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Formulation and *in-vitro* evaluation of aceclofenac pulsatile tablets as a oral - time controlled drug delivery system

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ABSTRACT

A tablet consisting of two layers of swelling and rupturable coatings was prepared and evaluated as pulsatile drug delivery system. Aceclofenac was used as model drug. The tablets were prepared by direct compression method. Different ratio of spray-dried lactose and microcrystalline cellulose were then coated sequentially with an inner swelling layer containing a super disintegrant (croscarmellose sodium) and an outer rupturable layer of ethyl cellulose. The effect of spray-dried lactose and microcrystalline cellulose on swelling layer and rupturable coating was investigated. In vitro dissolution was preformed using the USP paddle (type II) apparatus at speed of 50 rpm by using phosphate buffer pH 7.4 as a dissolution medium. The lag time of the pulsatile tablets of Aceclofenac decreased with increasing concentration of microcrystalline cellulose in the cores and increased with increasing levels of both swelling layer and ruputable ethyl cellulose coating. Increasing levels of water uptake by the ethyl cellulose coating causes bulging and become like gel and forms insoluble skeleton where the drug seems to be time-controlled release, and thus prolonged the lag time.

Keywords: Aceclofenac, pulsatile tablets, ethyl cellulose, lag time.

INTRODUCTION

Conventional controlled release drug delivery systems are based on single or multiple – unit reservoir or matrix system, which are designed to provide constant drug levels over an extended period of time. However, pulsatile delivery is desirable for drugs acting locally or having an absorption window in the gastro-intestinal tract or for drugs with an extensive first pass metabolism, which develop biological tolerance, where the constant presence of the drug at the site of action diminishes the therapeutic effect, or for drugs with special the pharmacokinetic features designed according to the circadian rhythm of human. A pulsatile release profile is characterized by a lag time followed by rapid and complete drug release.

Pulsatile drug delivery systems are generally classified into time - controlled and site - specific delivery system [3]. The release from the time controlled delivery is primarily controlled by the system, while the release from the site-specific group is primary controlled by the biological environment in the gastro-intestinal tract such as pH of the site of action or enzymes.

Most pulsatile drug delivery systems are reservoir devices covered with a barrier coating. The barrier can dissolve, erode or rupture during/after a certain lag time, after which the drug is released rapidly from the inner reservoir. The

rupturing of the barriers is induced by an expanding core upon water penetration through the barrier coating. The expansion can be caused by effervescent excipient or swelling agents.

The present study focuses on the development of pulsatile release tablets at a peroral, time - controlled single-unit dosage form. The proposed system consists of a core tablet coated with two layers, an inner swelling layer and an outer rupturable coating. The swelling layer is composed of croscarmellose sodium, a super disintegrant and polyvinyl pyrrolidone (PVP) as a binder, while the rupturable coating is an ethyl cellulose film [1].

MATERIALS AND METHODS

MATERIALS

Acelofenac was obtained as gift sample from Micro labs Ltd, Hosur, microcrystalline cellulose was obtained from Nice chemicals, ethyl cellulose from lobachemie Pvt Ltd, Mumbai, Magnesium stearate from S.D fine chemicals, Mumbai. Colloidal silicon dioxide Croscarmellose sodium, and spray- dried lactose monohydrate was obtained from Sarcen pharmaceutical, Pondicherry. All materials used were of analytical grade.

PREPARATION OF PULSATILE RELEASE TABLETS

The core tablets containing varying ratio of spray dried lactose monohydrate (Flowlac 100) and Microcrystalline Cellulose (Avicel pH 102) (100:0, 70:30, 50:50, 70:30, 0:100) were prepared by direct compression method [1]is given in the table 1.

