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Pulsatile Drug Delivery System of Theophylline for the Treatment of Nocturnal Asthma

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ABSTRACT:

The objective of this study was to prepare and characterize Pre-coated pulsatile tablet of Theophylline giving pulsatile release for asthma. Pre-coated pulsatile drug delivery gives highest concentration at the early morning when it is needed the most. So it increases the patient compliance and decreases the side effects. Press-coated pulsatile tablets were prepared by direct compression method using different polymer ratio of HPMC K4M:HPMC K15M, croscarmelose sodium polymers to achieve pulsatile drug release. Effects of all the polymers, with different concentrations, on physical properties of Pre-coated pulsatile tablets were investigated. To evaluate the effect of HPMC K4M: HPMC K15M concentrations, different trial batches of various polymeric concentration was employed. The optimization of core tablet was done on the basis of disintegration time. The optimization of Pre-coated pulsatile tablet was done based on the Pree-coated lag time & release rate. The core tablet formulation C5 and Pree-coated pulsatile tablet formulation PC1 were selected as optimum production formulation. The Pre-coated lag time , drug content, disintegration time and in-vitro drug release were found to be 3 hr, 99.21% , 35 sec, 99.67% respectively. From regression value it revealed that all formulations followed krosmeyer peppas and Weibull model, which indicates that the drug release follows swelling. Stability study at 400C±20C / 75 ± 5 % RH revealed that there was no significant change in disintegration time, drug content and % CDR after 30 days. So, prepared formulation was stable during stability study. The developed Pree-coated pulsatile tablet can be effectively used for oral administration in case of asthma as it releases the drug in a pulsatile manner up to 9 hours thus improving patient compliance.

KEY WORDS: Pre-coated pulsatile tablet, Theophylline, Chronotherapy, Asthma

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INTRODUCTION[1,2,4,11]

In recent year, 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. Many of pharmaceutical therapeutic agents are mostly effective when made available at constant rates or near to absorption sites. Much effort has been going on to develop sophisticated drug delivery systems such as osmotic devices for oral application. Oral drug delivery system is more favored on popular controlled drug delivery system in pharmaceutical research 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. Traditionally, 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 hourperiod, may be changing as researcher's report that some medications may work better if their administration is coordinated with other therapies for the treatment of nighttime bwetting (enuresis) in children with day-night patterns and biological rhythms. In the human body systems such as cardiovascular, pulmonary, hepatic and renal systems show variation in their function throughout a typical day. They are naturally followed by the internal body clocks and are controlled by the sleep wake cycle. However, a release pattern of drug is not suitable in certain disease condition. At that time release profile of a delivery system characterised 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. This system aims to deliver a drug via the oral route at a rate different than constant i.e., zero order release. The lag time is the time interval between the dosage form is placed into the aqueous environment and drug get to release from its dosage form after rupturing or eroding outer layer. The lag time between 0.5 hour to 4hour is desire for upper region of gastrointestinal tract and more than 4 hours for lower portion of small intestine. Pulsatile drug delivery capable of releasing its drug content at either a predetermined time or at a specific site in the gastrointestinal tract. Nocturnal and morning wheeze are common symptoms of patients with asthma. These patients have overnight decreases in peak expiratory flow rate or forced expiratory volume in one second. Because of this bronchoconstriction they can't sleep well and become more hypoxaemic during the night. Although regular inhaled treatment reduces the overnight fall in peak flow rates in those patients who have taken their treatment as required. Still some patients complain of nocturnal symptoms despite adequate inhaled treatment. As a result of this the therapeutic effect of theophylline has been studied which can improve nocturnal symptoms and the morning decrease in peak flow rates in patients.

Theophylline (dimethylxanthine) is methylated xanthine class of drug used in therapy for respiratory diseases such as chronic obstructive pulmonary disease (COPD) and asthma. It is a nonselective phosphodiesterase inhibitor, also a bronchodilator, which enhance the respiratory muscle function and mucociliary clearance. The aim of the present work was to develop a time controlled release formulation of theophylline based on a enteric coated time release press-coated technique for nocturnal asthma.

Materials and methods

The drug Theophylline was obtained as gift samples from five star pharma,vatwa, Ahmedabad. And Avicel 101pH, Croscarmellose Sodium, Sodium starch glycolate, HPMC K4M, HPMC K15M,Ethyl cellulose provided by L.J Institute of Pharmacy, Ahmedabad.

