International Journal of Pharmacy and Biological Sciences-IJPBS™ (2020) 10 (1): 50-57
Online ISSN: 2230-7605, Print ISSN: 2321-3272
Research Article | Pharmaceutical Sciences | Open Access | MCI Approved

# Design and *In-Vitro* Evaluation of Colon Targeted Delayed Release Tablets to Treat Ulcerative Colitis

**Gundati Sahithya*, K. Anie Vijetha[1], M. Sunitha Reddy[2] And N. Vijaykumar[3]**

**[*, 1, 2]Department of Pharmaceutics, Centre for Pharmaceutical Sciences, IST, JNTUH, Telangana, India.**

**[3]Deputy Manager, Neuheit Pharma Technologies Pvt. Ltd., Hyderabad, Telangana, India.**

Received: 14 Oct 2019 / Accepted: 18 Nov 2019 / Published online: 01 Jan 2020
***Corresponding Author Email:** sahithyagundati11@gmail.com

## Abstract

The aim of the present research investigation was to formulate and evaluate orally administered delayed release tablets of an anti-inflammatory drug for locally targeting the colon. Mesalamine is a BCS class IV drug intended for the treatment of Ulcerative Colitis. The developed product was designed to be pharmaceutically equivalent to Asacol HD - the Reference Listed Drug. The criticality of the formulation lies in hindering the API release in acidic environment and targeting to the colon. In the present study, the motto of delaying the drug release was achieved by incorporation of non-bio-degradable polymers with pH dependent solubility as enteric coating. Compatibility studies (40°C/75% RH) revealed that there were no physical as well as chemical interactions between drug and excipients. Trials of core tablets were carried out with varying proportions of binder (povidone), disintegrant (MCC) and lubricant (talc/Mg-stearate). The formulation with a similar release profile to that of coat removed innovator product was considered optimized (for core tablets). Coating trials were carried out with different proportions of enteric coating polymers, pore former, and plasticizer. A blend of equal proportions of Eudragit L 100 and Eudragit S 100 was found to be achieving the acid protection as that of innovator. The optimized coated formulation was charged to stability studies under accelerated storage conditions (40°C/75% RH) and the results were compared with initial results. It was concluded that the optimized formulation is pharmaceutically equivalent to innovator tablets and hence it shall be further evaluated for its bioequivalence.

**Keywords**

BCS class IV, delayed release, drug targeting, enteric coating polymers, ulcerative colitis, stability studies.

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## INTRODUCTION:

Colonic delivery of drugs can be achieved by oral route (through tablets, capsules) and rectal route (through suppositories, enemas). For controlled release systems, due to greater flexibility in designing a dosage form, the oral route has received the most attention. [1] If the drugs were directly targeted on the site of action, then the treatment might be more effective.

The one area that would benefit from the development and use of modified release technology is the colon. It is a site where both local and systemic drug delivery occurs.[2] CTDD is required for topical treatment of diseases associated with colon such as inflammatory bowel disease, Ulcerative colitis, Chron's disease, irritable bowel syndrome, colon cancer, and amoebiasis.[3] The most crucial challenge that CTDDS faces is protecting the formulation from dissolving in the acidic media of stomach and preventing the release of active ingredient from formulation until it arrives at colon with no – minimum loss of API during its passage through GIT.[4]

For many years, the use of enteric coatings has achieved site-specific delivery into small intestine. Suitable polymers are available in wide range. As the pH levels in terminal ileum and colon is higher than in any other areas of GIT, site-specific delivery into colon is possible by formulating a dosage form that disintegrates at higher pH levels. The main group of polymers used for the development of CTDDS are Eudragits as they have the ability to withstand different pH levels starting from low pH in stomach to neutral pH in small intestine for several hours. The systems formulated as solid oral dosage forms (tablets, capsules, pellets) are coated with pH sensitive polymers as an enteric coating. [5]

## MATERIALS AND METHODS:

### Materials:

Mesalamine was procured from Divi's laboratories, Lactose monohydrate (Pharmatose 200M®, Gravity), Povidone (Kollidon 30®, Evonik), Microcrystalline cellulose (Avicel pH 302, Signet), Talc (Luzenac Pharma), Magnesium stearate (Ligamed MF-2V®, Peter Grievens), Colloidal silicon dioxide (Aerosil 200 Pharma, Evonik), Eudragit L30D55® (Evonik), Eudragit L100® (Evonik), Eudragit S100® (Evonik), Dibutyl sebacate (DBS NF), Triethyl citrate (Zuhahi Rondu), Titanium dioxide (Zuhahi Pharma), PEG 6000, Iron oxide red (Zuhahi Pharma), Isopropyl alcohol (Emplura).

