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# Development and Evaluation of Bilayer Tablet of Metoclopramide HCl and Aceclofenac

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## Abstract

Bilayer tablets are basically used to administer a dosage form with dual release effect or to formulate two incompatible drugs. The main objective of the present research work was to prepare bilayer tablet of Metoclopramide hydrochloride (MTH) and Aceclofenac (ASF) for separate layers to avoid the degradation of the drug, with the desired release pattern and thus to maximize the efficacy of both drugs in combination for the effective treatment of migraine. MTH and ACF were formulated as immediate and conventional release layer respectively. ASF was formulated as conventional release layer using PVP K-30 and MCC as binder and disintegrants respectively. MTH was formulated as immediate release layer by using various disintegrants like Sodium starch glycolate (SSG), Cross carmellose sodium (CCS) and Pre-gelatinized starch (PGS). Mixture design technique was used to find out the optimized quantity of the super disintegrants. Disintegration time (DT) and drug release at 15 min ($Rel_{15min}$) were taken as dependent variables while quantity of super disintegrants was taken as independent variable. SSG and CCS in a concentration of 7.5% and 4.5% respectively gave a DT of 9 sec, and 98.67% release at 15 min ($Rel_{15min}$). Stability studies of bilayer tablets as well as physical mixture were carried out and the samples were evaluated with DSC, FT-IR and % content of drug. Bi-layer tablet was suitable for preventing direct contact of these two drugs and thus to maximize the efficacy of combination of two drugs for migraine.

**Keywords:** Bilayer tablet; Metoclopramide HCl; Aceclofenac; Superdisintegrants

## Introduction

Bilayer tablets are prepared with one layer of drug for immediate release while second layer designed to release drug, later, either as second dose or in an extended or conventional release manner. Bilayer tablet is suitable for sequential release of two drugs in combination and separate two incompatible substances. Each layer may contain a different medicinal agent with varying release profiles, and they are designed for many reasons such as to control the delivery rate of either single or two different active pharmaceutical ingredients and to separate incompatible active pharmaceutical ingredients from each other, to control the release of active pharmaceutical ingredients from one layer by utilizing the functional property of the other layer (such as, osmotic property) [1] (Figure 1). With the development of pharmaceutical research, dosage form of two or more active ingredients in combination have attracted much more interest because they can show synergistic cumulative effect and/or decreased side effects. But at the same time, there also exist some problems in the process of preparing such combinations solid dosage forms, such as incompatibility between the active ingredients or between active ingredients and excipients. The physical or chemical interaction between two or more drug components in same dosage form or between the active ingredient and pharmaceutically adjuvant can frequently occurs which results in toxic or no clinical effects [2].

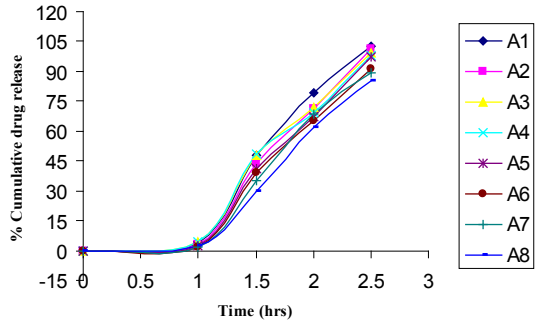


**Figure 1:** % drug release of ACF conventional layer (A1-A8).

Metoclopramide HCl (MTH) is an anti-emetic drug which was also effective in the treatment of nausea and pain associated with migraine while it also increases the gastric motility and reduces the gastric stasis problem associated with upper GI tract [3] (Figure 2).

Aceclofenac (ACF) is a non-steroidal anti-inflammatory drug with a potent anti-inflammatory and analgesic activity than those of Diclofenac sodium and Indomethacin. The incidences of adverse GI reactions are very much less than the NSAID's available in the market. The bioavailability of Aceclofenac is nearby 100%. It also has 99.97% protein binding property due to which the conventional dose of Aceclofenac may provide effect upto10-12 hrs. It has been also reported that NSAID's are very useful in the treatment of migraine. According to report, Metoclopramide shows unacceptable degradation with the acidic environment when given together with NSAID's [4].

The present work focuses on the immediate release dosage form of Metoclopramide HCl which gives faster onset of action by achieving

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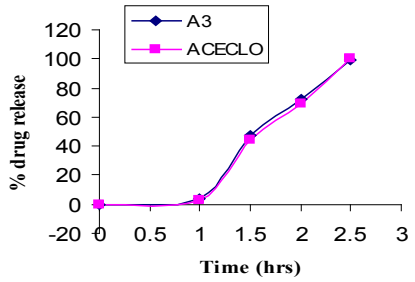


**Figure 2:** Comparison of the optimized formulation with ACECLO (marketed).

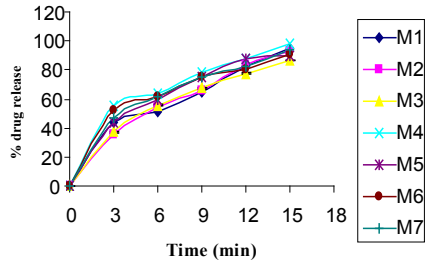


**Figure 3:** % Drug Release of MTH Immediate Release layer (M1-M7).

peak plasma concentration readily, also reduce the gastric stasis problem which is very common during the migraine attacks and causes Aceclofenac to be readily available in the small intestine which is its main site of absorption. To prepare conventional tablet of Aceclofenac, this synergizes the effect of Metoclopramide HCl to prevent pain of migraine with the desired release pattern and to avoid the degradation of the drug.

## Materials and Methods

### Materials

MTH was obtained as a gift sample from Ipca Laboratory (Mumbai, India). ASF was obtained as a gift sample from NuLife Pharmaceutical (Pune, India). PVP K30 was purchased from Sisco research Laboratories Pvt. Ltd (Mumbai, India). MCC, SSG and CCS were procured as a gift sample from Concept Pharmaceuticals Ltd. (Aurangabad, India). Magnesium Stearate, Lactose, Pre-gelatinized starch were purchased from S.D. Fine Chemical Ltd. (Mumbai, India). All others reagents and chemicals used were of analytical reagent grade (Figure 3).

### Methods

**Preparation of conventional release layer of ACF:** Weighed quantity of drug ACF, micro crystalline cellulose MCC, PVP K-30 and lactose were mixed uniformly with the help of mortar and pastel. A solution of alcohol and water (1:1) was prepared this water alcohol solution was added to drug excipient mixture to form a damp mass. This damp mass was forced manually to pass through the sieve no 16. Granules were obtained these granules were dried at 60°C for 4 hrs. Dried granules were passed through 18 # sieve. Granules were collected and to this 10% of the fines were added. The resulting granules were mixed with lubricant Magnesium stearate and colloidal silicon dioxide in a polyethylene bag for 5 min. The granules equivalent to 100 mg were compressed using a multi-station tablet compression machine (Rimek MINI, India) using 8 mm die. Composition of all batches was represented in Table 1 and Figure 4.

**Preparation of immediate release tablets of MTH:** MTH immediate release can be prepared by wet granulation as well as direct compression. But here intermediate addition technique was chosen for the addition of the superdisintegrants because of better results of it than intragranular (addition during preparation of dough mass) and extragranular (addition after preparation of granules) technique [5] (Figure 5).

The formulations were subjected to optimization techniques to identify the minimum quantity of super disintegrant required to get the desired release profile. In Design of Experiments approach, process variables are first 'screened' to determine which are important to the outcome (excipient type, percentage, disintegration time (DT), etc.). Next step is the 'optimization', when the best settings for the important variables are determined. It involves the use of 'mixture designs' for changing mixture composition and exploring how such changes will affect the properties of the mixture.

