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Research Article

Modified Polysaccharides as Fast Disintegrating Excipients for Orodispersible Tablets of Roxithromycin

Vijay Sharma,[1] Anil K. Philip,[1] and Kamla Pathak[1,2]

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Abstract. The purpose of this study was to develop a dosage form that was easy to administer and provides rapid release of the drug roxithromycin, using modified polysaccharides as rapidly disintegrating excipients. Modified polysaccharides co grinded treated agar (C-TAG) and co grinded treated guar gum (C-TGG) were prepared by subjecting pure polysaccharides namely agar and guar gum respectively to sequential processes of wetting, drying and co grinding with mannitol (1:1). The modified polysaccharides were characterized by Scanning Electron Microscopy and Diffuse Reflectance Spectroscopy and evaluated for particle size distribution, derived properties, swelling index and biodegradability. Optimization studies based on 2^2 factorial designs, with friability and disintegration time as response parameters were used to formulate orodispersible tablets of roxithromycin and evaluated for wetting time, water absorption ratio and *in vitro* drug release at salivary pH 6.4 and physiological pH 7.4. Results indicated that lower levels of modified polysaccharides namely C-TAG in F_3 and C-TGG in F_7 and higher levels of microcrystalline cellulose, exhibited least disintegration times without friability concerns. *In vitro* release of optimized formulations F_3 and F_7, both at salivary pH and physiological pH was found to be more than 90% within 30 min as compared to 27.82% at the same time point of conventional formulation. Stability studies carried out as per ICH Q1A guidelines suggested the formulations to be stable for a period of 6 months. Thus the approach of using modified polysaccharides as fast disintegrating excipient can be used to formulate a stable orodispersible formulation.

KEY WORDS: modified polysaccharides; orodispersible; roxithromycin; swelling index; 2^2 factorial design.

INTRODUCTION

Orodispersible tablet is a dosage form that is to be placed in the mouth where it disperses rapidly before swallowing. The significant aspects of this delivery system are rapid onset of action, enhanced bioavailability of the drug than those observed from standard dosage forms and improved patient compliance for pediatric, geriatric population, patients with poor physiological and physical abilities and traveling patients that may not have ready access to water. Of the various desirable features for orodispersible tablets like dissolution and disintegration in the mouth within seconds, it should be capable of high drug loadings, be compatible with taste masking approaches, be portable without fragility concern, have pleasant mouth feel after oral administration and lower sensitivity to environmental conditions of temperatures and humidity. One of the major concerns is manufacture of the tablet using conventional processing and packaging equipments with relatively inexpensive orodispersible excipients.

Currently available technologies for manufacture of orodispersible tablets can be broadly classified into two major categories namely conventional and patented technologies. Most of the technologies require specialized processing conditions and equipments except for some conventional cost effective technologies like direct compression and disintegrant addition. Disintegrant addition is one of the popular techniques for formulating orodispersible tablets whereby optimum concentrations of superdisintegrants are added to the formulation to achieve rapid disintegration accompanied with good mouth feel. Numerous literature reports suggest the use of relatively expensive semi synthetic polymeric superdisintegrants like crosspovidone (1,2), croscarmellose sodium (2), sodium starch glycollate (3), PVPK12 (4) and cross linked sodium carboxy methylcelluose (5). The reports on use of natural polysaccharides like treated agar (6) and guar gum (7) as disintegrants for rapidly disintegrating tablets are relatively fewer.

The present study was aimed to modify selected polysaccharides by simple techniques, characterize, and assess their orodispersible properties by formulating and evaluating orodispersible tablets of the model drug roxithromycin. Presumed mechanism of disintegration is that, the porous nature of the modified polysaccharides shall facilitate water

[1] Department of Pharmaceutics, Rajiv Academy For Pharmacy, NH#2, Delhi–Mathura bypass P. O. Chattikkara Mathura, 281001 Uttar Pradesh, India.
[2] To whom correspondence should be addressed. (e-mail: kamla_rap@yahoo.co.in)

absorption, thereby causing swelling of polysaccharides without forming gelatinous mass in water, which may lead to excellent disintegration of tablet.

Roxithromycin, Erythromycin 9-{*O*-[(2-methoxyethoxy) methyl] oxime} is a macrolide antibiotic used in the treatment of wide variety of infections like bronchitis, severe campylobacter enteritis, chancroid, diphtheria, legionnaires, pneumonia sinusitis and trench fever (8). Following oral administration, roxithromycin is absorbed with a bioavailability of about 50% and the peak plasma concentrations are reached in about 2 h, after a single dose. Absorption is reduced when taken after, but not before meals. An orodispersible tablet of roxithromycin may provide a dosage form that is easy to administer, provide rapid release of drug and also enhance bioavailability of the drug by pregastric absorption through mouth, pharynx and oesophagus, as the drug releases in saliva and passes down in to the stomach.

MATERIALS

Roxithromycin was supplied as gift sample by Torrent Pharmaceuticals Ltd., Indrad, India. Agar, spray dried lactose and mannitol were purchased from S MERCK, India. Guar gum was obtained gift from ACE International, India, Pepsin—1:3,000 was purchased from Titan Biotech Ltd., India and Potassium bromide IR grade was procured from Merck KGaA, Darmstadt, Germany.