Methods[9,12,22]:

Formulation of pulsatile tablets

Theophylline core tablets were prepared by direct compression method. All the ingredients were weighed and mixed properly as shown in Table 1. Magnesium stearate and talc were added in required quantity and mixed with powder mixture. The powder was added to feed and compressed by 5mm punch by single punch tablet machine. From the six formulations C1, C2, C3, C4,C5 and C6 the formulation C5 is selected as best formulation and press coated with the various compositions containing HPMC K4M, HPMC K15M, Ethyl cellulose 10FP with their various compositions Ratio. (**Table 2,2.1,2.2,2.3)**

Table 1: Formulation of Theophylline Core tablets

Ingredients	C1 (mg)	C2 (mg)	C3 (mg)	C4 (mg)	C5 (mg)	C6 (mg)
Theophylline	100	100	100	100	100	100
Sodium starch glycolate	4	8	16	-	-	-
Croscarmellose sodium	-	-	-	6	8	10
Microcrystalline cellulose	40	60	80	40	60	80
Lactose	50	26	-	48	26	5
Color	Trace	Trace	Trace	Trace	Trace	Trace
Magnesium-stearate	Trace	Trace	Trace	Trace	Trace	Trace
Talc	Trace	Trace	Trace	Trace	Trace	Trace

The formulations PC1, PC2, PC3 to PC21 different compositions were weighed and used as press-coating

material to prepare press-coated pulsatile tablet by direct compression method.

Table 2: Different Polymer Ratio for Coating Polymers

Ratio	90:10	80:20	60:40	50:50	40:60	20:80	10:90

Table 2.1: Trials of Theophylline Press-coated Tablet

Ingredients	PC1 (mg)	PC2 (mg)	PC3 (mg)	PC4 (mg)	PC5 (mg)	PC6 (mg)	PC7 (mg)
HPMC K4M	180	160	120	100	80	40	20
HPMC K15M	20	40	80	100	120	160	180
Total	200	200	200	200	200	200	200

Table 2.2: Trials of Theophylline Press-coated Tablet

Ingredients	**PC8 (mg)**	**PC9 (mg)**	**PC10 (mg)**	**PC11 (mg)**	**PC12 (mg)**	**PC13 (mg)**	**PC14 (mg)**
Ethyl cellulose 10FP	180	160	120	100	80	40	20
HPMC K15M	20	40	80	100	120	160	180
Total	200	200	200	200	200	200	200

Table 2.3: Trials of Theophylline Press-coated Tablet

Ingredients	**PC15 (mg)**	**PC16 (mg)**	**PC17 (mg)**	**PC18 (mg)**	**PC19 (mg)**	**PC20 (mg)**	**PC21 (mg)**
Ethyl cellulose 10FP	180	160	120	100	80	40	20
HPMC K4M	20	40	80	100	120	160	180
Total	200	200	200	200	200	200	200

EVALUATIONS:

Flow Properties of powder blend [4, 17]

The flow properties of powder blend were characterized in terms of angle of repose, compressibility index and Hausner ratio. Angle of repose was performed using funnel method by keeping a funnel vertically in a stand at a specified height above a paper placed on a horizontal surface. The funnel bottom was closed and 2 gm of powder was filled in the funnel. Then the funnel was opened to releases the powder on the paper to form a smooth conical heap. The radius of the heap (r) and the height of the heap (h) were measured. The tan-1 of the height of the pile / radius of its base gave the angle of repose. Bulk density (ρb) and tapped densities (ρt) were determined and thereby hausner ratio (HR) and compressibility index were calculated according to the following equations.

$$Compressibility\ index\ = \frac{\rho\ tapped - \rho\ bulk}{\rho\ tapped} \times 100$$

$$Hausner\ ratio = \frac{\rho\ tapped}{\rho\ bulk}$$

Hardness, Thickness, Weight variation, Disintegration time and Drug content of core tablets and pre-coated tablets[3,4]

Hardness of the tablets was tested using a Monsanto hardness tester (Monsaanto type). Thickness was determined by vernier calipers. Friability of the tablets was determined in a friability test apparatus (Roche Type). Disintegration time of the tablets was determined using a tablet disintegration test apparatus (Singhla Scientific Industries) using distilled water as fluid. For drug content the tablets was estimated by the spectrophotometrically at 272 nm (Shimadzu UV 1800).