### Methods:

### Preliminary studies:

The preliminary studies like characterization of API and compatibility studies of API and excipients were performed. Characterization of API includes physical parameters evaluation like Bulk density, Tapped density, Compressibility Index and, Hausner's ratio and solubility studies. [6]

**Table 1: Characterization of API**

| S.No | Test | | Result |
|---|---|---|---|
| 1 | Bulk density (g/mL) | | 0.34 |
| 2 | Tapped density (g/mL) | | 0.95 |
| 3 | Compressibility index (%) | | 63.79 |
| 4 | Hausner's ratio | | 2.76 |
| 5 | Solubility studies (mg/mL) | Purified water | 0.84 |
| | | 0.1N HCl | 9.38 |
| | | pH 6.0 phosphate buffer | 4.96 |
| | | pH 7.2 phosphate buffer | 17.35 |

### Compatibility studies of API and excipients

The compatibility studies of API and excipients were performed by physical observations. Mesalamine was mixed in equal ratios with all the excipients used in formulation and kept at 40°C/75% RH condition for one month. Physical properties of samples were monitored regularly for any changes in colour in the specific duration of storage and the results were reported in table 2. Along with these studies, FTIR studies were also conducted for the optimized formulation. The compatibility studies showed that there were no significant interactions between the drug and the excipients.

**Table 2: Physical observations of compatibility studies of API and excipients**

| S. No | Ingredients | Ratio | 40°C / 75 % RH | | |
|---|---|---|---|---|---|
| | | | Initial | 15 days | 30 days |
| 1 | Mesalamine (API) | NA | White to off-white coloured powder | No change | No change |
| 2 | API + Lactose monohydrate | 1:1 | White to off-white coloured powder | No change | No change |
| 3 | API + Povidone | 1:1 | White to off-white coloured powder | No change | No change |
| 4 | API + Microcrystalline cellulose | 1:1 | White to off-white coloured powder | No change | No change |
| 5 | API + Talc | 1:1 | White to off-white coloured powder | No change | No change |
| 6 | API + Magnesium stearate | 1:1 | White to off-white coloured powder | No change | No change |
| 7 | API + Colloidal silicon dioxide | 1:1 | White to off-white coloured powder | No change | No change |
| 8 | API + Eudragit L 100 | 1:1 | White to off-white coloured powder | No change | No change |
| 9 | API + Eudragit S 100 | 1:1 | White to off-white coloured powder | No change | No change |
| 10 | API + TEC | 1:1 | White to off-white coloured wet lump | No change | No change |
| 11 | API + Titanium dioxide | 1:1 | White to off-white coloured powder | No change | No change |
| 12 | API + PEG 6000 | 1:1 | White to off-white coloured powder | No change | No change |
| 13 | API + Iron Oxide Red | 1:1 | Light red coloured powder | No change | No change |
| 14 | API + Lactose monohydrate + Povidone + MCC + Talc + Magnesium stearate + Colloidal silicon dioxide+ Eudragit L 100 + Eudragit S 100 + TEC + Titanium dioxide + PEG 6000 + Iron Oxide Red | 1:1:1:1:1 :1:1:1:1: 1:1:1:1 | Light red coloured powder | No change | No change |