METHODS

Preparation of Modified Polysaccharides as Fast Disintegrating Excipients

Modified polysaccharides were prepared by suspending 5 g of selected pure polysaccharides—agar (AG) and guar gum (GG) in 100 ml of distilled water. The suspensions were stirred at 500 rpm using magnetic stirrer (Jindal Scientific Industries, India) for 24 h. Obtained swollen masses were spread out on enameled trays (10×12 in.), and dried at 40 °C for 72 h. The dried product was scrapped out and crushed in a glass pestle mortar to obtain coarse, non-free flowing and heterogeneous particles of treated polysaccharides—treated agar (TAG) and treated guar gum (TGG). Treated polysaccharides were then co-grinded with mannitol (1:1) in a glass pestle mortar for 20 min and passed through sieve (# 22) to get the modified polysaccharides—co-grinded treated agar (C-TAG) and co-grinded treated guar gum (C-TGG) respectively (9).

Evaluation and Characterization of Modified Polysaccharides

Measurement of Particle Size and Its Distribution

Particle size distribution studies for pure, treated and modified polysaccharides were carried out by the method of sieving using a nest of BSS sieves arranged in order of (# 10, 16, 22, 44, 60, 85, 100, 120, 200 and receiver) on a mechanical shaker (Jindal Scientific Industries, India) for 20 min. The weight of powder retained on each sieve was used for calculation of various micromeritic parameters—mean diameter, standard deviation (10), and IQCS (Intra quartile coefficient of skewness) (11).

Evaluation of Derived Properties

The derived properties of pure, treated and modified polysaccharides were obtained using bulk density apparatus (HICON, India) and the obtained values of loose bulk and tapped bulk densities were subjected to the calculation of Carr's index and Hausner ratio (11).

Surface Morphology

External surfaces of pure, treated and modified polysaccharides were studied for surface morphology by scanning electron microscope (Joel 6100, Tokyo, Japan). The samples were coated with gold palladium under argon atmosphere using a gold sputter module in a high vacuum evaporator.

Determination of Swelling Index

A modified fabricated apparatus (Fig. 1) (12) was used to measure water uptake and swelling index (S I) of pure and modified polysaccharides. Weighed quantity of test polysaccharide was subjected to the graduated arm A (internal diameter 10 mm) and the swelling medium, phosphate buffer pH 6.4 was poured in graduated arm B (internal diameter10 mm) to a level corresponding to the height of powder pile in arm A. The level of swelling medium was maintained constant during the entire experiment. The increase in the volume (cm^3) of test polysaccharide was recorded at different time intervals up to 24 h and SI was calculated by the following equation,

$$SI = \text{Final volume} - \text{Initial volume} / \text{Initial volume} \times 100 \quad (1)$$

The swollen mass from arm A, at the end of test period was removed and weighed (gram) to get the final weight and

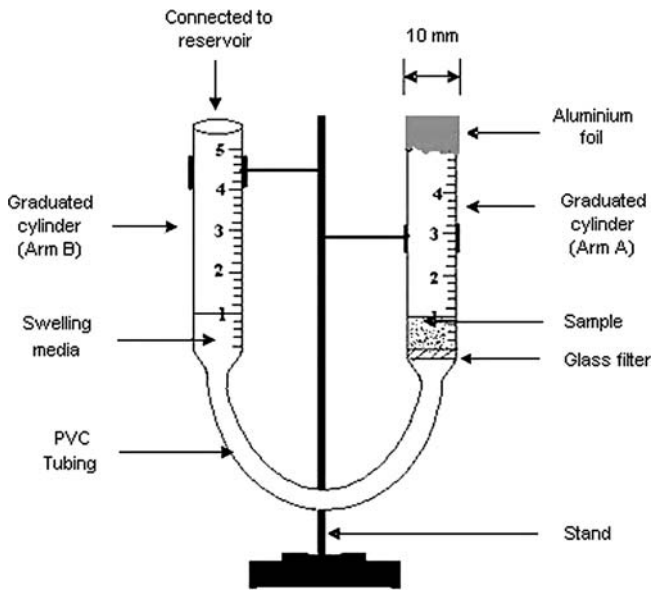

Fig. 1. Schematic diagram of modified apparatus for determination of swelling properties

Table I. Experimental Design for Formulation of Orodispersible Tablet of Roxithromycin

S. No.	Factor Combination	Concentration of Modified Polysaccharide (%wt/wt)	Concentration of MCC (%wt/wt)
1	F_1	5	10
2	F_2	10	10
3	F_3	5	15
4	F_4	10	15

percentage increase in weight was determined by use of following equation

$$\text{Increase in weight}(\%) = \text{Final weight} - \text{Initial weight}/\text{Initial weight} \times 100 \quad (2)$$

Percentage increase in weight was interpreted for water uptake capacity of the test polysaccharides. The reduction in SI of modified polysaccharides in comparison to pure polysaccharide was determined by the following equation

$$\text{Reduction in SI} = \text{SI of polysaccharide} - \text{SI of modified polysaccharide}/\text{SI of polysaccharide} \quad (3)$$

The results were subjected to Wilcoxon Rank Sum Test (13).