Drug content[3,4]

Tablet was finely powdered and powder was taken in a volumetric flask. It was dissolved and diluted to 100mL with 0.1N HCl. Further dilutions were made according to the need. The absorbance of the solution was measured at 267 nm using UV spectrophotometer.

Disintegration time[3,4,6]

For Core tablets:

In vitro disintegration time of six tablets from each formulation was determined using tablet disintegration apparatus. In vitro disintegration test was carried out at 37 ± 2 ^{0}C in 900 mL 0.1N HCl.

For Press-coated tablets:

In vitro dissolution studies were carried out using USP XXIII Type II (paddle method) apparatus. In order to simulate the pH changes along with the gastro intestinal tract (GIT), dissolution media with 0.1 N HCl and phosphate buffer (pH 6.8) were sequentially used. When performing the experiment, 0.1 N HCl medium was used for 2 h (since the average gastric emptying time is 2 h). Then removed and fresh phosphate buffer (pH 6.8) was added for subsequent hours. 900 mL of the dissolution medium was used at each time and stirred at 50 rpm at

37 ± 0.5 ºC. 5 mL of dissolution media was withdraw at predetermined time interval and fresh dissolution media was replaced. The withdrawn samples were analyzed at 272 nm using a UV spectrophotometer.

Stability studies [9]

Stability of a drug is defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specifications. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity an light and enables recommended storage conditions, re-test periods and shelf lives to be established.

ICH specifies the length of study and storage conditions:

- Long term testing 25°C ± 2°C / 60 % RH ± 5 % for 12 months
- Accelerated testing 40°C ± 2°C / 75 % RH ± 5 % for 6 months

In this investigation Preparation will be store for 30 days at 40°C ± 2°C / 75 % RH ± 5 %, every 15 days drug content of the preparation is check.

Results and discussion

Flow Properties of blend, Hardness, Thickness, Weight variation, Disintegration Time and Drug content of core tablets:

All the tablets passed weight variation test as the % weight variation was within the pharmacopeial limits of 5%. The thickness and diameter of the tablet was dimensionally measured by vernier caliper scale. Core tablet mean thickness of 6 formulations were found to be in range 3.64±0.8 to 3.87±0.1. The standard deviation values indicate that all formulation were within the range. Hardness of core tablets was found to be in the range of 3.1±0.22 to 3.4±0.41. The prepared tablets of all the formulations possessed good mechanical strength with sufficient hardness. The percent friability was less than 1% in all the formulations indicating that the friability was within the prescribe limits. The results of friability showed that the tablet exhibited good mechanical strength. In order to obtain burst release, disintegration time should be much lower. Disintegration time was in the range of 35.6±2.081 to 60.6±1.15. The disintegration time was dependent on the concentration of the sodium starch glycolate and Croscarmellose sodium. As the concentration of sodium starch glycolate increases and Croscarmellose sodium, there is decrease in the disintegration time. The % drug content of core tablets were in the range of 98.11±0.015 to 99.77±0.03. The result showed that the % drug content was found within the limit of USP (90%– 110%). C5 batch was optimized formula because its disintegration time was 35 sec and % drug content was found to be 99.77.

The screening of different disintegrants was done on the basis of disintegration time. The disintegration time of all the preliminary batches are depicted in Table 4. As shown in Table 4, C5 batch showed less disintegration time compared to other batches. Hence it was concluded that C5 batch was optimized batch amongst all others batches.

Table 3: Pre-compression studies of Core tablets

Formula No	Bulk Density (gm/cm3)	Tapped Density (gm/cm3)	Carr's Index (%)	Hausner Ratio
C1	0.563±0.010	0.667±0.009	15.59±2.696	1.18±0.037
C2	0.548±0.010	0.663±0.007	17.34±1.075	1.20±0.015
C3	0.567±0.007	0.656±0.005	13.56±1.936	1.15±0.025
C4	0.534±0.007	0.644±0.008	17.08±1.628	1.20±0.023
C5	0.563±0.008	0.684±0.006	17.69±1.777	1.21±0.026
C6	0.574±0.007	0.703±0.010	18.34±2.112	1.22±0.031

