Original Article

PULSATILE RELEASE OF KETOPROFEN FROM COMPRESSION COATED TABLETS USING EUDRAGIT® POLYMERS

HETAL PATEL[1], SONIA PANDEY[1], VIHARI PATEL[1], RITESH SHAH[1], SANJAY TIWARI[1]*

[1]Maliba Pharmacy College, Uka Tarsadia University, Bardoli Mahuva Road, Surat, Gujarat, India 394350
Email: tiwarisanju@gmail.com

ABSTRACT

Objective: The objective of the present research work is to develop compression coated tablet of ketoprofen as a pulsatile release system for treatment of rheumatoid arthritis.

Methods: Core tablets of ketoprofen were prepared using the wet granulation method and evaluated for appearance, hardness, friability, weight variation, thickness, disintegration time and % drug release. Core tablets were coated with Eudragit S100 and Eudragit L100 by compression coating method to achieve desired lag time. The blends of core and coating materials were evaluated for bulk density, tapped density, Hausner's ratio, % Compressibility index and angle of repose. Compression coated tablets were evaluated for appearance, hardness, friability, weight variation, thickness and % drug release.

Results: Core tablets, as well as compression coated tablets, showed acceptable Pharmaco technical properties. Optimized core tablets were disintegrated within 15s due to the effectiveness of super disintegrant, sodium starch glycolate. Dissolution studies of compression coated tablets in media with different pH (1.2, 6.8, and 7.4) showed that drug release could be modulated by changing the concentration of EudragitL100 and Eudragit S100. The optimized batch exhibited 80% drug release up to 6 h with a 4 h lag time. Stability study of the optimized formulation indicated no significant change in appearance, physical parameters, drug content and drug release profile at accelerated conditions for two months.

Conclusion: compression coated tablet of ketoprofen was successfully developed to achieve burst drug release after specific lag time.

Keywords: Chronomodulated drug delivery, Pulsatile release, Compression coated tablets, Lag time

INTRODUCTION

Oral route of drug administration is perhaps the most appealing route for the delivery of drugs. Of the various dosage forms administered orally, the tablet is one of the most preferred dosage forms because of its ease of manufacturing, convenience in administration, accurate dosing, better stability and tamperproof nature [1]. Chrono-modulated drug delivery is defined as the rapid and transient release of a certain amount of molecules within a short time period immediately after a predetermined off released period, i.e., lag time or these systems have a peculiar mechanism of delivering the drug rapidly and completely after a lag time, i.e., a period of no drug release. Such a release pattern is known as pulsatile release [2-7]. Chrono-therapeutics refers to a treatment method in which *in vivo* drug availability is timed to match the rhythms of disease in order to optimize therapeutic outcomes and minimize side effects. It is based on the observation that there is an interdependent relationship between the peak to trough rhythmic activity in disease symptoms & risk factors, pharmacological sensitivity and pharmacokinetics of many drugs [8].

Diseases, such as hypertension, asthma, peptic ulcer, arthritis, etc., follow the body's circadian rhythm. Many systems in the human body, such as cardiovascular, pulmonary, hepatic and renal systems show variation in their function throughout a typical day. They are naturally synchronized with the internal body clocks and are controlled by the sleep-wake cycle. Each body system exhibits a peak time of functionality that is in accordance with these rhythmical cycles. Similarly, disease states affect the function of some of these systems in the body and therefore, they too exhibit a peak time of activity within a circadian rhythm [9].

The compression coated tablet is a tab-in-tab concept which consists of core tablet completely surrounded by the coating material. Compression coating is a dry coating concept which omits usage of solvent & heat. The composition of core tablet & coating material regulates drug release pattern from the system [10, 11].

