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RESEARCH ARTICLE

Formulation of pulsatile drug delivery containing anti-asthmatic drug dosage form

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Abstract

The aim of the present research work was to develop Theophylline pulsatile tablet for the acute asthmatic attack. In the present study Theophylline Pulsatile tablet consisting of fast-swelling core tablet coated with a water-insoluble ethylcellulose were developed. Effects of coating material, the type of the disintegrants, and coating level on the release profiles were investigated. Rupture time increased with increasing the amount of coating level. Tablets with EC_{50} was most optimal in order to achieve a long lag time and followed by rapid release as compare to EC_{20}. The lag time of tablet containing different disintegrants increased in the following order: croscarmellose< sodium starch glycolate<low-substituted hydroxypropyl cellulose< Crospovidone. And the lag time increase with higher coating level. The results showed that EC_{20} was the best candidate polymer for pulsatile release tablet as compared to EC_{50} which has very long lag time.

Keywords : Pulsatile release; Theophylline; Lag time; Pulsatile tablet; Ethylcellulose.

INTRODUCTION

Many body functions that follow circadian rhythm, a number of hormones like renin, aldosterone, and cortisol show daily fluctuations in their blood levels. Circadian effects are also observed in case of pH and acid secretion in stomach, gastric emptying, and gastro-intestinal blood transfusion.

Diseases like bronchial asthma, myocardial infarction, angina pectoris, rheumatic arthritis, ulcer, and hypertension required time dependence drug delivery system. Such a condition demands pulsatile release of drug rather than maintaining constant plasma drug level. Drugs which exhibits biological tolerance should not be delivered at ,a constant rate since the drug effect decreases with time at constant drug level.

The lag time is essential for the drugs that undergo degradation in gastric acidic medium (e.g., peptide drugs) irritate the gastric mucosa or induce nausea and vomiting. These conditions can be satisfactorily handled by enteric coating, and in this sense, enteric coating can be considered as a pulsatile drug delivery system.

Increase patient compliance due to reduced doses. A pulsatile drug delivery system is characterized by a lag time that is an interval of no drug release followed by rapid and complete drug release. Pulsatile systems are basically time-controlled drug delivery systems in which the system controls the lag time independent of environmental factors like pH, enzymes, gastro-intestinal motility, etc [1].

Aim and Objectives

1. Extended daytime or night time activity
2. Reduced side effect.
3. Reduced dosage frequency.
4. Reduction in dose size.
5. Improved patient compliance.
6. Lower daily cost to patient.
7. Drug adapts to suit circadian rhythms of body functions.
8. Drug targeting to specific organ like colon.
9. Protection of mucosa from irritating drugs.
10. Drug loss is prevented by reducing extensive first pass metabolism [2-3].

Method of Preparation Of Core Tablets

The core tablets were prepared by using four different types of superdisintegrants namely Crospovidone (PVPP), Sodium Starch Glycolate, Low-substituted Hydroxypropyl Cellulose (L-HPC11), Croscarmellose. And various component like Microcrystalline Cellulose and lactose as inert

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filler, Polyvinyl Pyrolidone as binder and Magnesium Stearate and talc as lubricants [4]. The composition of core tablet is represented in Table 1.

Table 1. Composition of Core tablets

Ingredients (mg)	Formulation Code			
	F1	F2	F3	F4
Theophylline anhydrous (drug)	100 mg	100 mg	100 mg	100 mg
Crospovidone (PVPP)	16 mg	--	--	--
Sodium Starch Glycolate	--	16mg	--	--
Low-substituted Hydroxypropyl Cellulose (L-HPC11)	--	--	16mg	--
Croscarmellose	--	--	--	16mg
Microcrystalline cellulose (MCC PH101)	50 mg	50 mg	50 mg	50 mg
Lactose	10mg	10mg	10mg	10mg
Polyvinyl Pyrrolidone (PVPK 30)	20mg	20mg	20mg	20mg
Magnesium Stearate	2mg	2mg	2mg	2mg
Talc	2mg	2mg	2mg	2mg

Procedure

A manually granulated mixture of Theophylline anhydrous, MCC PH 101,lactose and a type of superdisintegrants (Crospovidone (PVPP), Sodium Starch Glycolate, Low-substituted Hydroxypropyl Cellulose (L-HPC11), Croscarmellose was combined with 10% PVP water solution as a binder and produce a wet mass. The wet mass was passed through 10 mesh sieve and granules were prepared .Granules were dried in the oven at 60°C and sieved through 22/44 mesh sieve. Magnesium stearate and talc were added and then compressed (The tablets punch size 8 mm, weight about 200 mg, biconcave shaped) with a single punch tablet compression machine.