Biodegradability Studies

Modified polysaccharides (100 mg) was suspended in 5 ml of isotonic saline solution (308 mOsmol/l) containing 10 mg of Pepsin (1:3,000) and was incubated at 37±0.5 °C for 96 h (14). The biodegradability was observed at 2, 7, 24, 48, 72 and 96 h.

Diffuse Reflectance Spectroscopy (DRS)

DRS studies were carried out, using FTIR Spectrophotometer with DRS attachment (Shimadzu FTIR-8400S Kyoto, Japan). The test sample diluted with KBr to get a final dilution of 1:400 was mounted in to the instrument. The measurements were made in transmittance mode in the range of 500–4,000 cm^{-1} against the background spectra of pure KBr.

Experimental Design

In the 2^2 factorial design (13) two independent factors namely, the concentration of modified polysaccharides and the concentration of microcrystalline cellulose were evaluated at two different levels (Table I). The disintegration time and friability were measured as dependent responses for all the formulations.

Blending and Tabletting

Modified polysaccharides, roxithromycin and other excipients (Table II) were mixed in a polyethylene bag for 15 min, lubricated with finely screened (# 120) PEG 6000 and compressed into tablets on an electrically operated single punch machine with 8-mm punch diameter (HICON, India).

Evaluation of Prepared Orodispersible Tablets

The disintegration time (n=6) of the orodispersible tablets was determined by employing a modified dissolution apparatus (15) and friability (n=20) was determined using Roche type friabilator (Jindal Scientific Industries, India).

Selection and Evaluation of Optimized Formulations

Optimized formulations (F_3 and F_7), selected on the basis of a disintegration time of less than 60 s and desirable friability were subjected to wetting time and water absorption ratio determinations (16). *In vitro* drug release characteristics were evaluated both in phosphate buffer pH 6.4 (salivary pH) and phosphate buffer pH 7.4 (physiological pH) separately in USP II paddle apparatus. Dissolution medium (900 ml) maintained at 37±0.5 °C was stirred at 100 rpm and samples withdrawn at predetermined intervals were analyzed spectrophotometrically. The data obtained was compared with the drug release profile of conventional tablet F_9 at pH 7.4.

Stability Studies

The optimized orodispersible tablets of each batch were separately stored in aluminium capped clear glass vials and subjected to the storage condition of 40±2 °C/75±5% RH (17) for 6 months. The samples were withdrawn at the time interval

Table II. Formulation and Response Parameters of Orodispersible Tablets of Roxithromycin

	Formulation Containing C-TAG				Formulation Containing C-TGG				Conventional
Ingredients by Weight (mg) /Response Parameter	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Roxithromycin	150	150	150	150	150	150	150	150	150
Modified polysaccharide	15	30	15	30	15	30	15	30	–
Microcrystalline cellulose	30	30	45	45	30	30	30	45	45
PEG 6000	6	6	6	6	6	60	30	6	6
Erythritol (%)	0.5	0.5	0.5	0.5	0.5	0.5	0.6	0.5	0.5
Spray dried lactose q.s	300	300	300	300	300	300	300	300	300
Disintegration time (s)	45	17	35	23	38	56	44	52	275
Friability	Pass	Pass	Pass	Pass	Fail	Pass	Pass	Pass	Pass

Table III. Micromeritic Properties of Pure, Treated and Modified Polysaccharides

S. No.	Name of Polysaccharide	Type of Polysaccharide	Statistical Parameters Evaluated		
			d_{mean} (μ_m)	Standard Deviation	I Q C S
1	AGAR	Pure	46.93	2.77	−0.20
		Treated	84.89	3.00	−0.13
		Co-grinded	40.30	2.20	−0.04
2	GUAR GUM	Pure	39.75	1.47	0.00
		Treated	199.81	1.49	0.32
		Co-grinded	41.96	2.12	0.00

of 0, 1, 3 and 6 months and evaluated for *in vitro* disintegration time, friability and percentage drug content and *in vitro* drug release. The chemical stability was also evaluated by DRS study.

RESULT AND DISCUSSION

Preparation of Modified Polysaccharides

Hydrophilic polysaccharides interact with aqueous solutions by three-dimensional swelling, to an equilibrium value and physically entrap a significant portion of water within their structure. Drying at this stage leads to evaporation of water leaving behind a porous structure. This structural modification does not allow the formation of gelatinous mass of the modified polysaccharides in water. However, the individual particles shall facilitate water uptake due to the porous structure, undergo independent swelling thus facilitating the process of disintegration. Therefore, selected polysaccharides AG and GG were subjected to sequentially controlled modifications of wetting and drying to obtain treated polysaccharides TAG and TGG