Table 4: Disintegration time of screening batch of core tablets

Batch	Weight variation	Thickness (mm)	Hardness	% Friability	% Drug content	Disintegration time(s)
C1	196.81±5.74	3.87±0.13	3.3±0.27	0.394±0.0011	98.11±0.015	60±1.154
C2	201.99±7.45	3.85±0.16	3.1±0.22	0.400±0.0018	98.27±0.012	54±0.577
C3	196.53±4.11	3.74±0.18	3.2±0.27	0.417±0.0020	99.13±0.011	50±2.081
C4	194.71±5.50	3.69±0.18	3.4±0.41	0.422±0.005	98.47±0.09	53±2.645
C5	**191.28±3.49**	**3.64±0.33**	**3.3±0.27**	**0.345±0.009**	**99.77±0.03**	**35±2.081**
C6	204.33±7.57	3.69±0.26	3.1±0.22	0.363±0.0033	99.63±0.019	45±1.527

Hardness, Thickness, Diameter, Friability, and Weight Variation of press coated tablets:

All the formulations showed almost uniform size, shape and appearance. The physico-chemical properties of all

the formulations (PC1-PC21) are shown in **Table 5, 6, and 7**. Thickness and weight Variation, the friability ranged hardness in different formulations, showed favorable results.

Table 5 Post-compression parameters Press-coated pulsatile tablets (PC1-PC7)

Batches	Weight variation ± SD	Thickness (mm)	Diameter (mm)	Hardness	% Friability
PC1	398±1.3	5.23±0.0012	10.35±00.32	4.5±0.02	0.546±0.0021
PC2	395±1.21	5.43±0.0032	10.28±0.0022	4.8±0.02	0.578±0.064
PC3	403±1.65	5.12±0.001	10.41±0.013	4.2±0.04	0.652±0.0032
PC4	401±0.06	5.15±0.0043	10.22±0.0017	4.9±0.03	0.582±0.021
PC5	391±1.47	5.34±0.0023	10.33±0.0025	4.2±0.03	0.416±0.012
PC6	402±1.69	5.29±0.0032	10.27±0.018	4.5.±0.05	0.432±0.0082
PC7	395±1.53	5.26±0.0017	10.43±0.015	4.0±0.03	0.421±0.0032

Mean ± S.D., n=3

Table 6 Post-compression parameters Press-coated pulsatile tablets (PC8-PC14)

Batches	Weight variation ± SD	Thickness (mm)	Diameter (mm)	Hardness	% Friability
PC8	399±1.87	5.12±0.02	10.37±0.004	5.5±0.06	0.416±0.0032
PC9	405±1.21	5.11±0.0012	10.38±0.0023	5.0±0.08	0.428±0.0021
PC10	396±1.33	5.32±0.0014	10.21±0.0019	4.9±0.06	0.352±0.0022
PC11	398±0.06	5.26±0.018	10.42±0.001	4.9±0.03	0.482±0.0061
PC12	410±1.11	5.34±0.0024	10.13±0.0014	4.7±0.09	0.316±0.0028
PC13	396±1.42	5.19±0.0033	10.17±0.0017	5.1.±0.3	0.532±0.0054
PC14	408±1.95	5.26±0.0015	10.23±0.0016	4.9±0.08	0.321±0.0035

Mean ± S.D., n=3

Table 7 Post-compression parameters Press-coated pulsatile tablets (PC15-PC21)

Batches	Weight variation ± SD	Thickness (mm)	Diameter (mm)	Hardness	% Friability
PC15	391±1.7	5.43±0.005	10.15±0.0019	5.3±0.019	0.446±0.0094
PC16	403±1.31	5.27±0.003	10.38±0.0015	5.2±0.021	0.378±0.032
PC17	402±1.45	5.32±0.008	10.11±0.006	4.8±0.08	0.552±0.0023
PC18	393±0.08	5.25±0.0012	10.42±0.00	4.5±0.0	0.682±0.00
PC19	406±1.47	5.14±0.0016	10.22±0.0041	5.5±0.032	0.516±0.0016
PC20	398±1.10	5.49±0.0031	10.42±0.0023	4.6±0.052	0.332±0.0012
PC21	401±1.53	5.36±0.004	10.47±0.007	4.9±0.035	0.621±0.0011

Mean ± S.D., n=3

In vitro drug release of core tablets and enteric coated tablets:

1) In-vitro Dissolution Profile of Press-coated tablet of Polymer Ratio (HPMC K4M : HPMC K15M)

The selection of Ratio of different coating polymers was done on the basis of % drug release. The % drug release of the trial batches are depicted in Table 8. The graph of %CDR Vs Time is shown in figure 1.

