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Chronomodulated drug delivery system of Montelukast sodium

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ABSTRACT

Many drugs have disadvantages like first pass metabolism, peak and valley absorptions at different absorption sites and drug instability problems. Pulsatile drug delivery systems (PDDS) are gaining interest as they can curtail most of the above mentioned disadvantages. Besides that, we can deliver the drug based on time dependent or site dependent theories as per requirement of the therapy. We can also treat those diseases which show dependency on chronopharmacology. Nocturnal asthma (NA) is one of such diseases that follow circadian rhythms where increasing of air way resistance and worsening of lung function is observed during the early morning time. So, in this research work we have done formulation and evaluation of simple orally applicable one pulse drug delivery system based on press coated tablet preparation taking Montelukast sodium as our drug molecule which have certain disadvantages like first pass metabolism and differences in absorption at different sites. This helps in obtaining worthy effects in treating NA as well as to curtail extensive first pass metabolism of the drug. Here first we have prepared (F1-F9) core tablet formulations. We have selected primojel, Ac-di-sol and polyplasdoneXL10 as swelling polymers in the core tablet composition and we have optimized F8 formulation with 7.5% polyplasdoneXL10 as the best immediate release core tablet. It accommodates a helping hand in obtaining burst release of the drug. The lag time was maintained by press coating the core tablets with barrier layer. Among the different barrier compositions from(X1-X12), X12 was found to show single pulse drug delivery with considerable drug release for 2 hrs after maintaining the pre expected 5 ½ hrs lag time.

Keywords: Pulsatile drug delivery systems (PDDS), Nocturnal asthma (NA), Chronopharmacology, Circadian rhythms, Burst release, Lag time.

INTRODUCTION

Montelukast sodium is chemically designated as [R-(E)]-1-[[[1-[3-[2-(7-chloro-2-quinolinyl) ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl) phenyl] propyl] thio] methyl] cyclopropaneacetic acid, monosodium salt, an orally administered drug of choice in the treatment of asthma in adults and children [1]. It is a potent, selective and orally acting leukotriene receptor antagonist used in the prophylaxis and treatment of asthma by inhibiting physiological actions of the cysteinyl leukotrienes (LTC4, LTD4and LTE4) [2, 3].But it has certain disadvantages like first pass metabolism, peak and valley absorptions at different absorption sites and drug instability problems. PDDS can curtail most of the above mentioned disadvantages.

We can also treat those diseases which show dependency on chronopharmacology [4, 5]. The diseases that can be justified by the PDDS include Asthma, Allergic rhinitis, Rheumatoid arthritis, Osteoarthritis, ulcers, myocardial infraction, hypercholesrolemia etc. Nocturnal asthma (NA) is one of the diseases that follow circadian rhythms where increasing of air way resistance and worsening of lung function is observed during the early morning time. A reduction in FEV1 that is forced expiratory volume in one second is found to be low during the late hours in patients with NA. So, by the application of PDDS [6] we can obtain worthy effects in treating NA.

We have selected single pulse system because of the advantage of ease of manufacturing as well as lacking further pan coating processes. Reason to select press coated technique [7] is it protects hygroscopic (one of the instability of Montelukast sodium), light sensitive oxygen liable drugs most effectively compared to the regular and pan coated techniques. But the disadvantage with these press coated technique is positioning of the core tablet exactly at the centre of the press coated layers which is a great challenge.

MATERIALS AND METHODS

Materials:
Montelukast sodium (obtained as gift sample from Cadila pharmaceuticals limited, Dholka, Ahmedabad) Pearlitol SD200, Polyplasdone XL10, Ac-Di-Sol, Primojel, colloidal silicon dioxide, Magnesium stearate, Ferric oxide (Red), Xanthan gum, Ethyl cellulose T10 (EC T10), Tamarind seed polysaccharide (TSP) used were of Pharmacopoeial grade.

Methods:
We have performed dissolution studies of pure drug in water with 0.5%SLS and the results reviled that the drug release was 92% for 60minutes and it is not sufficient to get the immediate release of the drug from the press coated tablet as the viscosities of the polymers that we have selected as the outer barrier layer were very high. So, in order to avoid the delay in the release of the drug after the lag time that is to get the drug release immediately, we decided to prepare immediate release cores which will help in burst release of the drug due to pressure by the disintegrants. So we have selected three disintegrants which have swelling property which in turn results in appliance of more pressure on the outer barrier layer of the press coated tablet and finally we optimized one formula as the core tablet.

Compatibility analysis:
All the exciepients used in different formulations were mixed with the drug separately in equal ratios and the samples of the final formula of the press coated tablet were analyzed through FT-IR and DSC studies and the graphs were shown under the **Blocks (A) and (B)** respectively.

(a) Fourier Transform Infra-red Spectroscopy (FTIR):
All the excipients used in different formulations were mixed with the drug separately in equal ratios and the samples of the final formula of the press coated tablet were analyzed through FT-IR and DSC studies. FT-IR spectra (400-4400cm^{-1}) were obtained on a Perkin-Elmer FT-IR spectrophotometer with a resolution of 4 cm^{-1} KBR pellets were prepared gently by mixing the 1 mg sample with 100 mg potassium bromide. The characteristic peaks were recorded.

(b) Differential Scanning Calorimeter (DSC):
Differential scanning calorimetry study was performed using Differential Scanning Calorimeter (DSC Q20, V24.2 Build 107). Samples were heated in an open aluminum pans at a rate of 10°C permin−1 under a nitrogen flow of 50 mL/min.

Preparation of mixed blend of drug and excipients of the immediate release core tablet:
All the ingredients were passed through mesh No.60. Required quantity of each ingredient was taken from each specified formulations that is from F1 to F9 as depicted in the **Table 1** and all the ingredients were dry blended. The powder blend was evaluated for flow properties like Angle of Repose, Bulk density, Tapped density, Compressibility index, and Haussner's ratio.

