FORMULATION AND EVALUATION OF ROXITHROMYCIN TABLETS

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ABSTRACT

The objective of the present study is to formulate and evaluate roxithromycin tablets employing roxithromycin (ROX) solid dispersions. Dispersions of ROX in mannitol were prepared by different techniques like physical mixing, melting method, melt solvent method, kneading technique and common solvent method with drug and carrier ratio of 1:1, 1:2, 1:4 and 1:9. ROX tablets were formulated employing 1:4 ratio of ROX-mannitol solid dispersions and their corresponding physical mixtures. The compressed tablets were evaluated for various tablet characteristics including dissolution rate and efficiency. Marked increase in the dissolution rate and efficiency was observed with tablets of dispersions in comparison to tablets formulated with physical mixtures and conventional tablets available commercially. Tablets prepared by dispersion of melt method have shown highest dissolution rate. Dissolution of ROX from these tablets obeyed first-order kinetics.

Keywords: Roxithromycin, solid dispersions, tablets, mannitol.

INTRODUCTION

Roxithromycin is erythromycin 9-[O-[(2)-methoxyethoxy) methyl]oxime, a semi synthetic macrolide antibiotic drug, very slightly soluble in water and aqueous fluids and its absorption is dissolution rate limited. ROX is used in the treatment of UTI, RTI, ENT, genital tract, skin and soft tissue infections[1,2]. The enhancement of oral bioavailability of drugs with poor water solubility remains one of the most challenging aspects of drug development. Solid dispersion techniques can be used to increase the dissolution and absorption of several insoluble drugs [3, 4]. Several insoluble drugs when prepared as solid dispersions showed improved solubility and dissolution when mannitol is used as a carrier [5, 6].

In the present investigation, solid dispersions of ROX were prepared employing physical mixing, melting method, melt solvent method, kneading method and common solvent method using mannitol which is a highly water soluble carrier at different drug to carrier ratios such as 1:1, 1:2, 1:4 and 1:9. The prepared solid dispersions and physical mixtures were formulated in to tablets and were evaluated. Solid dispersions having 1:4 ratio of drug and carriers showed more solubility. Hence, formulations are carried by using those solid dispersions.

MATERIALS AND METHODS

Materials

Roxithromycin was obtained as a gift sample from Acto Pharmaceuticals, Warangal. Mannitol was obtained from BDH chemicals, Mumbai. Starch, microcrystalline cellulose, polyvinyl pyrrolidone (PVP), talc and magnesium stearate were obtained from S.D. fine chemicals, Mumbai. All other ingredients used were of analytical grade.

Methods

Preparation of solid dispersions and physical mixtures:

Solid dispersions of ROX were prepared using mannitol as a carrier in 1:4 ratio using different preparation techniques such as physical mixing, melting method, melt solvent method, kneading method and common solvent method.

Physical mixtures of ROX and mannitol were prepared by trituration in a mortar and sifted through mesh no.120. In melting method, solid dispersions were prepared by melting the physical mixture of ROX and mannitol in a sand bath. The fusion temperature was controlled between 165-175°C. 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 desiccator. In melt solvent method, ROX was dissolved in methanol and the solution was incorporated into the melt of mannitol at 165°C by pouring into it. It was kept in an ice bath for sudden cooling. The mass was kept in a desiccator for complete drying. The solidified mass was scrapped, crushed, pulverized and passed through mesh no.120. In kneading method, ROX 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. In common solvent method, required quantities of ROX and mannitol were taken in a glass mortar and this mixture was dissolved in methanol. The prepared solution was triturated until methanol was completely removed. The powder obtained after complete removal of methanol was passed through sieve No-100 and was stored in dessicator.

Preparation of ROX Tablets:

Tablets each containing 150 mg of roxithromycin were prepared employing its physical mixtures and solid dispersions in mannitol (prepared by various methods melting method, melt solvent method, kneading technique and common solvent method) 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°C for 2h. The dried granules were again passed through sieve no. 16 to break the aggregates. The lubricants were added to the dry granules and blended. Tablets also prepared by direct compression technique by adding microcrystalline cellulose and lubricants. The blend was compressed into tablets on a Cadmach single punch tablet machine to a hardness of 4-5 Kg/Sq.cm. The prepared tablets were evaluated for the uniformity of weights, hardness, friability[7], drug content[8], disintegration time and in vitro release studies [9, 10].