Ketoprofen is used to treat rheumatoid arthritis. It is BCS (Biopharmaceutical Classification System) class II drug having a half-life of 1-3 h. Patients with rheumatoid arthritis have severe pain early in the morning [12-14]. Hence, there is a need to formulate ketoprofen pulsatile release tablet to provide the highest drug level during early morning hours. Khadabadi S [15] and Rane AB [16] *et al.* formulated press coated tablet for pulsatile drug delivery of ketoprofen using HPMC and a combination of hydrophilic (glycine max husk or sodium alginate) and hydrophobic polymers (micronized ethyl cellulose powder), respectively. Fan TY *et al.* prepared pulsatile release tablets using a combination of ethylcellulose and Eudragit L as film coating materials and cross-linked polyvinyl pyrrolidone (PVP) in the core tablets [17]. Pandey S *et al.* prepared "tablets in capsule" system for facilitating both immediate and pulsatile drug deliveries of theophylline to mimic the circadian rhythm of nocturnal asthma [18]. Aim of the present study was to achieve burst release of ketoprofen after specific lag time from compression coated tablets using Eudragit® polymers. Ketoprofen compression coated tablets having a combination of Eudragit L100 and S100 to achieve pulsatile release has not been reported yet.

MATERIALS AND METHODS

Materials

Ketoprofen was received as a gift sample from Neon Pharma, Mumbai, India. Eudragit L100, Eudragit S 100, microcrystalline cellulose, sodium starch glycolate, PVP K 30, talc and magnesium stearate was purchased from Balaji drugs, Surat, India.

Methods

Identification of ketoprofen

Drug identification was performed using melting point, UV analysis and Fourier transform infrared spectroscopy (FTIR) study (Bruker Optics Alpha, Germany). An IR spectrum of the drug was recorded in the range of 4000-500 cm^{-1}. Assay of ketoprofen was performed as per IP [19].

Bulk characterization of ketoprofen powder

Ketoprofen powder was characterized by appearance, colour, odour, and particle size and flow property. Particle size determination by sieve analysis and flow property characterization by Hausner's ratio, Carr's index and angle of repose was performed as per USP [20].

Formulation of compression coated tablet

Preparation of ketoprofen core tablets by direct compression method (batch P_1)

The composition of core tablet (batch P_1) is mentioned in table 1. The drug and excipients were passed through sieve no. 40; mixed and compressed into tablets using a tablet machine (Rimek mini press 1) equipped with 6.5 mm diameter punch.

Preparation of ketoprofen core tablets by wet granulation method (batches P_2 to P_6)

The composition of core tablet (batch P_2 to P_6) is mentioned table 1. The drug and excipients (previously passed through sieve no. 40) were mixed and granulated using PVP K30 solution as the granulating agent. The wet mass was passed through sieve no. 30 and the granules were dried and compressed into tablets using a tablet machine (Rimek mini press 1) equipped with 6.5 mm diameter punch.

Table 1: Compositions of core tablets of preliminary batches P_1 to P_6

Formulation	Batch P_1	Batch P_2	Batch P_3	Batch P_4	Batch P_5	Batch P_6
Drug (mg)	80	80	80	80	80	80
Microcrystalline cellulose (mg)	58	58	58	58	58	58
Sodium Starch Glycolate (mg)	6	6	6	6	6	6
Magnesium stearate (mg)	3	3	3	3	3	3
Talc (mg)	3	3	3	3	3	3
Polyvinyl pyrollidone K30 (mg)	-	1	2	3	4	5

Coating of core tablets using eudragit S100 (batch E_1)

The core tablets were coated using Eudragit S100 (batch E_1) (10%) by the compression coating method. The complete compression coated tablet was prepared by placing 50% of the outer layer powder mixture in the die, manually centering the previously prepared core tablets on the powder in the die & loading the remaining 50% of the outer layer powder mixture into the die, the contents were then compressed using a single press tableting machine fitted with a 8 mm diameter concave punch set.