The aim of the current study was to develop and optimize the fast disintegrating tablets of MTH with low friability and minimum DT,

| Formulation | A1 | A2 | A3 | A4 | A5 | A6 | A7 | A8 |
|---|---|---|---|---|---|---|---|---|
| Aceclofenac (ASF) | 66 | 66 | 66 | 66 | 66 | 66 | 66 | 66 |
| MCC | 8 | 10 | 12 | 14 | 8 | 10 | 12 | 14 |
| PVP K-30 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
| Cab-o-sil | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Magnesium Stearate | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Lactose | 17 | 14 | 11 | 8 | 13 | 10 | 7 | 4 |
| Total | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |

*Each values represented in mg

* MCC Microcrystalline cellulose, PVP Polyvinyl pyrolidone

**Table 1:** Composition of ACF conventional Layer.

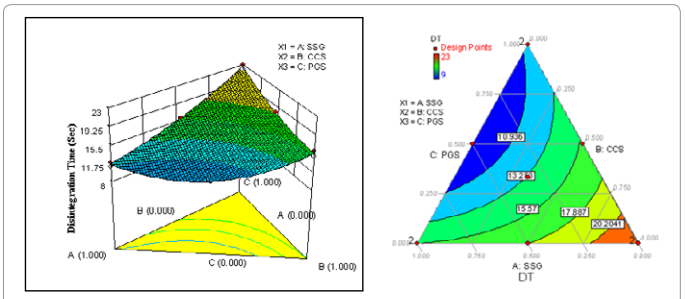


**Figure 4:** Response surface diagram and contour plot diagram for DT.

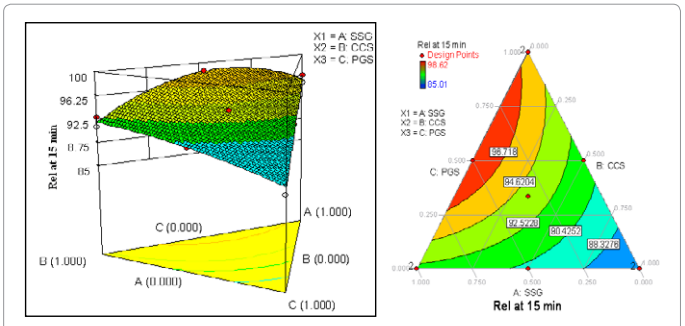


**Figure 5:** Response surface plot and contour plot diagram for Rel at 15 min.

prepared by wet granulation technique for oral delivery. A computer aided optimization process using a simplex centroid mixture design was employed to investigate the effect of three independent variable (factors) i.e.; amount of superdisintegrants: SSG, CCS and PGS. The DT and release after 15 minutes ($rel_{15min}$) were taken as the response variables.

A Simplex Centroid Mixture Design was selected for this experiment. It consists of 7 design points. This design generally involves independent variable X and dependent variables Y.

The independent variables selected for this study were SSG ($X_1$), CCS ($X_2$) and PGS ($X_3$) and dependent variables include Disintegration time ($Y_1$) and Release at 15 min ($rel_{15min}$) ($Y_2$). The design of the MTCL immediate release layer with different variables is as given in Tables 2 and 3. Firstly 7 trial formulations were prepared.

The raw materials were weighed (Table 4) and passed through 85# screen prior to mixing. 90% Alcoholic solution of PVP was prepared and added to the mixture of MTH, sodium lauryl sulphate (SLS), intragranular fraction of superdisintegrants (50%) and microcrystalline cellulose. The granules were obtained by passing the mass through 16 # sieve. These granules were dried at room temperature for 2-3 hours and were again passed through 18 # sieve. The dried granules were mixed with the extra granular fraction (remaining 50%) of superdisintegrant and lubricated with required amount of magnesium state (2% w/w). The granules equivalent to 100 mg were compressed using a multi-station tablet compression machine (Rimek MINI, India) using 8 mm die [6,7]. Composition of all batches was represented in Table 5 and Figure 6.

| Formulation | Independent Variables* | | |
|---|---|---|---|
| | A | B | C |
| **M1** | 1 | 0 | 0 |
| **M2** | 0 | 1 | 0 |
| **M3** | 0 | 0 | 1 |
| **M4** | 0.5 | 0.5 | 0 |
| **M5** | 0.5 | 0 | 0.5 |
| **M6** | 0 | 0.5 | 0.5 |
| **M7** | 0.33 | 0.33 | 0.33 |

**Table 2:** Preparation of MTCL HCl Immediate Release Tablets (Design Mixture).

| Coded level | Actual values† | | |
|---|---|---|---|
| | A | B | C |
| 0 | 0 | 0 | 0 |
| 0.33 | 4 | 4 | 4 |
| 0.5 | 6 | 6 | 6 |
| 1 | 12 | 12 | 12 |

**Table 3:** Coded level of MTCL immediate release formulation design and their actual values.

| Formulations | M1 | M2 | M3 | M4 | M5 | M6 | M7 |
|---|---|---|---|---|---|---|---|
| **Metoclopramide Hydrochloride (MTH)** | 15 | 15 | 15 | 15 | 15 | 15 | 15 |
| **SSG** | 12 | - | - | 6 | - | 6 | 4 |
| **CCS** | - | 12 | - | 6 | 6 | - | 4 |
| **PGS** | - | - | 12 | - | 6 | 6 | 4 |
| **SLS** | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 |
| **Magnesium Stearate** | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 |
| **MCC** | 70 | 70 | 70 | 70 | 70 | 70 | 70 |
| **Total** | 100 | 100 | 100 | 100 | 100 | 100 | 100 |

* Each values represented in mg

*SSG Sodium starch glycolate, CCS Cross carmellose sodium, PGS Pre-gelatinized starch

**Table 4:** Composition of MTH immediate release Tablet.

| Formulations | F1 | F2 | F3 | F4 | F5 | F6 |
|---|---|---|---|---|---|---|
| **SSG** | 6.6 | 7.8 | 6.3 | 6.9 | 8.1 | 7.5 |
| **CCS** | 5.4 | 4.2 | 5.7 | 5.1 | 3.9 | 4.5 |
| *All quantities are in mg | | | | | | |

*Each tablet contains MTH 15 mg, sodium lauryl sulphate 1.5 mg, microcrystalline cellulose 70 mg and magnesium stearate 1.5 mg.

**Table 5:** Composition of validated MTH immediate release layer (A1-A7)*.

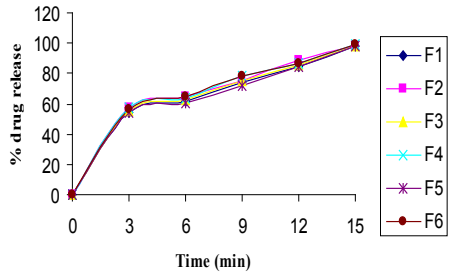


**Figure 6:** % drug $rel_{15min}$ of optimized formulation (F1-F6).

| Immediate Release Layer | Quantity F6 | Conventional Release Layer | Quantity A3 |
|---|---|---|---|
| MTH | 15 | ACF | 66 |
| SSG | 7.5 | PVP K-30 | 12 |
| CCS | 4.5 | MCC | 7 |
| SLS | 1.5 | Cab-o-sil | 2 |
| Magnesium Stearate | 1.5 | Magnesium Stearate | 2 |
| MCC | 70 | Lactose | 11 |
| **Total** | 100 | **Total** | 100 |

**Table 6:** Optimized bilayer tablet.

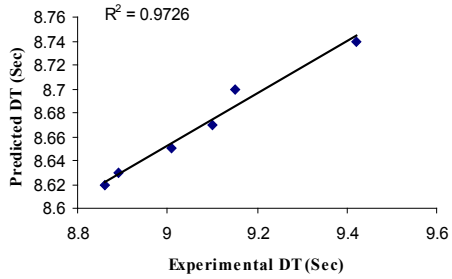


**Figure 7:** Graph of experimental v/s predicted values of DT F1-F6 formulation.

**Data analysis:** Design-Expert Software version 7.0 was used to model the shape of the surfaces. After producing and analyzing the formulations, physical–chemical responses were applied to fit the appropriate model. The model was tested for goodness of fit ($R^2$) and analysis of variance (ANOVA) was applied to verify the adequacy of the regression model in terms of a lack-of-fit test. Subsequently, grid search was performed to locate the composition of optimum formulations. Also, three-dimensional response surface graphs were drawn in MS-Excel using the output files generated by the Design Expert Software [8].

**Validation of optimization model:** Six optimum formulations (Table 6 and Figure 7) were selected by grid search, performed over the entire experimental domain, to validate the chosen experimental design and polynomial equations. The criterion for selection of formulation

was primarily based on the highest possible values of DT and $rel_{15min}$. The formulation corresponding to these formulations were prepared and evaluated for various responses. The resultant experimental data of responses were subsequently quantitatively compared with the predicted values. Also, linear regression plots between observed and predicted values of the responses were attempted using MS- Excel, forcing the line through the origin.

**Formulation of bilayered tablet:** The bilayer tablet was prepared by taking the optimized formulation of the individual layers as studied earlier. The optimized formulation of conventional release tablet and immediate release tablet, i.e. F6 and A3 respectively was used to formulate bilayer tablet formulation. Both the formulations were prepared separately as described in experiment I and II, bilayer tablets were prepared by double compression technique.