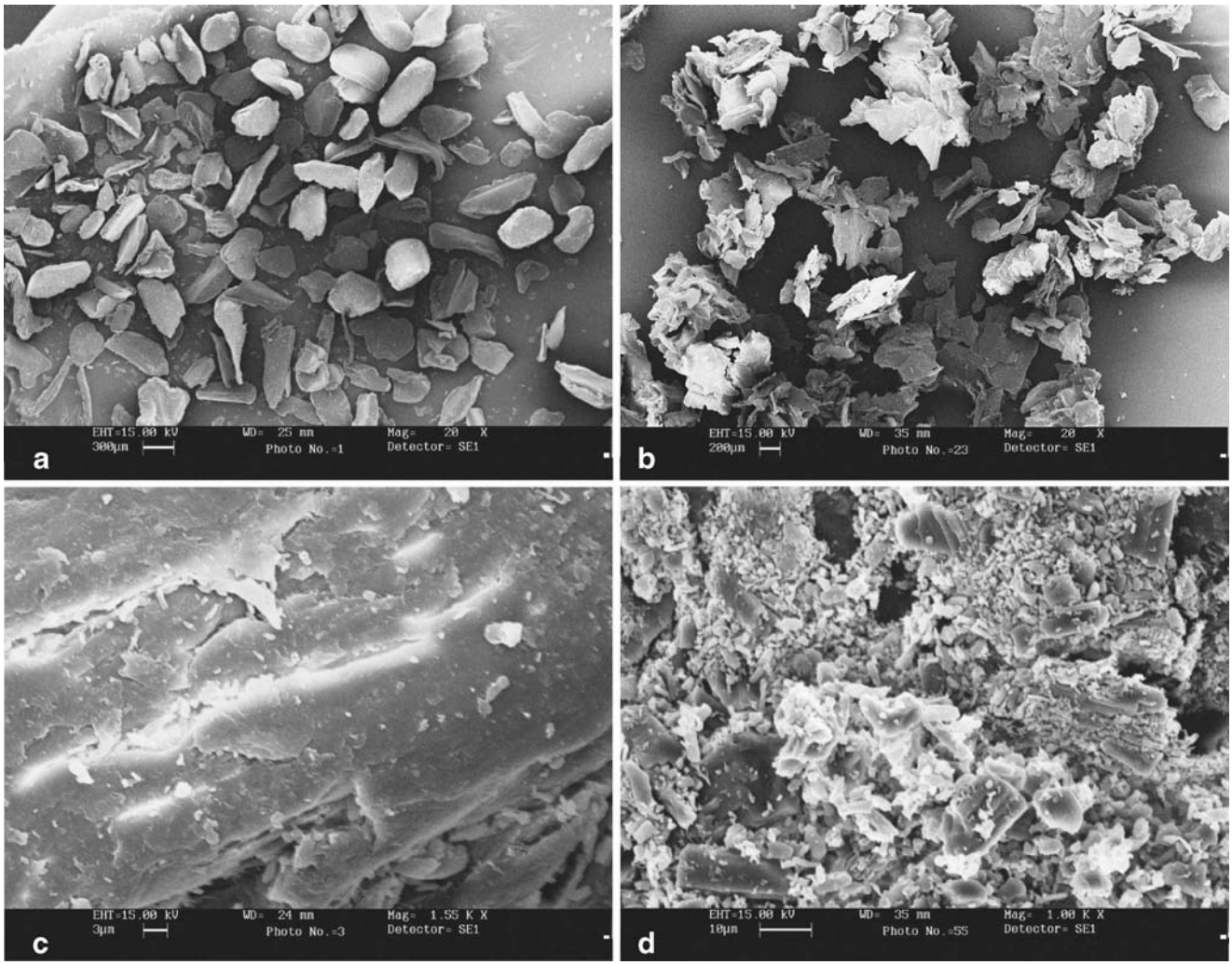

Fig. 2. Scanning electron micrographs of **a** AG, (original magnification ×20); **b** TAG, (original magnification ×20); **c** surface morphology of TAG, (original magnification ×500); **d** C-TAG, (original magnification ×20)

