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Formulation and Evaluation of Chronomodulated Drug Delivery of Montelukast Sodium

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Abstract

An oral press coated tablet containing Montelukast sodium was formulated with an outer barrier layer of different compositions of hydrophobic polymer eythyl cellulose and hydrophilic polymer hydroxyl propyl methyl cellulose. This press coated tablet was prepared by using direct compression and wet granulation methods in order to achieve the predetermined lag time.

Keywords: Pulsatile drug delivery systems (PDDS); Nocturnal asthma(NA); Chronopharmacology; Circadium Rhythms; Burst release; Lag time

Abbreviations: EC: Ethyl Cellulose; HPMC: Hydroxy Propyl Methyl Cellulose; FTIR: Fourier Transform Infra Red; SLS: Sodium Lauryl Sulphate; IR: Immediate Release; ChrDDS: Chrono Modulated Drug Delivery Systems; PCT: Press Coated Tablets

Introduction

Controlled drug delivery systems [1] have acquired a centre stage in the area of pharmaceutical R &D sector. Such systems offer temporal &/or spatial control over the release of drug and grant a new lease of life to a drug molecule in terms of controlled drug delivery systems for obvious advantages of oral route of drug administration. These dosage forms offer many advantages, such as nearly constant drug level at the site of action, prevention of peak-valley fluctuation, reduction in dose of drug, reduced dosage frequency, avoidance of side effects and improved patient compliance. In such systems the drug release commences as soon as the dosage form is administered as in the case of conventional dosage forms. However, there are certain conditions, which demand release of drug after a lag time. Such a release pattern is known as pulsatile release [2-5]. The diseases currently targeted for chronopharmaceutical formulations are those for which there are enough scientific backgrounds to justify ChrDDS compared to the conventional drug administration approach. These include asthma, arthritis, duodenal ulcer, cancer, diabetes, cardiovascular diseases, hypercholesterolemia, ulcer and neurological diseases [6,7].

If the organization in time of living system including man is borne in mind, it is easy to conceive that not only must the right amount of the right substance be at right place but also this must occur at the right time. In the last decade numerous studies in animals as well as clinical studies have provided convincing evidence, that the pharmacokinetics &/or the drug effects -side effects can be modified by the circadian time &/or the timing of drug application within 24 hrs of a day [8]. A pulsatile drug delivery system that can be administered at night (before sleep) but that release drug in early morning would be a promising chronopharmaceutic system. Drug targeting to colon [9] would prove useful where intentional delayed drug absorption is desired from therapeutic point of view in the treatment of disease that have peak symptoms in the early morning such as nocturnal asthma, angina, arthritis.

Circadian rhythms are self-sustaining, endogenous oscillation, exhibiting periodicities of about one day or 24 hours. Normally, circadian rhythms are synchronized according to the body's pacemaker clock, located in the suprachiasmic nucleus of the hypothalamus [8]. 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 airway 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. The worsening of asthma at night commonly referred to as nocturnal asthma (NA) [10]. A drug delivery system administered at bedtime but releasing drug during morning hours would be ideal in this case. Nocturnal asthma is a variable exacerbation of the underlying asthma condition associated with increases in symptoms, need for medication, airway responsiveness, and/or worsening of lung function. Generally, a reduction in peak flow or forced expiratory volume in one second (FEV1) of at least 20% is implicit in this definition. 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. . Consequently, the administration of a drug formulated in such a delivery system, i.e. taken at bedtime with a programmed start of drug release in early morning hours, could offer a more effective therapy than a typical controlled release drug delivery system, provided that the most appropriate drugs are administrated [11].

Pharmaceutical coatings [12] are an essential tool to achieve the desired formulation of pharmaceutical dosage forms. Coating techniques mostly used in pharmaceutical industry are aqueous or organic coating, which present some disadvantages: time consuming, stability for heat labile and hydrolysis of degradable drug and polluted environment problem. Thereby, non-solvent coating is introduced as alternative coating technique to overcome these disadvantages.

For the time controlled release system from compression-coated tablets, the amount of the outer shell is a key factor for controlling the lag time. Higher amount of the outer coating added would prolong the lag time of drug release [13].

