



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 superdisintegrant (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 performed 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 rupturable 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 system 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, Housur, microcrystalline cellulose was obtained from Nice chemicals, ethyl cellulose from Iobachemie 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, Pondecherry. 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, 30:70, 0:100) were prepared by direct compression method (1).

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).

The powder mixture was further blended for 5 min. The core tablets (diameter 10mm; biconvex, hardness 4 to 4.5 kg/cm² average tablets weight 450 mg) were compressed using a single rotary tablet press machine.

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 |

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/cm².

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 |

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 oven at 40°C for 2 h to remove the residual solvent.

Those tablets were then 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/cm² 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 electron 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.

$$\% \text{ water uptake} = \left[\left(\frac{w_t - w_0}{w_0} \right) \right] \times 100$$

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

Invitro Drug release Study (23)

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 withdrawn 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.

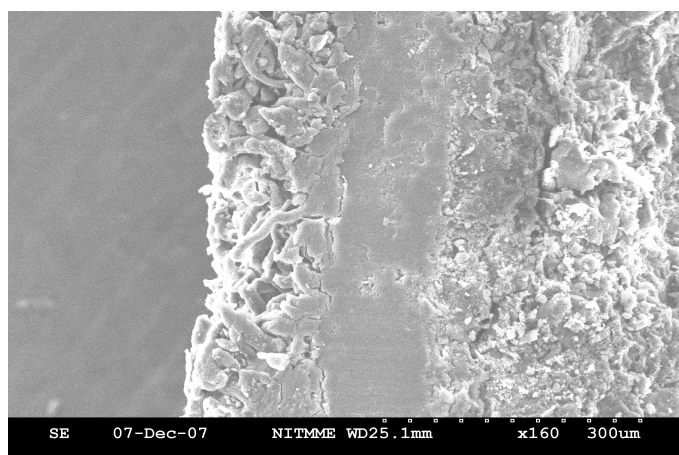
RESULTS AND DISCUSSION

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 shows a 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).

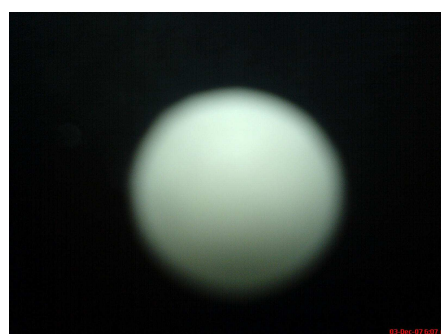
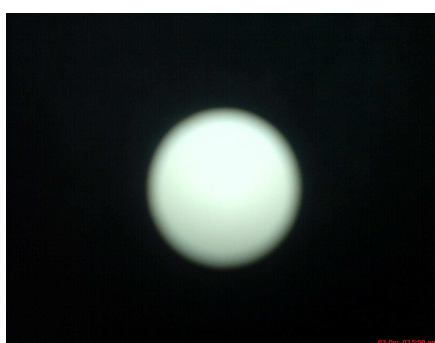
Figure 1: SEM Photograph of formulation F35



Water influx and the subsequent volume expansion of the swelling agent caused the rupturing of the ethylcellulose 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

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. The influence of core composition, Level of swelling layer and rupturable coating, water uptake study was investigated.

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

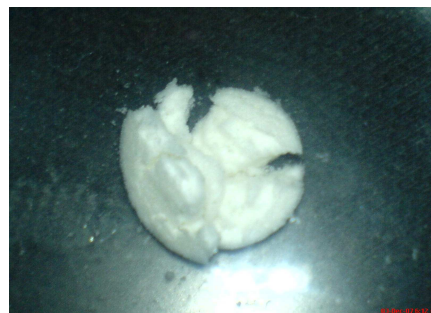


(a)

(b)



(b)



(d)

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/cm²) and rupturable coating consisting of ethylcellulose (theoretical coating levels 3,4,5 mg/cm²) 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.

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.