Coating of Tablet

The tablets were coated in a coating pan. The coating solution was prepared by dissolving ethyl cellulose in acetone and PEG 400 (1%), PG (2.5%) as a plasticizer. Coating was continued until the increase in weight up to 4%, 6% and 8% as calculated using the following equation:

Process conditions were as under:

Inlet temperature- 60°C,

Product temperature- 33-35°C,

Pan speed- 30 rpm,

Atomizing pressure- 1.2bar,

Spraying rate- 6ml/min.

The coating solution was applied when the tablet bed in the coating pan reached 60°C.

$$\%\text{Water gain} = \frac{W_t - W_0}{W_0} \times 100$$

Where W_t is the weight of the tablets after coating, W_0 is the initial weight of tablets.

Table. 2. Batch code for weight gain by coating on core tablets

Polymer	Weight gain		
	4.0%	6.0%	8.0%
EC20	F1-I	F1-II	F1-III
	F2-I	F2-II	F2-III
	F3-I	F3-II	F3-III
	F4-I	F4-II	F4-III
EC50	F1a	F1b	F1c

Evaluation Of Pulsatile Tablet

a) Weight variation
b) Tablet Thickness
c) Hardness
d) Disintegration of tablet
e) Drug content test
f) In vitro drug release
g) Stability study
h) Rupture test [5-7].

MECHANICAL PROPERTIES OF POLYMERIC FILM

a) Preparation of polymeric films

The coating polymer EC was dissolved in Acetone at a concentration of 2.5 % w/v and plasticizers PEG 400 (1% v/v) and PG (2.5%v/v) were added to form coating solution. The resulting solution was casted on polyethylene sheet, and dried for 4 h at 40°C. The dried films were carefully removed, and weighed with an analytical balance. The films were stored at room temperature for 48 h and cut into

size of 40mm x 40mm. The exact film thickness was measured at five different points using a Screw micrometer [6].

b) Water uptake study

The %water uptake capacity of polymeric films was determined by immersing the free films into phosphate buffer pH 6.8 at 37°C, Also this condition was used for dissolution study. At predetermined time intervals, the films were removed from the medium and weighed with an analytical balance after carefully removing the excess medium on the films with paper tissue. The water content at any time was calculated as follows:

$$\%\text{Water uptake} = \frac{W_t - W_0}{W_0} \times 100$$

Where, W_t is weight of wet film at time t and W_0 is weight of dry film.

c) Tensile strength

A measurement of the force required to break a polymeric film. The tensile strength of a material quantifies how much stress the material will endure before failing. This is very important in applications that rely upon polymers physical strength or durability.

Instrument: Shimadzu AG-100KNG.

Shape: Plate; Gauge length: 10 mms

Test Speed: 5 mm/min

d) Elongation at break

A measurement of the percentage elongation from the original sample at the movement when the material breaks during at tensile test.

Scanning Electron Microscopy

SEM was used to image of pulsatile tablet cross-sections. Sample was sputter coated with gold platinum and then imaged on an S-250 SEM at an accelerating voltage of 20Kv. SEM analysis of the pulsatile tablet internal and outer structure was also made after splitting the sample [6].

Evaluation tests

The results for Weight variation, Thickness, %Drug content, Hardness, disintegration time of all batches are shown in Table: 3-4.

a) weight variation: Results indicate that all formulations complies the pharmacopoeial standards. The value of average Weight obtained ranged from 196.4mg to 206.1 mg.

b) Thickness: Results indicate that thickness of all tablets batches varied in a narrow range 4.2mm to 4.5mm indicating that prepared tablets have uniform thickness.

c) %Drug content: On the basis of the obtaining the result of each batch drug content, all batch formulations complies as per pharmacopoeial standards (NLT: 90% and NMT: 110%).

d) Hardness: All the batch formulations having hardness range from 3.8 to 4.1 (Kg/cm2) Tablets have sufficient mechanical strength while handling tablet.

e) Disintegration time: Results indicate that disintegration time of tablets for all the batches were less than 15 min, so results complies pharmacopoeial standards.