The aim of the present investigation was to develop and evaluate an alternative, simple, orally applicable one pulse drug delivery system based on a press-coated tablet preparation. The PCT investigated in the current study consisting of a rapidly disintegrating core tablet presscoated by a barrier layer consisting of varying concentrations of Hydroxy propyl methyl cellulose (HPMC) and Ethylcellulose (EC). HPMC is a disintegrant and had been used to cause rapid disintegration of tablets. The other component of the barrier layer, Ethylcellulose (EC) is a well-known water-insoluble polymer that has long been used as a rate-controlling membrane in medication dosage forms to regulate drug release. Although EC has also been added in tablet formulations to act as a retarding material, few papers have focused on the use of EC as a directly compressible excipient. It was postulated that when the barrier layer was exposed to dissolution media, the HPMC particles swell and erode [14], a process which was retarded to varying degrees depending upon the quantity of EC present, demonstrating that manipulation of both components controls the erosion rate.

Materials and Methods

Table 1: List of chemicals

S.No	Name of chemicals	Source
1.	**Drug** Montelukast Sodium	Gift sample obtained from the Madras Pharmaceuticals Ltd, Chennai
	Polymer	
2.	HPMC K_4M	Drugs India, Hyderabad
3.	EC T10	Drugs India, Hyderabad
	Excipients	
4.	Lactose	Drugs India, Hyderabad
5.	Ac-di-sol	Drugs India, Hyderabad
6.	Primojel	Kawarlal & Co., Chennai
7.	Crospovidone	Ridesh Chemicals Pvt Ltd., Mumbai
8.	Magnesium Stearate	Harish Chemicals Pvt Ltd., Ahmadabad
9.	Colloidal sio_2	abot Sunmar Pvt Ltd., Naddoor

Preparation of core tablets by direct compression

The ingredients depicted in the table except colloidal silicon dioxide and magnesium stearate were dry blended for 15 minutes followed by addition of quitted ingredients and dry blended for another 5 minutes. The mixed blend of drug and excipients was compressed using a single punch CADMACH punching machine to produce round tablets weighing 100mg with a diameter of 6mm. A minimum of 50 tablets were prepared for each batch.

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Table 2: Formulation of the core tablet.

Ingredients (mg/100mg tab)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Montelukast sodium	10	10	10	10	10	10	10	**10**	10
Lactose monohydrate	83.6	81.1	78.6	83.6	81.1	78.6	83.6	**81.1**	78.6
Ac-di-sol	5	7.5	10	_	_	_	_	_	_
Primojel	_	_	_	5	7.5	10	_	_	_
Polyplasdone XL10	_	_	_	_	_	_	5	**7.5**	10
Colloidal SiO_2	0.4	0.4	0.4	0.4	0.4	0.4	0.4	**0.4**	0.41
Magnesium stearate	1	1	1	1	1	1	1	**1**	1

Preparation of press-coated tablets

The core tablets were press-coated with 400mg of prepared barrier blend as per the mentioned formulas from X1 to X5. 200mg of barrier layer material was weighed and transferred into a 13mm die then the core tablet was placed manually at the center. The remaining 200mg of the barrier layer material was added into the die and compressed.

Table 3: Formulation of Barrier layer (400mg) for press coated tablets.

Ingredients	Formulation (%W/W)				
	X1	X2	X3	X4	X5
EC T 10	100	87.5	0	50	25
HPMC K_{100} M	0	12.5	100	50	75

In vitro drug release study of core tablets

The in vitro release pattern of core tablets was studied as per method given by Chaudhari SP [15] Release pattern was studied visually by taking images of the core tablets in a petri plate containing dissolution medium at the specific time intervals 5sec, 10sec, 15sec. Also the sample was analyzed at 342nm using a UV spectrophotometer.

In vitro drug release study of press-coated tablets

In-vitro dissolution studies of press coated tablets were performed at 37 ± 0.5 °C using 0.5% w/v aqueous solution sodium lauryl sulfate in USP II paddle method at 50 rpm. 5 ml of filtered aliquot was manually withdrawn at pre-determined time intervals and replaced with 5 ml of fresh 0.5% sodium lauryl sulfate solution maintained at the same temperature. The samples were analysed at 342nm using a UV spectrophotometer. The lag time and percentage release was determined of the each formulation.

Results and Discussion

Design of Pulsatile release tablet

The pulsatile drug delivery system consisted of inner core tablet containing drug reservoir and outer coating layer with combination of water insoluble polymer Ethylcellulose and water soluble polymer HPMC. Ethyl cellulose was chosen because of its swelling and rupturable behavior. HPMC was chosen because of its eroding behavior.

