RESEARCH ARTICLE

Formulation and evaluation of dispersible taste masked tablet of roxithromycin

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Roxithromycin is a broad spectrum, semisynthetic macrolide antibiotic, having bitter taste. In the present study, an attempt has been made to mask the bitter taste of roxithromycin by complexation technique. Weak cation exchange resins Indion 214 and Amberlite IRP64, polymer carbopol 934P were used in formulation of complexes with the drug. The loading process was optimized for the pH of loading solution and resin or polymer:drug ratio. The complexes were evaluated for bulk density, angle of repose, taste masking, and *in vitro* drug release. *In vitro* drug release studies showed more than 80% drug release from the optimized formulation within 30 min. Amberlite IRP64 was found to be better complexing agent for masking the bitter taste of roxithromycin.

Key words: *Amberlite IRP64, Indion 214, ion-exchange resin, taste masking*

INTRODUCTION

Ion exchange resins are solid and suitably high molecular weight polyelectrolytes that can exchange their mobile ions of equal charge with surrounding medium reversibly and stoichiometrically.[1] Bitter drugs can get adsorbed onto ion exchange resins and carbopol to form complexes, which is nonbitter.[2] The resinates can be formulation as lozenges chewing gum, suspension or dispersible tablets. The complex of drug and resin does not break at pH 6.7 of saliva with cation concentration of 40 meq/l. But at high cation concentration of stomach and pH of 1-3, free drug is immediately released.[3] Roxithromycin is a dual-action macrolide. It acts by binding to the ribosomal units in the microorganism, blocking the incorporation of amino acid into forming essential highly polymerized peptides. In this study, weak cation exchange resins Indion 214, Amberlite IRP64, and carbopol 934P were used to mask the taste of bitter drug.

MATERIALS AND METHODS

Roxithromycin was provided as a gift sample by Wockhardt Ltd., Aurangabad, India, Indion 214 was gifted by Ion Exchange (India) Ltd., Amberlite IRP64 was obtained as a gift sample from Rohm and Haas, Philadelphia, and carbopol 934P was gifted by Novion, Mumbai, India. Other chemicals used were of AR grade.

Preparation of drug-resin complexes

The drug-resin complexes were prepared by batch process.[4] An accurately weighed amount of roxithromycin (1 gm) was taken in 100 ml of distilled water. The known weight of ion exchange resin was added to the slurry and stirred on magnetic stirrer until equilibrium was achieved. Time to reach equilibrium was determined by measuring concentration of drug in solution.[5] The resinates obtained were washed with copious amount of methanol to remove uncomplexed drug. The complexes were dried overnight in a hot air oven at 40°C and then stored in tightly closed dessicator. The amount of drug loading was determined by finding the difference between the amount of drug present in the stock solution and the amount remaining in filtrate at the end of equilibrium.[6]

Optimization of drug loading

Amberlite IRP64 and Indion 214 were subjected to different pH condition to find the optimum pH condition for loading of drug. The ratio of drug and resin complexes were 1:1, 1:2, 1:3, and 1:4, and the pH was maintained at 6.

Preparation of drug-carbopol 934P complex

An accurately weighed amount of roxithromycin was dissolved in 20 ml of methanol and this solution was added to the slurry containing known weight of carbopol in 50 ml distilled water, while stirring on magnetic stirrer. The resulting mixture was stirred overnight and dried in hot air oven 40°C. Four batches were prepared using drug:carbopol in the ratio of 1:1, 1:2, 1:3, and 1:4.

Determination of drug content in the complexes

About 100 mg complex was weighed and taken in a 100-ml volumetric flask, and volume was made with

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0.1 N HCl. The solution in the volumetric flask was then sonicated for 20 min and stirred further for 2 h on magnetic stirrer and then filtered using 0.2-μ membrane filter. From filtrate, 10 ml of solution was pipetted out and diluted up to 100 ml with the 0.1 N HCl, and absorbance was measured at 216 nm using UV double beam spectrophotometer.

X-ray diffraction

Studies were carried out to ascertain the formation of complexes of roxithromycin. The X-ray diffraction pattern for pure roxithromycin, Indion 214, Amberlite IRP64, and carbopol 934P complexes, and their physical mixture were obtained.

Determination of properties of complexes

Prepared complexes were evaluated for shape, angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio. Angle of repose was determined by funnel method. Bulk density was determined by taking weighed quantity of material in measuring cylinder tapped on hard surface 100 times and subtracting the volume occupied after tapping from the initial volume.

