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Research Article

Design and Evaluation of Press Coated Pulsatile Delivery of Doxofylline Tablets

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Abstract

The objective of this work was to develop and evaluate a pulsatile drug delivery system intended for chrono pharmacotherapy. The press-coated tablet (PCT) containing doxofylline in the inner core was formulated with an outer barrier layer by different compositions of hydrophilic polymer hydroxyl propyl methyl cellulose (HPMC E50) and hydrophobic polymer ethyl cellulose. The effect of formulation composition on the barrier layer comprising both hydrophilic and hydrophobic Polymers on the lag time of drug release was investigated. Among different barrier compositions from (F1 - F3), F3 was found to show single pulse drug delivery with considerable drug release for 6hrs after maintaining the pre expected 6hrs lag time.

Keywords: Pulsatile Drug Delivery; Press-Coated; Lag time; Doxofylline; HPMC; Ethyl Cellulose.

Introduction

Circadian phase dependent patterns have been well documented in conditions such as asthma, arthritis, epilepsy, migraine, allergic rhinitis, cardiovascular diseases, and peptic ulcer diseases with particular times where symptoms are more prominent or exacerbated [1]. Treating these diseases with immediate release dosage forms may be impractical if the symptoms of the diseases are pronounced during the night or early morning. Therapy with modified release dosage forms with zero order drug release theoretically leads to controlled and constant levels of drug in plasma throughout the day [2]. However, this is not providing extra therapeutic levels at the time of increased symptoms and unwanted plasma drug concentration at other times of day may produce adverse effects with little therapeutic benefit [3]. In order to optimize therapy in terms of safety, patient compliance and efficacy, chrono pharmaceutical formulations based upon the time controlled drug delivery systems (TCDDS) are considered to be potential therapeutic options [4]. TCCDS are dosage forms that are designed to mimic the circadian rhythm of the disease by releasing the drug appropriate time, by means of an internal pre-programmed clock that is initiated when the dosage forms come in contact with gastrointestinal fluids [5]. TCCDS have been formulated as pellets, capsules and tablets designed to release drug only after a defined lag time [6]. Tablet formulations generally consist of a rapid release core tablet encased in a barrier layer either formed by press-coating or liquid coating [7]. The press-coating offers advantages over liquid coating as it does not involve the use of solvents, requires a relatively short manufacturing process and allows greater weight gain to the core tablet. However common drawbacks of the press-coated technique are the multistep process involved and the requirement for reliable and reproducible central positioning of the core tablet within press-coated tablet, a major challenge for large scale industrial manufacturing [8].

The lag time of drug release from press-coated tablet depends upon the thickness and the composition of the barrier layer. Generally speaking, the thicker the barrier layer, the longer the lag time to drug releases [9]. The composition of the barrier layer controls the mechanism of effecting a lag time. In most instances where high viscosity grades of polymers such as hydroxypropyl methylcellulose (HPMC), hydroxy propyl cellulose, polyethylene oxide are used in the barrier layer, the polymer swells upon contact with GI fluids, then dissolves or erodes exposing the inner core tablet [10].

Doxofylline, a new generation xanthine analogue used in treatment of asthma and chronic obstructive pulmonary disease (COPD). The drug has less extra respiratory effects compared to that of theophylline [11]. Asthma is a chronic inflammatory disease of the airways, characterized by hyper responsiveness to a variety of stimuli. The role of circadian rhythms in the pathogenesis and treatment of asthma indicates that an airways resistance increases progressively at night in asthmatic patients. Circadian changes are seen in normal lung function, which reaches a low point in the early morning hours [12]. The worsening of asthma at night commonly referred to as nocturnal asthma (NA). A drug delivery system administered at bedtime but releasing drug during morning hours would be ideal in this case. Lung function (e.g., peak expiratory flow rate or FEV1) is usually highest at 4 PM and lowest at 4 AM the latter time is generally when asthma symptoms are most prevalent [13-30].

Materials and Methods

Materials

All the materials used in the current study were of pharmaceutical grade: Doxofylline was chosen as a model drug (Gift sample from Mars therapeutics, Hyderabad), crosspovidone (Nicolas primal, Mumbai), HPMC E15, HPMC E50 (colorcon asia, Goa), magnesium stearate (alpha chemicals), and talc (alpha chemicals).