In Vitro dissolution of core tablets

The core tablet shows 73.97 % of drug release within 9 minutes upon contact with dissolution medium, core tablet get erode and release the drug as given in Figure 1.

Analytical methods

From the standard stock solution (1000 µg/ml), appropriate aliquot were transferred to series of 10 ml volumetric flasks and made upto 10 ml with desired solvents so as to get concentration of 5,10,15,20… or 2,4,6,8… µg/ml. the absorbance of the solution were measured at 342 nm for Montelukast sodium. This procedure was performed in triplicate to validate calibration curve. A calibration curve was plotted.

Table 4: – Linearity values for Montelukast sodium

S.No	Concentration(µg/ml)	Absorbance (nm)
1	0	0
2	2	0.1706
3	4	0.3446
4	6	0.4886
5	8	0.6423
6	10	0.8206

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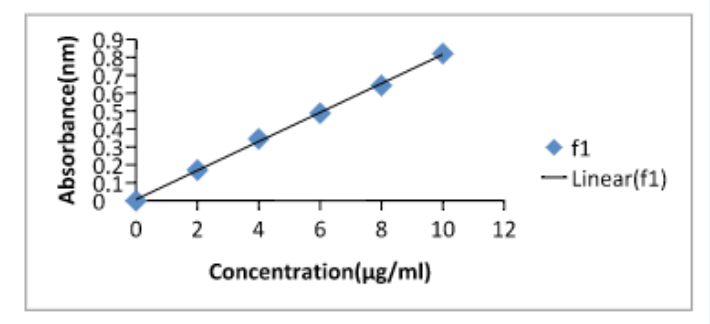

Figure 1: Standard plot of Montelukast sodium in 0.5% SLS at λ max 342 nm.

Compatibility Analysis

Fourier transform infra-red spectroscopy

FT-IR spectroscopy was employed to ascertain the compatibility of drugs with polymers. The individual drug and final formulation were scanned. Both the spectra were compared for confirmation of common peaks. Montelukast sodium with polymers showed no significant variation in height, intensity and position of peaks, suggesting that drug and excipients were compatible. There is no interaction between drug and polymer. Hence, it can be concluded that the drug is in Free State and can release easily from the formulation the spectra are reported in the Table no.6.3 and Figure 6.2-6.3.

Table 5: FTIR spectra data of Montelukast sodium and final formulation

	N-H	C-H	C=0	C-Cl
MONTEL pure drug	3442cm^{-1}	2929cm^{-1}	1715cm^{-1}	800cm^{-1}
Final formulation	3446cm^{-1}	2935cm^{-1}	1720cm^{-1}	746cm^{-1}