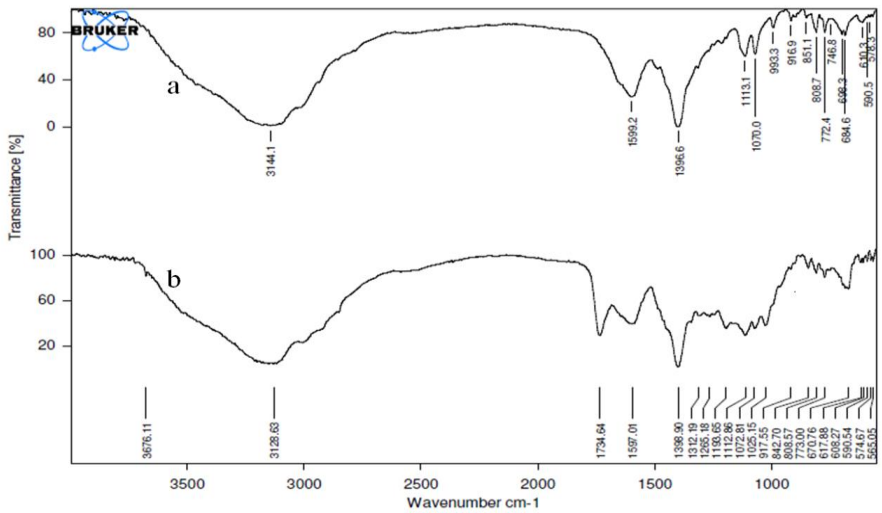



**Fig 1: IR overlay of Mesalamine and optimized formulation (a) Mesalamine (b) Optimized formulation**

**Formulation:**

Core tablets of Mesalamine were prepared by wet granulation method. [7] Prepared core tablets were then coated with prepared coating dispersions.

**Preparation of coating dispersion**

Prepare the solvent system by mixing isopropyl alcohol and water in 95:5 ratios and then divide it into 70 parts and 30 parts. To 70 parts solvent system, slowly add enteric polymers, Solubilizing agent and plasticizer and stir for 30min with magnetic stirrer. To 30 parts solvent system add remaining ingredients and homogenize for 10min. Add minor part to major part and stir for 15min. Finally pass the prepared dispersion through ATSM mesh #100.

**Table 3: Formulation of Mesalamine core tablets**

| Ingredients (mg/unit) | F1 |
|---|---|
| Mesalamine | 800 |
| Lactose monohydrate | 215 |
| Povidone | 20 |
| Purified water | 22.4%w/w |
| Microcrystalline cellulose | 24 |
| Talc | 5 |
| Colloidal silicon dioxide | 5 |
| Magnesium stearate | 5 |
| Total weight of core tablet | 1050 |

**Table 4: Formulations for coating trials:**

| Ingredients (mg/unit) | CF1 | CF2 | CF3 | CF4 | CF5 | CF6 | CF7 | CF8 | CF9 |
|---|---|---|---|---|---|---|---|---|---|
| Core tablet | 1050 | 1050 | 1050 | 1050 | 1050 | 1050 | 1050 | 1050 | 1050 |
| Eudragit L 30D 55 | 32 | 48 | 64 | - | - | - | - | - | - |
| Eudragit L100 | - | - | - | - | - | - | 10 | 22 | 16 |
| Eudragit S100 | | | | 64 | 32 | 32 | 22 | 10 | 16 |
| Dibutyl sebacate | 3 | 3 | 3 | - | - | - | - | - | - |
| Triethyl citrate | - | - | - | 3 | 3.2 | 3.2 | 3.2 | 3.2 | 3.2 |
| Talc | 20 | 20 | 20 | 20 | 17.8 | 17.8 | 17.8 | 17.8 | 17.8 |
| Ferric oxide Red | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Titanium dioxide | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| PEG 6000 | - | - | - | - | - | 1 | 1 | 1 | 1 |
| Isopropyl alcohol | 95 parts | 95 parts | 95 parts | 95 parts | 95 parts | 95 parts | 95 parts | 95 parts | 95 parts |
| Purified water | 5 parts | 5 parts | 5 parts | 5 parts | 5 parts | 5 parts | 5 parts | 5 parts | 5 parts |
| Total weight of coated tablet (mg/unit) | 1114 | 1130 | 1146 | 1146 | 1112 | 1113 | 1113 | 1113 | 1113 |
| % Buildup | 6.1 | 7.62 | 9.14 | 9.14 | 5.9 | 6.0 | 6.0 | 6.0 | 6.0 |