Table 1: Manufacturing formula of the core tablet

Ingredients(mg/100mg tab)	**F1**	**F 2**	**F 3**	**F 4**	**F5**	**F6**	**F7**	**F 8**	**F 9**
Montelukast sodium eq.to Montelukast	10.4	10.4	10.4	10.4	10.4	10.4	10.4	10.4	10.4
Lactose anhydrous (Super Tab 21AN)	82.95	80.45	77.95	82.95	80.45	77.95	82.95	80.45	77.95
Primojel	5	7.5	10	_	_	_	_	_	_
Ac-di-Sol	_	_	_	5	7.5	10	_	_	_
PolyplasdoneXL10	_	_	_	_	_	_	5	7.5	10
Colloidal silicon dioxide	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
Magnesium Stearate	1	1	1	1	1	1	1	1	1
Ferric oxide (Red)	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25

Formulation of core tablets by direct compression:
The ingredients depicted in **Table 1** except colloidal silicon dioxide and Magnesium stearate were dry blended for 15minutes followed by addition of quitted ingredients and dry blending for another 5minutes.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.

Evaluation of the immediate release core tablets:
All the prepared tablets were evaluated for Average weight, hardness, friability, drug content, invitro disintegration time, wetting time and invitro dissolution.

Dissolution rate studies:
Dissolution rate studies of Montelukast sodium from all formulations was performed using LABINDIA DISSO 2000 an eight stage dissolution rate testing apparatus with paddle. The dissolution fluid was 900ml of Distilled water with 0.5% SLS. The test was performed at a speed of 50rpm and at a temperature of 37±0.5°C. Samples of dissolution medium (5ml) were withdrawn through a filter of 0.45µm at different time intervals, suitably diluted and assayed for Montelukast sodium by measuring absorbance at 346 nm. The dissolution experiments were conducted in triplicate.

Formulation of mixed blend for barrier layer:
All the ingredients were passed through mesh No.60. Required quantity of each ingredient was taken from each specified formulations of the barrier layer that is from X1 to X12 as depicted in the **Table 2** and all the ingredients were dry blended. The blends were evaluated for flow properties like Angle of Repose, Bulk density, Tapped density, Compressibility index, and Haussner's ratio.

Table 2: Manufacturing formula of Barrier layer (300mg) for press coated tablets

Ingredient	Formulation (%W/W)											
	X1	X2	X3	X4	X5	X6	X7	X8	X9	X10	X11	X12
Xanthan gum	100	70	60	50	40	20	10	15	12.5	10	7.5	5
EC T10	-	30	40	50	25	15	5	15	15	15	15	15
Mannitol	-	-	-	-	35	65	85	65	65	65	65	65
TSP	-	-	-	-	-	-	-	5	7.5	10	12.5	15

Preparation of press-coated tablets:
The core tablets were press-coated with 300mg of prepared barrier blend as per the mentioned formulas from X1 to X12. 150mg of barrier layer material was weighed and transferred into a 13mm die then the core tablet was placed manually at the center. The remaining 150mg of the barrier layer material was added into the die and compressed at a pressure of 5 tons for 3min using KBr hydraulic press.

Evaluation of press-coated tablets:
All the prepared tablets were evaluated for Average weight, hardness, friability and swelling index**.**

Swelling index:
The tablets were weighed and placed in metallic baskets. These were immersed in 900ml of medium using USP basket method rotated at 50rpm.At specified time intervals, remove the tablets and lightly bottled with tissue paper to remove excess water and weighed.

$$\text{Swelling index (\%)} = [Ws\text{-}Wd / Wd]\ 100,$$

where Ws is weight of swollen tablet at time‘t’ and Wd is the weight of dry tablet.

Dissolution rate studies:
Dissolution rate studies were performed for all the press coated tablets using LABINDIA DISSO 2000 an eight stage dissolution rate testing apparatus with paddle. The dissolution fluid was 900ml of Distilled water with 0.5% SLS. The test was performed at a speed of 50rpm and at a temperature of 37±0.5°C. Samples were with drawn for every hour up to 15 hours and the lag times were observed for every batch tablet and the collected samples were analyzed for the drug released spectroscopically at 346nm in order to know whether the formulations show sigmoidal release.

RESULTS AND DISCUSSION

Compatibility analysis:
Fourier transform infra-red spectroscopy:
The FTIR spectrum of Montelukast exhibited peak at 3366.88cm^{-1} due to N-H stretching and at 2923.68 cm^{-1} due to alkane saturated peak. The FTIR spectrum of Montelukast with primojel has shown peaks at 3378.9 cm^{-1}and 2925.61 cm^{-1} where as drug with Ac-di-sol has shown at 3389.7 cm^{-1}and 2923.4 cm^{-1}and drug with Poly plasdone XL10 has shown peaks at 3379.72 cm^{-1}and 2924.17 cm^{-1}.The FTIR spectrums of individual drug and drug with primojel, Ac-di-sol, Poly plasdone XL10 as well as final formula of press coated tablet were shown in **Fig (a), (b), (c), (d)** and **(e)** of the **Block (A).**

