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# DESIGN DEVELOPMENT AND EVALUATION OF SUSTAINED RELEASE DOSAGE FORM OF ORNIDAZOLE USING DIFFERENT POLYMERS

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**ABSTRACT**

Ornidazole is a synthetic nitroimidazole used for treatment of infections caused by both anaerobic bacteria and protozoa. It has short half-life, makes the sustained release (SR) forms extremely advantageous. Sustained release tablets results in increased bioavailability. The purpose of the present study was to develop a sustain release matrix drug delivery system (SR) containing Ornidazole as a model drug by using various proportions of polymers such as HPMC E15, HPMC K15. The sustained release formulations of Ornidazole were prepared by direct compression method. Optimization of formulation was done by studying effect of drug to polymer ratio on drug release. FT-IR studies indicated absence of any interaction between Ornidazole, polymers (HPMC E15 and HPMC K15) and excipients. Ten formulations were prepared and Formulation F8 possesses good drug release property. The tablets were also evaluated for its hardness, friability and other *In-vitro* evaluation tests. All parameters complied with IP limits. Drug release was diffusion controlled and followed Zero order kinetics. Non-Fickian diffusion was the drug release mechanism for all the tablets formulated.

**Key words:** Ornidazole, Controlled Release, DSC, Characterization, *In-vitro*.

## INTRODUCTION

Sustained release systems that oral route of administration has been investigated the most, because of flexibility in dosage forms design that the oral route offers [1]. With many drugs, the basic goal of therapy is to achieve a steady-state blood level or tissue level that is therapeutically effective and nontoxic for an extended period of time. To achieve better therapeutic action various types of drug delivery systems are available, out of which sustained release systems are gaining much importance because of their wide advantages over others like ease of administration, convenience and non-invasiveness [2].

Matrix tablets are one of the most widely used dosage forms within controlled release techniques in pharmaceutical manufacturing standards, as drug release rates are matrix devices have a major advantage over other controlled release devices, as they cannot undergo sudden dose dumping. This gives a higher initial release rate and can be made to release at a nearly constant rate. The polymer when incorporated into pharmaceutical dosage forms such as tablets had shown a tendency to line arise the drug release curves and gives zero order release.

Sustained drug delivery system is behind investigated so as to alter the body distribution of a drug with a view to reduce the toxicity of the drug and/or deliver them more efficiently to their site of action. In generalized way, the sustained release or controlled release systems are intended to exercise control on drug release in the body, whether this be of a temporal or spatial nature or both: In other words, the system attempts to regulate drug concentrations within the tissue or cells.

The drug selected under the study is ornidazole and is an antibiotic, antifungal, antiprotozoal and can remain in the stomach for long periods and hence can release the drug over a prolonged period of time.

The present study is an attempt to formulate sustained release matrix tablets of ornidazole using different polymers, in order to improve the patient compliance, better therapeutic efficacy, less side effects

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and reduced dosage regimen with less toxicity for treatment of many diseases.

## MATERIALS

Ornidazole was obtained as gift sample from DR. Reddys Laboratory, Hyderabad, other Chemicals like Microcrystalline cellulose from SD Fine Chemicals Ltd., Mumbai, Magnesium Stearate and Talc were procured from Nice Chemicals Pvt. Ltd., Cochin, Polymers like HPMC E15, HPMC K15 were procured from S. Kant. Health Care Ltd., Gujarat and all other chemicals used for this study was analytical grade.

## METHODS

### Compatibility studies

The compatibility of drugs and excipients used under experimental condition were studied. The study was performed by taking 2 mg sample in 200 mg KBr (Bruker spectrum-100). The scanning range was 600 to 4000 cm-1 and the resolution was 1cm-1. This spectral analysis was employed to check the compatibility of drugs with the excipients used[5].

### Pre-Compression Characteristics

The pre-compression characteristics like angle of repose, bulk density, tapped density Hauser's ratio, Carr's index, Scale of Flow ability were determined and tabulated in the table no 3.