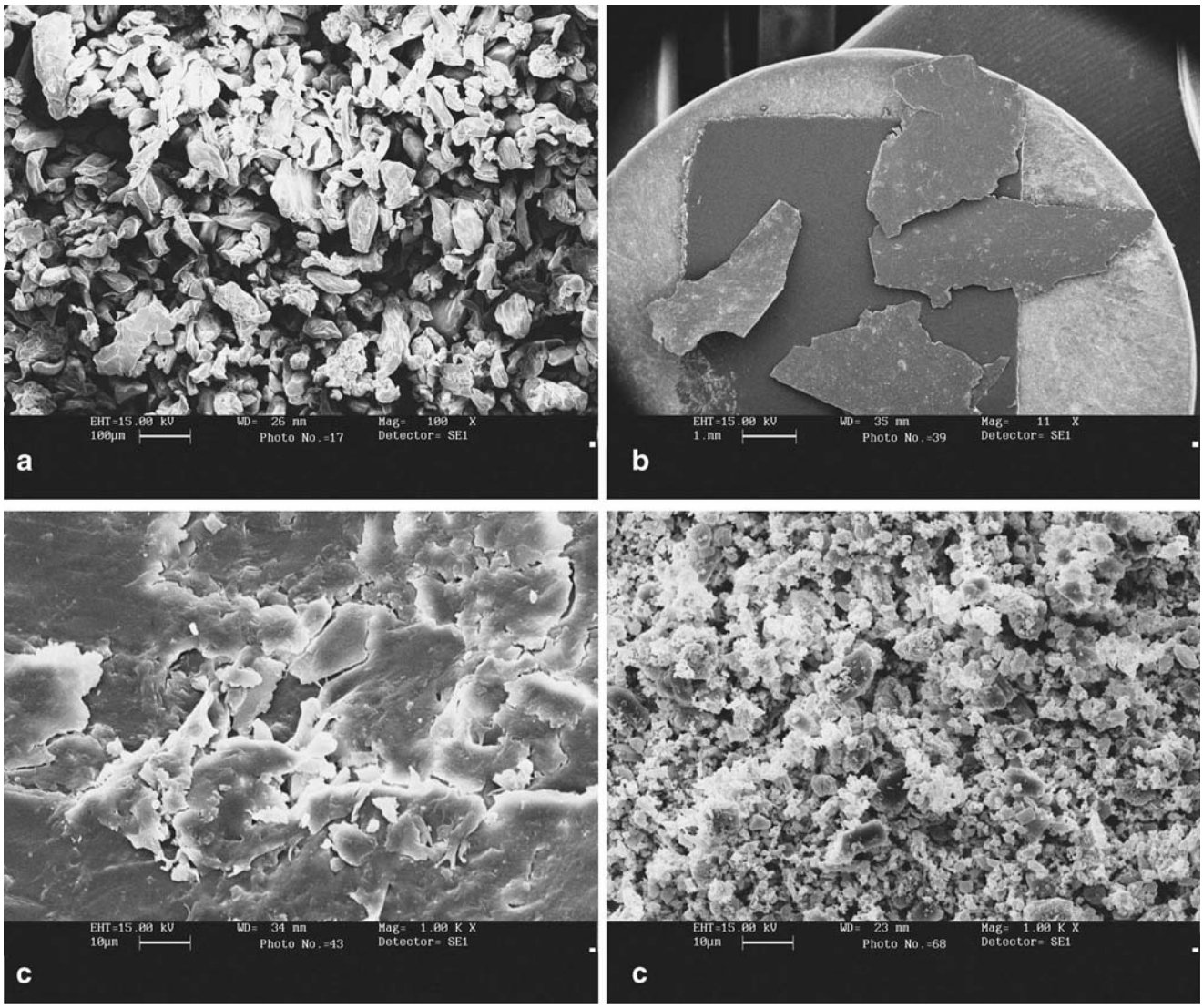

Fig. 3. Scanning electron micrographs of **a** GG, (original magnification ×100); **b** TGG, (original magnification ×11); **c** Surface morphology of TGG, (original magnification ×1,000); **d** C-TGG, (original magnification ×1,000)

that were sticky, non-free flowing aggregated lumps and presented handling problems. It is reported that grinding or milling not only reduces particle size but also causes changes in molecular behavior such as crystallinity and chemical reaction rate in the solid phase (10). Keeping in view these facts mannitol, a directly compressible water soluble sugar alcohol was selected as a grinding assistant as it imparts a cooling sensation in mouth due to its negative heat of solution, is an orodispersion aid and improves flow property of other materials (9). TAG and TGG were co-grinded with mannitol in 1:1 ratio to obtain free flowing, non-sticky powders of modified polysaccharides C-TAG and C-TGG respectively.

Evaluation and Characterization of Modified Polysaccharides

Particle Size Distribution Studies

The micromeritic data documented in Table III clearly indicates an increase in the d_{mean} of pure polysaccharides on treatment with water whereas co-grinding with mannitol led