Table 1: Effect Coating Thickness and Ratio of Spray Dried Lactose, Avicel on Pulsatile Tablets (Without Drug)

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
lactose : Avicel ratio In core	100 : 0			70 : 30			50 : 50			30 : 70			0 : 100		
1.aceclofenac	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2.spray dried Lactose lactose mono hydrate	445.5	445.5	445.5	311.85	311.85	311.85	222.75	222.75	222.75	133.85	133.85	133.85	-	-	-
3.avicel (mcc)	-	-	-	133.65	133.65	133.65	222.75	222.75	222.75	311.65	311.65	311.65	445.5	445.5	445.5
4.Aerosol	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25
5.mag. stearate	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25
6.Ac di - sol coating level (mg /cm^2)	13.5	22.5	31.5	13.5	22.5	31.5	13.5	22.5	31.5	13.5	22.5	31.5	13.5	22.5	31.5
7.outer E.C coating level (mg /cm^2)	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5

Ingredient (mg)	F16	F17	F18	F19	F20	F21	F22	F23	F24	F25	F26	F27	F28	F29	F30
lactose : Avicel ratio in core	100 : 0			70 : 30			50 : 50			30 : 70			0 : 100		
1.Aceclofenac	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2.spray dried lactose lactose mono hydrate	445.5	445.5	445.5	311.85	311.85	311.85	222.75	222.75	222.75	133.85	133.85	133.85	-	-	-
3.Avicel (mcc)	-	-	-	133.65	133.65	133.65	222.75	222.75	222.75	311.65	311.65	311.65	445.5	445.5	445.5
4.Aerosil	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25
5.Mag. stearate	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25
6.Ac di - sol coating level (mg /cm^2)	22.5	22.5	22.5	22.5	22.5	22.5	22.5	22.5	22.5	22.5	22.5	22.5	22.5	22.5	22.5
7.Outer E.C coating level (mg /cm^2)	3	4	5	3	4	5	3	4	5	3	4	5	3	4	5

The drug containing core tablets were prepared in a similar manner by replacing spray dried lactose monohydrate with aceclofenac (100 mg per tablet). The core tablet excipients were blended for 10 minutes, followed by the addition of magnesium stearate (0.5% w/w) and Aerosil 200 (0.5% w/w) is given in the table 2.

The powder mixture was further blended for 5 min. The core tablets (diameter 10mm; biconvex, hardness 4 to 4.5 kg/cm^2 average tablets weight 450 mg) were compressed using a single rotary tablet press machine.

Table 2: Formulation Variables For Pulsatile Tablets (With Drug)

Ingredients (mg)	F31	F32	F33	F34	F35	F36	F37	F38	F39
lactose : Avicel ratio in core	70 : 30								
1.Aceclofenac	100	100	100	100	100	100	100	100	100
2.spray dried	241.85	241.85	241.85	241.85	241.85	241.85	241.85	241.85	241.85
4.Avicel (mcc)	103.65	103.65	103.65	103.65	103.65	103.65	103.65	103.65	103.65
4.Aerosil	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25
5.Mag – Sterate	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25
6.Ac di – sol coating level (mg /cm^2)	13.5	13..5	13.5	22.5	22.5	22.5	31.5	31.5	31.5
7.outer E.C coating level (mg /cm^2)	3	4	5	3	4	5	3	4	5

COATING OF TABLETS

The core tablets were coated with two consecutive layers; Croscarmellose sodium as an inner swelling layer and ethyl cellulose as an outer reputable coating layer, AC-Di-sol and PVP (Kollidon 90F) was used as a binder (Ac–Di-sol: kollidon 90F 6:1w/w) kollidon 90F was dissolved in 96% v/v ethanol by stirring overnight until a clear solution was obtained.

Ac–Di-sol was dispersed into the kollidon 90F solution and agitated for at least 30 min to obtain a homogeneous dispersion prior to coating. The coating dispersion was then layered onto the core tablets in Glatt- drum coater to obtain swelling layer level of 13.5, 22.5 and 31.5 mg/cm^2.

The coated tablets were further dried in the coating pan for 15 min at 40°C after the coating process was finished. The tablets were then placed in the over at 40°C for 2 h to remove the residual solvent.