**Table 5: Equipment and process parameters**

| S.No | Process step | Equipment | Process parameters | |
|---|---|---|---|---|
| 1 | Wet granulation | Rapid mixer granulator | Impeller speed: 193 rpm<br>Chopper speed: 1440 rpm | |
| 2 | Drying | Fluid bed Dryer | Inlet temperature: 50˚C<br>Fluidization: 60cfm | |
| 3 | Dry milling | Mobile mini Multi Mill | Knives direction: forward<br>Speed: Medium | |
| 4 | Lubrication | Octagonal blender | Blender size: 2L<br>Rpm: 13 | |
| 5 | Compression | Compression Machine | Turret speed: 9rpm | |
| 6 | Coating | Auto coating machine | Inlet Temperature (°C)<br>Product Temperature (°C)<br>Exhaust Temperature (°C) | 25.4-30.4<br>22.9-25.6<br>26.9-28.3 |

| | |
|---|---|
| Pan RPM | 5-8 |
| Spray rate (g/min) | 2.56-7.45 |
| Atomization (bar) | 0.6-0.2 |
| Pattern air (bar) | 0.6-0.2 |

**Evaluation parameters [6]:**

The lubricated blend parameters were evaluated by bulk density, tapped density, compressibility index and Hausner's ratio and the results were reported in table 8. The core and coated tablets were evaluated for various parameters like weight variation, hardness, thickness, friability, disintegration in 0.1N HCl and dissolution and the results were reported in table 10 and table 11.

**Disintegration in 0.1N HCl**

To check the protective mechanism of polymer coat in acidic medium during dissolution, disintegration test is to be performed in acidic medium (0.1N HCl, 2 hours, 37°C±0.5°C). The disintegration results were reported in the table 10

**Dissolution [8]**

Subject 6 tablets to dissolution in OGD media as described in the table 6. Compare the release profiles of coated formulations with that of innovator product (RLD-Reference Listed Drug) in OGD media by means of similarity factor $f_2$. The composition which shows similarity with the RLD is considered as optimized formula for coating.

**Table 06: RLD dissolution studies protocol and specifications as per USP in OGD media**

| Stage | Acid stage | Buffer stage 1 | Buffer stage 2 |
|---|---|---|---|
| **Apparatus** | USP II (Paddle) | | |
| **Media** | 0.1N HCl | pH6.0Phosphate buffer | pH 7.2 Phosphate buffer |
| **RPM** | 100 | 100 | 50 |
| **Volume** | 500 mL | 900 mL | 900 mL |
| **Recommended time points** | 2 hrs | 1 hr | 120 minutes |
| **Dilutions** | - | - | Pipette 2mL of sample in 50mL VF and make up to volume with pH 7.2 phosphate buffer |
| **Blank** | 0.1N HCl | pH6.0Phosphate buffer | pH 7.2 Phosphate buffer |
| **Standard solution** | 0.1N HCl (20ppm) | pH6.0Phosphate buffer (20ppm) | pH 7.2 Phosphate buffer (40ppm) |
| **$\lambda_{max}$** | 302nm | 330nm | 332nm |
| **Specification limits** | No individual value exceeds 1% dissolved in 2Hrs. | No individual value exceeds 1% dissolved in 1Hr. | Q=80% at 1.5 hrs |

**Stability Studies:**

Pack the coated tablets of the optimized formulation in 120CC HDPE bottle, seal and load into a 40°C/75% RH condition stability chamber. Stability studies were done for 3 months. Withdraw samples at monthly intervals and subject to assay by HPLC method, water content by Karl Fischer titration method and dissolution.

**Assay by HPLC [8]**

Transfer 50.0g of Mesalamine standard in 50mL volumetric flask and add 5mL of 0.25N HCl. Sonicate to dissolve, dilute to volume and mix. Pipette out 4mL of this standard stock solution in 25mL volumetric flask dilute to volume and mix to obtain 160ppm standard solution. Filter using 0.45µm membrane filter. For the preparation of sample solution, take 20 tablets average weight and then crush them. Transfer accurately weighed powder equivalent to 800mg of Mesalamine to 500mL volumetric flask. Add 50mL 1N HCl solution, sonicate for 30min at below 30°C with intermediate shaking. Add 300mL water, sonicate for 20min at below 30°C with intermediate shaking and dilute to volume with water. Centrifuge a portion of this solution at 3500rpm for 5min and filter using 0.45µm membrane filter.