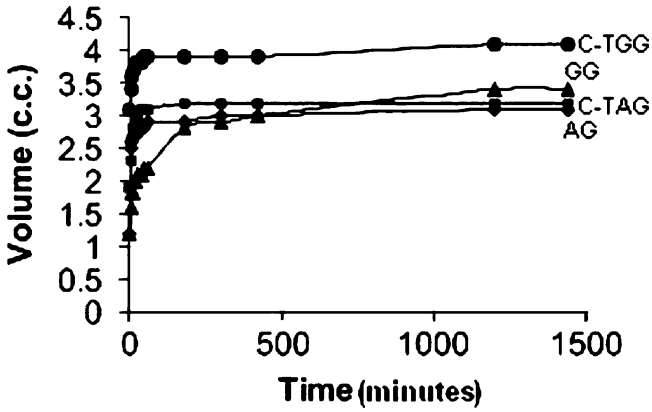

Fig. 4. Kinetic plots for swelling property of AG, C-TAG, GG and C-TGG

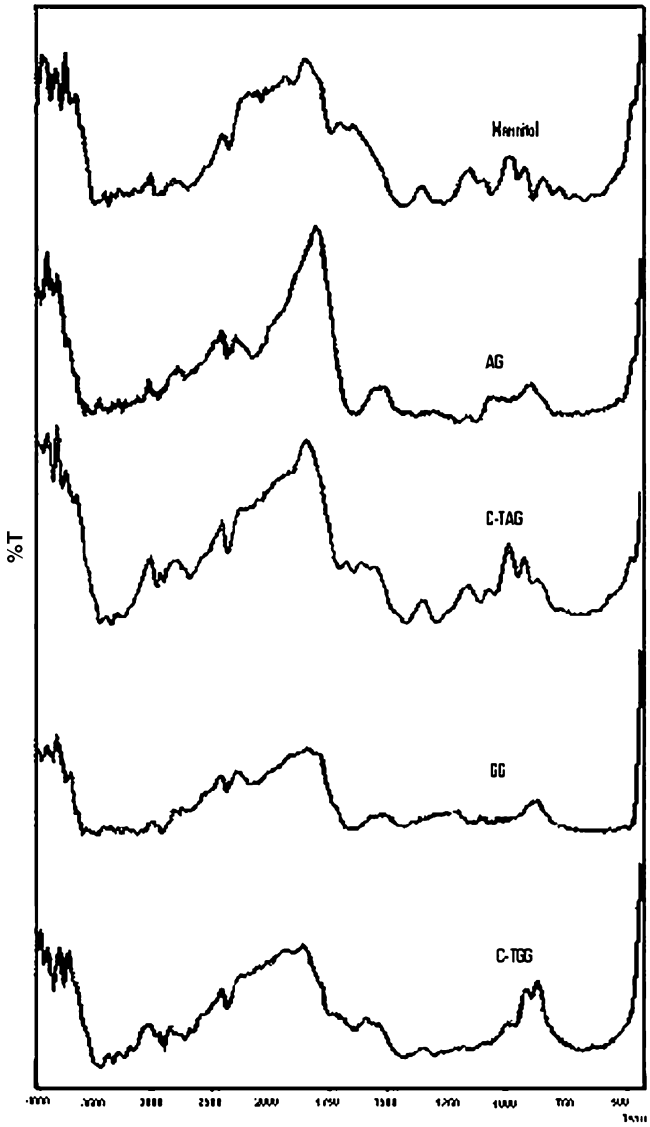

Fig. 5. Diffuse reflectance spectra of mannitol, pure polysaccharides and modified polysaccharides

to a decrease in particle size. Closer numerical values of d_{mean} for C-TAG (39.37 μm) and C-TGG (41.96 μm) assured the reproducibility of cogrinding process used for particle size reduction. Particle size distribution summarized using statistical methods indicated a high degree of skewness on treatment with water that approached zero values on co grinding suggesting normalization of the particle population.

Determination of Derived Properties

The bulk density of AG was found to be 0.40 g/cm^3 and that of C-TAG was found to be 0.32 g/cm^3, similarly the bulk density of GG found to be 0.40 g/cm^3 that got reduced to 0.30 g/cm^3 for C-TGG. A 20–25% reduction in bulk density values of modified polysaccharides indicated a higher bulk volume and thereby higher porosity when compared to pure polysaccharides, which is desirable to support rapid disintegration. The values of Carr's compressibility index in the range of 18–20 and Hausner ratio values of 1.35 and 1.23 for the modified polysaccharides C-TAG and C-TGG suggested fairly good flow properties that may be further improved by addition of flow activators.

Surface Morphology

The microscopic images showed small particles with smooth surface for AG and GG (Figs. 2a and 3a), whereas TAG and TGG exhibited aggregates of particles (Figs. 2b and 3b). The treated polysaccharides when co-grinded with mannitol was obtained as a relatively homogeneous dispersion with numerous pores, cracks and fissures (Figs. 2c,d and 3c,d) that are assumed to facilitate rapid water ingress and support rapid disintegration.

Determination of Swelling Index

The SI of AG (158.33%) significantly reduced after the modification, to a value of 68.42% for C-TAG. Similarly, for C-TGG the SI was 32.25% from an initial value of 183.33% of guar gum (Fig. 4). The reduction in SI may be attributed to higher water loading capacity of highly porous C-TAG and C-TGG when compared to their purer versions. The water loading capacity for C-TAG (84.32%) was higher than that of C-TGG (81.34%) and is a superior disintegrant. In order to act as an efficient fast disintegrant, the magnitude of swelling should be less than its water absorption capacity so as to avoid the formation of gelatinous mass that will retard orodipersion. The SI of C-TAG and C-TGG reduced to an order of 56.78 and 82.41% respectively, in comparison to the pure polysaccharides, which assures the use of modified polysaccharides as rapidly disintegrating excipients. The calculated Z value for AG versus C-TAG and GG versus C-TGG were 4.04 and 4.36 that is more than the tabulated Z value of 1.96 at 95% confidence level hence pure and co-grounded polysaccharides are assured to be statistically different.