Those tablets were than coated with ethanolic ethyl cellulose solution, using triethyl citrate as a plasticizer. The coating solution was prepared by dissolving ethylcellulose in 96%v/v ethanol (3.5% w/w solution) and was stirred overnight to obtain a clear solution. The plasticizer (5% w/w based on polymer solids) was further agitated for at least 30 min prior to coating to obtain a homogeneous solution.

The homogeneous dispersion was gently stirred throughout the coating process. The polymer solution was sprayed on to the tablets in a glatt – drum- coater to obtain coating levels of 3, 4 and 5 mg/cm^2 ethylcellulose.

The tablets were further dried in the coating pan for 15 min at 40°C after the coating process was finished and then placed in the oven at 40 °C for 2 h to remove residue solvent. The coated tablets were equilibrated at room temperature overnight and stored in a closed container prior to further experiments.

EVALUATION OF PULSATILE RELEASE TABLETS [10]

Scanning election microscopy

The morphology of a cross -section of the pulsatile release tablets was observed under a scanning electron microscope (model Hitachi - 3000 4 Japan). The dried samples were mounted onto the stages prior to coating with gold to a thickness is of about 3 nm under vacuum and were then observed with scanning electron microscope.

Rupture test

The lag time of pulsatile release tablets is defined at the time when the outer ethylcellulose coating starts to rupture. It was determined visually by using the USP XXIV paddle dissolution apparatus (900ml of phosphate buffer pH 7.4, 37.0± 0.5 °C, 50 rpm) in addition the rupture behavior of pulsatile release table was photographed by a digital camera [1].

Water uptake study [11]

The water uptake of pulsatile release tablets was determined in medium filled containers placed in a horizontal shaker (100 ml of phosphate buffer pH 7.4, 37°C, 74 rpm) at pre determined time points, the tablets were removed from the dissolution medium, carefully blotted with tissue paper to remove surface water, weighted and then placed

back in the medium up to the time when the coating of the tablet ruptured. The water uptake was calculated as follows.

$$\% \text{ water uptake} = \left[\left(\frac{w_t - w_0}{w_0} \right) \right] x100$$

Where w_t is weight of wet tablet at time t and w_0 is weight of drug tablet.

Invitro Drug release Study [23],[45]
The USP type (II) rotating paddle method (37.0±0.5 °C, 50rpm, 900ml of phosphate buffer pH 7.4) was used to study the drug release from pulsatile release tablets (lab India) [6]. Samples were with drawn after pre determined time intervals and the amount of aceclofenac released was assayed with a spectrophotometer (shimadzu- PC - 2201pc) at a wavelength of 275 nm.

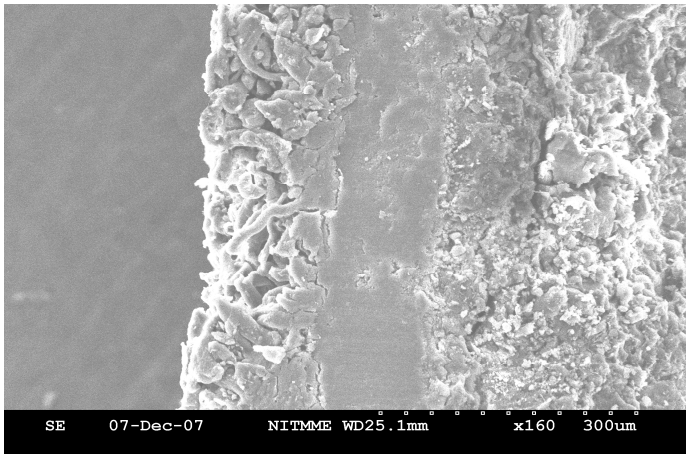
RESULTS AND DISCUSSION

The pulsatile release tablet system developed in the present study was a reservoir device, where the tablet cores were surrounded by two consecutive layers, a swelling layer and rupturable layer respectively.

The swelling layer consists of croscarmellose sodium as the swelling agent because of its superior swelling behaviors and PVP as a binder. The rupturable coating consisted of a plasticized ethylcellulose film. Ethylcellulose was chosen because it formed a mechanically weak and semi permeable film [1], which could rupture easily upon exposure to the dissolution medium and the resultant internal pressure developed within the tablet cores.