Block (A): Fourier Transform Infra-red spectrums

Figure (a): FTIR of Pure drug

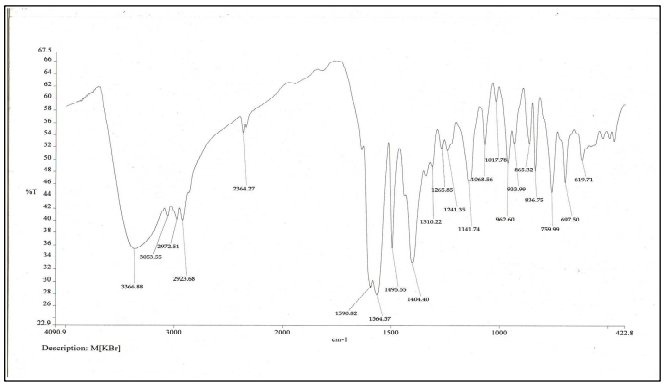


Figure (d): FTIR of Drug + Poly plasdone

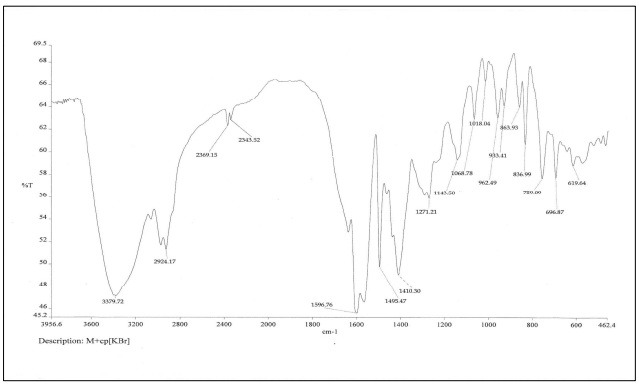


Figure (b): FTIR of Drug + primojel

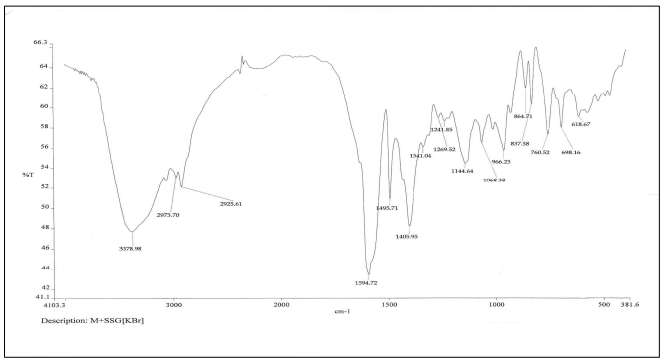


Figure (e): FTIR of Final formula

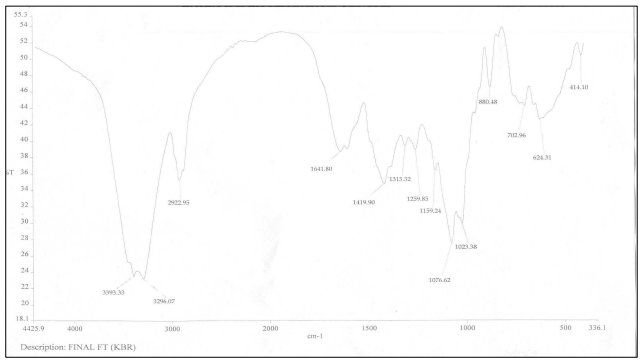
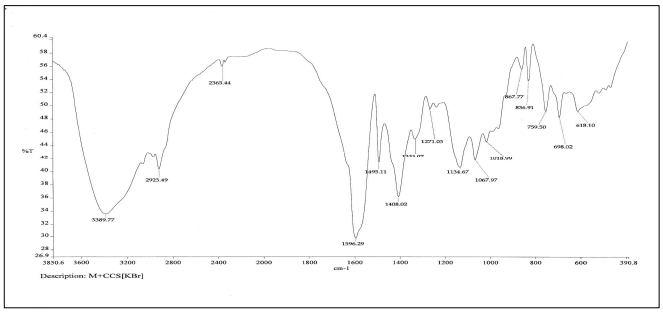


Figure (c): Drug + Ac-di-sol



Differential scanning calorimetry:

The DSC thermogram of Montelukast exhibited an endothermic peak at 69.81^{0}c corresponding to its melting point. The DSC thermograms of Montelukast with other exciepients doesnot show profound shift in peaks which indicates compatibility. The DSC thermograms of the individual drug and drug with lactose, mannitol, Poly plasdone XL10 as well as final formula were shown in **Fig (f), (g), (h), (i)** and **(j)** of the **Block (B).**

