3)

Table 09. Cumulative percent drug released of optimized formulation F4 before and after accelerated stability study

Time (h)	Cumulative % drug release			
	At initial	After 30 days	After 60 days	After 90 days
0	0	0	0	0
1	0	0	0	0
2	0	0	0	0
3	1.42±0.32	0.08±0.32	1.05±0.32	1.85±0.32
4	2.60±0.31	2.60±0.32	3.02±0.32	2.92±0.32
5	4.56±0.21	2.43±0.32	4.13±0.32	4.03±0.32
6	97.54±0.11	97.75±0.32	97.68±0.32	96.96±0.32
7	98.76±0.29	97.75±0.32	97.68±0.32	96.96±0.32

All the values are expressed as mean ± SD (*n*=3)

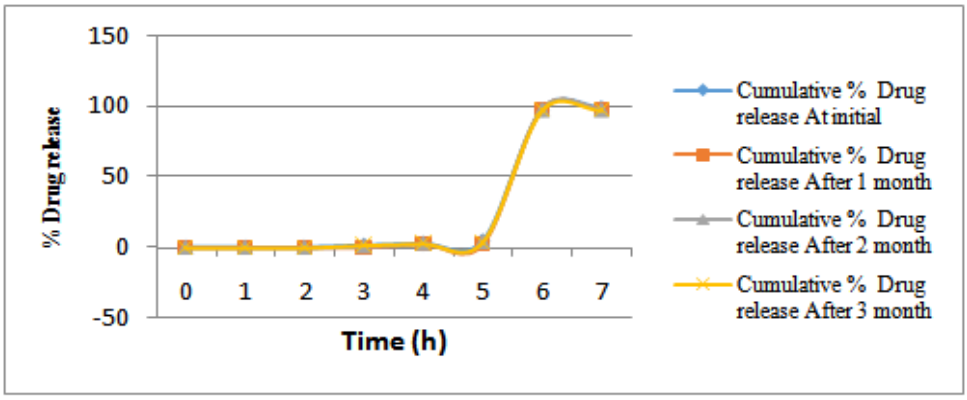

Figure 11.*In-vitro* drug release study of optimized formulation F4 before and after accelerated stability study.

From table 08 it was revealed that there were no considerable changes in thickness, hardness and drug content of F4 formulation before and after accelerated stability study. Also table 09 and figure 11 depicted that there was hardly any difference between dissolution profile of optimized formulation F4 before and after stability study. Hence press-coated tablets prepared were found to be stable at 90-day study.

IV. DISCUSSION

Chronotherapeutics is the discipline concerned with the delivery of drugs according to inherent activities of a disease over a certain period of time. For this purpose, pulsatile drug delivery system is required, it deliver the drug at the right site of action at the right time and in the right amount and have a peculiar mechanism of delivering the drug rapidly and completely after a "lag time," i.e., a period of "no drug release" and it is suitable for chronotherapy of nocturnal asthma. Press coating is the absolute dry coating without solvent and heat use and consists of a core tablet of drug and an outer layer, composed of single or different polymers, that is considerably thicker than typical tablet coats and which completely surrounds the core (inner) tablet.In a nocturnal asthma symptoms are increase at 4.00 am to 6.00 am and need for medication, increased airway responsiveness and worsening of lung function. Lung function (e.g. peak expiratory flow rate) is usually highest at 4.00 pm and lowest at 4.00 am. Patients with nocturnal asthma symptoms may have greater night time activation of inflammatory cells and mediators, lower levels of epinephrine and increased vagal tone.For the treatment of nocturnal asthma, *theophylline* anhydrous press-coated tablets were prepared by direct compression with 9 mm round concave punch using polymers and core by 8 mm round concave punch. Press coated tablet contains Swellable disintegrating agent in core to create internal pressure on hydration and achieve burst release. Hence for the chronotherapy of nocturnal asthma the time controlled press coated tablets may give very satisfactory results. UV light absorption spectrum in the range 200 nm to 400 nm of 0.0025% w/v solution of drug in 0.1 N $HCl_{(aq.)}$ and 7.2 pH phosphate buffer exhibits a maximum peak at about 271.0 nm and 272.0 nm respectively complies with pharmacopeial standards thus indicating purity of obtained drug sample.From the I.R. spectrum it was found that there were no changes in the main peaks in IR spectra of mixture of drug and polymers, which show there were no interactions. The peaks obtained in the spectra of drug and polymers mixtures correlates with each other. This indicates that the drug was compatible with the components used in the formulation. Angle of repose, loose bulk density, tapped bulk density; Carr's index and Hausner's ratio of the powder mixtures were found in the satisfactory range. Tablet hardness, weight variation test, friability, content uniformity, tablet thickness was found to be in the required range which complies with pharmacopeial standards thus indicated good strength of tablets. The main aim of the study was to release drug after 6 h from the time of administration of formulation. From *in-vitro* dissolution study of optimized formulation F4 was found that the HPMC K100LV used in 100 mg in coat give the lag time of 6 h.HPMC K4M and the combination of HPMC K100LV with HPMC K4M used also in 100 mg concentration it gives lag time of more than 6 h which was not acceptable as per the aim of study. But at higher and lower proportionsof these polymers the lag time was not desired. At the same time the amount cannot be lowered without minimizing the size of core which was not possible.Accelerated stability study of *theophylline* press coated tablets for 90 days were showed that there were no considerable changes in thickness, hardness, drug content and dissolution profile of F4 formulation before and after accelerated stability study. Hence press coated tablet prepared was found to be stable at 90-day study.

V. CONCLUSION

The present work showed that promising pulsatile time controlled release of *theophylline* anhydrous was successfully formulated by using press coting technique. Tablets (formulation 04) shows satisfactory results as they released the drug with predetermined lag time of 6 h but lag time get increases with increase in amount

of polymer. It indicated that release was directly related to polymer concentration. It was concluded that HPMC was suitable for use in systems to achieve a time to peak concentration of 6 h as required. As with HPMC K4M lag time was increased, it was concluded that viscosity grade of the polymer is particularly important. As viscosity and concentration of polymers increased, release rate of drug was retarded. Batches containing combination of HPMC K100LV and K4M controlled the drug release better at low concentration of high viscosity grade and it was used to optimize the formulation for pulsatile release. When mixtures of HPMC K100LV and K4M were used, drug release was inversely proportional to amount of HPMC K4M. Even a small percentage of HPMC K4M increased in combination with HPMC K100LV decreased release rate markedly. By combining HPMCs of low viscosity with higher viscosity grades, drug release rate was thus being adjusted. By using low viscosity grades of HPMC it was possible to obtain a drug plasma peak at 6 to 7 h after administrating i.e. to achieve the main aim of the studies.From accelerated stability study it was concluded that there was no much effect of the temperature and moisture on the hardness, drug content, and *in-vitro* drug release from pulsatile press coated tablet.

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Conflict-of-interest

No conflict-of-interest

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