***In vitro* dissolution rate study of tablets:**

The *in vitro* 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°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 0.1 N HCl and the absorbance of the diluted solutions was measured at 205 nm using spectrophotometer against 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 as suggested by Khan [11].

RESULTS AND DISCUSSION

All the tablets prepared were found to contain the medicament with in 100±3% of labeled claim. The drug content obtained was found to be within the required limits. Hardness of the tablets in all the batches was found to be in the range of 4-5 kg/cm^2. Friability of the tablets was less than 1%. All the tablets formulated by wet granulation and direct compression methods 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. Tablets prepared by wet granulation have exhibited less disintegration time compared to the tablets prepared by direct compression. The disintegration times were within 7.5 min. The evaluation data of tablets was given in Table 1.

Table 1: Evaluation of various parameters of roxithromycin tablets

S.No	Tablet	% drug content	Hardness (kg/cm^2)	Friability (%)	D.T. (minutes)
Tablets prepared by wet granulation method					
1	ROX-M (1:4) MLT	99.37±0.53	4.6±0.37	0.54±0.13	2.0
2	ROX-M (1:4) MSV	97.96±0.45	4.2±0.59	0.65±0.21	2.4
3	ROX-M (1:4) KNE	99.53±0.13	4.8±0.19	0.71±0.45	5.5
4	ROX-M (1:4) CSV	98.23±0.19	4.1±0.54	0.62±0.75	4.3
5	ROX-M (1:4) PM	97.29±0.28	4.9±0.16	0.85±0.13	6.5
Tablets prepared by direct compression method					
1	ROX-M (1:4) MLT	100.25±0.13	4.5±0.55	0.51±0.27	2.47
2	ROX-M (1:4) MSV	98.31±0.15	4.2±0.79	0.75±0.19	3.3
3	ROX-M (1:4) KNE	99.13±0.53	4.1±0.43	0.59±0.28	6.1
4	ROX-M (1:4) CSV	100.26±0.12	4.9±0.15	0.87±0.58	5.2
5	ROX-M (1:4) PM	97.29±0.16	4.7±0.23	0.71±0.15	7.5
Commercial tablet					
1	A	99.87±0.23	4.5±0.53	0.62±0.35	1.5
2	B	98.29±0.08	4.6±0.23	0.84±0.05	3.0

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. The tablets formulated employing solid dispersions gave rapid and fast dissolution of drug when compared to tablets prepared with physical mixtures. 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.

Table 2: Dissolution parameters roxithromycin tablets

Tablet	Zero order 'r' value	First order 'r' value	K_1 (min^{-1})	DE_{30} (%)	T_{50} (min)
Tablets prepared by wet granulation technique					
ROX-M (1:4) MLT	0.935	0.996	0.0472	63.92	14.68
ROX-M (1:4) MSV	0.951	0.994	0.0333	59.87	20.81
ROX-M (1:4) KNE	0.929	0.981	0.0242	49.63	28.63
ROX-M (1:4) CSV	0.954	0.993	0.0235	52.95	29.48
ROX-M (1:4) PM	0.965	0.987	0.0133	32.26	52.10
Tablets prepared by direct compression technique					
ROX-M (1:4) MLT	0.937	0.986	0.0283	58.76	24.48
ROX-M (1:4) MSV	0.963	0.997	0.0260	53.27	26.65
ROX-M (1:4) KNE	0.970	0.994	0.0200	32.58	34.59
ROX-M (1:4) CSV	0.974	0.997	0.0202	44.79	34.30
ROX-M (1:4) PM	0.972	0.983	0.0199	26.78	58.23
Commercial tablet					
A	0.932	0.995	0.0497	65.83	13.94
B	0.979	0.978	0.0293	57.24	23.73

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 prepared by wet granulation are showing higher dissolution rate. The release was nearly similar to the marketed tablet A and greater than marketed tablet B.