Figure 1 shows a SEM photograph of cross section of the pulsatile release tablet. The three parts of the systems are clearly visible, namely the dense tablet core (microcrystalline cellulose, lactose and drug) (C). The more layer of the Ac-DI-sol containing swelling layer (B) and the homogeneous ethyl cellulose coating as the outer rupturable coating (A).

Figure 1: SEM Photograph of formulation F35



Water influx and the subsequent volume expansion of the swelling agent caused the rupturing of the ethylcellose coating. The drug was then released rapidly with in a short period after a certain lagtime due to the strong rupturing of the coating [11]. The rupturing sequence of a pulsatile release tablet is shown in figure 2.

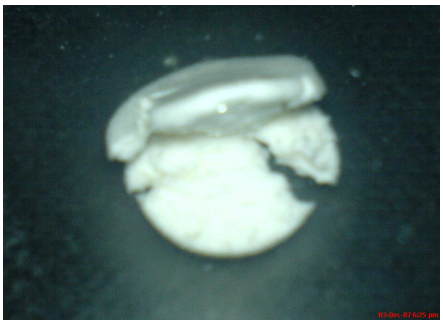
Effect of core composition (Spray dried lactose: Avicel) [11]
Drug - free core tablets containing varying ratio of spray - dried lactose monohydrate (Flowlac - 100) and microcrystalline cellulose (Avicel pH 102) (100;0, 70:30, 50:50, 30:70, and 0:100 w/w) were prepared by direct compression. The core tablets were coated with swelling layer consisting of AC-Di-sol (Theoretical coating levels of 13.5, 22.5, 31.5 mg/cm^2) and rupturable coating consisting of ethylcellulose (theoretical coating levels 3,4,5 mg/cm^2) as expected, increase the amount of microcrystalline cellulose in the core tablets decreased the lag time, this being almost independent of the amount of Ac-Di-sol .

Microcrystalline cellulose possesses a good disintegration property; higher amounts of microcrystalline cellulose, increased the disintegrating forces of the cores. Resulting in a shorter lagtime, increasing the ethylcellulose coating level increased the lag time for all microcrystalline cellulose concentration.

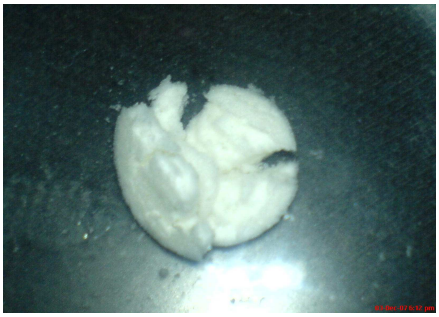
Figure 2: Rupture sequence of pulsatile release tablet at time (a) t= 0min, (b) t=90min, (c) t= 180min, (d) t=270min

(a)

(b)



(b)



(d)

To develop the pulsatile release tablet based on swelling and rupturable coatings, several studies were necessary to identify formulation variables, which provided the desired system properties, namely a rapid drug release after a certain lag time [44]is given in table 3, 4, 5. The influence of core composition, Level of swelling layer and rupturable coating, water uptake study was investigated.

Table 3: Lag time for Different Ac-Di-Sol Layer Level & Same E.C Layer Level With Different Mcc Ratio In Core F1 To F15 (13.5,22.5,31.5mg/Cm^2,//5mg/Cm^2)

Formulations	Ac-di-sol-layer level(mg/cm^2)	E.C layer level (mg/cm^2)	MCC ratio in core	Lag time (min)*
F1	13.5	5	0	420±2.0
F4	13.5	5	30	360±2.0
F7	13.5	5	50	90±3.0
F10	13.5	5	70	60±3.0
F13	13.5	5	100	30±2.0
F2	22.5	5	0	420±2.0
F5	22.5	5	30	450±2.6457
F8	22.5	5	50	60±1.7320
F11	22.5	5	70	60±2.6457
F14	22.5	5	100	60±2.6457
F3	31.5	5	0	510±4.3588
F6	31.5	5	30	510±5.1961
F9	31.5	5	50	120±3.0
F12	31.5	5	70	120±1.7320
F15	31.5	5	100	90±3.0