Coating of core tablets using mixture of eudragit S100 and Eudragit L100 (batches F_1 to F_9)

The core tablets were coated by compression method with different weight ratios of (% w/w) mixture of Eudragit S100 and Eudragit L100 (table 2). Agglomerates of a mixture of Eudragit S100 and Eudragit L100 were prepared using PVP K 30 (1%) as a binder.

Evaluation of powder blends and compression coated tablets

Evaluation of Powder blends of core tablets and coating layer

Micromeritics (angle of repose, bulk density, tapped density and percentage compressibility) of core and coat layer blends was determined prior to manufacturing of compression coated tablets [21].

Evaluation of core and compression coated tablets

Core and compression coated tablets were characterized for appearance, diameter, thickness, weight variation, hardness, friability and % drug content. Hardness, thickness and friability were determined by the Monsanto hardness tester, digital vernier calipers and friabilator respectively. Disintegration test of core tablets was performed in a USP disintegration apparatus using three different mediums (0.1 N HCl (Hydrochloric acid), pH 4.6 acetate buffer, pH 7.4 phosphate buffer).

Table 2: Coating composition of tablets of batches F_1 to F_9

Ingredients (mg)	Batches								
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Eudragit L100	20	20	20	40	40	40	60	60	60
Eudragit S100	40	60	100	40	60	100	40	60	100
Magnesium Stearate	3	3	3	3	3	3	3	3	3
Talc	2	2	2	2	2	2	2	2	2

In vitro release of drug from compression coated tablets was determined using 6-station USP dissolution-basket apparatus (TDT-06T, Electrolab) at 50 rpm at 37.0±0.5 °C. Dissolution of ketoprofen from compression coated tablet was monitored for 2 h in 900 ml 0.1 N HCl followed by 900 ml pH 4.6 acetate buffer solutions for 4 h followed by 900 ml pH 7.4 phosphate buffers for 22 h.

At predetermined time interval a 5 ml sample was withdrawn from each dissolution vent and replaced with fresh medium to maintain the sink condition. The samples withdrawn were filtered through Whatman filter paper and the drug content in each sample was analyzed by UV spectrophotometer after suitable dilution (UV-3092, Lab-India, India) at 260 nm. The dissolution test was performed in triplicate. Drug dissolved at specified time period was plotted as cumulative percent release versus time curve. The lag time of batches F_1 to F_9 were calculated based on drug release>10%

Stability studies

Compression coated tablets of the optimized batch were packed in alu-blisters and stored at accelerated conditions (40 °C/75 % Relative humidity) for 3 mo and evaluated for appearance, hardness, % drug content and *in vitro* drug release at an interval of one month up to three months [22].

RESULTS AND DISCUSSION

Identification of ketoprofen

The melting point of the ketoprofen was found to be in the range of 95-98 ºC, which complied with a standard reference. Identification peak of ketoprofen was present in the recorded UV spectrum at λ max 260 nm which complied with UV spectra of pure ketoprofen given in reference clerk [23]. IR spectra of ketoprofen showed a characteristic peak at 1693 cm^{-1} (C=O stretching), 1650 cm^{-1} (C=C stretching), 1281 cm^{-1} (C-N stretching). FTIR spectrum of drug was comparable with reference FTIR spectrum **(**fig. 1**)** [19]. Percentage drug content was found to be 99.49±0.64 which complied with the limit provided in Indian pharmacopeia, 2010.