In vitro release of roxithromycin

Complexes of roxithromycin with Indion 214, Amberlite IRP64, and carbopol 934P were subjected to *in vitro* dissolution studies using USP 24 method. Weighed quantity of complexes equivalent to normal dose was suspended in 0.1 N HCl using USP dissolution apparatus type II and the quantity of drug released was determined periodically.

Taste evaluation of complexes

The taste of complexes was checked by panel method.[7] For this purpose, 10 human volunteers were selected. About 50 mg of drug equivalent complex was placed on tongue and taste evaluated after 10 s.

Formulation of dispersible tablets

The tablet consist of resinate equivalent to 50 mg drug. Perlitol and spray-dried lactose were selected as diluents. All the six batches were prepared by direct compression method using single punch tablet machine. The hardness of tablet of each batch kept constant (3-4 kg/cm^2). The weight of tablet of each batch was adjusted to 300 mg.

RESULT AND DISCUSSION

For preparation of resinates, batch method was preferred because of its convenience. Time to reach equilibrium during drug loading was found to be 6 h. To investigate effect of pH on drug loading, the pH of drug-resin solution was varied keeping the drug:resin in the ratio 1:1, and results are recorded in Table 1. The results showed that lower loading of roxithromycin was observed at low pH, which might be due to the higher concentration of competing ions which may inhibit the interaction of resins. At pH 6, maximum loading of roxthromycin was seen onto both the resins Indion 214 and Amberlite IRP64. Hence, pH 6 was selected for complexation of roxithromycin with Indion 214 and Amberlite IRP64. Effect of drug:resin ratio on loading is shown in Table 2 and effect of drug:carbopol ratio on loading is shown in table 3. It shows that 1:1 drug:resin ratio shows maximum drug loading.

Increase in the amount of complexing agent increases the amount of drug adsorbed as number of sites increases, but the drug content per gram of the complex decreases.

Results of taste evaluation by panel method [Table 4] revealed that Amberlite IRP64 mask the bitter taste of drug completely at 1:3 and 1:4 ratios, whereas Indion 214 and carbopol 934P complexes mask the bitter taste of drug at 1:4 ratio. Evaluation of taste masked complexes [Table 4]. *In vitro* release profile of complex is shown in Figure 1. Studies in 0.1 N HCL using USP paddle apparatus at 50 rpm with drug-Amberlite IRP64 complex showed better release than that of drug-Indion 214 complex and drug-carbopol 934P complex. More than 80% of drug was released within 30 min from this complex. The complexation was confirmed by carrying out X-ray diffraction studies on Indion 214, Amberlite IRP64 and carbopol 934P, drug, resin, drug complex, and physical mixture of two. The X-ray powder diffraction (XRPD) showed crystalline peak characteristics of drug were masked and characteristic amorphous characteristics of the complex were prevalent confirming the complexation. Results of angle of repose, bulk and tapped density, Carr's index, and Hausner's

Table 1: Effect of pH on drug loading

pH	Roxithromycin loading on Indion 214	Roxithromycin loading on Amberlite IRP64
3	31.54 ± 1.89	27.20 ± 1.67
4	36.27 ± 1.69	29.53 ± 1.39
5	40.52 ± 2.42	37.10 ± 1.79
6	47.79 ± 1.15	40.74 ± 2.20
7	45.07 ± 1.37	38.69 ± 1.39
8	43.96 ± 1.53	36.78 ± 1.11

Mean ± SD; n = 3

Table 2: Effect of drug:resin ratio on loading

Drug:resin	% Drug content per gram of Indion 214 resinate	% Drug content per gram of Amberlite IRP64
1:1	47.01 ± 1.63	40.71 ± 2.01
1:2	38.10 ± 1.38	37.41 ± 1.68
1:3	31.12 ± 1.44	31.31 ± 1.65
1:4	26.89 ± 2.25	24.58 ± 1.72

Table 3: Effect of drug:carbopol ratio on loading

Drug:carbopol ratio	% Drug content per gram of drug carbopol complex
1:1	47.32 ± 1.84
1:2	34.53 ± 1.53
1:3	25.80 ± 2.08
1:4	16.96 ± 1.78

Table 4: Evaluation of taste of complexes

Volunteer		1	2	3	4	5	6	7	8	9	10
Pure drug		3	3	3	3	3	3	3	3	3	3
Drug-Indion	1:1	3	3	2	3	3	3	3	2	2	3
214 complex	1:2	2	3	2	3	2	3	3	2	1	2
	1:3	1	2	1	2	1	2	2	1	1	2
	1:4	0	0	0	1	0	0	1	0	0	1
Drug-Amberlite	1:1	2	2	3	2	3	2	2	2	2	2
IRP64 complex	1:2	1	1	1	2	1	1	2	1	1	1
	1:3	0	0	1	0	0	0	1	1	0	0
	1:4	0	0	0	1	2	0	0	0	0	0
Drug-carbopol	1:1	3	2	3	3	2	3	3	3	3	2
934P complex	1:2	2	1	2	2	3	2	2	2	2	3
	1:3	1	2	2	1	2	1	1	1	2	2
	1:4	0	0	0	0	0	1	0	0	1	0