The compression was carried out on Rimek compression machine using 8 mm standard round flat punch set. First, previously weighed quantity of conventional layer blend was fed to die cavity as the first layer and compressed very slightly to get uniform layer, then weighed quantity of immediate layer blend was fed to the die cavity as the second layer and compressed finally to get bilayer tablet. By this method, the immediate release layer was compressed once, so there is fast disintegration and avoidance of the double compression.

## Evaluation of bilayered tablet

The prepared bilayer tablets were evaluated as per standard procedure for hardness (n=3), weight variation (n=20), thickness (n=20), friability and drug content [9,10]. Hardness of the tablets was tested using a Strong-Monsanto tablet hardness tester. Friability test was conducted using Roche friabilator. The thickness of the tablets was measured by digital Vernier caliper. Drug content was analyzed by measuring the absorbance of standard and samples at λmax 292 nm (Aceclofenac) and 248 nm (Metoclopramide Hydrochloride) using UV/Visible spectrophotometer (Shimadzu UV-1700).

***In vitro* dissolution study:** *In vitro* dissolution study was carried out using the following operating variables. The in vitro release study for all formulations was carried out in dissolution rate test apparatus.

Apparatus : USP dissolution apparatus type 2 (paddle type) I.P.

Speed of the paddle : 75 rpm

Temperature : 37°C ± 0.5°C

Dissolution medium :

Acid stage: 900 ml 0.1 N Hydrochloric acid for 1 hr.

Buffer stage: 900 ml phosphate buffer of pH 6.8 for next subsequent hours.

One tablet previously weighed, was kept in the dissolution medium. 10 ml samples were withdrawn at half hour intervals, filtered and was diluted to 10 ml and analyzed by using UV-spectrophotometer (JASCO V-530) at specified wavelength (nm). Aliquots of sample removed were replaced with fresh dissolution medium. The absorbances were noted down for each aliquot. The concentration was calculated by using the software PCP Disso v2.08.

**Dissolution study of marketed formulation:** The dissolution study of the marketed formulation (ACECLO, ARISTO Pharma Ltd. Mumbai) was carreid out to study the release pattern of tablet.

# Results and Discussion

## Physical Properties

The following parameters were evaluated (Table 7) for the MTH, ACF, SSG, CCS, PGS, Lactose and microcrystalline cellulose (MCC).

## ACF conventional release layer

**1) Blend property:** The prepared granules were evaluated for the blend property like bulk density, tapped density, Carr's index [11], Hausner ratio and angle of repose [12].

The Carr's index of A1 was 12.95% while maximum was 20.05% for A8 formulation i.e. in the range of 10-20% which was considered as excellent to good flow property. Angle of repose less than 30° gives good flow property to the granules. All the formulations except A7 and A8 had an angle of repose of less than 30° indicating flow ability of granules (Table 8). This may be due to the concentration of the binder PVP K-30. The bulk density of all the formulation was in the range of 0.289 to 0.399. Hausner ratio of all formulation was below 1.5 indicates good compression characteristics. All the parameters were inter related to the tablet properties like hardness, friability etc. All these results indicate (Table 9) that, the granules possess satisfactory flow and compressibility properties.

| Material | Bulk Density (gm/ml) | Tapped Density (gm/ml) | Angle of Repose (θ) | Carr's Index (%) | Hausner Ratio |
|---|---|---|---|---|---|
| **MTH** | 0.29 | 0.231 | 17.37 | 1.209 | 26.12 |
| **ACF** | 0.25 | 0.280 | 10.71 | 1.120 | 30.21 |
| **SSG** | 0.24 | 0.290 | 17.10 | 1.209 | 25.74 |
| **CCS** | 0.22 | 0.246 | 19.24 | 1.210 | 27.64 |
| **PGS** | 0.23 | 0.264 | 12.24 | 1.120 | 24.21 |
| **Lactose** | 0.25 | 0.314 | 17.19 | 1.300 | 27.21 |
| **MCC** | 0.26 | 0.230 | 19.49 | 1.360 | 28.13 |

**Table 7:** Physical properties of drug and excipients.

| Formulations | Bulk Density (gm/ml) | Tapped Density (gm/ml) | Carr's Index (%) | Hausner Ratio | Angle of Repose (θ) |
|---|---|---|---|---|---|
| **A1** | 0.289 | 0.332 | 12.95% | 1.148 | 24.54 |
| **A2** | 0.339 | 0.364 | 14.36% | 1.073 | 21.89 |
| **A3** | 0.294 | 0.389 | 16.23% | 1.323 | 24.10 |
| **A4** | 0.321 | 0.362 | 12.77% | 1.127 | 25.54 |
| **A5** | 0.295 | 0.364 | 18.95% | 1.233 | 28.61 |
| **A6** | 0.293 | 0.355 | 17.46% | 1.211 | 29.78 |
| **A7** | 0.299 | 0.354 | 15.53% | 1.183 | 33.36 |
| **A8** | 0.308 | 0.366 | 20.05% | 1.188 | 32.73 |

**Table 8:** Blend properties of formulation of ACF conventional release layer.

| Formulations | Thickness (mm) | Hardness ($Kg/cm^2$) | % Friability | Disintegration Time (min) | % Drug Content |
|---|---|---|---|---|---|
| **A1** | 1.2 ± 0.3 | 3-4 | 1.249 | 0.53 | 99.23 ±1.7 |
| **A2** | 1.2 ± 0.5 | 3-4 | 1.009 | 1.12 | 99.57 ± 0.35 |
| **A3** | 1.2 ± 0.1 | 3-4 | 0.525 | 1.59 | 99.68 ± 0.48 |
| **A4** | 1.2 ± 0.4 | 3-4 | 0.496 | 2.13 | 99.23 ± 0.45 |
| **A5** | 1.2 ± 0.3 | 3-4 | 0.556 | 3.56 | 101.23 ± 0.25 |
| **A6** | 1.2 ± 0.4 | 3-4 | 0.493 | 5.29 | 98.53 ± 0.49 |
| **A7** | 1.2 ± 0.1 | 3-4 | 0.413 | 8.17 | 99.31 ± 0.15 |
| **A8** | 1.2 ± 0.3 | 4-5 | 0.493 | 11.26 | 101.44 ± 0.74 |
| **ACECLO (Marketed)** | 2.2 ± 0.1 | 3-4 | - | 1.43 | 101.67 ± 0.57 |

**Table 9:** Tablet properties of formulation of ACF conventional release layer.

### 2) Evaluation of ACF conventional release tablet

The compressed tablets were subjected for the test like thickness, hardness, tensile strength, friability, and disintegration time and % drug content. The results are as follows;

According to above data, all the formulations showed uniform thickness. In weight variation test, the pharmacopoeial limit for the percentage deviation (Tables 10 and 11) of more than 200 mg is ± 5%. Good uniformity in drug content was found among different batches of the tablets, and the percentage of drug content was between 95-105%.

The % friability for all the formulations was below 1%, indicating that the friability is within the prescribed limits. All forms complied with the in-house specifications for weight variation, drug content, hardness, and friability.

### 3) *In vitro* dissolution study

The dissolution was carried in two parts

- 0.1N HCl for first hour
- Phosphate buffer pH 6.8 for next subsequent hours

The release of ACF conventional release layer mainly depends on the quantity of binder PVP K-30 and disintegrant Micro-crystalline cellulose (MCC). The concentration range of PVP K-30 was 1-8% while that of MCC was 8-12%.