Bulk characterization of ketoprofen powder

Carr's index, Hausner's ratio and angle of repose of drug powder were 34.36%, 1.52 and 40.36°, respectively, which indicated a poor flow and compressibility of drug powder.
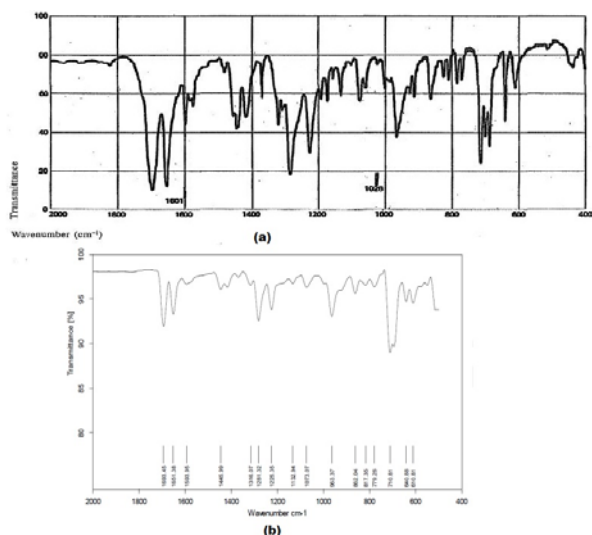
Fig. 1: FTIR spectra of a) reference ketoprofen as per IP and b) ketoprofen sample used for this study

Formulation and evaluation of dosage forms

Evaluation of powder blends of core tablets

Carr's index and Hausner's ratio blend of batch P_1 to P_6 is mentioned in table 3. Blend of batch P_1 exhibited poor flow property and compressibility of blend hence it was not suitable to prepare tablets by the direct compression method. Hence, wet granulation technique using PVP K 30 as a binder was employed to prepare core tablets. Powder blends of all batches (P_2 to P_6) indicated acceptable flow property and compressibility (table 3). Granulation process improved flow property and compressibility of the blend. *Consiglieri VO et al.* also proved that the production of granules of fluconazole with PVP improved flow and compressibility of fluconazole [24]. *Patel et al.* concluded that granulation could be an interesting method to improve the flow property of a poorly flowable Lactose Monohydrate when associated with a suitable binder and the granulation technique [25].

Evaluation of core tablets of ketoprofen

Results of parameters like weight variation, hardness, friability, Thickness and % drug content of core tablets are shown in table 4. All tablets were produced with an acceptable weight variation (<10%), uniform thickness, acceptable hardness (3-5 kg/cm^2) and acceptable friability (<1%). Percentage drug content of all tablets was in the range of 95–105. All tablets were disintegrated within 2 min due to the presence of super disintegrant sodium starch glycolate (table 5). Super disintegrant sodium starch glycolate absorbs water rapidly and swells in water to the extent of 200–300% and exert sufficient pressure inside the tablets to break up into particles [26, 27]. Batch P_2 exhibited faster disintegration among all the batches (P_2 to P_6) due to the minimum amount of binder in the formulation. Setty CM *et al.* compared acacia, PVP and starch paste as a binder in fast disintegrating tablets and concluded that PVP showed least disintegration time of tablets [28]. Binder Sharma D *et al.* also successfully developed fast disintegrating tablets using PVP and SSG as a binder-super disintegrant combination [26]. Tablets of batch P_2 were used for further studies to prepare compression coated tablets.

Table 3: Results of evaluation of powder blend of core tablets of preliminary batches (P_1 to P_6)

Parameter	P_1	P_2	P_3	P_4	P_5	P_6
Bulk density* (g/cm^3)	0.22 ±0.06	0.32±0.10	0.67 ±0.23	0.55 ±0.11	0.43 ±0.12	0.32 ±0.10
Tapped Density* (g/cm^3)	0.43 ±0.19	0.37 ±0.11	0.80 ±0.19	0.66 ±0.21	0.59 ±0.13	0.38 ±0.12
Hausner's ratio	1.95	1.14	1.19	1.19	1.17	1.17
Carr's index (%)	48.83	12.60	16.12	16.28	14.56	14.93
Angle of Repose(º)*	35± 0.56	25.80± 0.15	23.04± 0.10	25.45± 0.11	25.56± 0.21	23.96± 0.15

*mean±SD

Table 4: Results of evaluation of core tablets of preliminary batches (P_2 to P_6)