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/Cm²./5mg/Cm²)

| 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 |

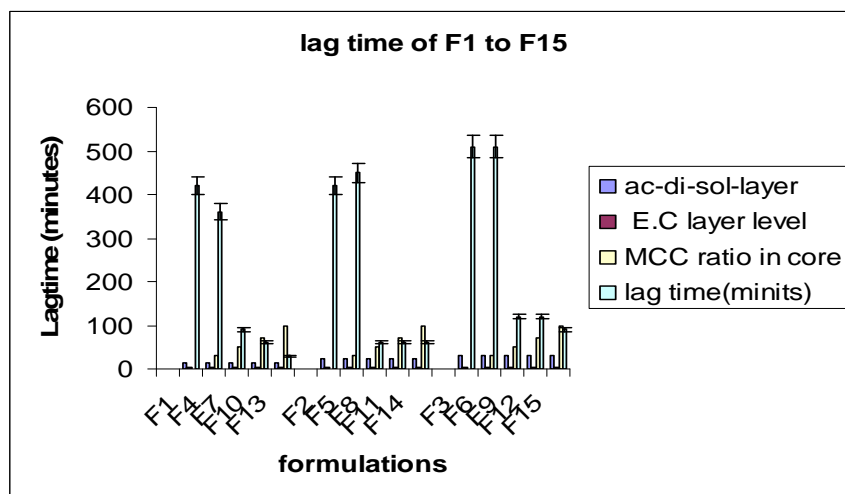


Figure 3: Lag time for Different Ac-Di-Sol Layer Level & Same E.C Layer Level With Different Mcc Ratio In Core F1 To F15 (13.5,22.5,31.5mg/Cm² //5mg/Cm²)

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/Cm² //3,4,5 Mg/Cm²)

| 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 |

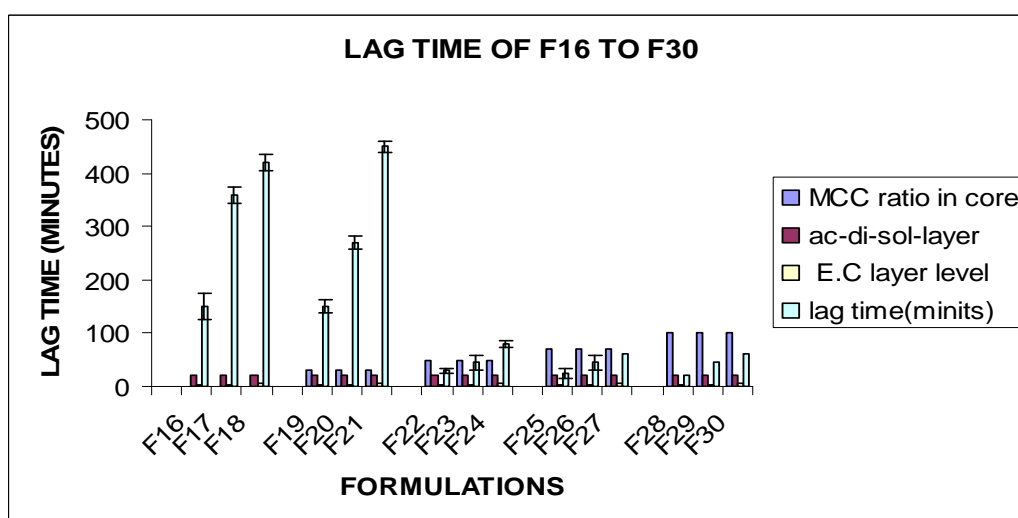


Figure 4:Lagtime for Same Ac-Di-Sol Layer Level And Different E.C Layer Level With Different Mcc Ratio In Core F16 To F30 (22.5mg/Cm² //3,4,5 Mg/Cm²)

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/cm², 22.5mg/cm², 31.5mg/cm² //3,4,5 mg/cm²)

| Formulation | MCC ratio in core | E.C layer level (mg/cm ²) | ac-di-sol-layer level(mg/cm ²) | lag time(min) |
|-------------|-------------------|---------------------------------------|--------------------------------------------|---------------|
| 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