Block (B): DSC Thermo grams

Figure (f): DSC of Pure drug

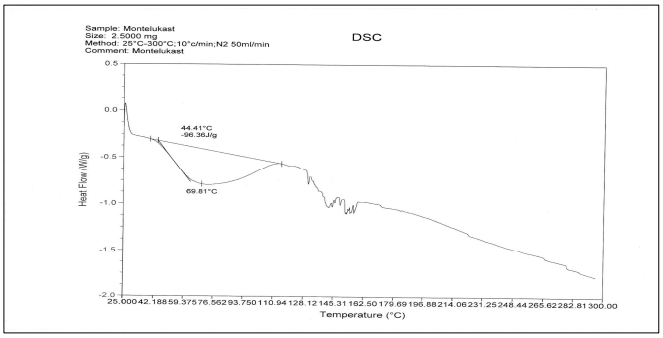


Figure (i): DSC of Drug + Ploy plasdone

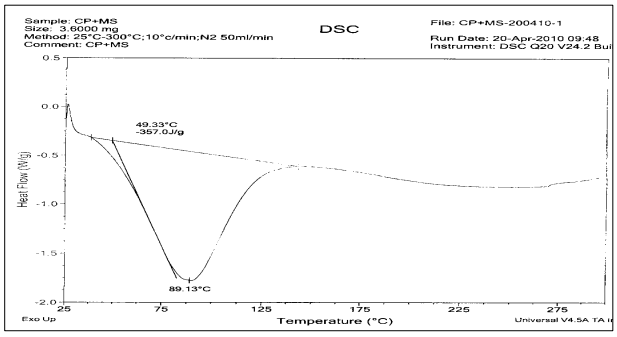


Figure (g): DSC of Drug + Lactose

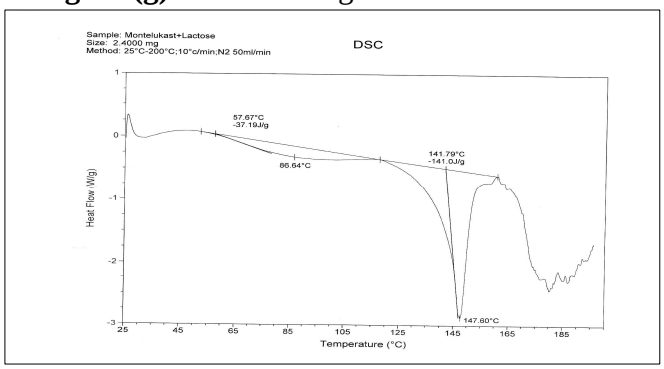


Figure (j): DSC of Final formula

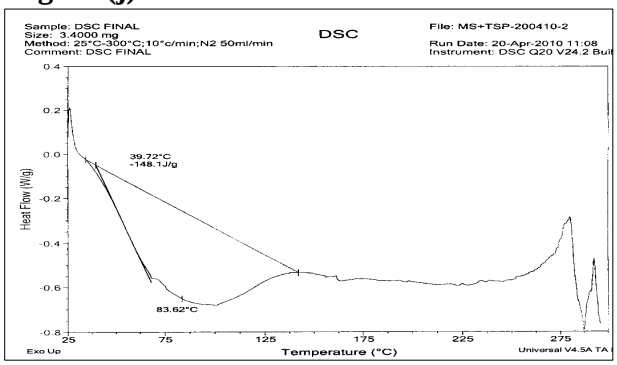
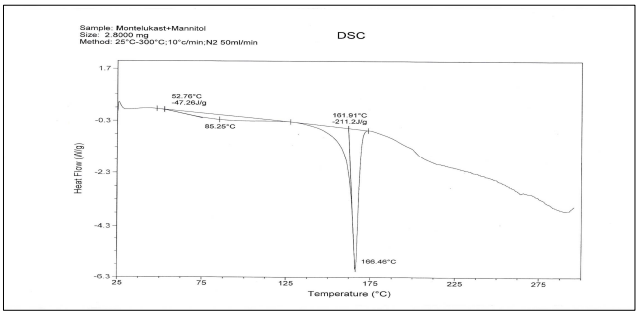


Figure (h): DSC of Drug + Mannitol



Evaluation of blends and tablets of immediate release cores:
The blends of all the formulations of the core tablet were evaluated for flow properties and were found that the flow property of the prepared powder blends was good and the results were given in the **Table 3**.Then the prepared core tablets were evaluated, and were found to exhibit satisfactory tablet characteristics as discussed in **Table 4**.The drug content of all the formulations was found to be existed between 90 and 100% and formulation **F8** was found to be with in the USP limits as per the drug content. The invitro disintegration time and wetting time were found to be very less for **F8** formulation that is 11minutes and 15minutes respectively and this batch tablets have also shown better dissolution profile when compared to remaining formulations as well as pure drug. The results of the dissolution profiles of all the formulations were represented graphically in **Figure 1**. The wetting time figures of the optimized core tablet were given in **Figure 3**.

The dissolution parameters of all batch formulations (F1-F9) calculated was shown in the **Table 5.** The T_{90}, DP_5 and DE_5 were found to be 10mins, 80% and 68.6% respectively for the formulation F8. For the remaining formulations it was found that the T_{90} values were high and DP_5 and DE_5 values were low when compared to the optimized formula that is **F8**. The Correlation Coefficient(R) Values of all formulations (F1-F9) were shown in the **Table 6** and from the (R) values it was found that the immediate release core tablets have followed the first order kinetics. The first order plots of the core tablets were given in the **Figure 6**.

Table 3: Evaluation of directly compressible blends of core tablet

Parameter	F1	F 2	F 3	F 4	F5	F6	F7	F 8	F 9
Angle of repose(◦)	32	29	33	32	30	31	34	33	34
Bulk density(gm/cm^3)	0.54	0.58	0.54	0.58	0.55	0.53	0.59	0.57	0.58
Tapped density(gm/cm^3)	0.63	0.71	0.66	0.67	0.69	0.65	0.73	0.67	0.68
% Compressibility	13	18	14	12	18	11	19	14	17
Haussner's ratio	1.16	1.21	1.20	1.13	1.17	1.15	1.22	1.18	1.19
Flow ability	Good	Good	Good	Good	Good	Good	Good	Good	Good

Table 4: Evaluation of Formulations of core tablet

Parameter	F1	F 2	F3	F 4	F 5	F6	F 7	F8	F 9
Average weight(mg)±S.D	99.8±0.2	99.1±0.51	99.8±0.2	99.5±0.26	99.1±0.26	99.1±0.51	99.16±0.5	99.56±0.25	99.15±0.5
Hardness(kg/cm^2) ±S.D	3±0.12	3.5±0.34	3.5±0.34	3±0.22	3±0.25	3±0.25	3±0.32	3.5±0.32	3±0.31
Friability (%)	0.19	0.21	0.18	0.17	0.20	0.19	0.18	0.16	0.16
InvitroDisintegration time(sec)	21	19	20	18	17	18	14	11	15
Drug content (%)	92	93	90	92	93	91	93	99	94
Wetting time(sec)	22	21	22	19	18	20	19	15	17
Drug dissolved in 10min (%)	59	61	60	62	65	65	79	91.3	90.3

Table 5: Dissolution parameters of the core tablet

Parameter	F1	F 2	F3	F 4	F 5	F6	F 7	F8	F 9
T_{90} (min)	25	20	20	18	15	16	15	10	10
DP5 (%)	65	70	68	72	77	73	75	80	77
DE5 (%)	56.1	59.8	60.4	61.2	65.5	63.3	64.3	68.6	66.1

Table 6: Correlation Coefficient(R) Values of immediate release core tablets of Montelukast sodium formulated employing different Super disintegrants as per Zero Order and First Order Kinetics.

