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A Study of Dissolution Enhancement and *Invitro* Evaluation of Roxithromycin Matrix Tablets of Solid Dispersions

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ABSTRACT

Tablets are compressed solid dosage form containing medicaments with or without excipients. Matrix tablets are used to produce controlled release of drugs in our body. Roxithromycin (ROX) is a broad spectrum, semisynthetic macrolide antibiotic, having bitter taste which elicits poor aqueous solubility within the GIT. In this present study, a design of an oral controlled release dosage form is carried out. ROX controlled release matrix tablets were prepared by solid dispersion technique and evaluated using various parameters. Solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles. In order to obviate its demerit and enhance dissolution rate of ROX, the solid dispersion was formulated by using mannitol as a carrier where the drug to carrier ratio is 1:3 and hydroxypropyl methyl cellulose (HPMC) as release retardant. The result shows that, the method of preparation of solid dispersion influences the physic-chemical characters of the tablets like hardness, friability, weight variation, disintegration time and *invitro* release profile. It was concluded that solid dispersion technique could be successfully used to improve the solubility of ROX using mannitol as carrier. Melt method can be selected as the method of preparation for highest improvement in solubility. Wet granulation method can be successfully used to prepare tablets of solid dispersions compared to direct compression for better drug release profile. The release rate of drug from controlled release tablet was followed by zero order kinetics. From huguchi and hixon-crowell law, the mechanism of drug release from solid dispersions was found to be diffusion.

Key words: Roxithromycin (ROX), Solid dispersion, Melt method, Matrix tablets & dissolution.

1. INTRODUCTION

Tablet is defined as a compressed solid dosage form containing medicaments with or without excipients. According to IP pharmaceutical tablets are solid, flat or biconvex dishes, unit dosage form, prepared by compressing a drug or mixture of drugs, with or without diluents. The oral route represents a convenient and safe way of drug administration. Compared to liquid dosage forms, tablets have general advantages in terms of the chemical, physical and microbiological stability of all the oral dosage forms. But Drugs with poor wetting, slow dissolution properties, intermediate to large dosages, optimum absorption high in the gastrointestinal tract, or any combination of these features may be difficult or impossible to formulate.

Over the past 30 years, as the expense and complications involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of controlled drug-delivery, greater attention has been focused on development of sustained or controlled-release drug-delivery systems. There are several reasons for the attractiveness of these dosage forms. It is generally recognized that for many disease states, a substantial number of therapeutically effective compounds already exist. The effectiveness of these drugs, however, is often limited by side effects or the necessity to administer the compound in a clinical setting. The goal is designing sustained- or controlled-delivery systems is to reduce the frequency of dosing or to increase effectiveness of the drug by localization at the site of action reducing the dose

required, or providing uniform drug delivery. Matrix tablets are the type of controlled drug delivery systems, which release the drug in continuous manner. These release the drug by both dissolution controlled as well as diffusion controlled mechanisms. To control the release of the drugs, which are having different solubility properties, the drug is dispersed in swellable hydrophilic substances, an insoluble matrix of rigid non-swellable hydrophobic materials or plastic materials.

Solid dispersions are group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug[1]. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles. Management of the drug release profile using solid dispersions is achieved by manipulation of the carrier and solid dispersion particles properties. Parameters, such as carrier molecular weight and composition, drug crystallinity and particle porosity and wettability, when successfully controlled, can produce improvements in bioavailability.

Major challenges to an oral controlled release medication:

1. Unpredictable gastric emptying time.
2. High variations in Gastric emptying due to factors such as age, race, sex, and disease states.
3. Limited contact time at the site of absorption.

Advantages of controlled drug delivery systems:

1. Achieve more effective therapies while eliminating the potential for both under and overdosing.
2. The maintenance of drug levels with in a desired change.
3. The need for fewer administrations, optimal use of the drug in question, and increased patient compliance.

Disadvantages of controlled drug delivery systems:

1. The possible toxicity or nonbioavailability of the materials used.
2. Undesirable byproducts of degradation.
3. The change of patient discomfort from the delivery device for instance if any surgery required to implant or remove the system.
4. The higher cost of controlled-release systems compared with traditional pharmaceutical formulations [2-6].

2. MATERIALS AND METHODS

Roxithromycin is a semi-synthetic macrolide antibiotic, obtained as a gift sample from Ajantha pharmaceuticals, Mumbai. To formulate the matrix tablet of solid dispersion Mannitol, Hydroxypropylmethylcellulose, Polyvinyl pyrrolidine (PVP), Starch Talc Magnesium stearate was purchased from National Scientific Products.