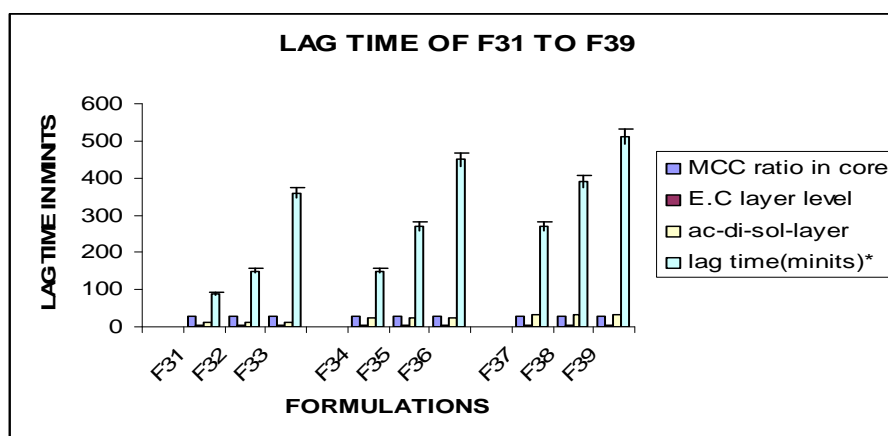


Figure 5:Lag time for Different Ac-Di-Sol Layer Level & Different E.C Layer Level With Same MCC Ratio in Core F31 TO F39 (13.5mg/cm², 22.5mg/cm², 31.5mg/cm² //3,4,5 mg/cm²)

Effect of the amount of swelling layer and rupturable coating(11)

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/cm² was 4.5, 5.2, 4.6 kg/cm² 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.

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.

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/cm² Ac - Di - S0 L layer was lower than that from the pulsatile release tablets with 22.5 mg/cm² Ac-Di - sol layer

A swelling layer level 13.5 mg/cm² 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/cm² Ac Di-sol layer showed a lower degree of rupturing then tablets with 22.5 mg/cm² Ac di-sol layer.

Next the drug release and the water uptake prior to rupture were investigated as function of the amount of rupturable ethylcellulose layer. The lag time increased with increasing ethylcellulose level, drug was released rapidly and

completely at ethylcellulose level of 3 mg/cm² at the higher ethylcellulose level 5 mg/cm², the drug released slower after the lag time, this was again caused by the lower degree of rupturing of the thickener coating. Higher ethylcellulose levels retarded the water uptake. The critical water uptake core was slightly higher at higher level ethylcellulose. This could be explained by higher mechanical strength of the thickener coating, requesting a higher degree of swelling (water up take) for rupturing.

Dissolution Profile of Pulsatile Tablets

Table 6: 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

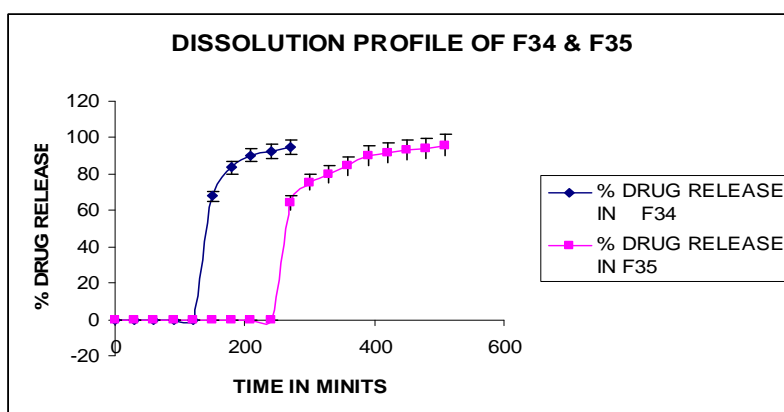


Figure 6: Dissolution Profile of F34 & F35

Water uptake study (11)