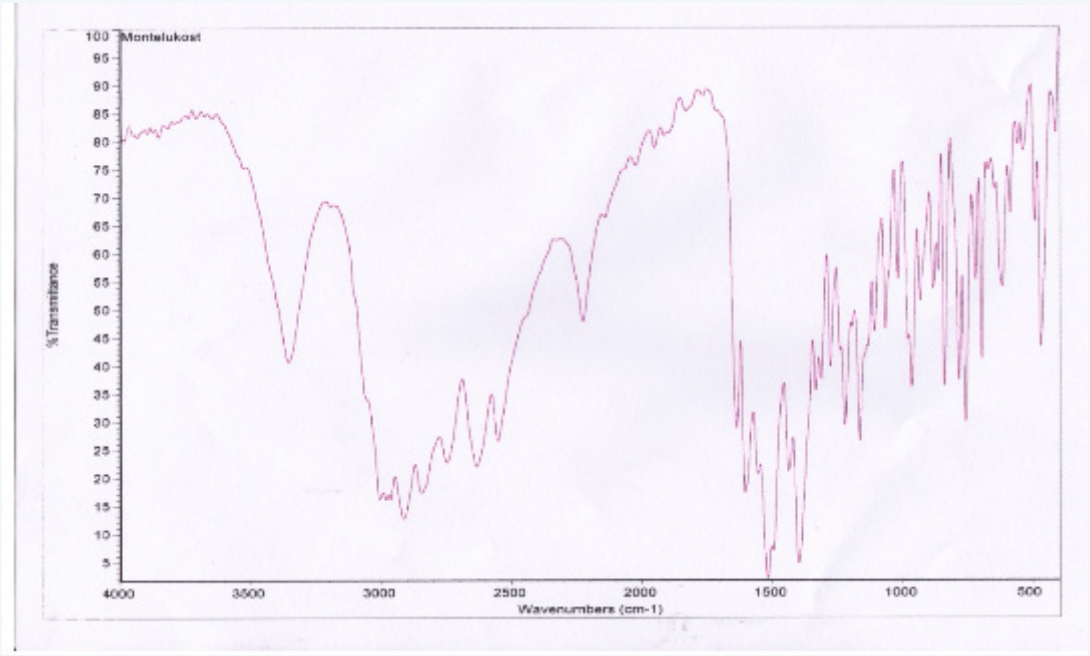

Figure 2: FTIR spectrum of Montelukast pure drug.

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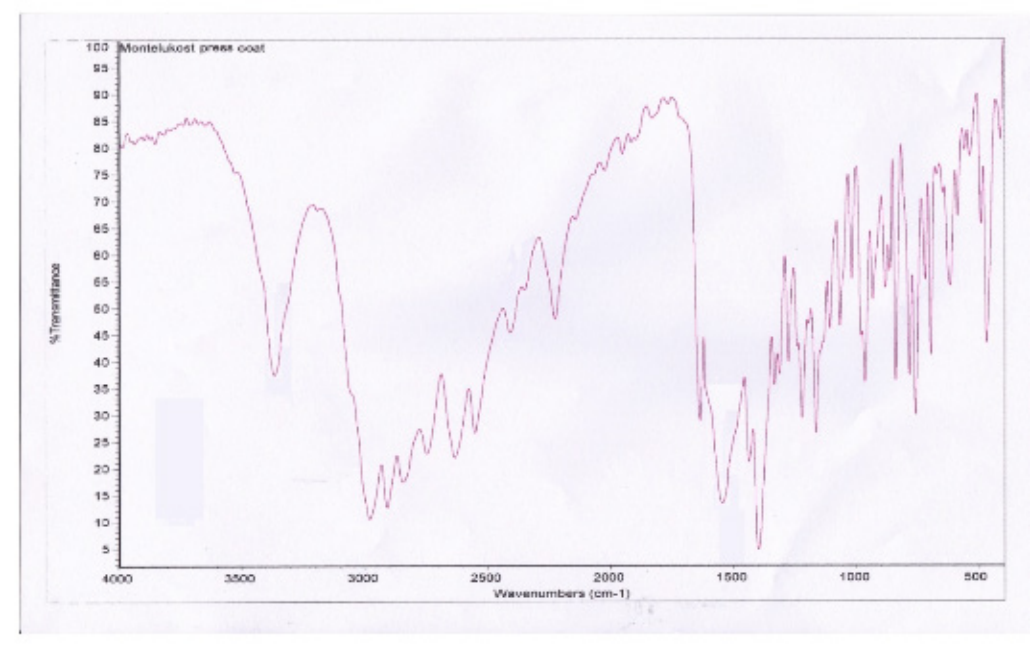

Figure 3: FTIR spectrum of Final formulation.

Table 6: Dissolution studies for core tablet.

	Cumulative % drug release								
Time (mins)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
3	31.27	34.22	29.32	30.34	32.43	35.55	37.33	39.65	33.26
6	54.31	49.34	52.64	54.51	47.54	56.41	53.24	60.24	50.75
9	65.67	56.55	65.09	63.11	59.43	63.62	66.68	73.97	62.75
12	79.33	68.05	81.87	87.13	75.32	70.22	78.65	87.47	73.97
15	88.11	79.66	92.68	93.14	91.25	89.72	94.43	98.96	86.26

Table 7: Correlation Coefficient r^2 Values of immediate release core tablets of Montelukast sodium formulated employing different Super disintegrants as per Zero Order and First Order Kinetics.