2.1. FORMULATION OF CONTROLLED RELEASE MATRIX TABLETS OF ROXITHROMYCIN

The dose of Roxithromycin in controlled release matrix tablet is 75mg. Its half-life is 12hrs. Composition of controlled release formulations of Roxithromycin is prent in the tabele.1.

2.2. PREPARATION OF SOLID DISPERSIONS OF ROXITHROMYCIN:

Solid dispersions of ROX were prepared by four different methods using mannitol which is a highly water soluble carrier where the drug to carrier ratio is 1:3. They include: Physical mixing, Melting method, Melt solvent method and Kneading method.

2.2.1. Physical mixing

Physical mixtures of Roxithromycin and mannitol were prepared by trituration in a mortar and sifted through mesh no 120.

2.2.2. Melting method

In Melting method, solid dispersions were prepared by melting the physical mixture of Roxithromycin and Mannitol in a sand bath. The fusion temperature was controlled between 165^0C to 175^0C. The molten mixture was immediately cooled and solidified in an ice bath with vigorous stirring. The solid obtained was scrapped, crushed, pulverized and passed through mesh no.120. The obtained product was stored in a desicator[7].

2.2.3. Melt solvent method

In melt solvent method, Roxithromycin was dissolved in methanol and the solution was incorporated into the melt of mannitol at 165^0C by pouring into it. It was kept in an ice bath for sudden cooling. The mass was kept in a desicator for complete drying. The solidified mass was scrapped, crushed, pulverized and passed through mesh no.120[8].

Table No.1: Composition of controlled release formulations of Roxithromycin

Ingredients (mg)	ROX_1 (Physical mixing)	ROX_2 (Melting method)	ROX_3 (Melt solvent method)	ROX_4 (Kneading method)
Roxithromycin	75	75	75	75
Mannitol	225	225	225	225
HPMC	66.3	66.3	66.3	66.3
PVP (2%)	Q.S	Q.S	Q.S	Q.S
Talc	2%	2%	2%	2%
Starch	15%	15%	15%	15%
Magnesium stearate	2%	2%	2%	2%

2.2.4. Kneading method

In kneading method, Roxithromycin was dissolved in methanol and this solution was added to aqueous solution of mannitol, which was prepared by dissolving mannitol in water. Then the mixture was triturated in a glass mortar until it was dried. The dried powder was passed through mesh no.120 and the final product was stored in a desiccator[9].

2.3. PREPARATION OF MATRIX TABLETS

Tablets each containing 75mg of ROX were prepared employing its physical mixtures and solid dispersions with mannitol by conventional wet granulation method using PVP solution in alcohol as binding agent at 2% concentration in the formula. The damp mass was then granulated by passing through sieve no. 10 and the granules obtained were dried in an oven at 60^0C for 2 hrs. The dried granules were again passed through sieve no. 16 to break the aggregates. The lubricants were added to the dry granules and blended.

2.3.1. Compression

The blend was compressed into tablets on a Cadmach single punch tablet machine to a hardness of 4-5 Kg/Sq.cm.

2.4. EVALUATION OF TABLETS

The various in-process control parameters that are performed are:

2.4.1. Hardness test

Three tablets were taken from each basket and tested for hardness using strong Cobb's tablet hardness tester.

2.4.2. Weight variation test

10 tablets selected at random were individually weighed and the average weight was determined. Not more than two of individual weights should deviate from the official standards (average weights±5%) and none deviate more than twice that percentage (10%).

2.4.3. Friability

10 pre-weighed tablets were placed in a chamber of Roche-Friabilator and it was operated for 4 min at the 25 revolutions per min. After 4 min, tablets were removed from the chamber, dusted and weighed again. The difference between the two weights was found out and the weight loss should not be more than 0.5% to 1.0% of their weights.

2.3.4. Drug content estimation

Twenty tablets were weighed accurately and powdered. The powder equivalent to 50 mg Roxithromycin was dissolved in glacial acetic acid (20 ml, 3 M), sonicated for 15 min and filtered through Whatman No. 41 filter paper. The residues were washed thoroughly with distilled water. The filtrate and washing were combined in 100 ml volumetric flask and diluted to mark. From the above solution 5ml was taken and it was diluted to 100ml. The solution (2.0 ml) was analyzed as above. Amount of ROX was computed by using UV spectrophotometer at 412nm.