Drug release study was done for the selection of optimize ratio of coating polymer that is Ethyl cellulose and HPMC K15M. Ratio of Ethyl cellulose and HPMC K15M showed different drug release as shown in figure 1. Ratio of two polymers taken as per table no. 2.1.

Release profile shows that higher the concentration of HPMC K4M and decrease the concentration of HPMC K15M give the drug release at specific period of time. All batches PC1, PC2, PC3, PC4, PC5, PC6, and PC7 Shows drug release after 2hr and give release upto 10hr.

Among the all batches PC1 to PC7, PC1 shows better drug release as per chronobiological need. So, PC1 that is ratio of HPMC K4M: HPMC K15M (90:10) is consider as best formulation.

Table 8: In-vitro Dissolution Profile of Trial batches of Press-coated tablet for selection of Polymer Ratio (HPMC K4M: HPMC K15M)

Media	Time (hr)	PC1	PC2	PC3	PC4	PC5	PC6	PC7
0.1 N HCL	0	0	0	0	0	0	0	0
	1	0	0	0	0	0	0	0
	2	0	0	0	0	0	0	0
Phosphate	3	1.32±0.011	3.3±0.015	2.65±0.022	3.2±0.03	3.76±0.05	1.97±0.011	2.13±0.022

buffer 6.8	4	8.12 ±0.02	7.32 ±0.02	6.22 ±0.021	8.12 ±0.021	5.62 ±0.021	5.02 ±0.021	4.82 ±0.024
	5	29.45 ±0.021	26.5 ±0.011	20.3 ±0.015	19.45 ±0.018	18.4 ±0.09	15.45 ±0.013	14.05 ±0.025
	6	56.22 ±0.023	48.32 ±0.03	46.81 ±0.013	42.42 ±0.012	40.78 ±0.05	40.43 ±0.012	39.23 ±0.022
	7	79.45 ±0.03	72.12 ±0.04	68.43 ±0.011	62.38 ±0.021	63.56 ±0.025	66.54 ±0.017	69.43 ±0.025
	8	90.94 ±0.022	89.02 ±0.011	82.45 ±0.04	81.87 ±0.017	73.65 ±0.04	77.78 ±0.11	76.32 ±0.014
	9	99.67 ±0.01	98.86 ±0.05	96.87 ±0.09	95.92 ±0.014	89.23 ±0.08	85.54 ±0.10	84.07 ±0.012
	10		99.4 ±0.09	99.36 ±0.010	99.11 ±0.012	99.88 ±0.06	98.21 ±0.009	98.01 ±0.011
	11							

Mean ± S.D., n=3

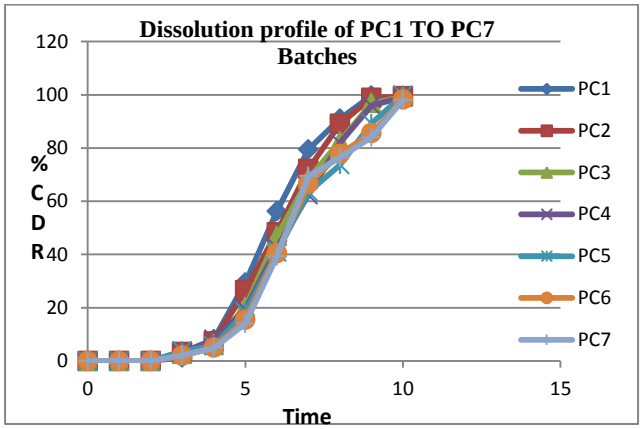


Fig. No. 1: Dissolution profile of PC1 to PC7 batches

2) In-vitro Dissolution Profile of Trial batches of Press-coated table for selection of Polymer Ratio (Ethyl cellulose : HPMC K15M)

The selection of Ratio of different coating polymers was done on the basis of % drug release. The % drug release of the trial batches are depicted in Table 5.15. The graph of %CDR Vs Time is shown in figure 2.