Parameter		F 1	F 2	F 3	F 4	F 5	F 6	F 7	F8	F 9
Zero order	r^2	0.9354	0.9757	0.9615	0.9362	0.9828	0.9779	0.9857	0.9891	0.9875
	k_0(µg/ml/hr)	1.08	1.07	1.1	1.13	1.45	1.09	2.01	2.21	1.90
First order	r^2	0.9447	0.9762	0.9719	0.951	0.985	0.978	0.986	0.9907	0.9876
	K_1(min^{-1})	0.037	0.032	0.033	0.038	0.062	0.04	0.088	0.13	0.095

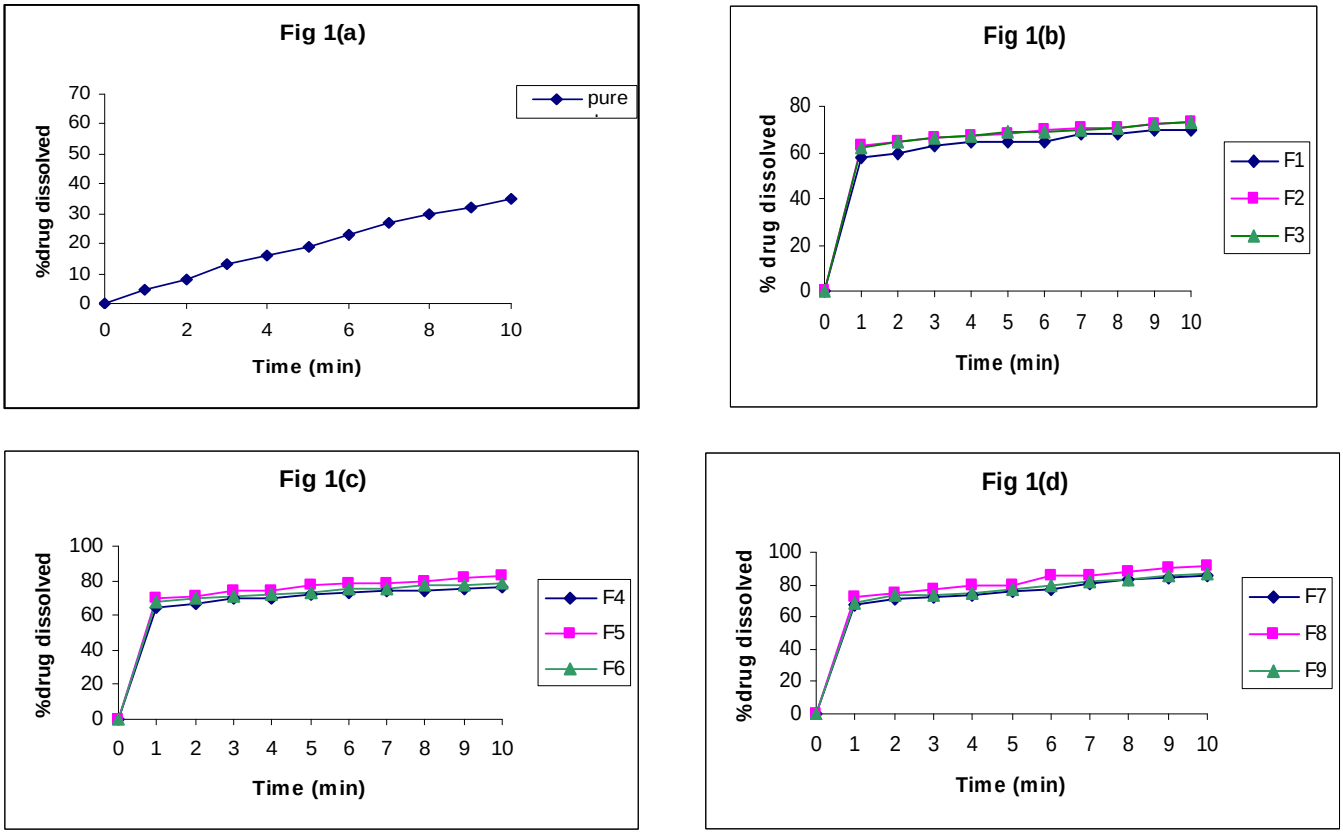
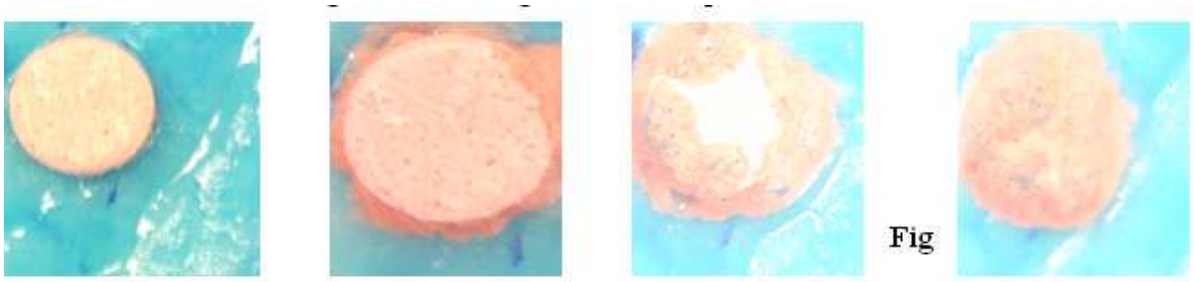


Figure 1: Dissolution profiles of all the core tablet formulations:

Fig 1(a): Dissolution profile of pure drug.
Fig 1(b): Dissolution profiles of F1, F2 and F3 formulations.
Fig 1(c): Dissolution profiles of F4, F5 and F6 formulations.
Fig 1(d): Dissolution profiles of F7, F8 and F9 formulations