The slope of this curve, the sensitivity of the lag time to the coating level decreased with increasing microcrystalline cellulose concentration the formulation. Therefore became more robust. The core without microcrystalline cellulose (Flowlac 100 : Avicel pH 102) w/w) showed the highest sensitivity (steepest slope), according to these results core tablets consists of lactose and microcrystalline cellulose with a 70: 30 w/w ratio was used for further studies.

Effect of the amount of swelling layer and rupturable coating [11], [45]
Besides the core composition, the amount swelling layer was another important variable influencing the rupturing unexpectedly, the lag time of tablets with a higher level of swelling layer increased at all ethylcellulose coating level.

However, this finding was in agreement with a study on time- controlled explosion system. The hardness of the core tablets coated with AC- di-sol levels of 13.5, 22.5 and 31.5 mg.cm^2- was 4.5, 5.2, 4.6 kg/cm^2 respectively, core tablets coated with higher levels AC- Di -sol (without rupturable membrane) had a higher hardness, which might retard the water penetration through this layer.

Figure 3: Lag time for Different Ac-Di-Sol Layer Level & Same E.C Layer Level With Different Mcc Ratio In Core F1 To F15 (13.5,22.5,31.5mg/Cm^2,//5mg/Cm^2)

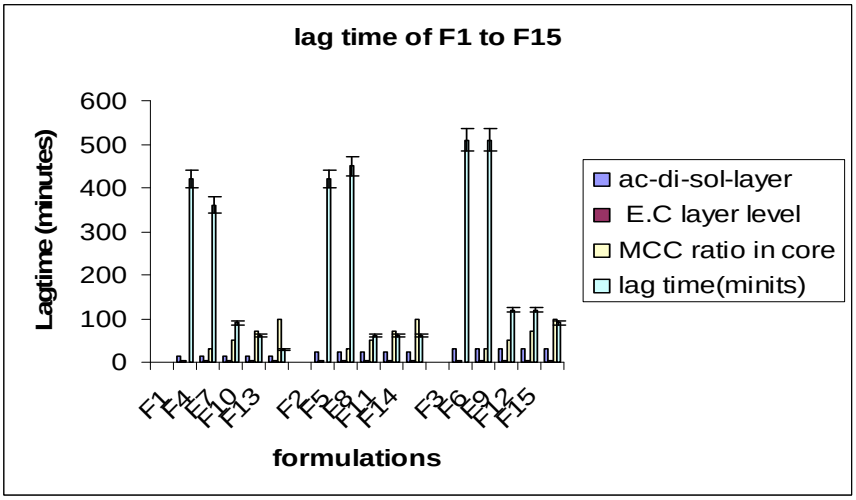


Table 4:Lagtime for Same Ac-Di-Sol Layer Level And Different E.C Layer Level With Different Mcc Ratio In Core F16 To F30 (22.5mg/Cm^2 //3,4,5 Mg/Cm^2)

Formulations	MCC ratio in core	Ac-di-sol-layer Level (mg/cm^2)	E.C layer level (mg/cm^2)	Lag time (min)*
F16	0	22.5	3	150±2.0
F17	0	22.5	4	360±3.4614
F18	0	22.5	5	420±3.0
F19	30	22.5	3	150±3.0
F20	30	22.5	4	270±2.0
F21	30	22.5	5	450±2.6457
F22	50	22.5	3	30±2.0
F23	50	22.5	4	45±1.7320
F24	50	22.5	5	80±2.0
F25	70	22.5	3	25±1.7320
F26	70	22.5	4	45±2.6457
F27	70	22.5	5	60±2.0
F28	100	22.5	3	20±2.0
F29	100	22.5	4	45±2.0
F30	100	22.5	5	60±1.7320

AC- Di-sol swelled when in contact with medium and therefore probably retarded the further water penetration into the core, which by itself had a high disintegration force resulting in short lag time.

