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Research Article

# FORMULATION AND EVALUATION OF BILAYER TABLET OF METRONIDAZOLE AND DICYCLOMINE HYDROCHLORIDE FOR TREATMENT OF IRRITABLE BOWEL DISEASE

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## ABSTRACT

The aim of the present study was to prepare bi-layer tablet of Metronidazole and Dicyclomine Hydrochloride for the effective treatment of Irritable Bowel Disease. Metronidazole and Dicyclomine Hydrochloride were formulated as immediate and sustained release layer respectively. The rational for formulation of bi-layer tablet of these two combinations was Metronidazole (immediate release) is strong antibiotic usually applied for antidiarrheal to treat inflammation of the large intestine and Dicyclomine Hydrochloride (Sustained release) is anticholinergic drug primarily used for irritable bowel disease. Bilayer tablet was suitable for maximize the efficacy of drugs in irritable bowel disease.

## INTRODUCTION:

In the last two decades, Irritable Bowel Syndrome (IBS) has gained considerable attention in the health-care field due to its increasingly high prevalence, sometimes debilitating effects and diverse symptom representation[1]. Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances, and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose[2]. Metronidazole 2-(2-methyl-5-nitroimidazol-1-yl)ethanol is a potent antibiotic usually applied for treatment of anaerobic infections and mixed infections, surgical prophylaxis requiring anaerobic coverage, Clostridium difficile-associated diarrhea and colitis diarrhea. The drug has potent activity and Well absorbed (at least 80%) with peak plasma concentrations achieved in 1-3 hours following oral administration of therapeutic doses of immediate release formulation. Dicyclomine Hydrochloride 2-(diethylamino) ethyl 1-cyclohexyl cyclohexane-1-carboxylate; hydrochlorideis a muscarinic antagonist used as an antispasmodic and in urinary incontinence. It antagonizes muscarinic receptors on smooth muscle in the gastrointestinal (GI) tract, thereby preventing the actions of acetylcholine and reducing GI smooth muscle spasms.

## MATERIAL AND METHODS:

### Materials

Dicyclomine Hydrochloride was a gift sample obtained from Shreepati Pharma, Indore, Metronidazole was a gift sample obtained from Modern Laboratories, Indore, Sodium Starch Glycolate, Poly vinyl Pyrollidone (PVP K-30), Magnesium stearate, Talc, Isopropyl alcohol were procured from Kasliwal Brothers Indore. All chemicals were used of analytical grade.
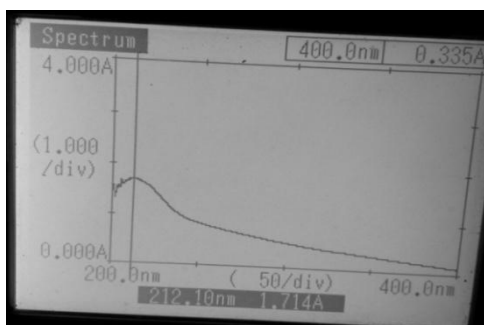
### Methods

### UV Analysis

### Calibration curve of Metronidazole

The calibration curve of Metronidazole was prepared in distilled water and 1.8 pH phosphate buffer by using Shimadzu 1800 UV visible spectrophotometer. Accurately weighed 50mg of Metronidazole was transferred into a 50ml volumetric flask and the volume was made up with methanol to obtain a 1000µg/ml stock solution of Metronidazole. From the stock solution 1ml was taken and transferred into a 10ml volumetric flask and rest of the volume was made up with methanol to obtain a 100µg/ml of solution from which 1 to 10µg/ml dilutions were prepared[3].

**Calibration curve of Dicyclomine Hydrochloride**

 

The calibration curve of Dicyclomine Hydrochloride were prepared in distilled water and 7.2 pH phosphate buffer by using Shimadzu 1800 UV visible spectrophotometer. Same procedure as mentioned above is utilized in phospate buffer 7.2 respectively.

**Solubility studies**

The solubility of both drugs in various medium was determined by shake flask method. In this method 2ml of each solvent was taken into a vial and an excess amount of drug was added. The vials were sealed properly and stirred for 10min. They were then kept on orbital flask shaker at 37°C for 24h. After solubilization of drug, an extra amount of drug was added to the vials containing drug-solvent mixture. The process was repeated until saturation solubility of drug, indicated by presence of undissolved drug. The mixtures were then kept at room temperature for 24 h. and centrifuged using Remi12C micro-centrifuge at 3000RPM for 15min. The supernatant were separated and diluted with respective solvents. The drug concentration was analyzed spectrophotometrically at 212 and 274 nm using UV-visible spectrophotometer (Shimadzu-1800)[3].