Biodegradability Study

Biodegradability is a primary concern when a GRAS listed excipient is subjected to modifications. Biodegradability studies on C-TAG and C-TGG in the presence of pepsin

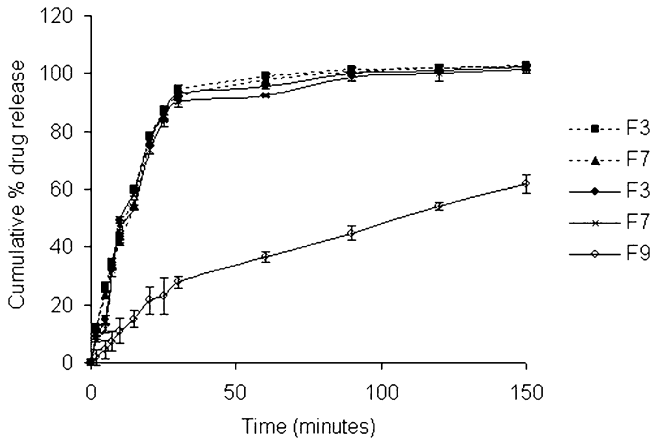

Fig. 6. *In vitro* drug release profile of (*filled square*) F_3 and (*filled triangle*) F_7 at pH 6.4, (*filled circle*) F_3, (*X symbol*) F_7 and (*open circle*) conventional tablet at pH 7.4

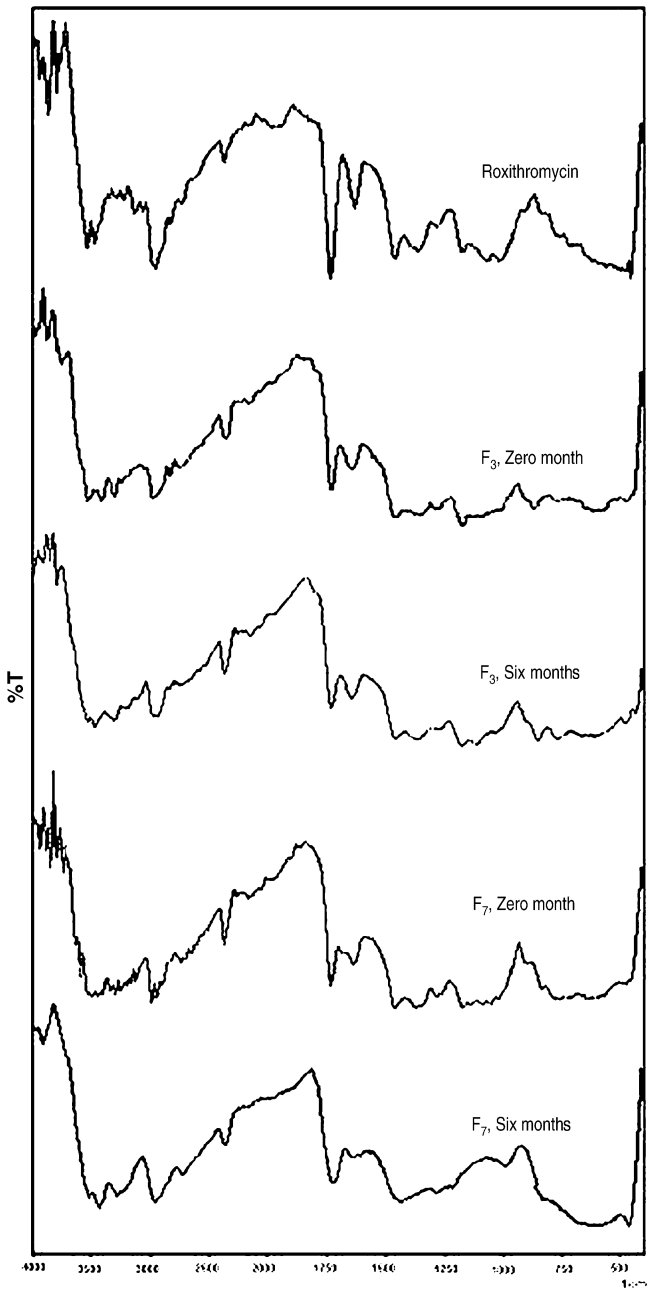

Fig. 7. Diffuse reflectance spectra of roxithromycin and optimized formulations at 0 and 6 months

(1:3,000), one of the enzymes present in gastric fluid exhibited gradual biodegradability within 96 h. The modified polysaccharides lost their definite physical appearance, became bulkier within 2 h, followed by formation of a suspension of fine particles that were digested at the end. C-TGG and C-TAG was completely digested within 24 and 72 h respectively.

Diffuse Reflectance Spectroscopy

Diffuse reflectance spectroscopy was carried out to determine the chemical changes if any, following the modifications of AG and GG. The DRS spectra of mannitol exhibited peaks between 3,000–2,900 cm^{-1} (C–H stretching), 3,700–3,600 cm^{-1} (O–H stretching) and 1,000–1,050 cm^{-1} (primary and secondary alcohols). The spectra of agar showed peaks at 1,080–1,150 cm^{-1} (C–O–C stretching) and for guar gum peaks were observed at 2,830–2,700 cm^{-1} (C–H stretching) and 1,700–1,750 cm^{-1} (C=O) The spectra of modified polysaccharides exhibited peaks at positions similar to that observed in the spectra of pure polysaccharides (Fig. 5) and hence, it can be concluded that the modification of the polysaccharides led to physical changes, with no evident chemical changes.