Table 7: Percentage water up take of F34, F35 (22.5mg/cm²/3.4mg/cm²)

| 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 | | |

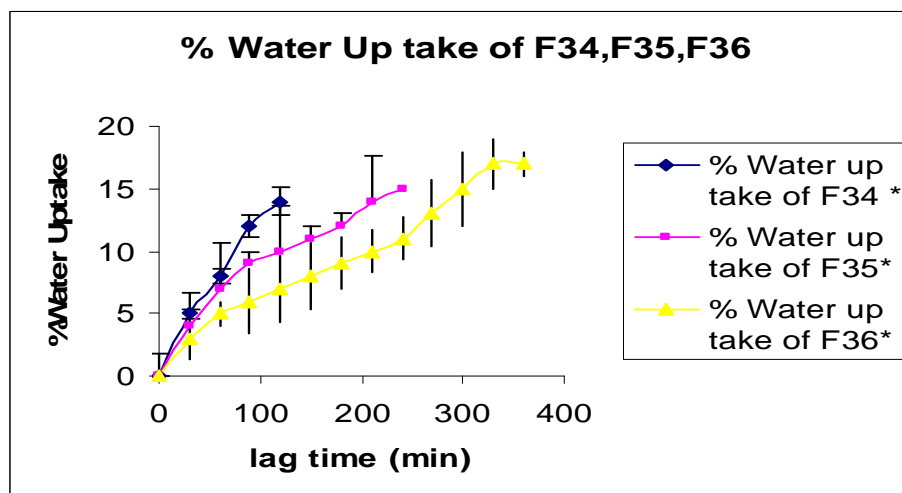


Figure 7: Percentage water up take of F34,F35 & F36 (22.5mg/cm²//3,4,5mg/cm²)

CONCLUSION

The present study was carried out to develop the pulsatile release tablet with a swelling layer and rupturable ethylcellulose coating. The system released the drug rapidly after a certain lag time due to the rupture of the ethylcellulose 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 tablets with different amount of ac-di-sol layer (13.5, 22.5, 31.5 mg/cm²) of 5.0mg/m² 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 tablets with different amount of E.C. layer (3, 4, 5 mg/cm) of 22.5mg/cm² 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 arthritiues

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/cm² Ac-Di-sol layer coating and 3, 4, 5 mg/cm² 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.

REFERENCES

- [1] Spvyas and RK Khar, Controlled drug Delivery – Fundamentals and application, Vallabh Prakashan – New Delhi, First Edition 2002.
- [2] Joseph R. Robinson, Controlled drug delivery, fundamentals and application, 2nd edition, page number 4, 5, and 6, 373,379.
- [3] Y.W. Chien, Novel drug delivery systems, 2nd edition.57-90
- [4] D.M. Brahmakar, Sunil B. Jaiwal, Biopharamcentics and pharmacokinetics, page number336, 337, 348.
- [5] Pharmaceutical dosage forms and drug delivery systems, Howard, Angle, Sixth edition, page number215.

