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Formulation and evaluation of chrono modulated pulsatile drug delivery system of doxofylline

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ABSTRACT

Chronotherapy defined as the treatment in which the drug release in the body is allowed to suite with the circadian rhythm of the disease, such that the involved action of the drug is shown with minimal side effects. Doxofylline core tablets prepared by direct compression method. These core tablets followed by preparation of pulsatile doxofylline tablets using press-coated technology. Doxofylline core tablets were prepared by using various excipients such as Sodium starch glycolate as superdisintegrant and MCC as diluents. The core tablets were then compressed into pulsatile tablets using combinations of HPMC K 100M and Eudragit L 100 in various concentrations. These Core tablets were evaluated for weight variation, thickness, drug content, disintegration and drug release studies. These core tablets evaluated based on the dissolution studies. The optimized formulation shows lower disintegration time and faster drug release. Then the pulsatile tablets were evaluated for various tests and drug release studies were conducted for pH 6.8 buffer and optimized formulation which showed satisfactory greater lag time of about 6 hours with satisfactory drug release which contains a combination of HPMC K15M , Eudragit L 100. Pulsatile tablets were formulated utilizing press coated technology and the combination of polymers provided required lag time with satisfactory dissolution profile.

Keywords: Pulsatile drug delivery, Doxofylline, Ethylcellulose, Eudragit and Tragacanth

INTRODUCTION

Chronotherapeutics discusses about the treatment method where the in vivo drug release is programmed to match the rhythms of disease such that to obtain the required therapeutic

outcomes and abate side effects [1, 2, 3].1-4 Circadian rhythms are self-sustaining, endogenous oscillations that occur with a periodicity of about 24 hours and are synchronized according to internal biologic clocks related to the sleep-wake cycle. The best-known circadian rhythms include body temperature, hormone secretion, metabolism, sleep or wake cycle [4, 5]. Hence the drug release should match the circadian rhythm of the disease hence variation in disease state and drug plasma concentration should be considered in the

development of drug delivery systems intended for the treatment of diseases with adequate dose at the appropriate time [5, 6]. Chronotherapeutic delivery system is required to be formulated to suit drug release conditions in various diseases like cardiovascular diseases, Asthma is disease of lung airways (bronchi) characterized by hyper active responsiveness to a variety of stimuli and in this condition the airways constricts and becomes inflamed with excess mucus lining the passage. The stimuli which may trigger the asthmatic condition includes exposure to allergens, cold air, moist air, emotional stress etc [7, 8]. Nocturnal asthma is condition where an exacerbation of the asthma is observed during the night times, such that worsening the functioning of the lung with increased airway response [9, 10, 11]. Usually, asthma attacks are more predominant in early mornings so it is annoying for a patient to take medicine at late night, hence in this condition there is a demand for pulsatile drug delivery system which release the drug at required time at proper site with efficient therapeutic action [12, 13]. Pulsatile drug delivery system offers various advantages like it provides extended activity, reduced side effects and dosage frequency, reduction in dose size, improved patient compliance, along with the main advantage of releasing the drug in required time in required quantity with satisfactory lag time [14, 15].

MATERIAL AND METHODS

Doxofylline was gifted by Hetero labs pvt limited, Hyderabad. Microcrystalline cellulose, Sodium starch glycolate, crosscarmellose sodium, Magnesium stearate, talc gifted by S D Fine chemicals. HPMC K15M, Eudragit L100, Eudragit S 100 and other chemicals were obtained from A.R. Chemicals.

METHODOLOGY 16, 17, 18

Method of preparation

Formulation of Doxofylline core tablets

Different matrix embedded formulations of Doxofylline hydrochloride were prepared by direct compression method using varying proportion of polymers either alone or in combination. The ingredients were passed through a 60 mesh sieve. Calculated amount of the drug, polymer (HPMC, Xanthan gum) and filler (MCC) was mixed thoroughly. Magnesium stearate was added as lubricant; the appropriate amount of the mixture was weighed and then compressed using a an Ten station rotary press at a constant compression force equipped with a 6-mm flat-faced punches at a compression force required to produce tablets of about 7–8 kg/cm2 hardness. All the tablets were stored in airtight containers for further study. Prior to compression, granules were evaluated for their flow and compressibility characteristics.

Formulation of pulsatile tablets

Formulation of Pulsatile Tablets by Press Coated Technology. The core tablets were compressed using polymer blend which has composition of HPMC K15 M and Eudragit L100 in different concentrations. Half of the coating polymer material was placed in the die cavity, then the core tablet was carefully sited in the centre of the die and cavity was filled on the top with the other half of the coating polymer material. Then the tablet was compressed using Rimek tablet machine, with 6 mm punch.