Selection of Optimized Orodispersible Formulation

From the results (Table II) obtained it was observed that, all the prepared formulations exhibited a disintegration time of less than 60 sec, but some of the formulations failed the friability test. Amongst the formulations (F_1–F_4) prepared using C-TAG, formulation F_2 showed the least disintegration time of 17 s but failed the friability test and F_3 with a disintegration time of 35 s passed the friability test and hence F_3 was considered as optimized formulation. Similarly for the formulations (F_5–F_8) made using C-TGG, friability test failed for the formulation F_5 exhibiting the least value of disintegration time 38 s and hence the formulation F_7 with the disintegration time of 44 s that passed the friability test was selected as the optimized formulation containing C-TGG. Thus formulations F_3 and F_7 (containing lower levels of modified polysaccharides and higher levels of MCC) that provided optimum friability and faster disintegration were identified as optimized formulations and subjected to further evaluations. F_1, F_4 F_6 and F_8 were rejected as these formulations failed the friability test.

Table IV. Stability Data for Optimized Formulations of Roxithromycin Orodispersible Tablet

Formulation Code	Parameters Evaluated	Time Interval (months)			
		0	1	3	6
F_3	Disintegration time (s)	35.1	34.2	34.1	32.6
	Friability	Pass	Pass	Pass	Pass
	Drug content (%)	102.7	102.4	101.5	101.2
	Percent drug release (30 min)				
	pH 6.4	94.9	94.7	93.9	93.6
	pH 7.4	93.0	92. 9	92.2	92.1
F_7	Disintegration time (s)	44.3	44.2	43.9	41.1
	Friability	Pass	Pass	Pass	Pass
	Drug content (%)	102.3	102.3	101.8	101.3
	Percent drug release (30 min)				
	pH 6.4	92.1	92.0	91.9	91.7
	pH 7.4	90.1	90.1	89.9	89.7

Evaluation of Optimized Orodispersible Formulation

Determination of Wetting Time and Water Absorption Ratio

The wetting time(s) of 6.5±0.4 and 6.6±0.5 s for F_3 and F_7 respectively were significantly lower due to the highly porous structure of modified polysaccharides and the presence of higher levels of MCC in the formulations (18). Water absorption ratio of the formulations F_3 and F_7 were found to be 1.4±0.1 and 1.3±0.2 respectively indicating that the formulations could uptake water approximately up to 1.5 times of their own weight. This could be again be attributed to numerous air filled pores present in modified polysaccharides that got displaced by water.

In Vitro Drug Release Study

In vitro drug release (n=6) studies of the optimized formulations were carried out at pH 6.4 and 7.4. The pH 6.4 was selected to assess any pregastric absorption that may take place when some of the particles from the orodispersible formulation get lodged into the denture and gradually may get absorbed through buccal mucosa. This in turn is suggested to increase the bioavailability of roxithromycin, as the hepatic metabolism of the drug absorbed through buccal cavity, is avoided. It was evident from Fig. 6, that in phosphate buffer pH 6.4, the percentage drug release from formulation F_3 and F_7 was found to be 94.91±1.10 and 92.06±1.24% respectively at 30 min, supporting the chances of absorption of the drug through buccal cavity. At pH 7.4 the percentage drug release from formulations F_3 and F_7 were found to be 93.04±0.77 and 90.13±1.90% (Fig. 6) respectively within 30 min which was many fold higher than the drug release of 27.82±1.98% from conventional tablets of roxithromycin, at the same time point. Faster dissolution for orodispersible formulations was due to larger surface area available for dissolution due to rapid disintegration of the formulation when compared to the conventional tablet, that required more time to disintegrate and hence to dissolute.

Stability Studies

The stability studies revealed (Table IV) that all the formulations were chemically stable when stored at 40±2 °C and 75±5% RH till the end of 6 months. Significant peaks of RXT at 1,685 cm^{-1} (ketone carbonyl), 1,730 cm^{-1} (lactone carbonyl), 1,000 and 1,200 cm^{-1} (ethers and amine functions), 1,340–1,460 cm^{-1} (–CH_2 bending) and 3,400–3,700 cm^{-1} (hydrogen bonded –OH and water) (19) in the DRS spectra at 0 months were retained in the samples withdrawn at sixth month (Fig. 7) and neither a shift, nor any new peak was observed indicating absence of any degradation product in the storage conditions tested. The tablets appeared to be physically stable and there was insignificant reduction in disintegration and friability for both the optimized formulations.

CONCLUSION

Modified agar and guar gum obtained were biodegradable, directly compressible and exhibited desirable swelling dynamics to be used as an excipient for the formulation of orodispersible tablets of roxithromycin. Formulations with lower levels of modified polysaccharides and higher levels of MCC were selected as the optimized orodispersible formulations that were stable for a period of 6 months.

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