- [6] Zydus recon, Health care ltd, Inac product Monograph, p.8 to 13.
- [7] The Remington, The Science and Practice of pharmacy, 20th edition vol.1 Mack Publication, p.903-913.
- [8] M.E. Alton, Pharmaceutics, The Science of dosage form design ,p. 229, 247.
- [9] BP **2006** page No.41 volume -I.
- [10] Leon Lachman, Herbert A, Lieberman, The Theory and practice of Industrial pharmacy, 3rd edition, Indian edition, Varghese publishing house, Bombay, 1990, p.67, 297, 298, 299, 318, 453.
- [11] Srisagul sangthongjeen et al, *journal of controlled release* 95 (**2004**) 147-159.
- [12] Anilk Anal et al Time – controlled pulsatile delivery system for bio active compound, recent patents on drug delivery & formulation 2007, 1, 73 - 79.
- [13] Shweta Arora, J. Ali et al, *Indian Journal of pharmaceutical Sciences* May – June **2006**.
- [14] Jason T.Mc Conville et al. *International National of pharmaceutics* 313 (**2006**) 150-158.
- [15] Efentakias. M. etal *International Journal of pharmaceutics* 311 (**2006**) 147-156.
- [16] Sharaddha S. Badva, Praveen sher et al, Development of hollowporows calcium pectinate beads for floating – pulsatile drug delivery, *Journal of controlled release* 21 July **2006**.
- [17] Andrei dashevsky and Ahmad Mohamad et al, *Journal of pharmaceuticals*,320,1-21,31 Aug **2006**, 179
- [18] Sameer Sharma and Atmaram pawar et al, *International Journal of pharmaceutics*, 313, 1-2,26April **2006**, 150-158.
- [19] T.Bussemer, N.A.peppas et al, *European Journal of pharmaceuticals and Biopharmaceutics* 50, April **2003**,261-270.
- [20] Srisagul sunthongjeen puttipakthachron et al, *Journal of controlled release*, 95, and **2004**, 147-159.
- [21] Akihiko kikuchi, Teruookano et al, pulsatile release control using hyrogels, advanced drug delivery reviews, 54, **2002**, 53-77.
- [22] Michael cardamone, Shari A. lofthouse et al. *international journal of pharmaceutics*, 10 November **1998**.
- [23] Rhoda M.Brand, Richard H.guy et al, *journal of controlled release* 33,**1995** ,285-292.
- [24] Bussemer. T et al, *Journal of controlled release* 93(**2003**) 331-339.
- [25] Bussemer. T. et al *International Journal of pharmaceutics* 267 (**2003**) 59-68.
- [26] T. Bussemer et al, *European journal of pharmaceuticals and Biopharmaceutics* 56 (**2003**) 261-270.
- [27] Akihiko. F kikuchi etal, *Advanced drug delivery reviews* 54 (**2004**) 53-77.
- [28] Xiaohva Tiu, Glenda. J. Pettway et al, *Biomaterial* 28 (**2007**) 4124 – 4131
- [29] V.S. Mastihotimath et al, *journal of pharmaceutics* 328 (**2007**). 49-56.
- [30] Shraddha S. Badva et al, *European journal of pharmaceuticals and Biophamaceutics* 65 (**2007**) 85 – 93.
- [31] Ahmad Mohmad et al, *European journal of pharmaceuticals and Biopharmaceutics* 64 (**2006**) 173-179.
- [32] Andrei Dashevsky et al, *International Journal of Pharmaceutics* 318 (**2006**) 124 – 131.
- [33] Inakrogel, Roland Bodmeier et al, *International Journal pharmaceutics* 187 (**1999**) 178 – 187.
- [34].Parinya Arunothayanum et al, *Journal of controlled release* 60 (**1999**) 391 -397.
- [35] Michael cordomone et al, *Journal of controlled release* 60 (**1999**) 391-397.
- [36] Michael cardamone et al *Journal of controlled release* 47 (**1997**) 2005 – 219.
- [37] Pulsatile delivery of amoxicillin against streptococcus pneumonia. Anti – infective research laboratory, May **2004**.
- [38] Sanglli. M.E. et al, *European Journal of pharmaceutical sciences* 22 (**2004**) 469 – 476.
- [39] Fan. T.Y et al, *Journal controlled release* 77 (**2001**) 245 – 251.
- [40] Sangalli, M.E, et al *journal of controlled release* 73(**2001**) 103-110.
- [41] Jonathan C.D. Sutch et al. *Journal of controlled release* 92(**2003**) 341-347.
- [42] Peter C puhultz, poeter kleinebudde et al, *Journal of controlled release* 47 (**1997**) 181 –189.
- [43] Rouge. N.; P. Buri et al *International Journal of pharmaceutics* 136 (**1996**) 117-139.