**Table 7: Chromatographic conditions for assay by HPLC**

| S.No. | Chromatographic parameters | |
|---|---|---|
| 1 | Column | Hypersil BDS C18 (150×4.6)mm, 5µm |
| 2 | Wavelength | 230nm |
| 3 | Flow rate | 1.2mL/min |
| 4 | Sample temperature | 25°C |
| 5 | Column temperature | 40°C |
| 6 | Injection volume | 20µL |
| 7 | Run time | About 30 min |
| 8 | Standard concentration | 160 ppm |
| 9 | Blank | Diluent |
| 10 | Diluent | 0.25N HCl |

**RESULTS AND DISCUSSION:**

**Dissolution:**

The dissolution profiles of innovator product and formulations CF1-CF9 were tabulated in table 11. The drug release profile shows that when Eudragit L100 and Eudragit S100 are used in 1:1 ratio in optimized formulation CF9, the drug release of test formulation matches with the drug release of innovator product.

**Table 8: Lubricated blend parameters of formulation F1**

| Bulk Density (g/ml) | Tapped density (g/ml) | Carr's index (%) | Hausner's ratio |
|---|---|---|---|
| 0.4444±0.021 | 0.5263±0.099 | 15.5555±0.034 | 1.1842±0.016 |

**Table 9: Core tablets evaluation of formulation F1**

| Weight variation | Hardness (kp) | Thickness (mm) | % Friability |
|---|---|---|---|
| 1051±0.87 | 15.3±1.80 | 6.32±0.27 | 0.18 |

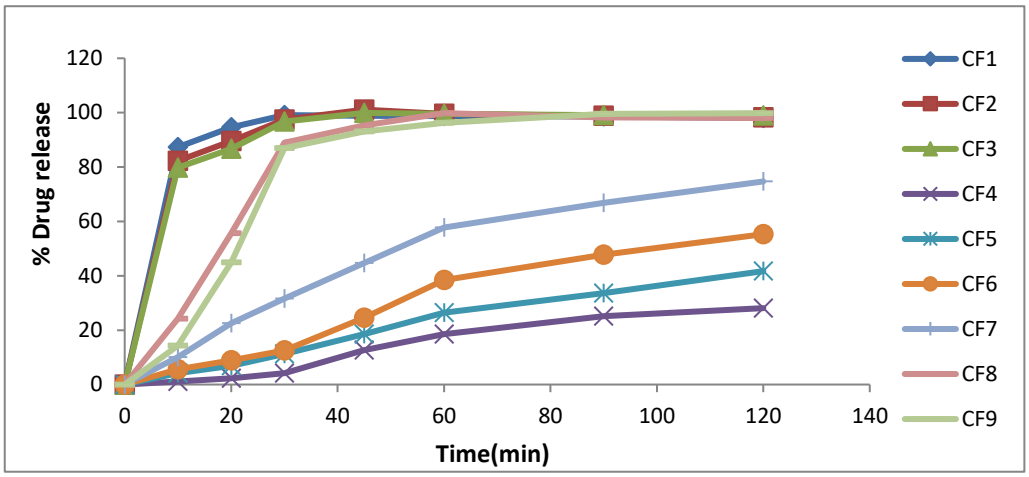
**Table 10: Coated tablets evaluation of formulations F10-F18:**

| Formulations | Weight variation | Hardness (Kp) | Thickness (mm) | Disintegration time (min) |
|---|---|---|---|---|
| **CF1** | 1112±0.87 | 12.9±1.65 | 6.66±0.13 | 70-78 |
| **CF2** | 1116±0.98 | 12.7±1.23 | 6.68±0.32 | 75-79 |
| **CF3** | 1148±0.45 | 12.5±1.88 | 6.53±0.41 | 80-94 |
| **CF4** | 1112±1.14 | 15.3±1.12 | 6.69±0.54 | 89-97 |
| **CF5** | 1114±0.97 | 13.9±1.54 | 6.69±0.37 | 86-93 |
| **CF6** | 1113±0.83 | 13.5±1.32 | 6.66±0.26 | 89-97 |
| **CF7** | 1115±0.59 | 14.3±1.49 | 6.57±0.19 | 158-179 |
| **CF8** | 1111±0.81 | 16.0±1.57 | 6.72±0.76 | 95-102 |
| **CF9** | 1113±0.93 | 17.4±1.87 | 6.82±0.62 | 96-103 |