Formulations Table

Table no 1: Formulation of sustained release tablets of Doxofylline

Ingredients(mg)	D1	D2	D3	D4	D5
Drug	10	10	10	10	10
HPMC K_4M	-	-	25	50	-
Sodium alginate	-	50	-	-	-
Xanthan Gum	-	-	-	-	50
Eudragit	50	-	25	-	-
Talc	2	2	2	2	2
Magnesium Stearate	2	2	2	2	2
MCC	33	33	33	33	33

EVALUATION STUDIES

Pre compression parameters

The powder blend was evaluated and bulk density in between 0.497-0.520, tapped density in between 0.637-0.642, Compressibility index in between 21.58-17.72, Hausner's ratio in between 1.215-1.291 and angle of repose in between 29.22-31.2.

Pre compression parameters

Core tablets were evaluated for various tests like the weight variation and the tablet weight was found between 88.7-90.81mg, the hardness was found to be 4.8kg/cm2, thickness was found up to 3.17mm, the friability was found up to 0.198 to 0.328% and the disintegration time was between 20 to 82 sec and content uniformity between 96.9 to 99.4% and all the results were tabulated as shown in Table

Table no 2: Characterization of Formulation

S. no	Bulk density	Tapped density	Compressibility index	Hausner ratio	Angle of repose(0)
D1	0.497	0.637	21.97	1.281	29.70
D2	0.503	0.642	21.65	1.276	29.22
D3	0.501	0.638	21.47	1.273	30.70
D4	0.497	0.642	22.58	1.291	30.10
D5	0.520	0.632	17.72	1.215	31.2

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Table no 3: Evaluation parameters of core tablets of each batch

B. No.	Weight variation (mg)*	Thickness (mm)*	Hardness (kg/cm^2)*	Friability (%)	Drugcontent (%)	Disintegration time(sec)
D1	98	3.27	5.90	0.44	96.82	66.32
D2	96	3.28	5.65	0.385	98.41	57.12
D3	99	3.28	5.92	0.321	98.76	67.21
D4	87	3.26	5.91	0.382	97.20	61.15
D5	90 ±1.81	3.25 ±0.04	5.61	0.410	97.74	59.65

EVALUATION PARAMETERS OF COATED TABLETS

Weight variation

All the formulated (D1 to D5) tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of ±7.5% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values.

Thickness

The thickness determined for formulated tablets were tabulated in Table No 7. Tablets mean thickness (n=3) were uniform in D1 to D5 formulations and were found to be in the range of 2.45 mm to 2.55 mm.

Hardness

The measured hardness of tablets of each batch ranged between 6.5 to 7 kg/cm^2 .This ensures good handling characteristics of all batches.

Friability

The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

Content Uniformity

The percentage of drug content for D1 to D5 was found to be between 96.82% and 98.76% of Doxofylline, it complies with official specifications. The results were shown in Table No. 7.

Table no 4: Evaluation parameters of Press coated pulsatile tablets of Doxofylline

B. No.	Weight variation (mg)*	Thickness (mm)*	Hardness (kg/cm^2)*
D1	203	4.15	6.72
D2	204	3..42	6.75
D3	203	4.25	6.93
D4	205	3.59	6.72
D5	202	4.10	6.64

Dissolution studies

All the three formulation of prepared matrix tablets of Doxofylline were subjected to in vitro release studies these studies were carried out using dissolution apparatus.

The dissolution medium consisted of 900 ml of Standard buffer pH 6.8 for period of time.

Table no 5: Dissolution Profile of batch no. D1 to D5

B. NO.	Time in hours (cumulative % drug release)											
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
D1	12.79	29.43	43.63	57.56	65.23	78.64	87.40	96.65				
D2	17.53	31.60	40.14	51.17	63.20	71.85	82.51	95.67				
D3	17.53	31.32	40.69	52.72	65.50	72.61	83.68	92.21	93.2	95.54	96.20	97.23
D4	12.08	25.61	31.47	42.30	49.13	55.74	62.54	68.56	75.15	80.21	84.22	88.59
D5	33.02	52.22	66.52	74.17	85.92	94.04						