Table 3. Results for Weight variation, Thickness, %Drug content, Hardness

Formulations	Avg weight of tablet (mg)±SD	Thickness in mm±SD	% Drug content	Hardness Kg/cm²
F1	200.5±0.49	4.5±0.09	103.55±2.31	3.8±0.056
F2	201.1±0.57	4.3±0.11	99.25±1.67	3.9±0.042
F3	201.6±0.71	4.2±0.27	102.35±1.11	4.1±0.037
F4	202.2±0.46	4.3±0.13	104.52±2.89	3.8±0.045

Table 4. Results for Disintegration time

Batch code	Disintegration time (min)						
	Tablet-1	Tablet-2	Tablet-3	Tablet-4	Tablet-5	Tablet-6	Mean
F1	5.30	5.45	5.30	5.55	5.30	5.45	5.38±0.107
F2	2.80	2.85	2.70	2.80	2.85	2.80	2.80±0.06
F3	3.40	3.60	3.85	3.60	3.40	3.85	3.6±0.201
F4	45sec	40sec	45sec	40sec	55sec	40sec	44.16±5.84

EVALUATION OF COATED TABLET

The results for Average weight and thickness of all batches are shown in Table: 5

Table 5. Results of weight variation & Thickness after coating

Batch Code	Average weight after coating (mg)	Thickness after coating (mm)
F1-I	208.5	4.58
F1-II	212.4	4.72
F1-III	216.3	5.09
F2-I	209.4	4.53
F2-II	213.5	4.78
F2-III	217.4	5.20
F3-I	210.2	4.56
F3-II	214.7	4.89
F3-III	218.9	5.12
F4-I	209.5	4.44
F4-II	213.2	4.70
F4-III	217.3	4.95
F1a	208.7	4.54
F1b	214.8	4.99
F1c	218.2	5.15

***IN VITRO* DRUG RELEASE PROFILE FROM PULSATILE TABLETS**

The percentage drug release of anhydrous Theophylline from different batches of tablets is shown in table: 6-10.

Table 6. *In vitro* drug release profiles from batch F1-I-F1-III

Time (min)	Mean % drug Dissolved		
	Formulations		
	F1-I	F1-II	F1-III
0	0.00	0.00	0.00
20	0.67	0.55	0.72
40	0.79	0.74	0.85
60	0.88	0.82	0.99
80	1.09	1.77	1.52
100	1.79	1.92	1.89
120	2.67	2.04	2.00
140	3.98	2.52	2.30
160	4.49	4.22	3.35
180	5.04	5.00	4.50
200	6.78	6.60	4.75
220	7.55	7.05	4.96
240	9.06	8.73	5.06
260	9.50	9.00	5.74
280	92.98	9.55	6.32
300	93.22	10.00	6.59
320	93.50	10.58	6.70

340	-	10.85	8.55
360	-	92.50	9.05
380	-	94.27	9.79
400	-	-	9.97
420	-	-	94.76

Table 7. In vitro drug release profiles from batch F2-I-F2-III

Time (min)	Mean % drug Dissolved		
	Formulations		
	F2-**I**	F2-**II**	F2-**III**
0	0.00	0.00	0.00
20	0.92	0.52	0.29
40	1.87	1.50	0.67
60	3.69	2.97	1.35
80	4.76	3.88	2.02
100	5.45	4.06	2.20
120	6.50	4.98	2.99
140	6.87	5.05	3.79
160	7.05	6.30	4.03
180	8.50	7.03	4.47
200	93.30	8.76	4.99
220	95.20	9.00	6.35
240	95.34	10.92	6.97
260	-	11.80	7.50
280	-	94.03	7.92
300	-	95.72	8.33
320	-	-	11.50
340	-	-	11.79
360	-	-	96.05
380	-	-	96.20