Figure 4:Lagtime for Same Ac-Di-Sol Layer Level And Different E.C Layer Level With Different Mcc Ratio In Core F16 To F30 (22.5mg/Cm^2 //3,4,5 Mg/Cm^2)

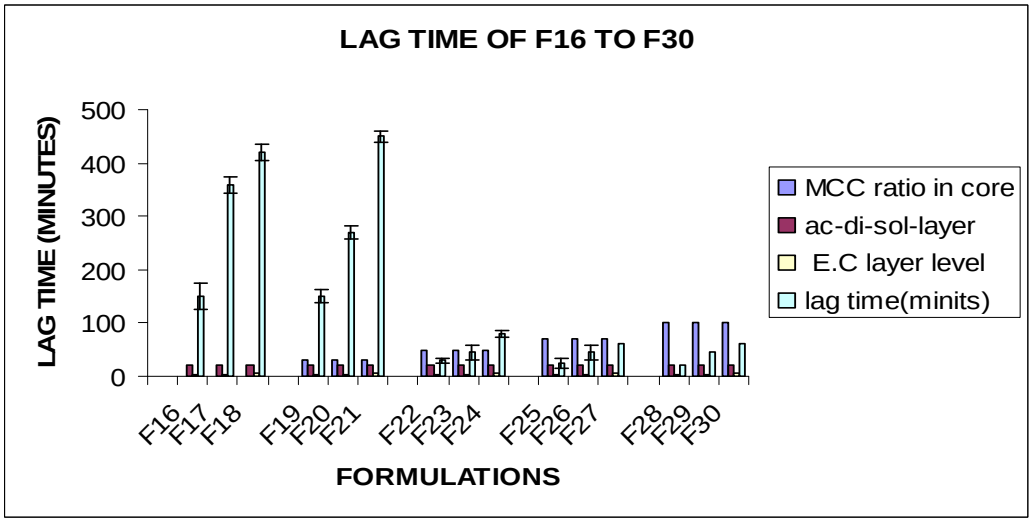
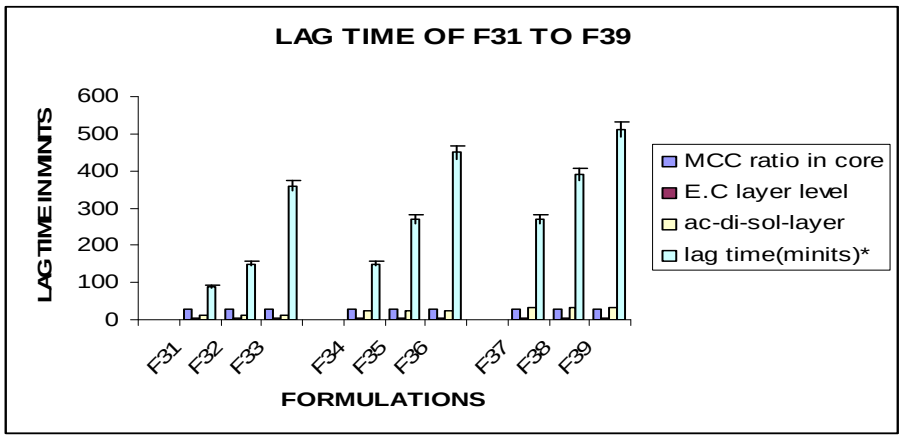


Table 5:Lag time for Different Ac-Di-Sol Layer Level & Different E.C Layer Level With Same MCC Ratio in Core F31 TO F39 (13.5mg/cm^2, 22.5mg/cm^2, 31.5mg/cm^2 //3,4,5 mg/cm^2)

Formulation	MCC ratio in core	E.C layer level	ac-di-sol-layer	lag time(min)
		(mg/cm^2)	level(mg/cm^2)	
F31	30	3	13.5	90±2.0
F32	30	4	22.5	150±3.0
F33	30	5	31.5	360±2.6457
F34	30	3	13.5	150±3.6055
F35	30	4	22.5	270±2.0
F36	30	5	31.5	450±2.0
F37	30	3	13.5	270±2.0
F38	30	4	22.5	390±2.6457
F39	30	5	31.5	510±1.0