Batch	Hardness* (kg. cm^{-2})	Friability* (%)	Average* Weight (mg)	Thickness* (mm)	%Drug Content*
P_2	4±0.5	0.410±0.010	150.05±0.66	2.1+0.05	98.8+0.45
P_3	4±0.1	0.354±0.050	155.1±1.33	2.0+0.02	98.83+1.6
P_4	4±0.3	0.423±0.011	149.9±0.66	2.1+0.01	99.07+0.94
P_5	3.5±0.09	0.356±0.020	150.05±0.66	2.1+0.05	98.89+1.5
P_6	5±0.4	0.349±0.021	151.05±2.66	2.1+0.04	100.66+1.8

*mean±SD

Table 5: Disintegration time of the core tablet of ketoprofen

Batch	Disintegration time in dissolution medium		
	0.1 N HCl* (pH 1.2) (s)	pH 6.8 Buffer*(s)	pH 7.4 buffer*(s)
P_2	33±1.9	17±1.5	15±3.3
P_3	57±6.4	54±3.8	52±1.6
P_4	59±4.3	58±6.2	60±4.5
P_5	58±1.8	58±4.1	59±1.1
P_6	60±8.1	118±3.5	120±4.5

*mean (n=6)±SD

Coating of core tablets using eudragit S100 (Batch E$_1$)

Hausner's ratio (1.32) and Carr's index (24.24%) of the blend indicated good flowability and compressibility. Only 49% of the drug was released up to 8 h and lag time was 5 h. These clearly indicated that tablet coated with Eudragit S100 alone could provide satisfactory lag time but failed to provide complete drug release. Such release profile was not desirable, so the further study was performed in which combination of Eudragit S100 and Eudragit L100 was coated on core tablets. Cheng G *et al.* coated pellets with Eudragit S100 alone and observed that the dissolving process of the coating layer of S100 alone was rather slow, resulting in very slow drug release [29].

Coating of core tablets using mixture of Eudragit S100 and Eudragit L 100 (batches F$_1$-F$_9$)

Hausner's ratio (1.45) and compressibility index (31.19%) of coating powder blend showed poor flow property and compressibility of the blend. A mixture of Eudragit S100 and L100 was granulated to improve flow property and compressibility of the blend.

Evaluation of compression coated tablets of batches F$_1$ to F$_9$

Powder blends of batches F$_1$ to F$_9$ exhibited good flow characteristic (table 6). Core tablets, as well as compression coated tablets, showed acceptable Pharmaco-technical properties (table 7).

Table 6: Results of evaluation of powder blend of core tablets of batches F$_1$ to F$_9$

Parameter	Batches								
	F$_1$	F$_2$	F$_3$	F$_4$	F$_5$	F$_6$	F$_7$	F$_8$	F$_9$
Bulk density* (g/cm³)	0.64± 0.10	0.61± 0.06	0.39± 0.08	0.65± 0.11	0.76± 0.10	0.76± 0.01	0.67± 0.01	0.60± 0.02	0.62± 0.10
Tapped density* (g/cm³)	0.73± 0.11	0.73± 0.18	0.76± 0.01	0.79± 0.15	0.22± 0.02	0.79± 0.18	0.78± 0.03	0.71± 0.02	0.73± 0.18
Hausner's ratio	1.14	1.13	1.22	1.21	1.81	1.21	1.30	1.70	1.25
Carr's index (%)	12.3	18.6	18.1	17.7	18.6	17.7	23.2	15.1	15.4
Angle of repose*(º)*	22.96± 0.22	21.64± 0.15	27.9± 0.28	22.45± 0.31	27.96± 0.62	23.45± 0.19	22.20± 0.09	21.04± 0.18	26.89± 0.11