Table 8. *In vitro* drug release profiles from batch F3-I-F3-III

Time (min)	Mean % drug Dissolved		
	Formulations		
	F3-I	**F3-II**	**F3-III**
0	0.00	0.00	0.00
20	0.79	0.67	0.59
40	2.07	1.88	0.93
60	3.56	2.07	1.79
80	4.69	3.99	2.92
100	5.79	4.56	3.34
120	6.33	5.82	3.95
140	7.77	6.70	4.50
160	8.03	7.66	4.77
180	9.56	8.23	5.75
200	10.05	9.59	5.98
220	92.00	11.78	7.00
240	94.34	12.55	7.33
260	95.90	13.06	9.00

280	-	93.23	9.85
300	-	94.93	10.09
320	-	95.22	11.22
340	-	-	13.22
360	-	-	14.03
380	-	-	92.23
400	-	-	94.33

Table 9. *In vitro* drug release profiles from batch F4-I-F4-III

Time (min)	Mean % drug Dissolved		
	Formulations		
	F4-**I**	F4-**II**	F4-**III**
0	0.00	0.00	0.00
20	0.54	0.93	0.76
40	1.96	3.29	0.92
60	2.52	4.45	1.98
80	3.96	5.79	2.67
100	4.20	6.20	3.55
120	5.77	6.63	4.03
140	7.93	7.98	5,80
160	8.23	9.08	6.12
180	93.89	10.29	6.79
200	95.00	11.92	7.55
220	96.69	93.72	8.05
240	-	95.23	9.88
260	-	96.90	11.09
280	-	-	12.96
300	-	-	91.00
320	-	-	93.92
340	-	-	95.88

Table: 10 *In vitro* release profiles from batch F1a-F1c

Time (min)	Mean % drug Dissolved		
	Formulations		
	F1a	F1b	F1c
0	0.00	0.00	0.00
20	0.24	0.20	0.18
40	0.38	0.26	0.23
60	0.62	0.53	0.45
80	0.96	0.76	0.98
100	1.44	1.32	1.21
120	2.45	2.05	1.89
140	3.07	2.97	2.50
160	4.64	4.24	3.89
180	4.83	4.55	4.03
200	5.60	5.00	4.98
220	6.51	6.40	5.79
240	7.89	6.98	6.07
260	12.09	9.82	8.29
280	20.20	9.72	10.06
300	22.97	11.88	11.79
320	26.92	14.23	13.19
340	30.43	22.28	15.23
360	32.20	27.26	20.19
380	34.35	30.51	25.50
400	38.40	31.23	28.21
420	44.07	32.37	30.98