### Angle of Repose

The angle of repose of powder mix was determined by the funnel-method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted to a height of 2 cm in such a manner that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone measured and angle of repose was calculated using the following equation.

$$\tan \theta = h/r$$

Where h and r are the height and radius of the powder cone, θ is the angle of repose.

Angle of repose values less than 25, 25-30, 30-40, and more than 40 indicates excellent, good, passable, and poor flow properties respectively [3-7].

### Bulk Density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 2 g of powder from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a 10ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 second intervals. The tapping was continued until no further change in volume was noted. LBD and TBD were calculated using the following formula [4,5].

LBD = weight of the powder/volume of the packing

TBD = weight of the powder/tapped volume of the packing.

### Compressibility Index:

The compressibility index of the granules was determined by Carr's Compressibility index.

$$\text{Carr's index (\%)} = [(TBD-LBD) * 100] / TBD$$

Where, LBD: Weight of the powder/volume of the packing. TBD: Weight of the powder/Tapped volume of the packing.

### Hausner's Ratio:

Hausner's ratio can be determined by the following equation5,

$$\text{Hausner's ratio} = TBD / LBD$$

Where, TBD -Tapped bulk densities & LBD- Loose bulk densities

### Formulation Ornidazole Matrix Tablets

All the formulations were prepared by direct compression method using HPMC E15, HPMC K15 polymers in various ratios and other excipients microcrystalline cellulose, Magnesium Stearate and talc are used. Ornidazole and all other ingredients were individually passed through sieve ≠ 60. All the ingredients were mixed thoroughly by triturating up to 15 min. The powder mixture was lubricated with magnesium stearate and talc.

### Post-Compression Characteristics

The post-compression characteristics like Weight Variation, Thickness, Hardness, and Friability were determined and tabulated in the table no 4.

### Thickness and Diameter:

Control of physical dimension of the tablet such as thickness and diameter is essential for consumer acceptance and tablet uniformity. The thickness and diameter of the tablet was measured using Vernier calipers. It is measured in mm [6].

### Tablet Hardness:

Tablet hardness of the tablets for shipping or breakage under conditions of storage, transportation and handling depends on hardness which was determined using Monsanto hardness tester. For each formulation, the hardness of 10 tablets was determined. The tablet was held along its oblong axis in between the two jaws of the tester. At this point, reading should be zero kg/ cm2. Then constant force was applied by rotating the knob until the tablet fractured. The value at this point was noted in kg/cm [2-8].

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**Weight Variation**

This is an important In-process quality control test to be checked frequently (every half an hour). Corrections were made during the compression of tablets. Any variation in the weight of tablet (for any reason) leads to either under medication or overdose. So, every tablet in each batch should have a uniform weight. 20 tablets were weighed individually. Average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight. The percentage difference in the weight variation should be within the permissible limits (7.5%). The percent deviation was calculated using the following formula. The limits are mentioned in the below table as per Indian pharmacopoeia (I.P) [9,10].

**Friability Test:**

For each formulation, 6 tablets were weighed. The tablets were placed in a Friabilator (Roche Friabilator) and subjected to 100 rotations in 4 minutes at 25 rpm. The tablets were then reweighed. The friability was calculated as the percentage weight loss [11,12].

**% Friability = (Loss in weight/Initial weight) x 100**

***In vitro* drug release studies**[13, 14]

Drug release studies were conducted using USP-22 dissolution apparatus-2, paddle type (Lab India) at a rotational speed of 50 rpm at 37±0.5º. The dissolution media used were 900 ml of 0.1 mol / l HCl for first 2 h followed by pH 6.8 phosphate buffer solutions for 22 h. Sink condition was maintained for the whole experiment. Samples (10 ml) were withdrawn at regular intervals and the same volume of pre-warmed (37±0.5º) fresh dissolution medium was replaced to maintain the volume constant. The samples withdrawn were filtered through a 0.45 µ membrane filter and the drug content in each sample was analyzed after suitable dilution with a UV spectrophotometer (Shimadzu UV-1700) at 276nm. The dissolution test was performed in triplicate. Drug dissolved at specified time periods was plotted as cumulative percent release versus time (h) curve and results obtained were tabulated in table no 5 .