3 = Very bitter; 2 = bitter; 1 = slightly bitter; 0 = normal

Table 5: Physical properties of taste masked complexes

Parameter	Drug-Indion 214 complex	Drug-Amberlite IRP64 complex	Drug-carbopol 934P complex
Shape	Irregular	Irregular	Irregular
Angle of repose	36.02	32.47	27.55
Bulk density	0.6329	0.6578	0.5813
Tap density	0.7692	0.7812	0.6756
Carr's index	17.71	15.79	13.95
Hausner's ratio	1.215	1.187	1.162

Table 6: Physical properties of formulated tablets

Batch	Disintegration time (s)	Weight uniformity	% Friability	Content uniformity	Uniformity of dispersion
B_1	182 ± 2.12	303.1 ± 1.99	0.87	48.85 ± 0.73	Passes
B_2	206 ± 2.58	301.2 ± 2.37	0.68	49.38 ± 0.82	Passes
B_3	107 ± 1.2	302.7 ± 1.19	0.82	49.88 ± 0.62	Passes
B_4	120 ± 1.94	300.5 ± 1.70	0.66	48.16 ± 0.46	Passes
B_5	48 ± 1.62	301.3 ± 2.15	0.63	49.03 ± 1.18	Passes
B_6	63 ± 2.46	302.4 ± 0.85	0.71	48.33 ± 0.76	Passes

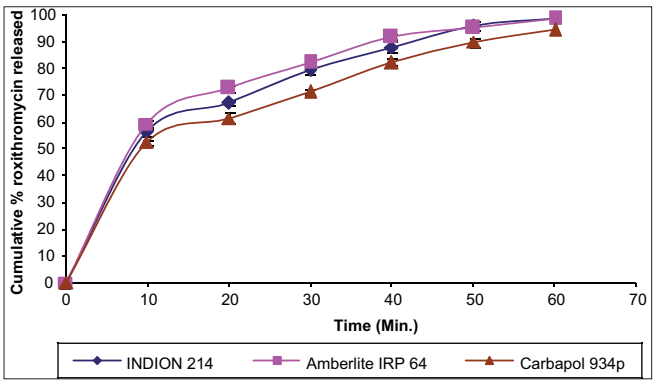

Figure 1: *In vitro* release profile of complexes

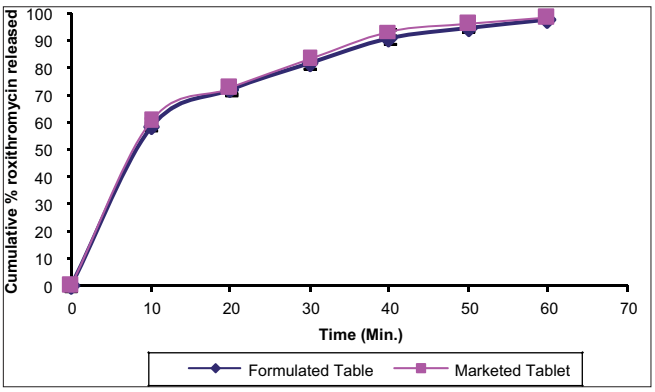

Figure 2: *In vitro* release of roxithromycin

ratio are depicted in Table 5.

Then, the formulated dispersible tablets were evaluated for disintegration time, weight uniformity, %friability, and content uniformity as shown in Table 6. After evaluation, batch B5 with 5% sodium starch glycolate and spray-dried lactose as filler was found to be optimum batch as it shows lowest disintegration time with desired friability value. Figure 2 shows that both formulated and marketed tablets released more than 95% of drug within 60 min. Thus, formulated tablets have comparable released profile with that of the marketed tablets. Formulated tablets masked

the bitter taste of drug completely, whereas marketed tablets failed.

CONCLUSION

Use of cation exchange resin offers good method for preaparing taste-masked substrates of roxithromycin. Results obtained in this work shows that drug-resin complexes and drug-carbopol complexes effectively masked bitter taste of roxithromycin. Formulated dispersible tablets showed comparable release profile with that of the marketed dispersible tablets and having additional advantage of complete taste masking. Thus, complexation of roxithromycin with Amberlite IRP64 increases acceptability and palatability of formulated dispersible tablets.

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