Fig 1. *In Vitro* Drug Release Profile From Batch F1-I-F1-III

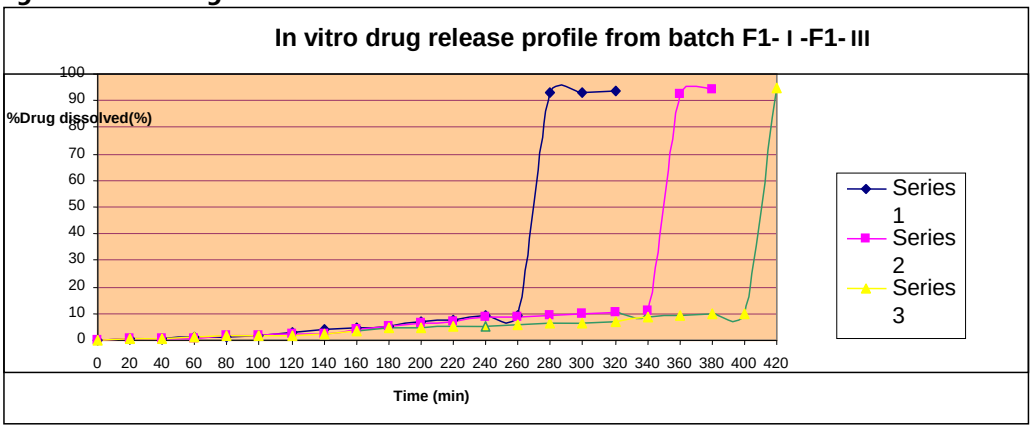


Fig 2. *In vitro* drug release profiles from batch F2-I-F2-III

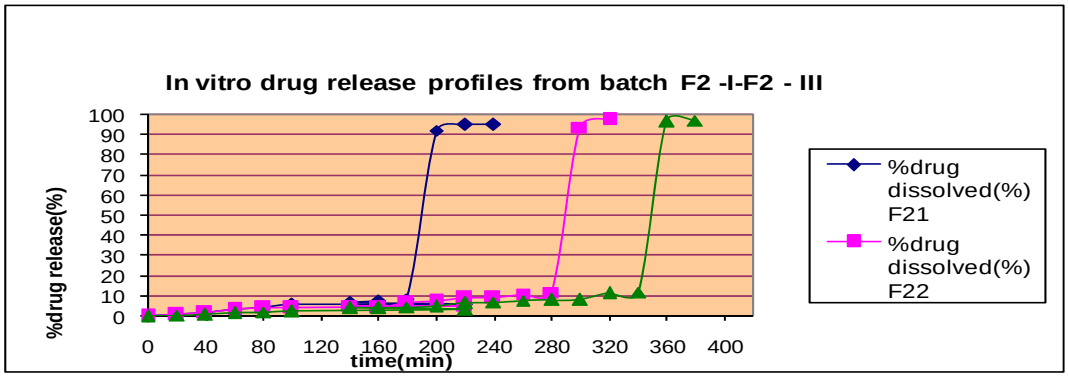


Fig 3. in vitro drug release profiles from batch F3 -I -F3 -III

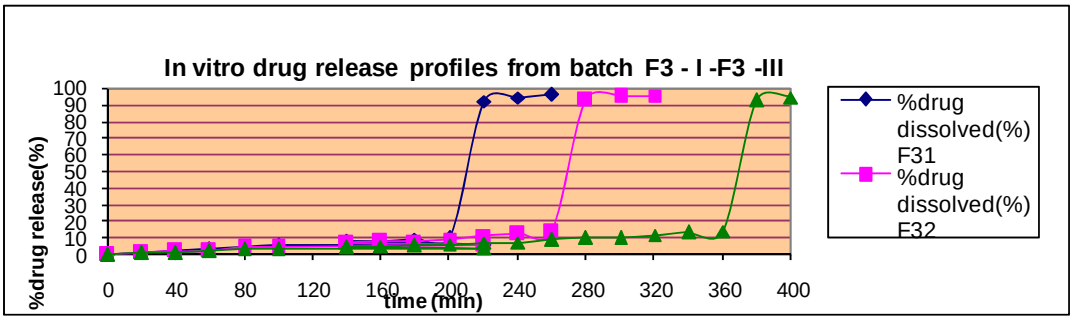


Fig 4. *In vitro* drug release profiles from batch F4-I-F4-III

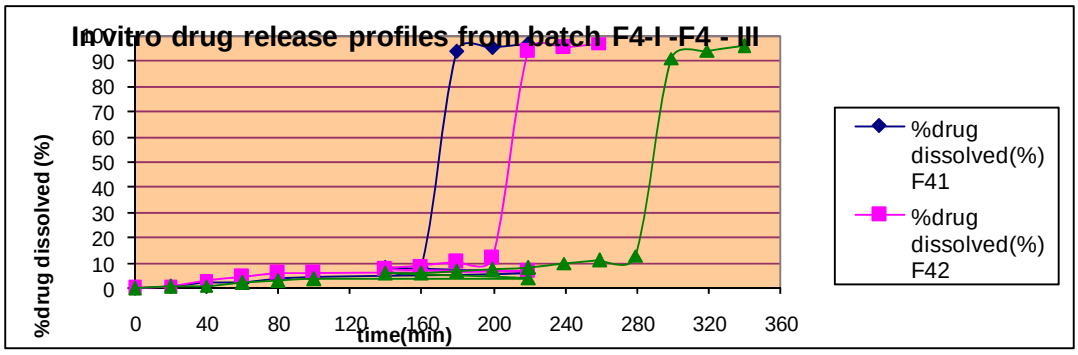
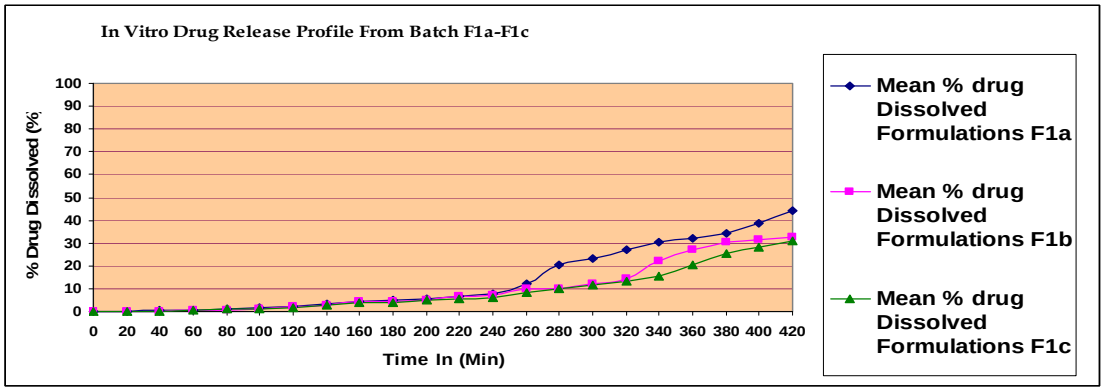