Table 2 enlists the dissolution parameters of ROX tablets. The dissolution data is shown in the Figure 1, 2 and 3. 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 is following first order kinetics.

Figure 1: *In vitro* dissolution profile of roxithromycin from tablets formulated by wet granulation method using various solid dispersions

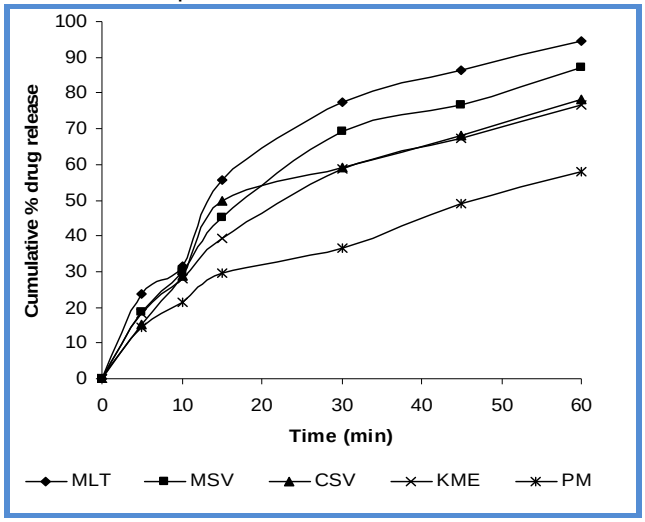


Figure 2: *In vitro* dissolution profile of roxithromycin from tablets formulated by direct compression method using various solid dispersions

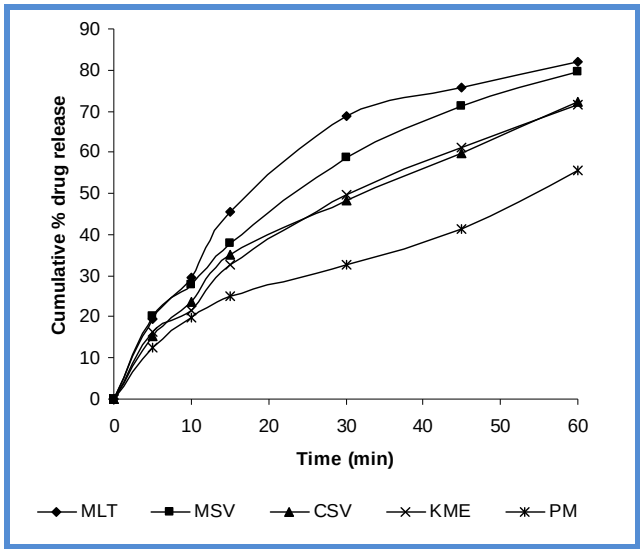
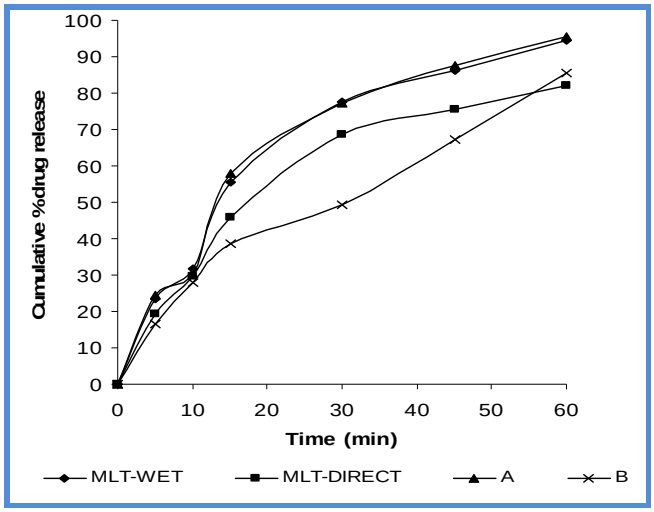


Figure 3: Comparative *In vitro* dissolution profile of roxithromycin from tablets formulated and commercial



Thus fast disintegrating roxithromycin tablets can be formulated by using solid dispersions of roxithromycin with mannitol in 1:4 ratio in melting method by wet granulation technique.

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