**Table 1. Formulations**

| Ingredients (mg) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| Ornidazole | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 |
| HPMC E15 | 100 | 200 | 300 | - | - | - | 150 | 200 | 100 |
| HPMC K15 | - | - | - | 100 | 200 | 300 | 150 | 100 | 200 |
| MCC | 330 | 230 | 130 | 330 | 230 | 130 | 130 | 130 | 130 |
| Talc | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Mg stearate | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| **Total** | **650** | **650** | **650** | **650** | **650** | **650** | **650** | **650** | **650** |

**Table 2. Calibration curve for Estimation of Ornidazole**

| S.NO | Concentration(µg/ml) | Absorbance | |
|---|---|---|---|
| | | 0.1 N HCl | 6.8 pH |
| 1 | 0 | 0 | 0 |
| 2 | 5 | 0.134 | 0.127 |
| 3 | 10 | 0.261 | 0.245 |
| 4 | 15 | 0.382 | 0.388 |
| 5 | 20 | 0.512 | 0.523 |
| 6 | 25 | 0.628 | 0.641 |

**Table 3. Physical properties of blend**

| F.CODE | Angle of Repose± SD* | Bulk Density (g/ml) ±SD* | Tapped Density (g/ml) ±SD* | Carr's Index (%)±SD* | Hausner's Ratio ±SD* |
|---|---|---|---|---|---|
| F1 | 26.25±0.23 | 0.488±0.0202 | 0.5091±0.0252 | 8.61±1.9083 | 1.0416±0.0088 |
| F2 | 27.96±0.15 | 0.5055±0.0055 | 0.5170±0.012 | 8.222±0.2266 | 1.02227±0.0052 |
| F3 | 26.65±0.34 | 0.4859±0.0069 | 0.5329±0.0051 | 8.8235±0.3054 | 1.0967±0.0321 |
| F4 | 28.93±0.12 | 0.3463±0.068 | 0.3810±0.0093 | 9.0909±0.1994 | 1.1000±0.004 |
| F5 | 27.36±0.15 | 0.3127±0.056 | 0.3528±0.0009 | 9.3636±0.6143 | 1.1082±0.0481 |
| F6 | 29.45±0.64 | 0.4650±0.0019 | 0.5093±0.001 | 8.6956±0.1499 | 1.0952±0.1191 |
| F7 | 27.54±0.15 | 0.5161±0.0050 | 0.5704±0.0014 | 9.6774±0.4180 | 1.1071±0.021 |
| F8 | 28.62±0.17 | 0.5000±0.0007 | 0.5577±0.0008 | 9.5750±0.3041 | 1.1034±0.0071 |
| F9 | 28.74±0.25 | 0.4706±0.0031 | 0.5333±0.0017 | 8.7647±0.9171 | 1.0933±0.0025 |

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**Table 4. Evaluation of Post Compression Parameters**

| Trial | Weight variation ±SD*** | Thickness (mm) ±SD** | Hardness (Kg/cm²) ±SD* | Friability (%w/w) ±SD** |
|---|---|---|---|---|
| F1 | 649±1.422 | 5.81±0.049 | 8±0.331 | 0.32±0.02 |
| F2 | 659±2.772 | 5.84±0.036 | 8.5±0.338 | 0.44±0.01 |
| F3 | 650±1.631 | 6.68±0.033 | 9±0.378 | 0.37±0.05 |
| F4 | 658±1.744 | 6.04±0.029 | 9±0.318 | 0.49±0.03 |
| F5 | 657±1.713 | 5.9±0.027 | 11±0.347 | 0.51±0.01 |
| F6 | 654±1.313 | 6.01±0.025 | 8.5±0.314 | 0.53±0.05 |
| F7 | 659±1.080 | 5.9±0.027 | 9.5±0.313 | 0.54±0.03 |
| F8 | 651±1.005 | 6.1±0.032 | 10.5±0.383 | 0.52±0.02 |
| F9 | 649±1.426 | 5.8±0.028 | 9.5±0.357 | 0.47±0.05 |