Fig 5. *In vitro* drug release profiles of batch F1a-F1c



Effect of the Type of Disintegrants and Coating Level on the drug Release Profiles

The lag time of the pulsed tablets was investigated and could be mainly controlled by the disintegrates which has different swelling behaviour and coating level which is related to the permeation and mechanical properties of the polymer coating.

Different formulations containing different disintegrates(crospovidone, sodium starch glycolate, low-substituted hydroxypropyl cellulose, croscarmellose) were prepared to characterise their potential. Results in Fig: 1-5 showed that lag time depend on the types of disintegrant. The lag time of tablets containing different disintegrants increased in following order: Croscarmellose < Sodium starch glycolate < Low-substituted hydroxypropyl cellulose < Crospovidone, which means croscarmellose, had a superior effectiveness as a disintegrant when compared with other materials.

Result shows that, EC20 provide pulse release while EC50 does not provide any pulse release. Drug release was slow in case of coating with higher molecular weight polymer EC50, due to increased puncture strength and especially elongation of the films.The rupture time increased with the higher coating level because of the increased mechanical strength of the coating and the reduced medium permeation rate at higher coating thickness. A similar trend was observed for all the disintegrants studied.

RUPTURE TEST

Table 11. Results of Lag time of different batches

Batch Code	Lag Time (min)
F1-I	275
F1-II	370
F1-III	412
F2-I	193
F2-II	273
F2-III	253
F3-I	214
F3-II	270
F3-III	378
F4-I	170
F4-II	214
F4-**III**	292

Mechanical Properties Of Polymeric Film Thickness

Table:12 shows thickness of polymeric film from 5 different places in mm (millimetre).

Table 12. Thickness of EC20 & EC50 films

S. NO	Thickness (mm)	
	EC20	EC50
1.	0.11	0.15
2.	0.12	0.14
3.	0.11	0.13
4.	0.13	0.14
5.	0.12	0.15
Mean±SD	0.118±0.00826	0.142±0.0084

Water uptake study of film.

Table 13. Percentage water uptake studies of polymeric films of EC20 & EC50

Time (hr)	%Water uptake	
	EC20	EC50
1	14.00	09.00
2	16.50	11.76
3	18.76	13.66
4	22.00	15.57
5	24.00	17.00
6	28.00	19.50

c) Tensile strength

Table 14. Tensile strength and Percentage elongation of EC20 and EC50

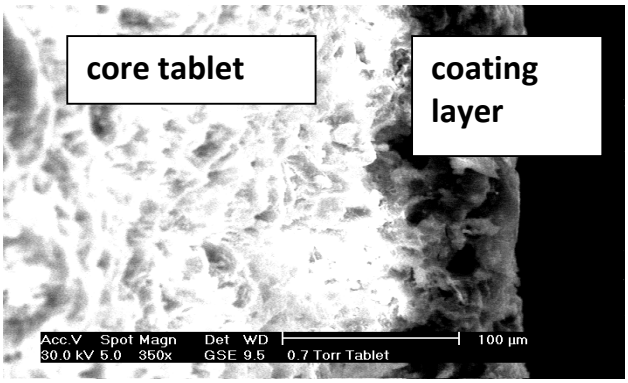
Polymer	Tensile Strength	% Elongation
EC20	17.22	8.54
EC50	24.54	21.50

The tensile strength and percentage elongation of EC50 is more than EC20. Outer membrane, formed using EC20 was brittle and ruptured sufficiently to ensure fast drug release. While coating with EC50, drug release was extremely slow due to increased tensile strength and especially elongation of films.