**Table 11: Dissolution profiles of coated tablets of test formulations CF1-CF9**

| Time (hr) | CF1 | CF2 | CF3 | CF4 | CF5 | CF6 | CF7 | CF8 | CF9 |
|---|---|---|---|---|---|---|---|---|---|
| 02 | **% drug release in Acid stage** | | | | | | | | |
| | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| 01 | **% drug release in Buffer stage I** | | | | | | | | |
| | 45.2±3.43 | 44.3±2.66 | 42.9±3.76 | 0.1 | 0.1 | 0.1 | 0.1 | 0.2 | 0.1 |
| **Time (min)** | **% drug release in Buffer stage II** | | | | | | | | |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 10 | 87.3±5.22 | 82.3±5.21 | 79.8±2.25 | 1.1±2.15 | 4.2±3.12 | 5.6±3.43 | 10.1±2.87 | 24.2±3.45 | 14.3±3.11 |
| 20 | 94.6±3.02 | 89.6±4.15 | 86.7±2.02 | 2.3±1.16 | 6.9±2.55 | 8.9±2.97 | 22.5±2.54 | 55.6±3.11 | 44.9±2.54 |
| 30 | 99.1±2.55 | 97.4±3.27 | 96.7±1.65 | 4.2±1.14 | 11.3±2.13 | 12.5±2.32 | 31.6±1.98 | 88.9±2.16 | 87.0±2.12 |
| 45 | 98.9±2.23 | 101.1±2.11 | 99.9±1.33 | 12.7±1.13 | 18.5±1.03 | 24.6±1.76 | 44.7±1.56 | 95.3±1.79 | 93.1±1.02 |

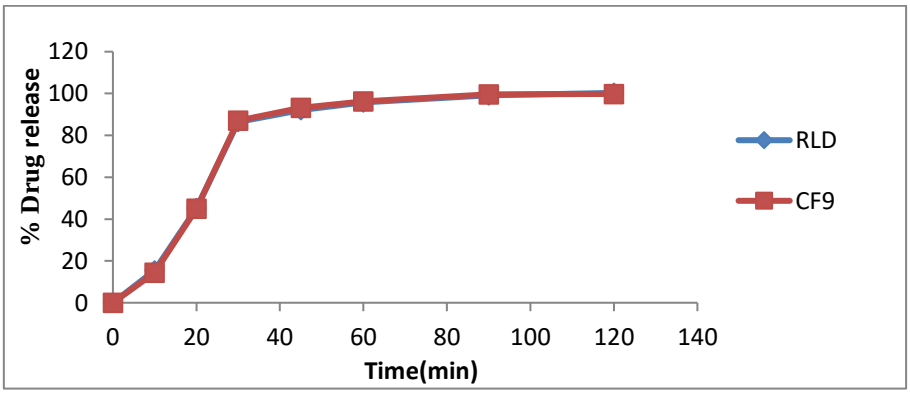
| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 60 | 98.7±2.07 | 99.6±3.15 | 99.6±1.24 | 18.5±0.86 | 26.4±1.01 | 38.4±1.00 | 57.8±1.23 | 99.8±1.45 | 96.2±1.00 |
| 90 | 98.6±1.17 | 98.8±2.22 | 99.1±1.02 | 25.1±0.84 | 33.6±0.54 | 47.7±0.76 | 66.8±0.98 | 98.3±0.86 | 99.6±0.53 |
| 120 | 98.0±1.11 | 98.3±1.18 | 99.0±0.54 | 28.1±0.53 | 41.7±0.53 | 55.3±0.65 | 74.7±0.63 | 98.0±0.55 | 99.8±0.52 |
| **f2** | 23.8 | 25.5 | 26.6 | 8.6 | 11.1 | 13.9 | 22.3 | 62.1 | 95.8 |