*mean±SD

Not more than 10% of the drug was released in 0.1 N HCl due to the presence of Eudragit in the coating layer. Dangi P *et al.* [30] also stated that Eudragit prevented drug release in stomach pH. Less than 80% of the drug was released at 6 h in batches F$_1$, F$_2$ and F$_3$; whereas batches F$_4$ to F$_8$ exhibited more than 80% drug release at 6 h (fig. 2 and 3).
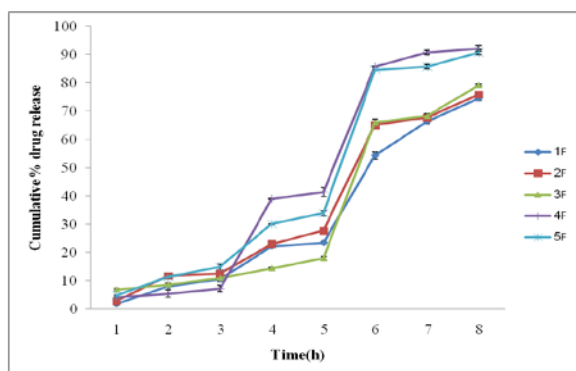

Fig. 2: Dissolution study of ketoprofen from compression coated tablets (n= 06) of batches of batches F$_1$ to F$_5$ for 2 h in 900 ml 0.1 N HCl followed by 900 ml pH 4.6 acetate buffer solutions for 4 h followed by 900 ml pH 7.4 phosphate buffer for 22 h

Fig. 3: Dissolution study of ketoprofen from compression coated tablets (n= 6) of batches F$_6$ to F$_9$ for 2 h in 900 ml 0.1 N HCl followed by 900 ml pH 4.6 acetate buffer solutions for 4 h followed by 900 ml pH 7.4 phosphate buffer for 22 h
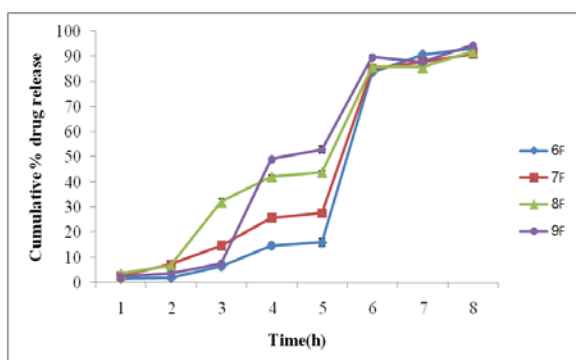
Lower level of Eudragit L100 could not rovide a desirable burst drug release at 6 h. Among Batches F$_1$, F$_2$ and F$_3$, F$_3$ exhibited maximum lag time i.e. 4 h which indicated that as Eudragit S100 increases there is an increment in lag time. Mehta R *et al.* also supported the same findings [31]. Batches F$_4$, F$_5$ and F$_6$ released more than 80% of the drug at 6 h and batch F$_6$ exhibited maximum lag time. Batches F$_7$, F$_8$ and F$_9$ could release more than 85% drug at 6 h but could not achieve desirable lag time.

Most commonly used pH dependent coating polymers Eudragit L100 and Eudragit S100 which dissolve at pH 6.0 and 7.0, respectively. Since pH varies in the different parts of GT tract, if these two polymers are combined with each other at various ratios, it would be possible to achieve drug release within the pH range of 6.0-7.0 [32]. Hence, only batch F$_6$ could provide desirable attributes, i.e. more than 80% drug release at 6 h and 4 h lag time hence, Batch F$_6$ was considered as optimized batch. Batch F$_6$ exhibited maximum lag time i.e., 4 h which is considered to be ideal as indicated in fig. 4.
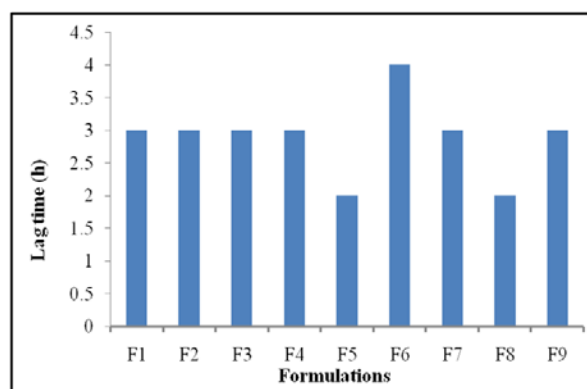

Fig. 4: Mean Lag time (n=6) of compression coated tablets of batches F$_1$ to F$_9$

Results of stability study of optimized batch indicated no significant change in appearance, physical parameters, and drug release profile at accelerated conditions for two months (table 8).