Figure 3: Wetting time of the optimized core tablet



3(a):0 sec Fig 3(b): 5sec Fig 3(c): 10sec Fig 3(d): 15sec

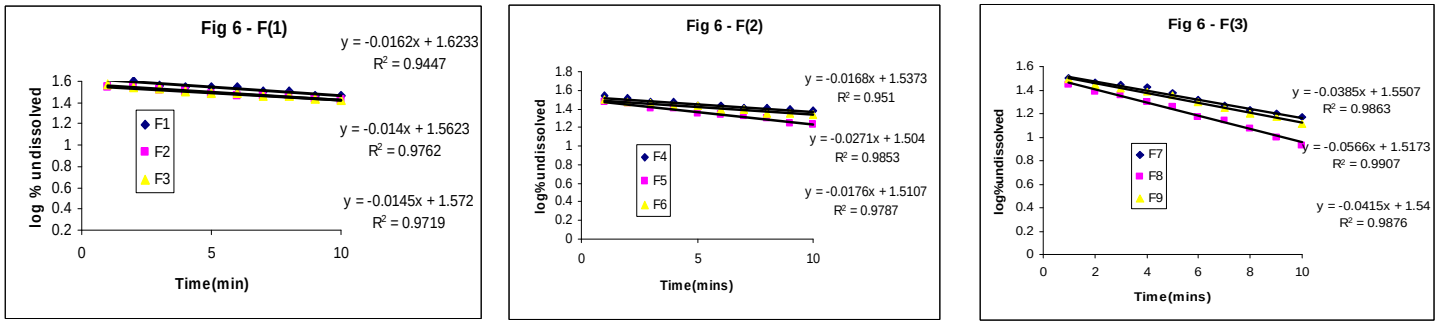


Figure 6: First order plots of all the core tablet formulations

Fig 6 - F (1): First order plots of F1, F2 and F3 formulations.
Fig 6 - F (2): First order plots of F4, F5 and F6 formulations.
Fig 6 - F (3): First order plots of F7, F8 and F9 formulations.

Evaluation of blends and tablets of press-coated formulations:

The blends of all the press coated barriers of all the formulations (X1-X12) depicted in **Table 2** were evaluated for flow properties and were found that the flow property of the prepared barrier layer blends of X1 and X2 were fair where as the flow ability of the remaining blends was good and the results were given in the **Table 7.** Then the prepared press coated tablets were evaluated, and were found to exhibit satisfactory tablet characteristics as discussed in **Table 8.** The water uptake was found to be optimum and the rupturing property was found to be good for the formulation **X12 and** this **X12** batch was found to maintain the predetermined lag time that is **5 ½ hrs** where as remaining formulations have shown lag times of more than 6hrs. The results of the dissolution profiles of all the formulations (X1-X12) were represented graphically in **Figure 2**. The wetting time figures of the optimized Press coated tablet were given in **Figure 4**. The Swelling index and the figures showing the lag times of the optimized Press coated tablet were given in the **Figures 5 and 5**[1] respectively. The kinetic parameters and the lag times of all batch formulations (X1-X12) calculated were shown in the **Table 9** and from the (R) values it was found that the drug release was following the first order kinetics after their maintained corresponding lag times. The first order plots of the finalized Press coated tablet was given in the **Figure 7**.

Table 7: Evaluation of directly compressible blends of barrier layer

Parameter	**X1**	**X 2**	**X 3**	**X 4**	**X5**	**X6**	**X7**	**X 8**	**X9**	**X10**	**X11**	**X 12**
Angle of repose(◦)	38	37	33	32	30	31	34	33	32	32	33	34
Bulk density(gm/cm^3)	0.50	0.52	0.54	0.58	0.56	0.56	0.57	0.55	0.55	0.54	0.53	0.54
Tapped density(gm/cm^3)	0.60	0.61	0.62	0.65	0.65	0.64	0.67	0.64	0.63	0.62	0.62	0.63
% Compressibility	18	16	14	12	13	12	14	14	15	15	14	15
Haussner's ratio	1.21	1.19	1.15	1.13	1.17	1.15	1.18	1.18	1.15	1.16	1.17	1.17
Flow ability	Fair	Fair	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good

Table 8: Evaluation of press coated tablets

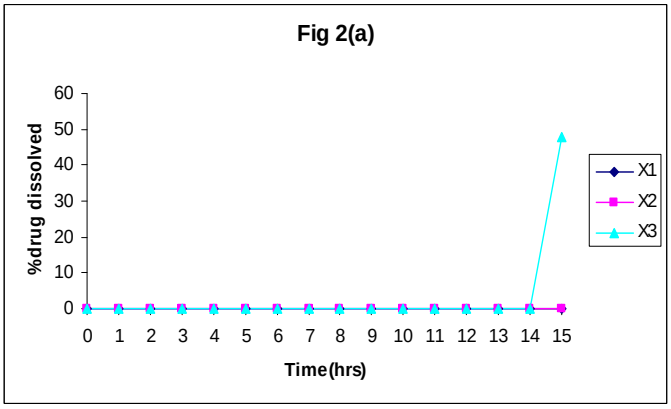
Parameter	X1	X 2	X3	X 4	X 5	X6	X 7	X8	X9	X10	X11	X12
Average weight(mg)±S.D	399.8 ±0.21	399.1 ±0.32	399.8 ±0.21	399.5 ±0.23	399.1 ±0.33	399.1 ±0.32	399.16 ±0.31	399.56 ±0.22	399.16 ±0.33	399.4 ±0.24	399.1 ±0.34	399.8 ±0.21
Hardness(kg/cm^2) ±S.D	5±0.12	5±0.34	5±0.34	5±0.22	5±0.26	5±0.25	5±0.32	5±0.32	5±0.34	5±0.34	5±0.26	5±0.26
Friability (%)	0.21	0. 11	0.11	0.14	0.12	0.13	0.10	0.10	0.11	0.12	0.16	0.12
Swelling index (%)	3.2	3.3	3.5	3.3	3.7	3.8	5.2	4.2	4.3	4.6	4.7	4.8