Drug release study was done for the selection of optimize ratio of coating polymer that is Ethyl cellulose and HPMC K15M. Ratio of Ethyl cellulose and HPMC K15M showed different drug release as shown in figure 2. Ratio of two polymers taken as per table no. 2.2.

Release profile shows that lower the concentration of ethylcellulose and increase the concentration of HPMC K15M give the drug release at specific period of time. PC8 shows drug release after 4hr and all other batches PC9, PC10, PC11, Shows drug release after 3 hr. same as PC12, PC13, and PC14 Shows drug release at 3 hr up to 10hr.

According to burst effect PC12 and PC13 and PC14 Shows best effect that is at 3 hr as per expected but PC13 shows better drug release than the PC12 and PC14. So, among the batches PC8 to PC14, PC13 that is ratio of Ethyl cellulose:HPMC K15M (20:80) is consider as best formulation.

Table 9: In-vitro Dissolution Profile of Trial batches of Press-coated table for selection of Polymer Ratio (Ethyl cellulose : HPMC K15M)

Media	Time (hr)	PC8	PC9	PC10	PC11	PC12	PC13	PC14
0.1N HCL	0	0	0	0	0	0	0	0
	1	0	0	0	0	0	0	0
	2	0	0	0	0	0	0	0
	3	0	0	0	0	2.11 ±0.013	1.3 ±0.06	3.1 ±0.06
Phosphate buffer 6.8	4	0	1.5 ±0.031	2.53 ±0.021	1.9 ±0.011	3.21 ±0.013	3.45 ±0.014	6.1 ±0.08
	5	1.73 ±0.023	3.23 ±0.02	5.94 ±0.032	4.40 ±0.023	13.91 ±0.010	15.32 ±0.010	17.98 ±0.04
	6	10.12 ±0.02	10.34 ±0.031	19.21 ±0.011	24.94 ±0.011	34.02 ±0.009	37.03 ±0.009	36.91 ±0.03
	7	29.95 ±0.04	30.42 ±0.021	39.43 ±0.017	56.91 ±0.022	48.45 ±0.022	63.54 ±0.07	61.56 ±0.04
	8	54.38 ±0.012	59.23 ±0.034	68.31 ±0.015	74.9 ±0.041	79.54 ±0.014	79.34 ±0.05	75.45 ±0.05
	9	76.88 ±0.015	79.23 ±0.012	84.32 ±0.017	89.29 ±0.013	88.12 ±0.013	90.45 ±0.03	94.34 ±0.04
	10	95.39 ±0.014	96.9 ±0.011	97.75 ±0.013	98.42 ±0.011	98.3 ±0.013	99.69 ±0.02	99.56 ±0.03
	11	98.21± 0.01	98.33 ±0.009	99.14 ±0.007	99.33 ±0.001	99.43 ±0.015		

Mean ± S.D., n=3

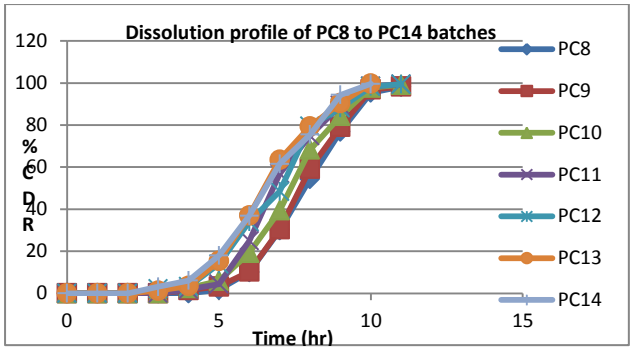


Fig. No. 2: Dissolution profile of PC8 to PC14 batches

3) In-vitro Dissolution Profile of Trial batches of Press-coated tablet for selection of Polymer Ratio (Ethyl cellulose : HPMC K4M)

The selection of Ratio of different coating polymers was done on the basis of % drug release. The % drug release of the trial batches are depicted in Table 5.16. The graph of %CDR Vs Time is shown in figure 3.

Drug release study was done for the selection of optimize ratio of coating polymer that is Ethyl cellulose and HPMC K4M. Ratio of Ethyl cellulose and HPMC K4M showed different drug release as shown in figure 3. Ratio of two polymers taken as per table no. 2.3.