Comparable release rates for the tablets based on the different ratio of binder as well as disintegrant were obtained for the period of 2.5 hrs.

| Time (Hrs) | A1 | A2 | A3 | A4 | A5 | A6 | A7 | A8 | ACECLO (Marketed) |
|---|---|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 3.56 | 3.51 | 4.05 | 4.56 | 2.21 | 2.03 | 1.96 | 2.11 | 3.40 |
| 1.5 | 45.77 | 43.75 | 46.81 | 44.32 | 41.29 | 39.45 | 38.16 | 39.46 | 44.04 |
| 2 | 79.13 | 71.32 | 72.16 | 69.23 | 67.28 | 65.09 | 66.34 | 65.91 | 69.19 |
| 2.5 | 102.83 | 100.03 | 99.51 | 98.26 | 97.61 | 94.37 | 95.38 | 93.15 | 99.84 |

**Table 10:** % Cumulative drug release profile of ACF conventional release layer.

| Formulation | Bulk Density (gm/ml) | Tapped Density (gm/ml) | Angle of Repose (θ) | Carr's Index (%) | Hausner Ratio |
|---|---|---|---|---|---|
| **M1** | 0.418 | 0.469 | 21.75 | 10.87 | 1.122 |
| **M2** | 0.438 | 0.521 | 22.86 | 15.93 | 1.189 |
| **M3** | 0.421 | 0.482 | 26.04 | 12.65 | 1.144 |
| **M4** | 0.431 | 0.504 | 28.27 | 14.48 | 1.169 |
| **M5** | 0.427 | 0.499 | 27.20 | 14.42 | 1.168 |
| **M6** | 0.435 | 0.517 | 25.69 | 15.86 | 1.188 |
| **M7** | 0.459 | 0.532 | 30.04 | 13.72 | 1.159 |

**Table 11:** Blend properties of MTH Immediate release layer.

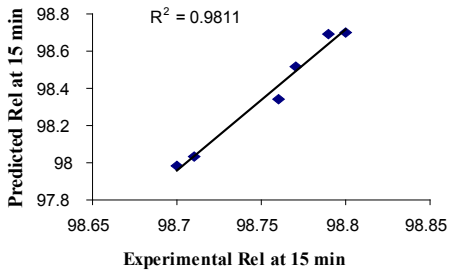


**Figure 8:** Graph of experimental v/s predicted values of $rel_{15min}$ of optimized formulations.

From the dissolution profile of tablet as shown in Figure 8, it can be concluded that, the formulation A3 which showed %CDR of 99.51% which was selected for preparation of optimized formulation. Also it has f2 value of 68.23 with the marketed formulation which resembles its similarity factor. The reason for this is use of optimum quantity of binder (7%) and disintegrants (12%). Low concentration of binder causes tablets to be friable and also it does not show a release pattern similar to that of marketed type (A1 and A2). On the other hand, higher the concentration of binder causes the tablet take longer time to disintegrate and hence slowing the release of the drug (93-94%) in 2.5 hrs for A6-A8.

From the dissolution profile, it was observed that the release of drug ACF in 0.1N HCl is very poor i.e. it releases the drug upto 2-3% which is very negligible. But when the dissolution medium was changed to phosphate buffer pH 6.8, there was a significant change in release profile, which showed a steep increase. This is also the reason why NSAID's show maximum absorption in the intestine.

## MTH Immediate Release Layer

### 1) Blend Property

All the formulations were evaluated for the blend property like bulk density, tapped density, compressibility index and Hausner ratio.

The above result predicts that, the Carr's index of all the formulations was in the range of 10-15% which was considered as excellent flow property. Angle of repose less than 30° gives good flow property to the granules and all formulations have angle of repose less than 30°. Hausner ratio of all formulations was below 1.5 gives good compression characteristics. All these results indicate that, the granules possess satisfactory flow and compressibility properties.

### 2) Evaluation of MTH Immediate Release Tablet

MTCL immediate release tablet was evaluated for the physical parameters like thickness, hardness, friability, disintegration time (DT), wetting time and uniformity of weight.

The obtained results of above evaluation test are depicted in Table 12.

The immediate release tablet of MTH was evaluated and above result predicts that, all the formulations were found to exhibit satisfactory tablet properties. The disintegration time of tablet ranged from 9-22 sec in which formulation M4 containing SSG and CCS in equal proportions was found to have minimum DT of 9 sec.

The mechanism of action of SSG is rapid uptake of water followed by rapid and enormous swelling, whereas CCS acts by the way of wicking and swelling ability.

The mechanism of disintegration was considered to be by drawing water into the tablet, swelling and causing the tablet to burst apart.

| Formulation | Thickness (mm) | Hardness ($kg/cm^2$) | % Friability | DT (Sec) | Wetting Time (Sec) | % Drug Content |
|---|---|---|---|---|---|---|
| **M1** | 0.6 | 2-3 | 0.198 | 12 | 3.17 | 99.23 ± 0.17 |
| **M2** | 0.6 | 2-3 | 0.2 | 15 | 3.42 | 99.45 ± 0.02 |
| **M3** | 0.6 | 2-3 | 0.261 | 22 | 4.89 | 99.18 ± 1.08 |
| **M4** | 0.6 | 2-3 | 0.176 | 9 | 3.04 | 99.56 ± 1.12 |
| **M5** | 0.6 | 2-3 | 0.148 | 18 | 4.56 | 98.79 ± 0.56 |
| **M6** | 0.6 | 2-3 | 0.211 | 16 | 4.08 | 99.08 ± 0.73 |
| **M7** | 0.6 | 2-3 | 0.357 | 13 | 3.97 | 98.90 ± 1.15 |

**Table 12:** Tablet properties of formulation of MTH immediate release layer.

As the drug has excellent water solubility, dissolution will not be rate limiting.

The formulation with SSG, CCS or PGS separately showed greater disintegration time as compared to the formulation M4 containing SSG and CCS in combination. M1 had showed less DT than M2 which indicates that concentration of SSG in the formulation is more pronounced to reduce the DT with CCS. M3 which contains only PGS had showed very poor profile as its DT is 22 sec which gives the significance that comparatively it is poor superdisintegrant. M7 have DT of 13 second and wetting time of 3.97 seconds as it contains all the three super-disintegrants.

The incorporation of wetting surfactant SLS favored the disintegration of the tablet by decreasing the interfacial tension and aiding absorption of water by forming the pores in tablet.

Wetting time: The wetting time gives out the significance of time required for the tablet to acquire moisture and also the minimum volume of liquid required for it. The tablets with combination of SSG and CCS had shown minimum time (3.04) to acquire moisture while the tablet with PGS only had shown maximum time (4.89).

**3) *In vitro* release studies of immediate release layer**

Different formulations with varying amount of drug: disintegrant ratios, employing wet granulation technique for immediate release layer were formulated. The in vitro release data is as follows:

From the dissolution profile of immediate release layer tablet formulation (M1-M7), as shown in Table 13 and in Figure 9, it was concluded that formulation M4 was considered to be the optimized formula, as it had highest % CDR of 98.31% of all formulations. This may be attributed to combination of two superdisintegrants like SSG and CCS along with the diluents MCC which also acts as a disintegrant.

| TIME (min) | M1 | M2 | M3 | M4 | M5 | M6 | M7 |
|---|---|---|---|---|---|---|---|
| **0** | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **3** | 43.38 | 34.97 | 37.22 | 55.31 | 43.33 | 52.56 | 47.45 |
| **6** | 51.62 | 53.98 | 55.79 | 63.53 | 59.92 | 62.04 | 61.46 |
| **9** | 65.066 | 66.23 | 67.54 | 78.24 | 75.36 | 74.91 | 75.12 |
| **12** | 82.42 | 83.12 | 77.67 | 87.96 | 87.63 | 80.29 | 81.94 |
| **15** | 95.229 | 92.75 | 87.05 | 98.31 | 89.84 | 91.24 | 93.89 |

**Table 13:** Dissolution profile of MTH immediate release tablet.

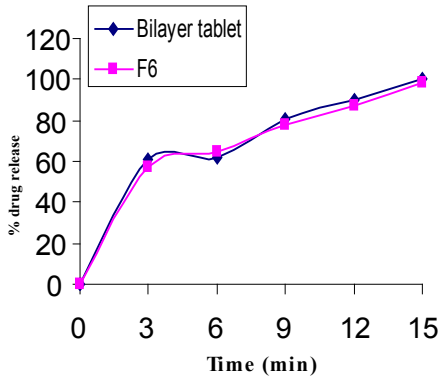


**Figure 9:** Comparison of dissolution profile of MTH of bilayer tablet with F3 formulation.

M3 had shown least CDR of 87.05%. The obvious reason may be the use of pregelitanized starch which showed poor superdisintegrants property. The combination of both the superdisintegrants showed good disintegrant behavior. It showed complete dissolution within 15 minutes. The formulation M7 containing mixture of all three superdisintegrants showed 93.89% drug release in 15 minutes.

## Analysis of Variance of the Super Cubic Model for the Responses

Screening is used in the beginning of the experimental procedure for investigating large numbers of factors aiming to reveal the most important among them. Optimization is applied for finding a factor combination matching an optimal response profile. The design supporting a linear model is useful when the experimental objective is screened.

The above value predicts that, the super cubic model is best fitted model for the mixture design. The value of $R^2$ was near to 1 which signifies that, formulations were following the Super Cubic model. The other two models as linear and quadratic does not give the significant values for both the parameters as DT in sec and $rel_{15min}$.

From the above data, coordinate system for the mixture design is called a simplex coordinate system. With three components (SSG, CCS, PGS) the coordinate can be plotted on a triangular graph.