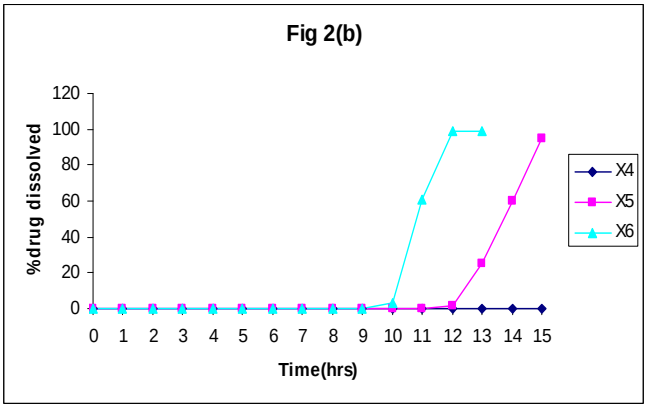
Table 9: In-vitro release kinetic parameters for press coated tablets

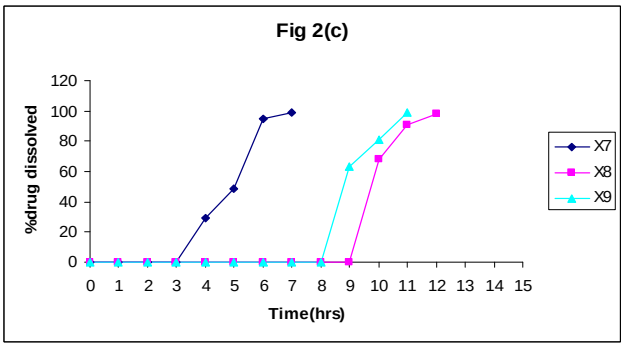
Formulation code	Lag time (hrs)	Zero - order model		First-Order Model	
		r^2	k_0	r^2	k_1
X1	>15	NA	NA	NA	NA
X2	>15	NA	NA	NA	NA
X3	14	NA	NA	NA	NA
X4	>15	NA	NA	NA	NA
X5	12	0.8973	0.530	0.8990	0.010
X6	10	0.9044	0.420	0.9601	0.011
X7	<5	0.9343	0.801	0.9503	0.030
X8	9	0.9045	0.471	0.9847	0.013
X9	8 ½	0.9117	0.480	0.9861	0.014
X10	8	0.9164	0.470	0.9880	0.014
X11	7	0.9226	0.930	0.9899	0.032
X12	5 ½	0.9361	0.931	0.9948	0.034

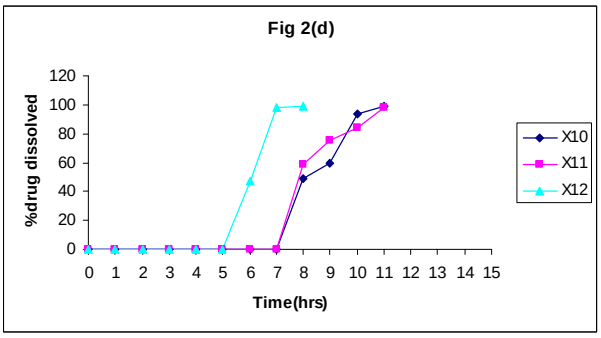
Figure 2: Dissolution profiles of all the core tablet formulations:

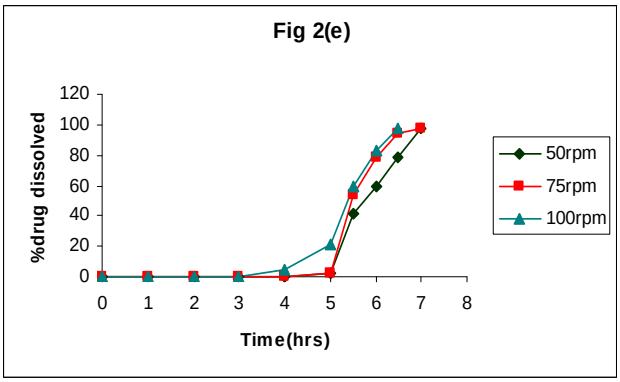
Fig 2(a): Dissolution profiles of X1, X2 and X3 formulations.
Fig 2(b): Dissolution profiles of X4, X5 and X6 formulations.
Fig 2(c): Dissolution profiles of X7, X8 and X9 formulations.
Fig 2(d): Dissolution profiles of X10, X11 and X12 formulations.
Fig 2(e): Dissolution profile of X12 formulation at different RPM's.
Fig 2(f): Dissolution profile of X12 formulation in different dissolution mediums.











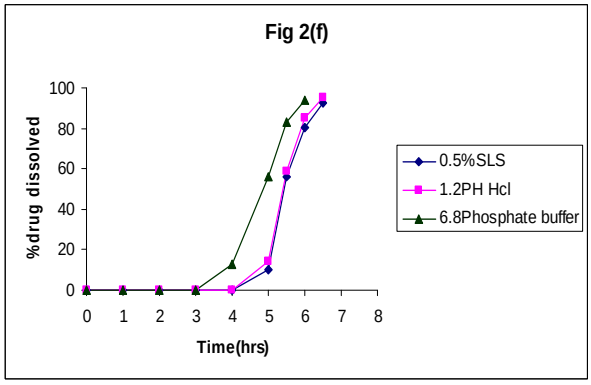


Figure 4: Wetting time of the optimized press coated tablet

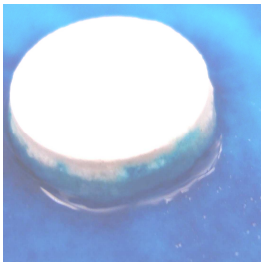


Fig 4(a):20min

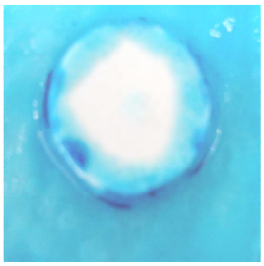


Fig 4(b):40min

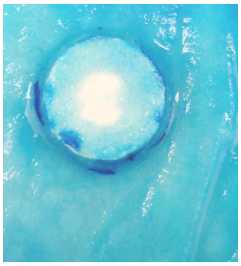
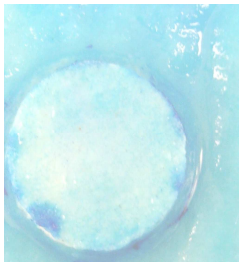