2.3.5. Disintegration time

It was carried out in the disintegration test apparatus. Six tablets were taken and kept in the basket having 10 mesh bottoms; a disc was placed over the tablet in each test tube. Immersion liquid used was water and the time for disintegration was noted.

2.3.6. *Invitro* drug release studies

2.3.6.1. Construction of standard curve of Roxithromycin

Roxithromycin (400 mg) was accurately weighed and transferred to a 100 ml volumetric flask. The final solution was prepared using glacial acetic acid & reaction between potassium permanganate with oxalic acid. Absorbance of the coloured solution was scanned on Shimadzu UV-visible spectrophotometer from 600 nm to 200 nm against reagent blank. Standard solutions of ROX (0.625, 1.25, 1.875, 2.5, 3.125, 3.75ml (400 µg/ml) were pipetted out into a series of 100 ml volumetric flasks and analyzed as above. Absorbance of the coloured solution was measured at 412 nm. It was found that the Beer's law is obeyed in the concentration range of 10-75 µg/ml of ROX.

2.3.6.2. *Invitro* Dissolution studies

Invitro dissolution studies were carried out in USP XXI dissolution rate test apparatus employing paddle stirrer. In 900 ml of distilled water, one tablet, a speed of 50 rpm and a temperature of 37±0.5^{0}C were employed in each case. A 5 ml aliquot was withdrawn at different time intervals and 5 ml of fresh dissolution

medium was replaced to maintain the constant volume of dissolution medium. From the samples collected, 1 ml was taken and diluted to 5 ml with 0.1N HCL as blank. The amount of ROX released was calculated from the standard graph. The dissolution experiments were conducted in triplicate. Dissolution efficiency values were calculated from the dissolution data.

The dissolution profiles of various tablets formulated employing physical mixture and solid dispersions are studied by using USP XXIII six- station dissolution rate test apparatus. The dissolution data obtained were subjected for model fitting and the model that fits the observed dissolution data was evaluated by correlation coefficient (r) between the variables involved[10]. The results were given in Table No: 2.

3. RESULTS AND DISCUSSION

The matrix tablets of Roxithromycin were formulated. The results of the evaluation study were given below.

3.1. EVALUATION OF TABLETS

3.1.2. Hardness

It was performed as per procedure in methodology section. The tablets in all the batches was found to be in the range of 4-5 kg/cm^2 & the tablet formulations was found to be within limits.

3.1.3. Weight variation test

It was done as per the procedure. All the batches of tablets were found to pass the weight uniformity test. Since, the tablets were compressed after manually pouring the accurately weighed portions of granules; the chances of weight variation were greatly reduced.

3.1.4. Friability

It was performed and it was found to be less than 1%.

3.1.5. Drug content:

All the tablets prepared were found to contain the medicament with in 100±5% of labeled claim. The drug content obtained was found to be within the required limits.

3.1.6. Disintegration time

All the tablets formulated by wet granulation employing physical mixtures and solid binary systems disintegrated rapidly. There is a large difference in disintegration time of tablets prepared by solid dispersions and physical mixtures. The solid dispersions prepared by melt method were found to have faster disintegration time when compared with all other methods. The disintegration time was found to be within the limits for all the formulations.

3.1.7. *Invitro* release studies

The dissolution profiles of various tablets formulated employing physical mixture and solid dispersions are studied by using dissolution rate test apparatus. The dissolution data obtained were subjected for model fitting and the model that fits the observed dissolution data was evaluated by correlation coefficient (r) between the variables involved. The tablets formulated employing solid dispersions gave rapid and fast dissolution of drug when compared to tablets prepared with physical mixtures (ROX_1). The possible mechanisms responsible for increased dissolution rate form these tablets are rapid disintegration of tablets and presence of drug in amorphous form in tablets, amorphous form is the highest energy form of a compound, which produce faster dissolution. The dissolution rate of ROX from tablets was strongly depends upon the method of preparation of tablet and technique used for the preparation of solid dispersions. Among the prepared solid dispersion tablets, tablets of melt method (ROX_2) prepared by wet granulation are showing higher dissolution rate.