## RSM Optimization Results

### Mathematical modeling

Mathematical relationships generated using ANOVA for the studied response variables are expressed as equation 1 and 2.

$$\mathbf{DT} = 11.52A+15.52B+22.52C-18.76AB-4.76AC-4.76BC-8.24ABC \quad (1)$$

$$\mathbf{rel}_{15min} = 95.84A+92.00B+86.23C+18.79AB+1.66AC+3.45BC-6.04ABC \quad (2)$$

All the polynomial equations were found to be statistically significant ($P<0.01$), as determined using ANOVA, as per the provision of Design Expert software shown in Table 14. The polynomial equation comprises of the coefficient for intercept. The sign and magnitude of the main effects signify the relative influence of each factor on the response. In the eq. 1, (-) sign indicates decrease in DT. From the eq. 1, the formulations with compositions AB, AC, BC and ABC had showed the minimum DT as compared to formulations A, B and C. the coefficient value of each denotes DT in seconds. Coefficient of AB had lowest polynomial value of -18.76 which had lowest DT of 9 sec whereas coefficient of C has the highest polynomial value of + 22.25 indicating higher DT of 22 sec. Coefficients of AC and BC had the same polynomial value of -4.76 indicating nearby same DT as 18 and 16 seconds respectively.

In the eq. 2, the coefficient value depends upon the no. of variables i.e. A, B, and C. for the formulations containing single component had shown polynomial values above 85 in first three coefficient A have highest polynomial value 9 i.e. 95.84 will give highest % of drug as 95.22% while C will give lowest % drug release 87.05% as it has a polynomial value of 86.23. In the next three coefficients, there is mixture

| Model | Disintegration time | $rel_{15min}$ |
|---|---|---|
| $R^2$ | 0.9907 | 0.9676 |
| *F* value | 85.35 | 14.94 |

**Table 14:** Analysis of variance of the super cubic model for the responses.

of two superdisintegrants. The polynomial value obtained for these coefficients are below 20 and coefficient AB has highest polynomial value of 18.79 which gives highest % drug release of 98.79%. The coefficient of formulation containing all the three superdisintegrants showed polynomial value in – 6.04 and having a % drug release of 93.89% which is less than the formulation having coefficient AB.

The value obtained for main effects of each factor in equation 1 and 2 that is concentration of superdisintegrants as SSG ($X_1$), CCS ($X_2$) and PGS ($X_3$) used separately or in combination has rather more pronounced effect on DT ($Y_1$) as well as $rel_{15min}$ (Y2). The use of $X_1$ and $X_2$ in combination has given the prominent results for the factors $Y_1$ and $Y_2$. At a given set of factor levels however, these higher-order polynomials yield results as the net effect of all the coefficient terms contained in the polynomial. In equation 2, the value predicts the release of the drug. In combination the coefficient value of AB is highest giving the higher % drug release.

## Response Surface Analysis

Response surface diagrams illustrating model equations and showing the effects of superdisintegrants on DT and $rel_{15min}$ of MTCL IR tablets were created to interpret the mixture region (Figures 10 and 11). In the response surface, each factor (pure mixture component) is represented in a corner of an equilateral triangle; each point within this triangle refers to a different proportion of components in the mixture. The maximum percentage of each ingredient considered by the regression is placed at the corresponding corner while the minimum is positioned at the middle of the opposite side of the triangle.

In the diagram, (Figure 12) the DT was decreased for $X_1$ and $X_2$ as compare to $X_3$; the apex point of triangle for $X_3$ goes upward denoting

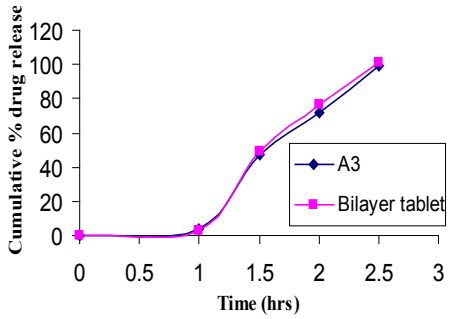


**Figure 10:** Comparison of dissolution profile of ACF of bilayer tablet with A3 formulation.

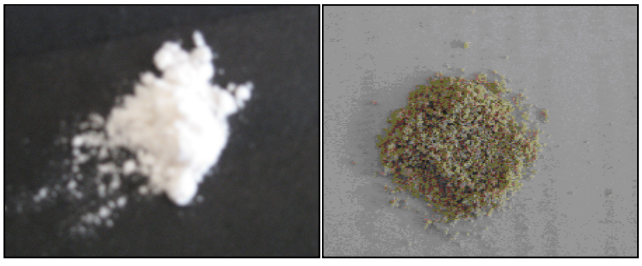


**Figure 11:** Photograph of samples of physical mixture (ACF + MTH) at (A) 0 days and at (B) 45 days.

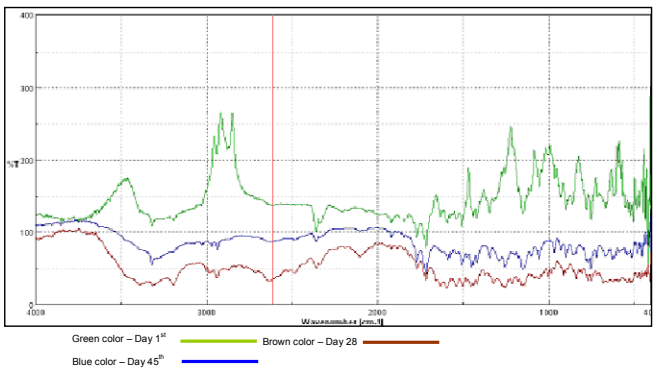


**Figure 12:** FT-IR spectrum of physical mixture subjected to stability study.

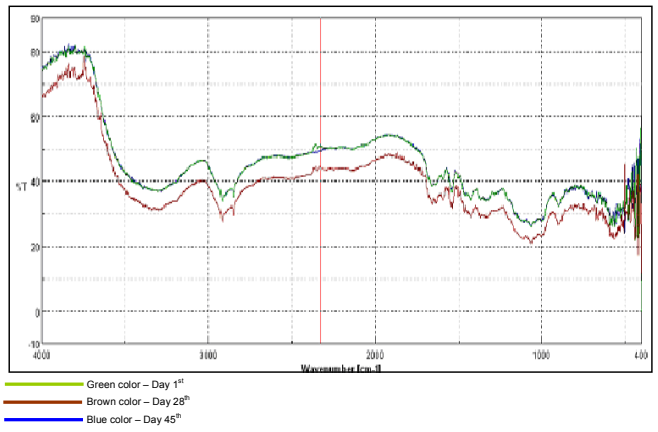


**Figure 13:** FT-IR spectrum of bilayer tablet at different days intervals.

increased DT. On the other hand, the use of these parameters in combinations as $X_1X_2$, $X_2X_3$, and $X_1X_3$ also showed different DT denoted on the side of triangle. The lowest value obtained for the combination of $X_1X_2$ as 9 seconds. The inclination of curves in Figure 13 shows that effect of $X_1$ is more pronounced to reduce the DT than that of $X_2$.

The above triangular countour plot diagrams for DT indicates that the concentration of the superdisintegrant in the blue colored region gives the minimum DT i.e. less than 10.936 sec. whereas the concentration of superdisintegrant in the orange colored region gives DT more than 20.2041 sec.

Figure 14 showing the release of drug after 15 min shows highest possible release for the combination $X_1X_2$ of 98.311%, while the lowest release value obtained for $X_3$ of 87.05% The curve seems to be inclined towards C which indicates that, the release profile of PGS is poor as compares to SSG and CCS.

The contour plot diagrams in Figure 5 for Rel at 15 min indicates, the red colored region having maximum % drug release i.e. above 96.718% where the concentration of SSG and CCS is more, while the blue colored region gives minimum % drug release of less than 88.3276%.

## Search for the Optimum Formulation

The optimum formula for MTH immediate release layer was searched by grid search. Varying the concentration of the superdisintegrant, the following results were obtained.