Formulation of core tablet

The inner core tablets were prepared by using direct compression method. As shown in table 1 powder mixture of Doxofylline (400 mg) and crosspovidone (60 mg) were dry blended for 10 minutes. Followed by addition of magnesium stearate and talc were added to the mixture and mixed for a further 10 minutes., 470 mg of resultant powder blend was compressed using rotary tableting machine (karnavati machinery Ahmadabad, India) with 9.5 mm punch and die to obtain core tablet.

Ingredients (mg)	F1	F2	F3
Doxofylline	400	400	400
Crosspovidone (5%, 10 and 15%)	20	40	60
Magnesium stearate (1%)	5	5	5
Talc (1%)	5	5	5
Total weight (mg)	430	450	470

Table 1: Formula used to prepare of core tablet.

Formulation of mixed blend for barrier layer

As given in the table 2 the various compositions containing HPMC E15, HPMC E50 and ethyl cellulose. F1 to F6 different compositions were weighed and dry blended at about 10 minutes and used as press-coating material to prepare press-coated pulsatile release tablets respectively by direct compression method.

Formulation codes						
Ingredients (mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
HPMCE15	300	300	350	_	_	_
HPMCE50	_	_	_	300	300	350
Ethyl cellulose	_	20	20	_	20	20
Magnesium state	5	5	5	5	5	5
Talc	5	5	5	5	5	5
Core tablet	470	470	470	470	470	470
Total weight (mg)	780	800	850	780	800	850

Table 2: The core tablet of (F3) 470 mg was press-coated with varying ratios of HPMC and ethyl cellulose polymers. The components were shown in table.

Each blend was evaluated for its Angle of repose and refers to as pre-compression parameters. Static angle of repose was determined according to the fixed funnel and freestanding cone method, whereby accurately weighed granules (3g) were carefully poured through the funnel with its tip at 2 cm height, H, until the apex of the conical heap so formed just reached the tip of the funnel. The mean diameter, 2R, of the base for the powder cone was measured and the angle of repose (θ) was calculated using the following equation. The results are shown in table 4.

Preparation of press-coated tablets

The core tablets were press-coated with 380 mg of prepared barrier mixed blend, 190 mg of barrier layer material was weighed and transferred in to a 12.7 mm die then the core tablet was placed manually at the center. The remaining 190 mg of barrier layer material was added in to the die and compressed using rotary tabletting machine.

Evaluation of press-coated tablets

Tablets were evaluated for friability test, hardness test and drug content. These parameters were referring to as post-compression parameters.

The friability of all the tablets studied was determined using a Roche friabilator. Pfizer hardness tester was used for the determination of hardness of tablets. The tablet was placed in contact between the plungers and handle was pressed. The force of fractured was recorded. Six tablets were tested from each formulation.

The determinations of drug content, a total tablet was weighed and powder equivalent to 10 mg of Doxofylline was weighed and dissolved in distilled water then filtered through what man filter paper. Solution was analysed for Doxofylline content by UV-Spectrophotometer at 274 nm using distilled water as a blank.

Evaluation pre-compression parameters

The pre-compression parameters like angle of repose, bulk density, tapped density, carr's index (CI) and Hausner ratio were calculated and tabulated.

Formulation code	Angle of repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index	Hausner ratio
F1	21.32°	0.54	0.69	13.6	1.24
F2	26.05°	0.49	0.63	12.2	1.10
F3	23.8°	0.57	0.66	14.8	1.12
F4	25.2°	0.52	0.68	12.43	1.15
F5	22.7°	0.53	0.59	15.8	1.19
F6	21.19°	0.50	0.64	13.42	1.21

Table 4: Pre-compression parameters for polymeric blend.

Formulation code	Average weight of tablets (mg)	Hardness (kg/cm²)	Disintegration time (sec)	Drug content (%w/w)
F1	428 ± 2.51	2.5 ± 0.251	30 ± 2	93.45 ± 0.74
F2	448 ± 2.08	2.8 ± 0.152	19 ± 1.5	96.12 ± 0.71
F3	468 ± 3.25	2.6 ± 0.1	10 ± 1	98.5 ± 0.85

Table 3: Evaluation parameters of doxofylline core tablets (RRT).