Fig 4(c):60min



Fig(d):80min

Figure 5: Swelling index of the optimized press coated tablet

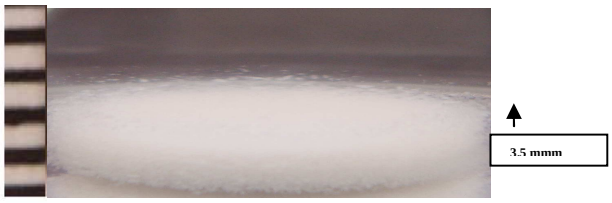


Fig 5(a): 1st hour

Fig 5(b): 2nd hour

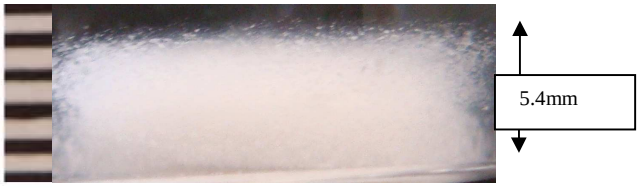


Figure 5[1]: optimized Press coated tablet showing drug release after lag time

Fig 5[1] (a): 1 ½hr

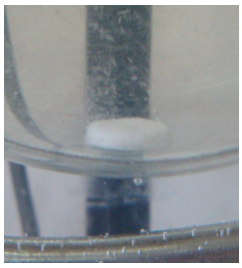


Fig 5[1] (b): 2 ½hr

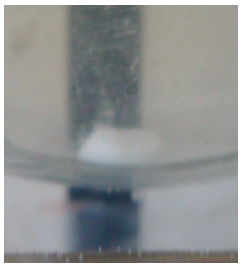


Fig 5[1] (c): 3 ½hr

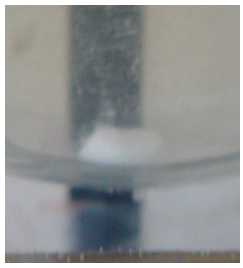
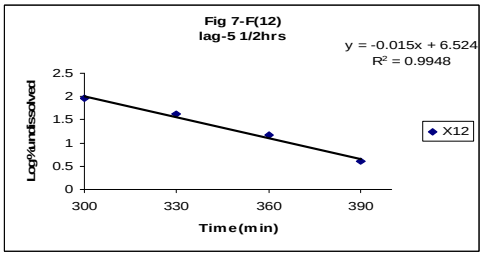


Fig 5[1] (d): 4 ½hr

Fig 5[1] (e):5 ½hr

Figure 7: First order plots of finalized press coated tablet.

Figures 7 - F (12) are First order plots of X12 formulation.



In the case of formulation **X1**, where only Xanthan gum was used as a barrier layer the lag time of more than **15hrs** was maintained when dissolution was performed at 50 rpm. But on increasing the rpm inspite of high viscosity and better cross linking property of Xanthan gum [8,9,10] it was certainly ruptured with in no time after its exhaustive swelling time of 3hrs.In the next three formulations that are **X2, X3** and **X4** we have added different percentages (30%, 40% and 50%) of EC T10 which has certain plastic deformation property made the formulations uninterrupted by the increased rpm's and have shown resolution. But the lag times were beyond the expected ones with these three formulations. Amongst **X3** where 40% of EC T10 was added with a simultaneous decrease in the amount of Xanthan gum has shown some what less lag time that is **14hrs** compared to fore formulations. This shows that the more the amount of the Xanthan gum, the lower the porosity. So, in order to decrease the lag times we have chosen Mannitol as a pore former and we have added different percentages like 35%, 65% and 85% in formulations **X5, X6** and **X7** respectively. We also proceeded with simultaneous decrease in Xanthan in each formulation. Amongst **X6** has shown appropriate lag time of **10hrs** where as X7 with more percentage of mannitol falls below the expected lag. In such wise, we have optimized 65% of mannitol and kept it constant through out later formulations.

In the next formulations we have tried addition of TSP which has some erosion property. By varying the ratios of Xanthan and TSP keeping the EC T10 and Mannitol in constant percentages we found a decrease in the lag times. Final formula that is **X12** with 5%Xanthan, 15%TSP,15%EC T10 and 65%Mannitol has shown considerable drug release for **2hrs** after maintaining the expected **5 ½ hrs** lag time. It was also found that the finalized formula had shown almost same lag time even the invitro dissolution rpm is increased.

CONCLUSION

Here we have optimized **X12** formulation by taking all the parameters observed in to consideration and it was found that **X12** had shown considerable drug release for 2hrs after maintaining the 5 ½ hrs lag time and it was found to be successful in achieving pulsatile drug delivery. By this work we would like to conclude that inspite of high viscosity and better cross linking property of Xanthan gum it can be certainly ruptured at high RPM with in no time after its exhaustive swelling time of 3hrs during invitro dissolution. The addition of EC T10 made it possible to come up the situation of easy rupturing at high pressures where as the addition of mannitol contrives in decreasing lag time and TSP assisted mannitol in decreasing further lag time since it has some erosion property. From the obtained results it can be concluded that our optimized formula **X12** could resist the RPM pressures as well as pH differences.

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