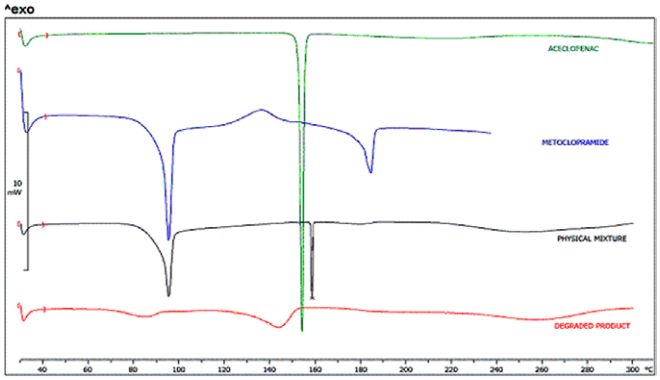


**Figure 14:** DSC thermogram of (a) ACF, (b) MTH, (c) physical mixture and (d) sample subjected to stability.

| DT (Seconds) | | | | | | | |
|---|---|---|---|---|---|---|---|
| **SSG** | **CCS** | **PGS** | **DT (Sec)** | **SSG** | **CCS** | **PGS** | **DT (Sec)** |
| 0 | 1 | 0 | 15.52 | 0 | 0.8 | 0.2 | 16.1584 |
| 0.2 | 0.8 | 0 | 11.7184 | 0 | 1 | 0 | 15.52 |
| **0.4** | **0.6** | **0** | **9.4176** | 0.6 | 0 | 0.4 | 14.7776 |
| **0.6** | **0.4** | **0** | **8.6176** | 0.4 | 0 | 0.6 | 16.9776 |
| **0.8** | **0.2** | **0** | **9.3184** | 0.2 | 0 | 0.8 | 19.5584 |
| **0.7** | **0.3** | **0** | **8.7804** | 0 | 0 | 1 | 22.52 |
| 0.5 | 0.5 | 0 | 8.83 | 0.6 | 0.2 | 0.2 | 11.5072 |
| 1 | 0 | 0 | 11.52 | 0.3 | 0.7 | 0 | 10.3804 |
| 0 | 0 | 1 | 22.52 | 0.6 | 0.3 | 0.1 | 10.0148 |
| 0 | 0.2 | 0.8 | 20.3584 | 0.9 | 0.1 | 0 | 10.2316 |
| 0 | 0.4 | 0.6 | 18.5776 | 0.85 | 0.15 | 0 | 9.7281 |
| 0 | 0.6 | 0.4 | 17.1776 | 1 | 0 | 0 | 11.52 |
| | | | | 0.8 | 0 | 0.2 | 12.9584 |
| **Rel at 15 min** | | | | | | | |
| **SSG** | **CCS** | **PGS** | **Rel at 15 min** | **SSG** | **CCS** | **PGS** | **Rel at 15 min** |
| 0 | 1 | 0 | 92 | 0 | 0.8 | 0.2 | 91.398 |
| 0.2 | 0.8 | 0 | 95.7744 | 0 | 1 | 0 | 92 |
| **0.4** | **0.6** | **0** | **98.0456** | 0.6 | 0 | 0.4 | 92.3944 |
| **0.6** | **0.4** | **0** | **98.8136** | 0.4 | 0 | 0.6 | 90.4724 |
| **0.8** | **0.2** | **0** | **98.0784** | 0.2 | 0 | 0.8 | 88.4176 |
| **0.7** | **0.3** | **0** | **98.6339** | 0 | 0 | 1 | 86.23 |
| **0.5** | **0.5** | **0** | **98.6175** | 0.6 | 0.2 | 0.2 | 95.59704 |
| 1 | 0 | 0 | 95.84 | 0.3 | 0.7 | 0 | 97.0979 |
| 0 | 0 | 1 | 86.23 | 0.6 | 0.3 | 0.1 | 97.20358 |
| 0 | 0.2 | 0.8 | 87.936 | 0.9 | 0.1 | 0 | 97.1471 |
| 0 | 0.4 | 0.6 | 89.366 | 0.85 | 0.15 | 0 | 97.659725 |
| 0 | 0.6 | 0.4 | 90.52 | 1 | 0 | 0 | 95.84 |
| | | | | 0.8 | 0 | 0.2 | 94.1836 |

**Table 15:** Feasibility Search for the MTH immediate release tablet for response variables as DT and release at 15 min. (Region I) ■ Optimized formulations.

## Optimization

The process was optimized for the response DT ($Y_1$) and $rel_{15min}$ ($Y_2$.) For selection of optimum formulations the following maximizing criteria was adopted: $rel_{15min}$>97%; DT<9 sec. Upon the subsequently exhaustive grid searches, the formulation composition with superdisintegrants levels of SSG ($X_1$) and CCS ($X_2$) fulfilled maximum requisites of an optimum formulation due to better regulation of release rate and minimum DT. The formulations showed $rel_{8h}$ as 98.67 and 8.86 sec as DT Table 15.

| DT in seconds | | | | | | | |
|---|---|---|---|---|---|---|---|
| **SSG** | **CCS** | **PGS** | **DT (Sec)** | **SSG** | **CCS** | **PGS** | **DT (Sec)** |
| 0.45 | 0.55 | 0 | 9.0769 | 0.775 | 0.225 | 0 | 9.148725 |
| **0.55** | **0.45** | **0** | **8.6769** | 0.45 | 0.55 | 0 | 9.0769 |
| **0.65** | **0.35** | **0** | **8.6521** | 0.35 | 0.65 | 0 | 9.8521 |
| 0.75 | 0.25 | 0 | 9.0025 | 0.25 | 0.75 | 0 | 11.0025 |
| **0.525** | **0.475** | **0** | **8.741725** | 0.475 | 0.525 | 0 | 8.941725 |
| 0.425 | 0.575 | 0 | 9.235525 | 0.275 | 0.725 | 0 | 10.679725 |
| 0.725 | 0.275 | 0 | 8.879725 | 0.425 | 0.575 | 0 | 9.235525 |
| 0.475 | 0.525 | 0 | 8.941725 | 0.325 | 0.675 | 0 | 10.104525 |
| **0.575** | **0.425** | **0** | **8.635525** | 0.375 | 0.625 | 0 | 9.623125 |
| **0.675** | **0.325** | **0** | **8.704525** | 0.225 | 0.775 | 0 | 11.348725 |
| **0.625** | **0.375** | **0** | **8.623125** | | | | |
| **Rel at 15 min** | | | | | | | |
| **SSG** | **CCS** | **PGS** | **Rel at 15 min** | **SSG** | **CCS** | **PGS** | **Rel at 15 min** |
| 0.45 | 0.55 | 0 | 98.378525 | 0.775 | 0.225 | 0 | 98.25250625 |
| **0.55** | **0.45** | **0** | **98.762525** | 0.45 | 0.55 | 0 | 98.378525 |
| **0.65** | **0.35** | **0** | **98.770725** | 0.35 | 0.65 | 0 | 97.618725 |
| 0.75 | 0.25 | 0 | 98.403125 | 0.25 | 0.75 | 0 | 96.483125 |
| **0.525** | **0.475** | **0** | **98.70175625** | 0.475 | 0.525 | 0 | 98.50975625 |
| 0.425 | 0.575 | 0 | 98.22380625 | 0.275 | 0.725 | 0 | 96.80225625 |
| 0.725 | 0.275 | 0 | 98.53025625 | 0.425 | 0.575 | 0 | 98.22380625 |
| 0.475 | 0.525 | 0 | 98.50975625 | 0.325 | 0.675 | 0 | 97.37005625 |
| **0.575** | **0.425** | **0** | **98.79980625** | 0.375 | 0.625 | 0 | 97.84390625 |
| **0.675** | **0.325** | **0** | **98.71405625** | 0.225 | 0.775 | 0 | 96.14050625 |
| **0.625** | **0.375** | **0** | **98.80390625** | | | | |

**Table 16:** Feasibility Search for the MTH immediate release tablet for response variables as DT and release at 15 min with Region I values. (Region II) ■ Optimized formulations.

| TIME (min) | F1 | F2 | F3 | F4 | F5 | F6 |
|---|---|---|---|---|---|---|
| **0** | 0 | 0 | 0 | 0 | 0 | 0 |
| **3** | 54.75 | 57.84 | 55.39 | 57.05 | 54.15 | 56.75 |
| **6** | 61.12 | 64.81 | 62.26 | 64.84 | 60.20 | 64.31 |
| **9** | 73.80 | 75.36 | 74.67 | 78.24 | 72.51 | 77.92 |
| **12** | 84.75 | 88.18 | 85.78 | 87.08 | 84.00 | 86.92 |
| **15** | 98.34 | 98.52 | 97.98 | 98.64 | 98.03 | 98.70 |

**Table 17:** Dissolution profile of optimized formulation of MTH immediate release tablet.

### 4) *In vitro* dissolution study of optimized formulation

The dissolution study of optimized formulation of MTH immediate release tablet was carried out in 0.1N HCl. The results were as follows

From Table 16 and Figure 6 it is evident that, formulation F6 containing 7.5 mg SSG and 4.5 mg CCS gave maximum drug release i.e. 98.70% within 15 minutes whereas formulation F3 containing 6.3 mg SSG and 5.7 mg CCS showed % of drug release of 97.98% within 15 minutes. Table 17 indicates that, the concentration of SSG in the range of 6.9 mg to 7.8 mg while concentration of CCS in the range of 4.2 mg to 5.1 mg in combination will give the minimum DT with higher % of drug release.