SCANNING ELECTRON MICROSCOPY (SEM)

Imaging technique of scanning electron microscopy (SEM) can offer useful information about the surface characterisation of the tablet surface. SEM was used to image cross section of pulsatile tablet.In the SEM image light part shows the pulsatile tablet core and dark part shows coating of EC20.

Fig 6. Cross section of Pulsatile Tablet coated with EC20



STABILITY STUDY

Stability studies on formulations F1-III was carried out at, room temperature (25°C±2°C/60%±5°CRH) and accelerated temperature (40°C±2°C/75%±5°CRH) conditions for 2 months. The formulations were evaluated for drug content and lag-time. It was found that there was no significant change in percentage drug content and in Lagtime.

Table 15. Results of Stability Study (Based On ICH Guidelines)

Formulations	Parameters	Storage Condition	
		25°C±2°C/60%±5RH	40°C±2°C/75%±5RH
F1-**III**	%Drug content	101.2	100.7
	Lag time (min)	412	405

The work carried in the present study can be summarized as follows:

Identification of anhydrous Theophylline was carried out by Melting point determination by capillary fusion method & IR spectroscopy by FTIR Spectrophotometer, Perkin Elmer, Spectrum GX, FTIR system, which was found to be in accordance to references. The λ_{max} of anhydrous Theophylline in phosphate buffer pH 6.8 corresponds to 272 nm and R^2 value from calibration curve was found to be 0.9996. Drug, polymers and excipients interaction was investigated by DSC. The DSC thermograms of pure drug and its physical mixture were recorded over a temperature range of 53°C – 300°C at the temperature were increase rate of 10°C/min. The thermograms did not show any major change in the endothermic peaks indicating no strong interaction between drug, polymers and excipients. The IR spectra of pure drug and tablet were recorded in the range of 4000-400 cm^{-1} .This study suggests that there was not a strong interaction between drug & excipients.

In vitro release profile of drug from pulsatile tablets prepared using EC20(Batch F1-III) has shown maximum lag time compared to other batches. Pulsed release was not observed for the batches (F1a-F1c) prepared using coating material EC50. The lag time of tablets containing different disintegrants increased in following order: croscarmellose < Sodium starch glycolate < Low-substituted hydroxypropyl cellulose < Crospovidone, It means croscarmellose had a superior disintegrant property compared to other disintegrants. Drug release was slow when tablets were coated with higher molecular weight ethyl cellulose (EC50), due to increased puncture strength and especially elongation of the films. The rupture time increased with the higher coating level (8%) because of the increased mechanical strength of the coating and the reduced medium permeation rate at higher coating thickness. A similar result was observed for all the disintegrants, which were studied.

SEM was used for image of pulsatile tablet cross section. The cross section of F1-III batch shows light part core and coated dark part which indicates perfect coating of tablet with EC20.

Stability studies of formulations F1-III was carried out at, room temperature (25°C±2°C/60%±5°CRH) and accelerated temperature (40°C±2°C/75%±5°CRH) conditions for 2 months. The formulations were evaluated for lag-time. No significant changes were observed in drug content (103.2, 101.4) and lagtime (412, 405) . Hence the selected formulation is stable under the conditions according to the ICH guideline.

Bronchial asthma requires time dependence drug delivery system. Such a condition demands considerations of diurnal progress of the disease rather than maintaining constant plasma drug level. A drug delivery system administered at bedtime, but releasing drug well after the time of administration (during morning hours), would be

ideal in this case. Same is true for preventing asthmatics attacks in the middle of the night.

The pulsatile release tablets composed fast-disintegrating tablet core coated with EC20 film, which could release theophylline anhydrous rapidly and completely after the lag time (F1-III -412min). Formulation screening studies showed that EC20 was the best candidate polymer for pulsatile release tablets. The lag time of tablets containing different disintegrants increased in the following order: croscarmellose < sodium starch glycolate < low-substituted hydroxy propyl cellulose < crospovidone and the rupture time increased with a higher coating level.

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