Formulation code	Correlation coefficient (r^2)			
	Zero order	First order	Higuchi	Peppas
F1	0.935	0.952	0.986	0.883
F2	0.975	0.936	0.983	0.882
F3	0.943	0.950	0.983	0.889
F4	0.832	0.952	0.897	0.861
F5	0.957	0.980	0.976	0.864
F6	0.841	0.969	0.954	0.865
F7	0.963	0.987	0.871	0.839
F8	0.856	0.999	0.964	0.816
F9	0.973	0.986	0.985	0.869

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Table 8: First order linear regression equations, rate of drug release of different formulations

Formulation Code	Zero order	First order
	K_0	K_1
F1	1.08	0.037
F2	1.38	0.032
F3	1.41	0.033
F4	1.30	0.038
F5	1.36	0.062
F6	1.13	0.043
F7	1.41	0.088
F8	1.90	0.138
F9	1.45	0.095

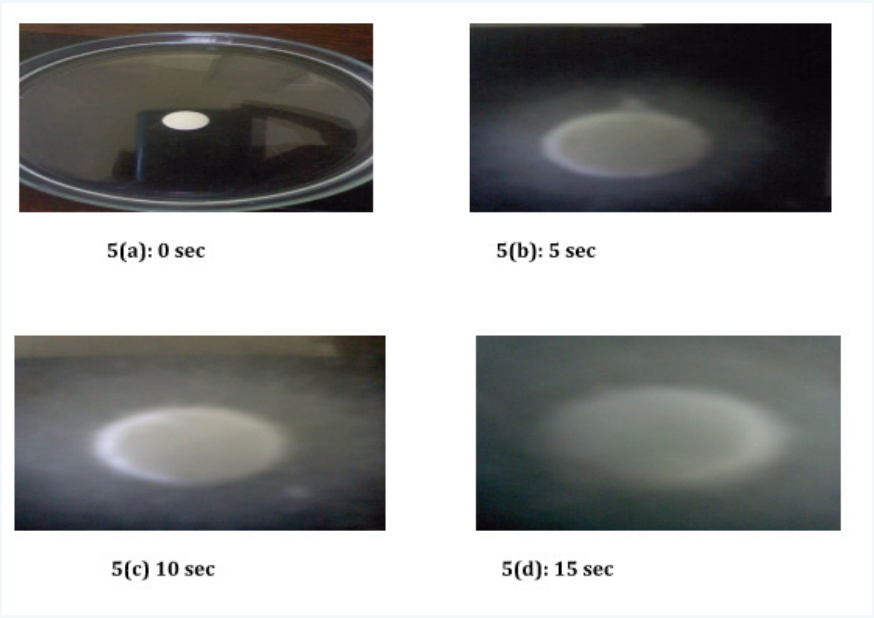

Figure 4: Wetting time of the optimized core tablet.

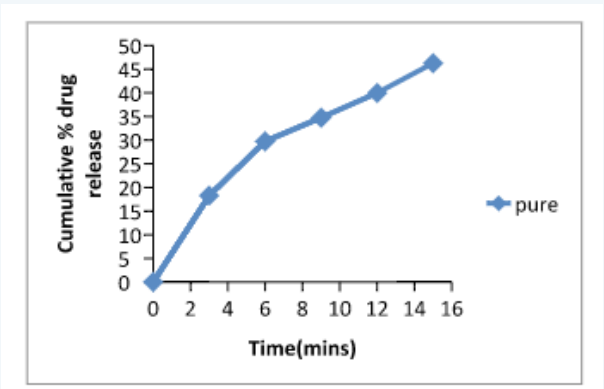

Figure 5: Plot of time vs cumulative % drug release of pure drug.

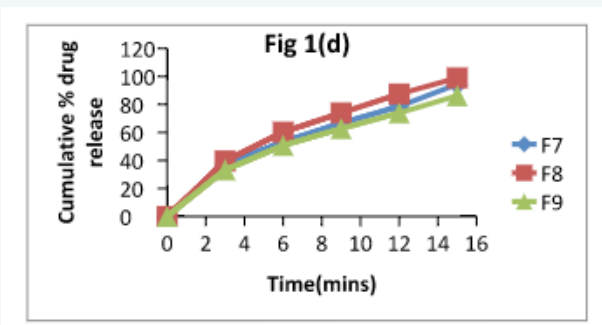

Figure 6: Plot of time vs cumulative % drug release of F7, F8, F9 formulations.

Based on the drug release within the required time period F8 was optimized and further formulated for press coating.

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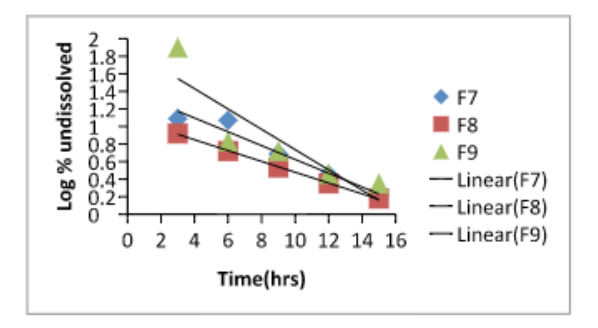

Figure 7: Plot of time vs log % undissolved of F7, F8, F9 formulations.