** Mean of three determination ±S.D*

Figure 5:Lag time for Different Ac-Di-Sol Layer Level & Different E.C Layer Level With Same MCC Ratio in Core F31 TO F39 (13.5mg/cm^2, 22.5mg/cm^2, 31.5mg/cm^2 //3,4,5 mg/cm^2)



While with the pulsatile release tablets of this study, both the tablet core and the swelling layer influenced the rupturing process, as expected higher levels of the rupturable ethylcellulose layer increased the lag time.

Release studies were carried out to examine the pulsatile release characteristics of the system. Aceclofenac was used as a model drug. The drug was not released prior to the rupturing of the coating. After rupturing, the drug release

from the pulsatile release tablets with 13.5 mg/cm^2 Ac - Di - S0 L layer was lower than that from the pulsatile release tablets with 22.5 mg/cm^2 Ac-Di - sol layer

A swelling layer level 13.5 mg/cm^2 might not be enough for the complete rupture of the tablets (flowlac 100: Avicel pH 102, 70:30 w/w core) as observed visually, tablets with 13.5 mg/cm^2 Ac $^-$ Di-sol layer showed a lower degree of rupturing then tablets with 22..5 mg/cm^2 Ac $^-$di-sol layer.

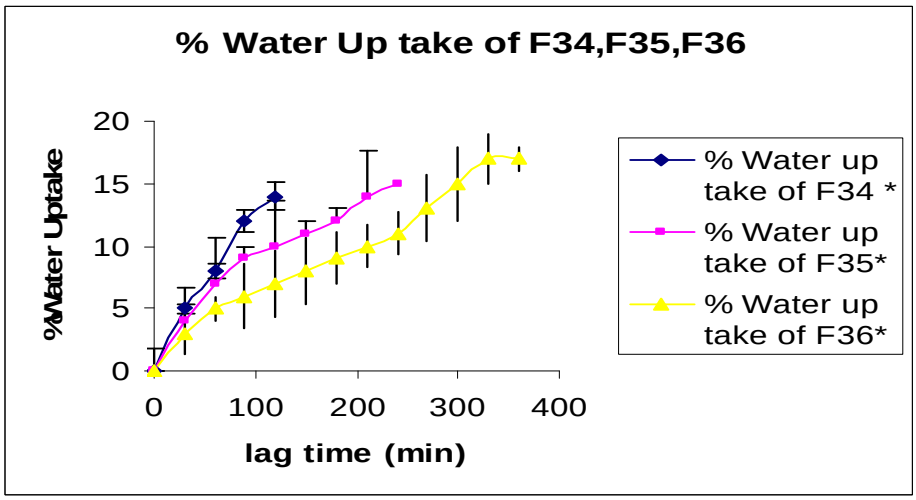
Next the drug release [45] and the water uptake prior to rupture were investigated as function of the amount of rupturable ethyl cellulose layer. The lag time increased with increasing ethyl cellulose level, drug was released rapidly and completely at ethyl cellulose level of 3 mg/cm^2 at the higher ethyl cellulose level 5 mg/cm^2, the drug released slower after the lag time, this was again caused by the lower degree of rupturing of the thickener coating. Higher ethyl cellulose levels retarded the water uptake. The critical water uptake core was slightly higher at higher level ethyl cellulose. This could be explained by higher mechanical strength of the thickener coating, requesting a higher degree of swelling (water up take) [45]for rupturing is given in table 6.