Table No. 2: Table showing comparative release profile of Roxithromycin from all tablet formulations

	Percentage Drug release (in %)			
Time(Hrs)	ROX_1	ROX_2	ROX_3	ROX_4
0.5	18.21	29.18	24.68	22.62
1.0	22.62	35.29	31.2	28.28
1.5	28.80	54.75	47.28	44.11
2.0	32.58	65.61	58.88	52.03
2.5	36.20	72.40	64.44	58.88
3.0	40.72	79.18	69.68	64.44
3.5	42.42	85.07	74.66	68.32
4.0	46.15	89.36	80.09	724.
4.5	48.07	90.05	85.07	74.66
5.0	51.11	92.76	88.23	78.00

Figure No. 1: Graph showing comparative release profile of Roxithromycin from all tablet formulations

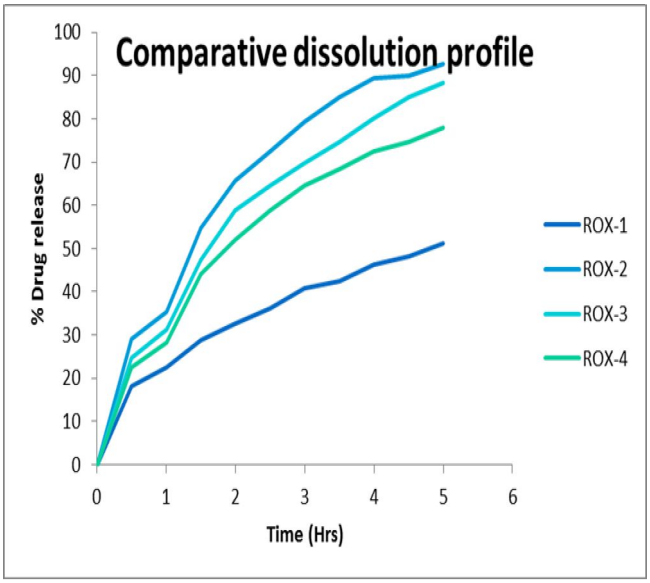

Table No. 3: Data showing regression co-efficient for zero and first order plots.

Formulation	Regression coefficient of zero order plot	Regression coefficient of first order plot	Order of drug releases
ROX_1	0.9612	0.7905	Zero
ROX_2	0.9555	0.7848	Zero
ROX_3	0.9743	0.7999	Zero
ROX_4	0.9638	0.7974	Zero

Table No.4: Data showing regression co-efficient for Higuchi and Hixon-Crowell models

Formulation	Regression coefficient of Higuchi (Diffusion)	Regression Coefficient of Hixon-Crowell (Erosion)	Main mechanism of drug release
ROX_1	0.9612	0.5147	Diffusion
ROX_2	0.9555	0.5243	Diffusion
ROX_3	0.9789	0.5476	Diffusion
ROX_4	0.9638	0.5174	Diffusion

3.1.8. Kinetics of drug release

This was carried out as per the procedure given in introduction and the results were tabulated. From the data, it was observed that, the regression coefficient of zero order plot is higher than that of first order plot & All the formulations of ROX follow zero order kinetics (table .3.)

3.1.9. Mechanism of drug release

This was carried out the regression coefficient of higuchi plot is higher than that of hixon-crowell plot. All the formulations of Roxithromycin follow diffusion as their mechanism of drug release (table.3.).

4. CONCLUSION

This work was done with an aim to increase the solubility of very poorly water soluble ROX by solid dispersion technique, to make a controlled release oral dosage form of ROX and evaluation of the tablets including *invitro* drug release.

The highly water soluble carrier was selected to increase the solubility of ROX by using various methods. The drug carrier ratio for the preparation of solid dispersion was 1:3. The hydrophilic polymer HPMC was chosen to control the release rate of drug. The method of preparation of tablet is simple wet granulation of drug with excipients followed by single stage compression which assures reproducible batches of tablets. The result shows that, the method of preparation of solid dispersion influences the physico-chemical characters of the tablets like hardness and *invitro* release profile.

Under formulation study, all the tests such as friability, hardness, drug content and disintegration were found to be within limits. The tablets formulated employing solid dispersions gave rapid and fast dissolution of drug when compared to tablets prepared with physical mixtures (ROX_1). The possible mechanisms responsible for increased dissolution rate form these tablets are rapid disintegration of tablets and presence of drug in amorphous form in tablets, amorphous form is the highest energy form of a compound, which produce faster dissolution.

From the above investigation, it was concluded that solid dispersion technique could be successfully used to improve the solubility of ROX using mannitol as carrier. “MELT METHOD” can be selected as the method of preparation for highest improvement in solubility. Wet granulation method can be successfully used to prepare tablets of solid dispersions compared to direct compression for better drug release profile. The release rate of drug from controlled release tablet was followed by zero order kinetics. From Huguchi and Hixon-crowell law, the mechanism of drug release from solid dispersions was found to be diffusion.

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