### 5) Validation of optimized formulations

For all 6 checkpoint formulations, the results of the physical evaluation and tablet assay were found to be within limits. Table 18 lists the composition of the checkpoints, their predicted and experimental values of all the response variables, and the percentage error in prognosis. Validation was carried out by verifying the predicted values obtained from the software with the experimental values of the

| Composition | | Dependant Variable | Experimental Value | Predicted Value | Percentage Error |
|---|---|---|---|---|---|
| $X_1$ (mg) | $X_2$ (mg) | | | | |
| 6.6 | 5.4 | DT | 9.10 | 8.67 | 4.505 |
| | | $rel_{15min}$ | 98.34 | 98.76 | -0.427 |
| 7.8 | 4.2 | DT | 9.01 | 8.65 | 3.99 |
| | | $rel_{15min}$ | 98.52 | 98.77 | -0.253 |
| 6.3 | 5.7 | DT | 9.12 | 8.74 | 4.166 |
| | | $rel_{15min}$ | 97.98 | 98.70 | -0.734 |
| 6.9 | 5.1 | DT | 8.89 | 8.63 | 2.92 |
| | | $rel_{15min}$ | 98.64 | 98.79 | -0.101 |
| 8.1 | 3.9 | DT | 9.15 | 8.70 | 4.91 |
| | | $rel_{15min}$ | 98.03 | 98.71 | -0.693 |
| 7.5 | 4.5 | DT | 8.86 | 8.62 | 2.70 |
| | | $rel_{15min}$ | 98.67 | 98.80 | -0.131 |

*DT Disintegration time, $rel_{15min}$ Drug release at 15 min

**Table 18:** Validation of optimized formulation.

| Formulation | Thickness (mm) | Hardness ($kg/cm^2$) | % Friability | DT in sec. |
|---|---|---|---|---|
| **AF*** | 1.7 | 4-5 | 0.66 | 131 |
| **A** | 1.2 | 3-4 | - | 122 |
| **F** | 0.6 | 1-2 | - | 9 |

*A=conventional release layer and F=immediate release layer

**Table 19:** Tablet properties of bilayer tablet formulation.

optimized formulations and percent error mean was calculated. Figure 7 and 8, shows linear correlation plots between the observed and predicted response variables, the residual plots showing the scatter of the residuals versus observed values. The linear correlation plots drawn between the predicted and observed responses demonstrated higher values of $r^2$ (ranging between 0.9726 and 0.9811), indicating excellent good fitting of model ($P<0.001$). Upon validation, the optimum formulations exhibited percentage error for various response variables, varying 2.70 to 4.505% (DT) and -0.734 to -0.101% ($rel_{15min}$). Thus, the low magnitudes of error as well as the significant values of $r^2$ in the current study indicate a high prognostic ability of RSM for MTH IR tablet.

An optimized formulation F6 of immediate release tablets was found to give minimum disintegration time (8.62 sec) and higher drug release at 15 minutes (98.67%) which will give ready onset of action. The higher value of SSG in combination with CCS gave out better result. Design and analysis of experiments were used as good tools to obtain the optimal formulation, which showed minimum friability, no lamination and that also met all official pharmaceutical specifications.

The validated data of the optimized formulation is given in Table 18.

## Bilayer Tablet of ASF and MTH

### 1) Properties of bilayer tablet

The tablet was evaluated for the physical parameters like thickness, hardness, % friability and DT. It was also checked for capping and lamination problem. There was no capping and lamination for any formulations.

Thickness of bilayer tablet was found to be decrease due to double compression pressure. Hardness was found to be within the range Table 19.

% friability was below 1% and it was found to decrease for bilayer tablet because of double compression. DT of bilayer tablet was found to be 131 sec inclusive of immediate release layer and conventional release layer. Above data concludes that, there is no interference of double compression pressure on the properties of bilayer tablet Table 20.

### 2) *In vitro* dissolution study of bilayer tablet

The dissolution of the bilayer tablet was carried out in two steps as described in the experimental. The results are as follows.

On comparing the release profile of MTH from immediate release layer of bilayer tablet formulation with formulation F6 (Figure 9 and Table 21), higher values for % cumulative drug release of 99.26% of MTH was observed

Similarly, the dissolution profile of ACF of bilayer tablet was compared with the optimized A3 formulation and results are as shown below.

From Figure 10 and Table 22 it was observed that the drug release profile decreases somewhat (98.03%) for the ACF conventional release layer of bilayer tablet as that of the formulation A3 with similar composition due to the double compression on the lower layer of bilayer tablet. In the first hour there was only 3-4% drug release from the conventional layer of bilayer tablet which is due to the dissolution medium 0.1 N HCl.

From the dissolution profile of the bilayer tablet, dissolution being conducted in two parts as described earlier, the formulation gives almost

| Time (Minutes) | % Cumulative Drug Release (% CPR) | |
|---|---|---|
| | Bilayer Tablet | F6 |
| 0 | 0 | 0 |
| 3 | 58.69 | 56.75 |
| 6 | 62.69 | 64.31 |
| 9 | 80.58 | 77.92 |
| 12 | 88.92 | 86.92 |
| 15 | 99.26 | 98.70 |

**Table 20:** Comparison of dissolution profile of MTH of bilayer tablet with F6 formulation.

| Time (Hours) | % Cumulative Drug Release (% CPR) | |
|---|---|---|
| | A3 | Conventional layer of bilayer tablet |
| 0 | 0 | 0 |
| 1 | 4.05 | 3.26 |
| 1.5 | 46.81 | 44.34 |
| 2 | 72.16 | 68.09 |
| 2.5 | 99.51 | 98.03 |

**Table 21:** Comparison of dissolution profile of ACF of bilayer tablet with A3 formulation.

| MTH | | | | ACF | | | |
|---|---|---|---|---|---|---|---|
| IR Ranges | Day 1st | Day 28th | Day 45th | IR Ranges | Day 1st | Day 28th | Day 45th |
| 3200 | + | + | - | 3318 | + | + | + |
| 3300 | + | + | + | 1717 | + | + | + |
| 2860 | + | - | - | 1590 | + | + | - |
| 2500 | + | + | - | 1507 | + | + | + |
| 1600 | + | + | + | 750 | + | + | + |
| 1540 | + | + | - | 717 | + | + | + |
| 1270 | + | - | - | | | | |
| 700 | + | - | - | | | | |

**Table 22:** Comparison of the IR spectra of MTH and ACF for physical mixture subjected to stability study.

same results. The formulation did not show any capping or lamination. The reason for this could be the use of easily fragmenting materials like lactose and MCC. Thus volume reduction by fragmentation seems to be more efficient means of producing larger surface areas that will promote inter-particulate attraction in the compacts. Interfacial bonds formed between two layers are strong. Thus high fragmentation of tablet components will facilitate the formation of mechanically strong bilayer tablets.

## Stability Studies

### 1) Physical changes

The mixture which was subjected to stability study at 40°C/75%RH shows brown discoloration (Figure 11) at the end of 45 days indicating photo-oxidative degradation of the sample. The data is supported by FT-IR, DSC and quantitative analysis.

FT-IR study

In the FT-IR study, the samples ACF, MTH, physical mixture at 0 days and physical mixture at 45 days were checked at 1st , 28th, and 45th day. The results were as follows

From the above results it can be concluded that, the degradation of the physical mixture was mostly checked at 1st, 28th and 45th day. MTH is getting more degraded as its characteristics peaks like 3200, 2500, 1540 (N-H), 3340 (O-H), 2860 (C-H), 1270 (C-O-C), 700 (C-Cl) are absent while only 2 peaks as 3300 (N-H) and 1600 (C=O) are present at the 45th day. In the spectra of ACF, only one peak as 1590 (N-H deformation) is absent at the 45th day. This concludes that, there is degradation of both the drugs and MTH getting more degraded as compare to ACF in the acidic environment. NH bonding was found to be mainly affected in the IR spectra of physical mixture of both the drugs which confirms that there is complex of the amino group with other acidic moiety.

The IR spectra of bilayer tablet had shown all the prominent peaks of both the drugs are present at the end of 45th day, which confirms that bilayer tablet does not show any degradation of the tablet and confirms its stability (Figure 13).

### 2) DSC study

The differential scanning colorimetry study was carried out on the four samples to study the degradation of the drug. The obtained results were as follows.