Water uptake study [11], [45]

Table 6: Percentage water up take of F34,F35 (22.5mg/cm^2//3,4mg/cm^2)

Time (min)	% Water up take of F34 *	% Water up take of F35*
0	0	0
30	5±1	4±1.7320
60	8±2.6457	7±2.6457
90	12±2.6457	9±3.6855
120	14±2.6457	10±1.0
150		11±3.6055
180		12±1.0
210		14±1.0
240		15±3.6055
270		
300		
330		
360		

Figure 6: Percentage water up take of F34, F35 &F36 (22.5mg/cm^2//3,4,5mg/cm^2)



Dissolution Profile of Pulsatile Tablets

Figure 7: Dissolution Profile of F34 & F35

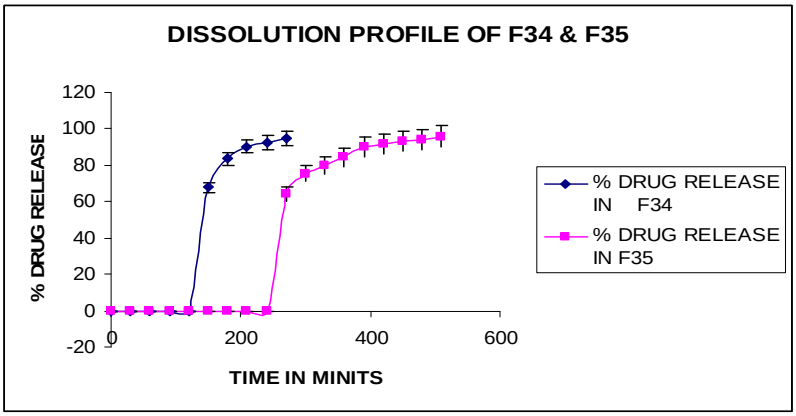


Table 7: Dissolution Profile of F34 & F35

Time(min)	% Drug release in F34	% Drug release in F35
0	0	0
30	0	0
60	0	0
90	0	0
120	0	0
150	68±3.6055	0
180	83.5±2.0	0
210	90.4±3.2908	0
240	92.6±3.4394	0
270	95±4.09267	64±0.5
300		75.5±7.0887
330		80±1.8027
360		84.5±5.0744
390		90±2.29128
420		91.5±1.5
450		93±2.6457
480		94±3.1224
510		96±2.5

** Mean of three determination ± S.D*

CONCLUSION

The present study was carried out to develop the pulsatile release tablet with a swelling layer and rupturable ethylcellose coating. The system released the drug rapidly after a certain lag time due to the rupture of the ethyl cellulose coating layer. The lag time of the system could be modified by several factors such as core composition, level of swelling layer and rupturable layer.

In first study for determined effect of core composition [(100:0), (70:30), (50:50), (30:70), (0:100) on the lag time of pulsatile tables with different amount of ac-di-sol layer (13.5, 22.5, 31.5 mgcm^2) of 5.0mg/m^2 E.C.

In another study for determined effect of core composition [(100:0), (70:30), (50:50, (30:70), (0:100) on the lag time of pulsatile tables with different amount of E.C. layer (3, 4, 5 mg/cm) of 22.5mg/cm^2 ac-di-sol coating.

The above study demonstrated that composition of (70:30) could be successfully employed for good lag time for treatment of rumatoid authritiues

Hence it was planned to time –controlled drug release by using composition of 70% spray dried lactase & 30% micro crystalline cellulose (avicel PH 102) in core tablet.

Pulsatile core tablets (70:30) coated with 13.5, 22.5, 31.5mg/cm^2 Ac-Di-sol layer coating and 3, 4, 5 mg/cm^2 E.C layer coating were prepared and evaluated. The results show that F35 formulation was able to time-controlled. The

drug release up to 510 minutes. This can be expected to reduce the frequency of administration and decrease the dose dependent side effects associated with repeat administration of conventional aceclofenac tablets.

The time –controlled release pulsatile tablet was found to be beneficial in terms of reduction in frequency of administration.

While patients suffering from rheumatoid arthritis feel more pain in the morning hours. The release of drug is preferred in pulses.

Hence it can be concluded that once-daily time-controlled release pulsatile tablets of aceclofenac having short half-life was found to exert a satisfactory time-controlled release profiles which may provide an increased therapeutic efficacy.

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