**Figure 1. Calibration curve of Ornidazole in 0.1 N HCl**

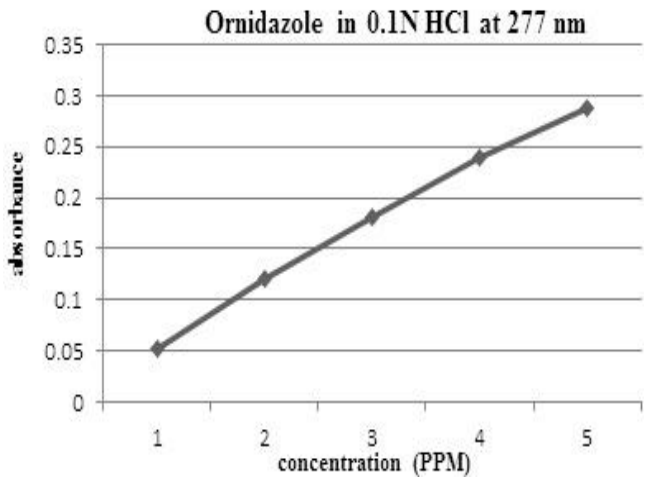
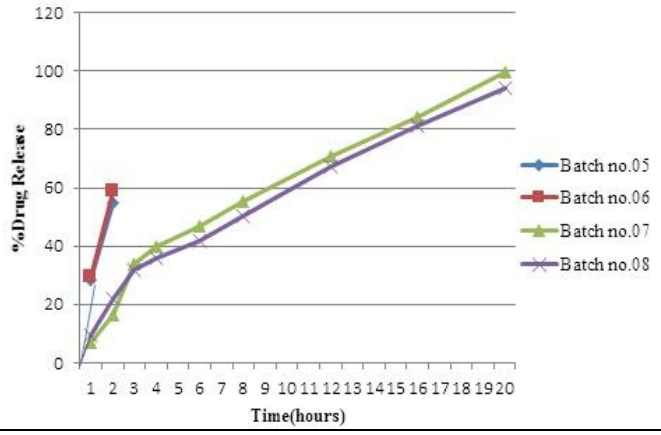



**Figure 2. Comparison of In vitro release profile of Batch no.05, 06, 07 and 08 in 0.1M HCl for 1st and 2nd hrs and in pH 6.8 phosphate buffer solution after 2nd hr**




## CONCLUSION

Suitable analytical method based on UV-Visible spectrophotometer was developed for Ornidazole. $\lambda_{max}$ of 277 nm(0.1 N HCl) and 230 nm(pH 6.8 buffer) was identified. All the excipients used did not interfere with the estimation of Ornidazole hydrochloride at analytical wavelength 277 nm (0.1 N HCl) and 230 nm (pH 6.8 buffer). Procedure to manufacture matrix tablets was established. Matrix tablets of Ornidazole (batch 07) were successfully prepared using microcrystalline cellulose, HPMC K100 M and HPMC K4M as excipients and by wet granulation method. The tablets were evaluated for pharmacopoeial and non-pharmacopoeial (industry specified) tests. Based on the results, batch 07 was identified as better formulations amongst all formulations for matrix tablets.

The manufacturing procedure was standardized and found to be reproducible. In case of matrix tablets the procedure was economical too. After one month accelerated stability developed formulations were found to be stable. Presence of water soluble ingredients in sustained release formulations increases porosity there by leads to increase in swelling of polymer and water uptake capacity of tablet.

The conclusions arrived in this thesis indicated that the sustained release formulations of Ornidazole developed in this investigation was found to be stable and is following USP, based on *in vitro release* studies.

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