**Graph1: Dissolution profiles of coated tablets of test formulations CF1-CF9**

**Table 11: Comparative dissolution profile of RLD and optimized formulation**

| **Time (hr)** | **RLD** | **CF9** |
|---|---|---|
| 02 | **% drug release in Acid stage** | |
| | 0.0 | 0.0 |
| 01 | **% drug release in Buffer stage I** | |
| | 0.1 | 0.1 |
| **Time (min)** | **% drug release in Buffer stage II** | |
| 0 | 0 | 0 |
| 10 | 15.4 ±2.13 | 14.3±3.11 |
| 20 | 45.3±2.05 | 44.9±2.54 |
| 30 | 86.5±1.29 | 87.0±2.12 |
| 45 | 92.1±1.05 | 93.1±1.02 |
| 60 | 95.7±1.12 | 96.2±1.00 |
| 90 | 99.2±0.85 | 99.6±0.53 |
| 120 | 100.3±0.43 | 99.8±0.52 |
| **f2** | | |




**Graph 2: Comparative dissolution profile of RLD and optimized formulation**

**Stability Studies:**

Stability studies results were reported in the table 12. The stability results show that the assay, dissolution studies and water content are within the specifications.

**Table 12: Stability data compilation of the optimized formulation**

| **Time points of loaded sample** | | | **Initial** | **1M** | **2M** | **3M** |
|---|---|---|---|---|---|---|
| **Assay (**90-110%) | | | 100.10% | 100.20% | 98.30% | 99.50% |
| **Dissolution** | **Time (min)** | **Limit** | **% Drug release** | **%Drug release** | **% Drug release** | **% Drug release** |
| **Acid stage** | 2hrs | NMT1.0% | 0 | 0 | 0 | 0 |
| **Buffer stage I** | 1hr | NMT1.0% | 0.1 | 0.1 | 0.2 | 0.1 |
| **Buffer stage II** | 10 | NLT 80% in 90min | 14.3±3.11 | 16.5±3.72 | 15.8±3.44 | 17.8±3.13 |
| | 20 | | 44.9±2.54 | 47.0±3.04 | 46.8±2.33 | 44.9±2.38 |
| | 30 | | 87.0±2.12 | 85.3±2.22 | 85.3±2.02 | 84.3±2.15 |
| | 45 | | 93.1±1.02 | 90.3±1.10 | 93.2±1.70 | 92.7±0.99 |
| | 60 | | 96.2±1.00 | 96.5±1.00 | 97.9±1.24 | 96.8±0.91 |
| | 90 | | 99.6±0.53 | 98.3±0.31 | 99.2±0.35 | 99.2±0.49 |
| | 120 | | 99.8±0.52 | 99.4±0.12 | 102.1±0.22 | 100.3±0.34 |
| **Water content** | | NMT 4.0% | 3.1 | 3.1 | 3.2 | 3.6 |

**CONCLUSION:**

Mesalamine is a BCS class IV drug intended for the treatment of Ulcerative Colitis. The developed product was designed to be pharmaceutically equivalent to Asacol HD - the Reference Listed Drug**.** In the present study, the motto of delaying the drug release was achieved by incorporation of non-bio-degradable polymers with pH dependent solubility as enteric coating. Compatibility studies (40°C/ 75% RH) for 1 month revealed that there were no physical as well as chemical interactions between drug and excipients**.** Optimization of core tablets was achieved by the use of MCC as disintegrant. Coating composition optimization was achieved by the use of blend of Eudragit S100 and Eudragit L100. A blend of equal proportions of Eudragit L 100 and Eudragit S 100 was found to be achieving the acid protection as that of innovator. The optimized coated formulation (CF9) was charged to stability studies under accelerated storage conditions (40°C/ 75% RH) and the results were compared with initial results. It was concluded that the optimized formulation is pharmaceutically equivalent to innovator tablets and hence it shall be further evaluated for its bioequivalence. Furthermore, *in vitro* studies in multimedia and *in vivo* studies in human volunteers are to be performed in order to confirm the delay in release of drug and to compare it with the performance of innovator product.

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