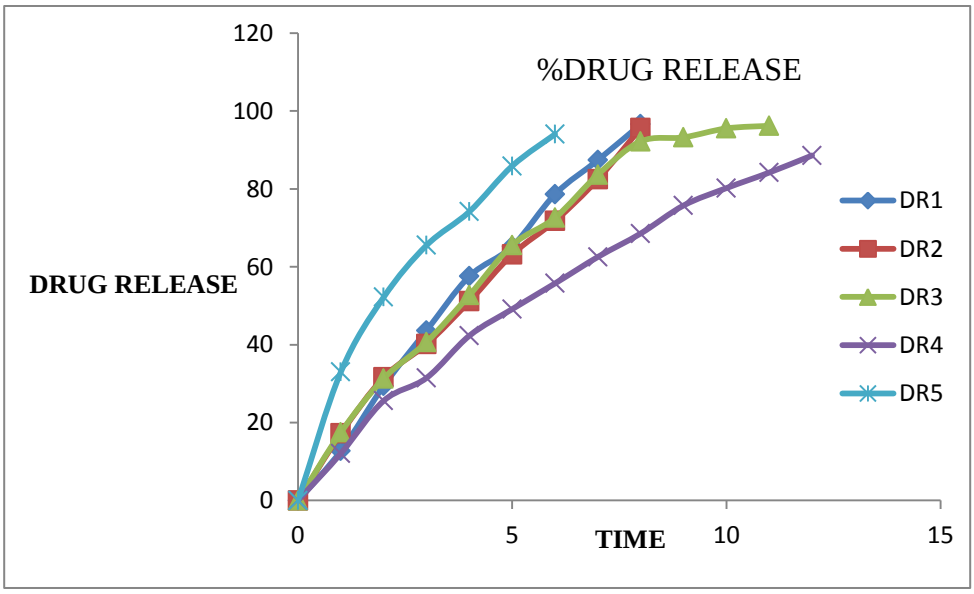

Fig no 1: Percentage drug release

Lag Time Determination by Rupture Test

The time taken for the outer coating to rupture is defined as the lag time of the pulsatile tablet. It was determined by using the USP II paddle dissolution apparatus. initially 900 ml of 6.8 phosphate buffer was taken as media and was carried for 12 hrs at 37.0 ± 0.5°C, 50 rpm. The time at which the outer coating layer starts to rupture was noted and considered as the lag time.

Tableno6: Evaluation of Lagtime

Formulation	Time (min)
D1	98
D2	160
D3	220
D4	289
D5	300

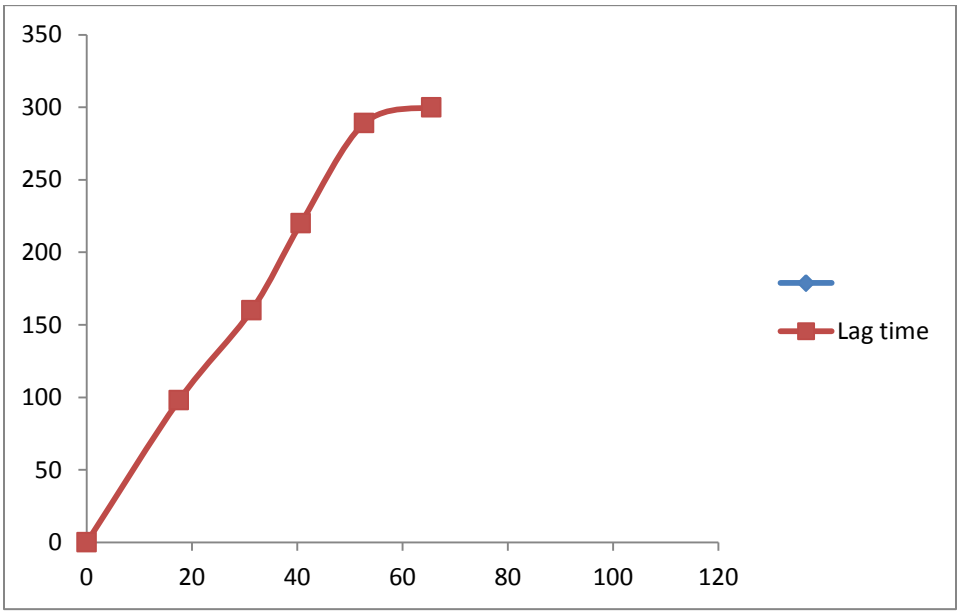

Fig no 2: Lag time of all formulations

Stability Study

There was no significant change in physical and chemical properties of the tablets of formulation F-3 after 30 days. Parameters quantified at various time intervals were shown;

Table no 7: Results of stability studies of optimized formulation F-3

Formulation Code	Parameters	Initial	1st Month	Limits as per Specifications
F-3	25^{0}C/60%RH % Release	99.61	99.53	Not less than 85 %
F-3	30^{0}C/75% RH % Release	99.47	99.54	Not less than 85 %
F-3	40^{0}C/75% RH % Release	99.61	99.56	Not less than 85 %

Table no 8: Stability dissolution profile of F-3 for 30 days

S.NO.	TIME(Hrs)	F-3 1M
1	0	0
2	1	5.73
3	2	7.22
4	3	8.6
5	4	9.62
6	5	10.2
7	6	72.3
8	7	79
9	8	99.61

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