In the DSC analysis, samples were subjected to thermal study to check the degradation of sample.

The thermogram of pure ACF showed a single sharp endothermic peak at 153.25°C with an onset temperature of 152.42°C with the peak width of 1.28°C which confirms its purity. MTH also showed its sharp endothermic peak at 94.90°C which is its melting point with an onset temperature of 92.17°C confirming its purity. In the physical mixture (PM) at 0 day, both the drugs showed the characteristic sharp endothermic peaks at their respective melting points i.e. 152.84°C and 95.15°C of ACF and MTH respectively which is approximately similar to the peaks obtained for pure drug as described earlier. The thermogram of PM at 45 days showed broadening as well as shifting of the peak at 143.93°C with onset temperature 132.97°C for ACF and 85.81°C with onset temperature 74.99°C for MTH. The height of the peak of both the drugs in the PM at 45th day was found to be decreased as shown in Figure 15.

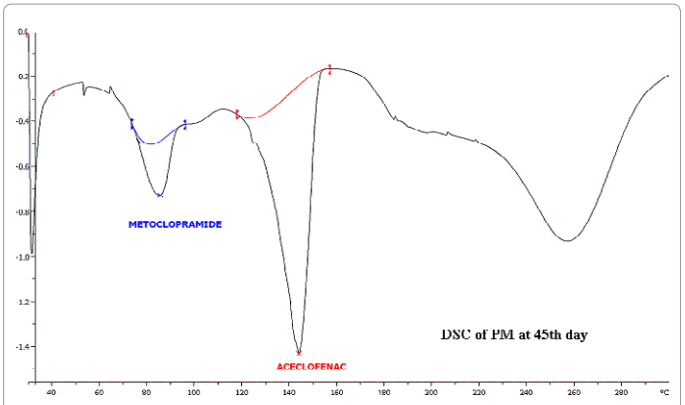


**Figure 15:** DSC thermogram of physical mixture (PM) at 45th day.

| Sample | Onset (To°C) | Peak (Tp°C) | Endset (Te°C) | Peak width (°C) |
|---|---|---|---|---|
| ACF | 152.42 | 153.25 | 154.16 | 1.28 |
| MTH | 92.17 | 94.90 | 97.41 | 2.96 |
| Physical mixture (0 days) | ACF–151.05 | ACF–152.84 | ACF–153.87 | ACF–1.48 |
| | MTH–92.02 | MTH–95.15 | MTH–97.56 | MTH–3.21 |
| Physical mixture (45 day) | ACF–132.97 | ACF–143.93 | ACF–151.50 | ACF–12.79 |
| | MTH–74.99 | MTH–85.81 | MTH–91.68 | MTH–9.92 |

**Table 23:** Thermal characteristics of samples.

The thermal characteristics of samples are summarized in Table 23.

The peaks have almost disappeared. There was a change in the peak width of both the drugs. The peak width of ACF was found to have changed drastically as mentioned in Table 15.

Also one exothermic peak was observed which may be due to oxidative degradation of the mixture (Figure 15).

The above all data predicts that, there is degradation of the drug in the sample which was subjected to stability study. The degradation might be due to the amide group of MTH with the carboxylic group of ACF.

### 3) Quantitative analysis of samples:

The % drug content study was carried out to study the degradation of the drug quantitatively. The physical mixture and bilayer tablet were evaluated for % drug content at the time interval of 7, 14, 21, 28, 45 day. In the present study quantification was carried out at two different conditions as

- At ambient conditions
- At 40°C/75% RH

The above result (Tables 24 and 25) concludes that, there was not a significant change in the value of % drug content of ACF as well as MTH at the 7th day and at 45th day which indicates stability of drug under given conditions. In the evaluation of bilayer tablet, the % drug content of ACF at 7th day was found to be 99.29% whereas and at the 45th day it was 99.31% while % drug content of MTH at 7th day was 99.16% and 98.81% at 45th day which is not a very significant change confirming the stability of bilayer tablet for longer period. Results of PM had changed significantly. The % drug content of ACF was changed from 99.09% to 82.17% at 7th and 45th day respectively whereas % drug content of MTH was found to be changed from 99.52% to 74.09%. This significant change predicts that, there is degradation of the physical

| Time (Days) | % Purity (At 40°C/75% RH) | | | |
|---|---|---|---|---|
| | ACF† | MTH‡ | Bilayer Tablet | Physical Mixture |
| 7 | 99.79 | 99.61 | ACF-99.29 | ACF-99.09 |
| | | | MTH-99.16 | MTCL-99.52 |
| 14 | 99.57 | 99.48 | ACF-99.21 | ACF-98.46 |
| | | | MTH-99.10 | MTCL-98.07 |
| 21 | 99.63 | 99.27 | ACF-99.37 | ACF-93.32 |
| | | | MTH-99.25 | MTCL-92.67 |
| 28 | 99.59 | 99.10 | ACF-99.46 | ACF-87.35 |
| | | | MTH99.07 | MTCL-79.48 |
| 45 | 99.48 | 99.31 | ACF-99.31 | ACF-82.17 |
| | | | MTH-98.81 | MTCL-74.09 |

**Table 24:** Quantitative % degradation of the physical mixture and bilayer tablet at 40°C/75% RH.

| Time (Days) | % Purity (At ambient temperature) | | | |
|---|---|---|---|---|
| | ACF† | MTH‡ | Bilayer tablet | Physical mixture |
| 7 | 99.83 | 99.77 | ACF-99.53 | ACF-99.67 |
| | | | MTH-99.60 | MTH-99.28 |
| 14 | 99.71 | 99.74 | ACF-99.36 | ACF-99.07 |
| | | | MTH-99.52 | MTH-96.22 |
| 21 | 99.65 | 99.68 | ACF-99.31 | ACF-93.43 |
| | | | MTH-99.58 | MTH-87.59 |
| 28 | 99.69 | 99.73 | ACF-99.38 | ACF-87.57 |
| | | | MTH99.49 | MTH-80.19 |
| 45 | 99.72 | 99.54 | ACF-99.45 | ACF-85.71 |
| | | | MTH-98.96 | MTH-77.34. |

**Table 25:** Quantitative % degradation of the physical mixture and bilayer tablet at ambient temperature.

mixture while the bilayer tablet formulation was found to be stable [13-18].

## Conclusion

In ACF conventional release layer, maximum drug release is achieved in 2.5 hrs. Conventional layer release very low amount of drug in 1st hour i.e. 3-4% in 0.1N HCl. Different concentrations of PVP K-30 as binder and MCC as disintegrant were used to formulate the conventional layer which showed different release pattern. The concentration of PVP K-30 significantly affected the release pattern of the drug than that of MCC which acts as disintegrant. Formulation A3 having PVP K-30 (7%) as binder and MCC (12%) as disintegrant had shown 99.15% drug release in 2.5 hrs. The optimized formula was compared with marketed formulation ACECLO (ARISTO Pharma) which showed good correlation.

In MTH immediate release layer, different concentration of superdisintegrants like SSG, CCS and PGS separately or in combination have shown different release pattern and different DT. With the use of mixture design 7 formulations were prepared in which M4 with combination of SSG and CCS showed minimum DT of 9 sec and maximum drug release of 98.31% in 15 min. Grid searches of above formulation gave 6 optimized formulations (F1-F6) in which formulation F6 containing SSG (7.5%) and CCS (4.5%) showed 98.70% drug release in 15 min. and DT of 8.86 sec. Concentration of SSG was found to be more significant than concentration of CCS in the optimized formulations of immediate release layer. Validated optimized formulation fulfilled all requisites of immediate release layer with good release rate and minimum DT.

Above two optimized formulations as ACF conventional release layer and MTH immediate release layer were used to compare bilayer tablet which showed good correlation of release profile and also fulfills all evaluation parameters with long time stability. A stability study of physical mixture at 45 days and bilayer tablet was studied in which physical mixture was found to be degraded whereas bilayer tablet remains stable at 40°C/75% RH as well as at ambient conditions. FT-IR study indicated loss of characteristic peak like N-H, C-H. C-Cl etc. of MTH while N-H peak was found to absent for ACF in the physical mixture. In DSC study, broadening and shifting of characteristic melting point peak was observed which indicate the degradation of physical mixture at 45 days. Quantitative analysis of physical mixture as well as bilayer tablet at different time intervals showed the decrease in drug content of physical mixture while % drug content of bilayer tablet was within the range. Finally, Optimized immediate release layer of MTH and conventional release layer of ASF show satisfactory pre and post compression parameters. Bi-layer tablet of MTH and ASF might be suitable for treatment of migraine by sequential release of the drug.

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