**Preparation of Metronidazole Immediate release layer by Direct Compression**

Weigh all Ingredients as per the quantities shown in table no. 1. Pass all the ingredients through sieve #80 and collect individuals in polybags. Mix measured quantity of Metronidazole, SSG and PVP-K30 for 15 minutes in a polybag. Magnesium stearate and talc was added to it and blend for 5 min in pastle mortar. Compress final blend using B-Tooling, multiple rotatory compression machine using 8 mm round shaped punches and corresponding dies.
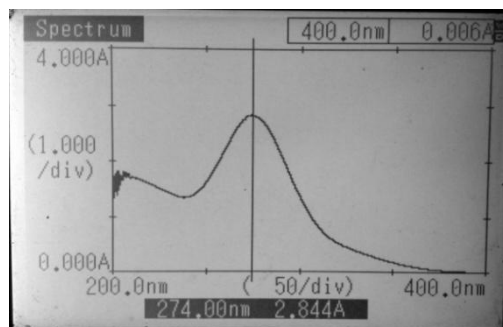
**Table 1:** Formula for immediate release layer

| S. N. | Ingredients | Quantity Per 10 Tablets (in mg) |
|-------|-------------|---------------------------------|
| 1. | Metronidazole | 2500 |
| 2. | Sodium starch glycolate | 300 |
| 3. | PVP K-30 | 150 |
| 4. | Magnesium Stearate | 50 |
| 5. | Talc | 50 |

**Preparation of Dicyclomine Hydrochloride Sustained release layer by Wet Granulation**

Weigh all Ingredients as per the quantities defined in tablet no. 2. Pass all the ingredients through sieve no #80 and collect in separate polybags. Prepare binder solution by dissolving PVP-K30 in Isopropyl alcohol. Mix all material expect lubricant for 15 min. Add binder solution to the above step and mix until uniform dough mass granules are formed. Pass all granules through #12 no. sieve. Dry all the granules at 50-55°C temperature. Add Magnesium stearate and Talc and blend it for 5 Minute. Compress final blend using B-tooling, multiple rotatory compression machine uses 8 mm round shape punches and corresponding dies.

**Selection of polymers and suitable experimental design**

A central composite design for two factor three level was selected to optimize the variable response. The two factors, viz. Polymer $X_1$ Eudragit RSPO and Polymer $X_2$ PVP-K30 of each polymer blend, were required by the experimental design and the factor level were suitably coded. The amount of Magnesium stearate was kept constant, while Isopropyl alcohol was taken in a sufficient quantity to maintain a constant tablet mass of 200mg. time taken to release 50% of drug were taken as the variable response[4].

**Table 2:** Formulation optimization data

| S.No. | Ingredients | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|-------|-------------|----|----|----|----|----|----|----|----|----|
| 1. | Dicyclomine Hydrochloride | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 |
| 2. | Eudragit RSPO | 400 | 400 | 400 | 500 | 500 | 500 | 600 | 600 | 600 |
| 3. | Microcrystalline cellulose | 800 | 800 | 800 | 800 | 800 | 800 | 800 | 800 | 800 |
| 4. | PVP-K30 | 80 | 100 | 120 | 80 | 100 | 120 | 80 | 100 | 120 |
| 5. | Magnesium Stearate | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 |
| 6. | Talc | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 |
| 7. | Isopropyl alcohol | QS | QS | QS | QS | QS | QS | QS | QS | QS |

### Evaluation of Granules

To find out physiochemical properties and release characteristics of the granular blend, all formulations are subjected to pre-formulation studies like bulk density, tapped density, Angle of repose, compressibility index and Hausner's ratio.

### Preparation of Bilayer tablets of Metronidazole and Dicyclomine Hydrochloride

Optimized batch of Metronidazole and Dicyclomine Hydrochloride were selected for formulation of bilayer tablet. As previously reported procedure for granules of immediate and sustained release layer were blended separately. One by one both layer was filled in rotatory compression machine and compressed.

### Evaluation of compressed tablets

The tablets prepared were evaluated for weight variation, disintegration test, dissolution test, thickness, hardness of individual dose and friability.

### Weight variation

The weight variation was performed by weighing 20 tablets individually, then individual weight of tablet is compared with average weight of 20 tablets.

### Hardness

The hardness of each batch of tablet was checked by using Monsanto hardness tester. The hardness was measured in terms of kg/cm2.

### Friability

The friability was determined by first weighing 10 tablets before placing in friability tester (Roche friabilator), which was rotated for 4 min at 25 rpm. After dusting, the remaining weight of tablet was determined.

### Thickness

The thickness of tablet was determined by vernier caliper.

### Disintegration

The test was performed by introducing one tablet in each tube and adds a disc to each tube. Suspend the assembly in the beaker containing purified water and operate the apparatus until the tablet completely disintegrates.

### *In Vitro* Dissolution test

The in-vitro dissolution studies were carried out using USP apparatus type II at 50 rpm. The dissolution medium (900 ml) consisted of simulated gastric fluid (pH 1.2 HCL buffer) was used for the first 2 hour and then replaced with phosphate buffer (pH 7.2) for 3 to 8 hours (900 ml), maintained at 37±0.5ºC. The drug release at different time interval was measured by UV-visible spectrophotometer at 212 nm and 274 nm. The release studies were conducted on six tablets in each batch and the mean values were plotted versus time [4].

### RESULT AND DISCUSSION:

Metronidazole and Dicyclomine Hydrochloride Bilayer tablet was formulated. Total nine batches were prepared for sustained release layer. All the formulations were subjected to evaluation, Tablet weight of sustained release layer varied from 155 to 189 mg, and thickness 3 to 4.1 mm. All the tablets exhibited friability values between 0.22 to 0.3, all immediate release layer disintegrated in less than 1 minute.

### CONCLUSION:

The present study was carried out to prove that bi-layer tablet of Metronidazole and Dicyclomine Hydrochloride as Immediate and Sustained release layer can be formulated. The concept explains the application of IR/SR from single dosage form which results in cost effectiveness and reduces the problems of irritable bowel disease.

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