Table 7: Evaluation of core and compression coated tablets of batches F_1 to F_9

Batch ⟹		F1	F2	F3	F4	F5	F6	F7	F8	F9
% Friability	**Compression coated**	0.42±	0.35±	0.42±	0.35±	0.41±	0.42±	0.35±	0.41±	0.42±
	Tablets*	0.05	0.04	0.05	0.02	0.04	0.05	0.04	0.02	0.05
	Core	0.41±	0.35±	0.42±	0.35±	0.34±	0.35±	0.41±	0.35±	0.41±
	Tablets*	0.01	0.05	0.01	0.02	0.02	0.05	0.01	0.02	0.01
Hardness (Kg/cm^2)	**Compression coated**	6.2±	6.2±	5.3±	5.6±	5.9±	5.4±	6.2±	6.2±	5.7±
	Tablets*	0.07	0.11	0.09	0.04	0.05	0.05	0.07	0.01	0.04
	Core tablets*	04±	04±	04±	3.5±	05±	04±	04±	05±	3.5±
		0.1	0.1	0.1	0.09	0.4	0.1	0.1	0.4	0.9
Thickness (mm)	**Compression coated**	4.27±	4.22±	4.09±	4.17±	4.20±	4.2±	4.08±	4.16±	4.09±
	Tablets*	0.01	0.03	0.003	0.02	0.02	0.01	0.04	0.04	0.03
	Core	2.66±	2.00±	2.1±	2.66±	2.1±	2.1±	2.1±	2.1±	2.0±
	Tablets*	0.02	0.005	0.05	0.02	0.056	0.05	0.05	0.05	0.05
Average weight (mg)	**Compression coated**	250.02±	247.1±0	250.05±	249.9±	253±	250±	249±	250±	252±
	Tablets*	0.66	0.06	0.6	0.66	0.56	0.052	0.66	0.001	0.064
	Core	150.05±	152.1±	149.9±	155.05±	150.05±	149.9±	155.05±	151±	150.05±
	Tablets*	0.66	1.33	0.66	2.66	0.66	0.66	0.2.66	0.001	0.66

Table 8: Results of stability study of ketoprofen compression coated tablet

Time	Physical change in appearance	Hardness (Kg/cm^2)	Friability (%)	%Drug release Lag time(h)	Q_6*
Initial	No change	5.4±0.05	0.42±0.05	4	83.26±0.60
One month	No change	5.3±0.05	0.42±0.05	4	81.61±0.98
Two month	No change	5.1±0.05	0.41±0.05	4	84.87±2.87

Q_6*means % drug release at 6^h

CONCLUSION

The chrono therapeutic dosage form of ketoprofen was formulated by a compression coating technique which could provide the drug release in the early morning hours if the tablet is taken at late night. The concentration of Eudragit S 100 and Eudragit L100 can regulate lag time, whereas; the amount of super disintegrant in core tablet can regulate burst drug release. Optimized batch (F_6) consisted of a combination of Eudragit S100 and Eudragit L100 in a ratio of 100:40 could release about 80-85% of the drug within 6 h with a lag time of 4 h. Lag time can be improved from 4 h to 6 h for better patient compliance. Thus, pulsatile release of ketoprofen can be achieved from compression coated tablets using Eudragit® polymers.

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CONFLICT OF INTERESTS

Declared none

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