Release profile shows that lower the concentration of Ethylcellulose and increase the concentration of HPMC K4M give the drug release at specific period of time. PC15, PC16, PC17, PC18, and PC19 Shows drug release after 3 hr. same as PC20, PC21, Shows drug release at 3 hr up to 10hr.

According to burst effect PC20 And PC21 Shows best effect at 3 hr as per expected but PC21 shows better drug release than the PC20. So, among the batches PC15 to PC21, PC21 that is ratio of Ethyl cellulose:HPMC K4M (10:90) is consider as best formulation.

Table 10: In-vitro Dissolution Profile of Trial batches of Press-coated tablet for selection of Polymer Ratio (Ethyl cellulose : HPMC K4M)

Media	Time (hr)	PC15	PC16	PC17	PC18	PC19	PC20	PC21
0.1N HCL	0	0	0	0	0	0	0	0
	1	0	0	0	0	0	0	0
	2	0	0	0	0	0	0	0
Phosphate buffer 6.8	3	0	0	0	0	0	2.95 ±0.014	2.34 ±0.011
	4	1.6 ±0.011	1.89 ±0.018	2.51 ±0.013	4.21 ±0.012	3.21 ±0.017	5.32 ±0.017	5.98 ±0.012
	5	2.34 ±0.016	3.06 ±0.013	8.43 ±0.021	11.32 ±0.013	17.29 ±0.018	16.27 ±0.018	19.52 ±0.013
	6	10.65± 0.020	11.23 ±0.015	24.12 ±0.022	25.61 ±0.021	35.71 ±0.016	38.43 ±0.07	40.04 ±0.017
	7	28.52± 0.018	35.43 ±0.016	48.3 ±0.020	65.34 ±0.022	65.34± 0.015	53.45 ±0.08	66.23 ±0.016
	8	46.23± 0.011	74.23 ±0.013	67.45 ±0.019	89.34 ±0.023	88.45± 0.012	84.32 ±0.015	86.32 ±0.013
	9	78.56± 0.019	86.34 ±0.018	83.34 ±0.012	93.32 ±0.024	95.67± 0.012	97.55 ±0.018	98.65 ±0.012
	10	93.21± 0.021	96.93 ±0.014	97.34 ±0.021	99.44 ±0.026	99.65± 0.011	99.76 ±0.015	99.88 ±0.017
	11	97.65± 0.014	98.15 ±0.011	99.32 ±0.015				

Mean ± S.D., n=3

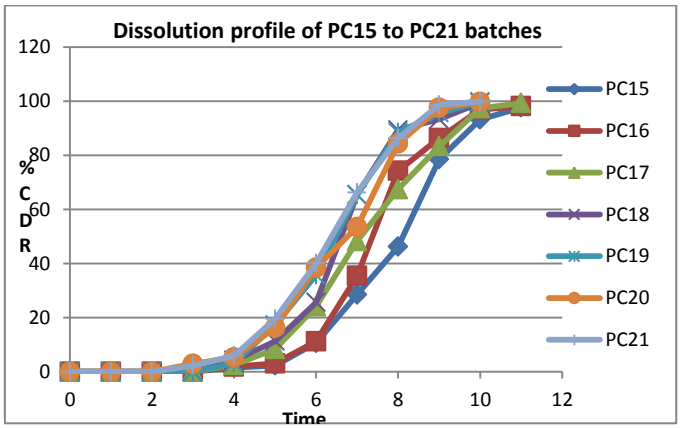


Fig. No. 3: Dissolution profile of PC15 to PC21 batches

Stability Studies:

Stability study of optimized batch PC1 was done at Accelerated testing 40°C ± 2°C / 75 % RH ± 5 %, interval of 15, and 30 days.