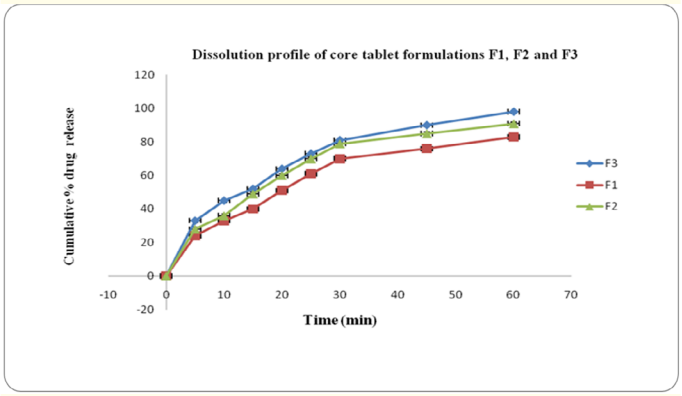

Figure 1: *In vitro* dissolution profile of core tablets in distilled water.

Dissolution profile of core tablets

Formulation code	Weight variation (mg)	Hardness (kg/cm²)	Thickness (mm)	Friability (%)	Lag time
F1	774 ± 2.08	7 ± 0.28	4 ± 0.026	0.51	2.5hr
F2	769 ± 3.60	7.5 ± 1	4.4 ± 0.029	0.49	3hr
F3	840 ± 2.51	6.3 ± 1.2	4.7 ± 0.023	0.56	3.5hr
F4	774 ± 2.64	6.9 ± 0.9	4.1 ± 0.028	0.42	3hr
F5	769 ± 2.08	5.5 ± 0.76	4.5 ± 0.019	0.57	5hr
F6	840 ± 2.8	6 ± 0.8	4.8 ± 0.021	0.62	6hr

Table 5: Evaluation of post compression parameters of PRT.

Dissolution profile of press-coated formulations F1, F2, F3, F4, 5 and F6.

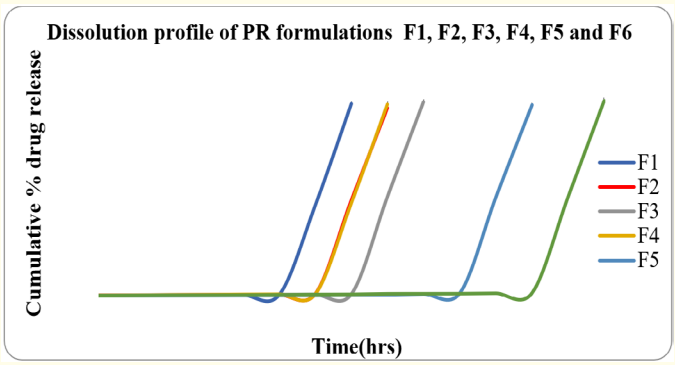

Figure 2: *In vitro* dissolution profile of core tablets in distilled water.

Discussion and Conclusion

A chrono modulated drug delivery system for doxofylline for the treatment of nocturnal asthma was successfully developed. The system was found to be satisfactory in terms of release of the drug after a lag time of 6hrs. The dosage form can be taken at bed time and will release the contents in the early hours of morning when the asthmatic attacks are more prevalent. The release of the drug was sharp and complete after the lag time, which is necessary for pulsatile drug delivery system.

- The formulation (F6) HPMC E50 (350 mg) and ethyl cellulose (15 mg) gave satisfactory release lag time of 6 hrs and it was found to be successful in achieving pulsatile drug delivery.
- The technology (press-coating) used for the preparation of press-coated pulsatile tablets (PCPT) is a relatively simple manufacturing process which can be easily adopted in industrial units on a commercial scale.
- However, there is further need for investigation for the clinical acceptance of this novel delivery system (by pharmacoscintigraphic study) to determine *in vitro* and *in vivo* correlation of the press-coated tablet formulations.

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