Table 9: Dissolution profile of Press coated tablets.

Time(hrs)	Cumulative % drug release				
	X1	X2	X3	X4	X5
0.5	_	_	_	_	_
1	_	_	2.74	_	_
1.5	_	_	79.7	_	_
2	_	_	82.3	4.8	_
2.5	_	_	84.1	42.6	_
3	_	_	86.1	71.6	3.58
3.5	_	_	86.8	75.3	47.11
4	_	6.33	89.3	78.4	68.86
4.5	_	83.57	91.1	80.5	74.9
5	4.09	98.63	92.4	82.6	79.5
5.5	36.44	98.95	92.6	86.4	85.3
6	76.17	_	93.9	89.1	90.7

Table 10: Correlation coefficient (r2) values in the analysis of release data of Montelukast sodium Press coated tablets as per various kinetic models.

Formulation Code	Correlation coefficient (r^2)				
	Zero order	First order	Higuchi	Peppes	n value of peppas
F1	0.870	0.782	0.684	0.856	0.641
F2	0.839	0.991	0.626	0.740	0.740
F3	0.949	0.822	0.843	0.895	0.895
F4	0.976	0.826	0.829	0.864	0.864
F5	0.874	0.893	0.672	0.672	0.731

Table 11: First order linear regression equations, rate of drug release of different formulations of Montelukast sodium press coated tablets.

Formulation code	Zero order	First order
	K_0	K_1
X1	0.138	0.010
X2	0.202	0.034
X3	0.224	0.013
X4	0.220	0.030
X5	0.130	0.014

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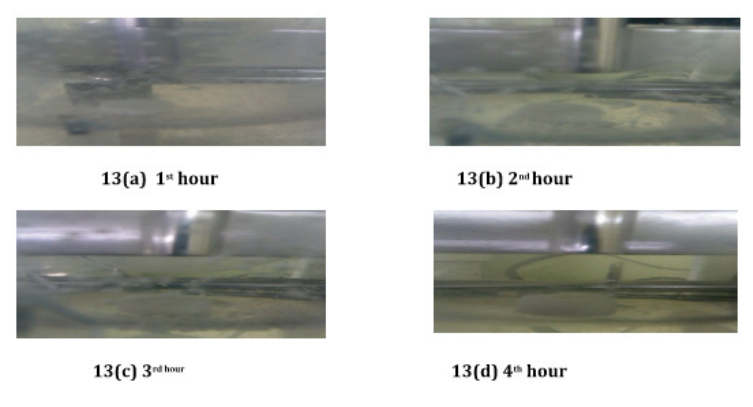

Figure 8: Optimized press coated tablet showing drug release after lag time.

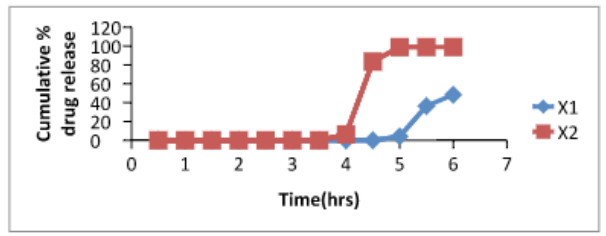

Figure 9: Plot of time vs cumulative % drug release of X1, X2 formulations.

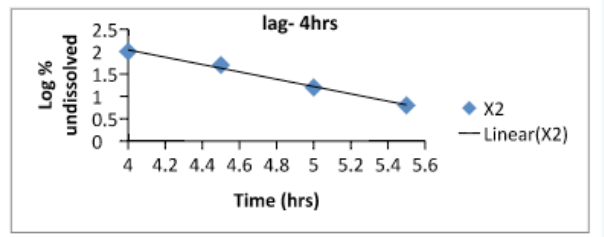

Figure 10: Plot of time vs log % undissolved of the optimized X2 formulation.

Conclusion

In the 5 trials, the optimized formulation was X2 trial which releases the Montelukast sodium immediately after a lag time. The core was compared with the pure drug where it showed 46.26 % of drug release in 15 minutes whereas core exhibited 98.96% in 15 minutes.

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