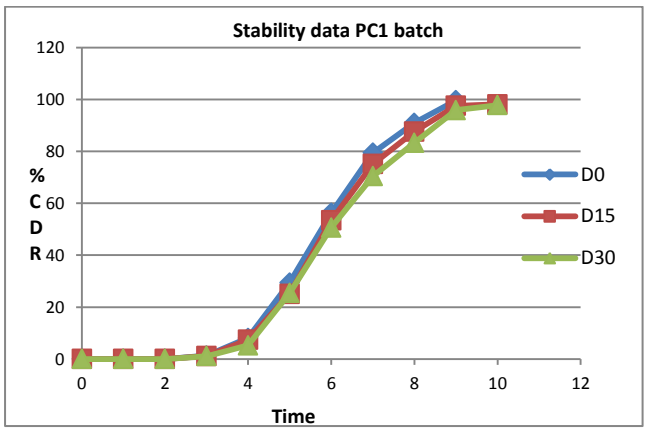
Table 5.22: Stability data of optimized batch PC1

Batch PC1	Disintegration time (sec)	Drug content (%)
D15	35.34±0.23	99.21±0.1
D30	37.56±0.43	98.85±0.3
D45	37.97±0.37	98.76±0.23

Table 5.23: Stability data of Cumulative % drug release of batch PC1

Time	D0	D15	D30
0	0	0	0
1	0	0	0
2	0	0	0
3	1.32	1.22	1.15
4	8.12	7.42	5.23
5	29.45	25.09	25.44
6	56.22	53.41	50.65
7	79.45	75.09	70.41
8	90.94	87.63	83.3
9	99.67	97.53	95.89
10		98.12	97.8

Figure 4: Drug release profile of optimizes batch at zero day, after 15th, 30th.



After 15, and 30 of interval Drug content, disintegration, percentage drug release of pulsatile was measured and it was found that percentage drug release of the tablet was 98.12, and 97.8% respectively, drug content was found to be 98.21,and 98.85 respectively and disintegration time was found to be 35.34, and 37.56 respectively. Result shows that the batch PC1 was stable for 30 days at accelerated condition.

CONCLUSION

The bronchodilating action of theophylline renders the drug useful in the chronic treatment of bronchial asthma. However, as its therapeutic concentration range is narrow (10–20 µg/ml), and as its absorption is prone to the effects of meals, the dosing management of the drug has been difficult. Mechanism of thophylline is Relaxes bronchial smooth muscle, causing bronchodilation and increasing vital capacity that has been impaired by bronchospasm and air trapping; actions may be mediated by inhibition of phosphodiesterase, which increases the concentration of cyclic adenosine monophosphate; in concentrations that may be higher than those reached clinically, it also inhibits the release of slow-reacting substance of anaphylaxis and histamine. During Preformulation studies, solubility analysis revealed that Theophylline was freely soluble in 0.1 N HCl and sparingly soluble in water. Ultraviolet spectroscopic method was performed for estimation of Theophylline. Theophylline showed λmax 267nm in 0.1 N HCl. Regression coefficient for calibration curve was found 0.995 in 0.1N HCl. Infrared spectra of pure drug and physical mixture of drug with other excipients confirmed the compatibility between drug and other excipients. Press-coated pulsatile tablet were prepared by direct compression method using different polymer ration of HPMC K4M and HPMC K15M, avicel PH101, sodium starch glycolate and Croscarmellose sodium polymers to achieve pulsatile drug release. Effects of all the polymers, with different concentrations, on physical properties of press-coated pulsatile tablet were investigated. The optimization of core tablet was done on the basis of disintegration time. The optimization of Press-coated pulsatile tablet was done based on the lag time & release rate. The core tablet formulation C5 and pree-coated pulsatile tablet formulation PC1 was selected as optimum production formulation. The lag time , drug content, disintegration time and *in-vitro* drug release were found to be 3 hrs, 99.77%,35 sec, 99.67% respectively . The FTIR results reveal that drug & polymers were chemically compatible. From regression value it revealed that all formulations followed Weibull model and korsmeyer peppas which indicates that the drug release follows swelling, and release from matrix type.

Stability study at $40^0C \pm 2^0C$ / 75 ± 5 % RH revealed that there was no significant change in disintegration time, drug content and % CDR after 30 days. So, prepared formulation was stable during stability study. The developed press-coated pulsatile tablet can be effectively used for oral administration in case of asthma as it

releases the drug in a pulsatile manner up to 9 hours thus improving patient compliance.

Thus, it can be concluded that the present work can be considered as one of the promising formulation for preparing press-coated pulsatile drug delivery system of Theophylline and can be effectively used in chronotherapeutic management of asthma by opening a new therapeutic dimension to an existing drug molecule.

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