

DESIGN, OPTIMIZATION, AND STATISTICAL EVALUATION OF ORAL RECONSTITUTED SUSPENSION OF CLARITHROMYCIN USING ION-EXCHANGE RESINS

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ABSTRACT

Objectives: The objective of the present study is taste masking of bitter clarithromycin using Indion 204, Indion 234, and Tulsion 335 as ion-exchange resins, which forms insoluble complexes, inhibiting the drug release in saliva as ion-exchange resins are cross-linked polymers, water-insoluble that contains salt-forming groups in repeating positions on the polymer chain. Drugs that are bitter and cationic get adsorbed onto weak cationic exchange resins of carboxylic acid functionality such as Indion 204, Indion 234, and Tulsion 335 to form non-bitter complexes.

Methods: The drug-resin complex loading process was optimized for the resin content, activation, swelling time, stirring time, influence of pH, and temperature for maximum drug loading and the formed complex was evaluated by differential scanning calorimetry (DSC) to confirm complex formation. The drug-resin complex was also characterized by their micromeritic and rheological properties. These complexes were used to prepare oral reconstituted suspensions and the taste was evaluated. The formulation was evaluated for various parameters such as sedimentation volume, pH, redispersibility, viscosity, drug content, and *in vitro* drug release.

Results: Acid-activated resins comprising Indion 204, Indion 234, and Tulsion 335 with the drug:resin ratio of 1:2, stirred in a solution of pH 7–8 at 70° for 6 h had a maximum drug loading and masked the bitter taste of clarithromycin. DSC of the drug-resin complex (DRC) revealed that there was interaction leading to complex formation. The drug-resin complex was formulated into suspension formulations (S1-S9) and evaluated. Various parameters were found to be within permissible limits. Formulations S3, S6, and S9 containing 1:2 ratios of the drug-resin complex of Indion 204, Indion 234, and Tulsion 335 revealed maximum taste masking. This was further confirmed by treatment of taste evaluation scores obtained from the volunteers by ANOVA, Dunnett's multiple comparison test, and Tukey's multiple comparison test. All the three optimized formulations had a significant difference of $p < 0.001$ when compared to control S10. S6 formulation was widely accepted.

Conclusion: Ion-exchange complexation could efficiently mask the bitter taste of clarithromycin and achieve palatable taste suitable for pediatric use.

Keywords: Ion-exchange resins, Drug-resin complex, Taste masking, Indion 204, 234, Tulsion 335, Dunnett's test, Tukey's test, ANOVA.

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INTRODUCTION

The ease of administration is the criterion for the preference of oral dosage forms. The bitterness of active pharmaceutical ingredients (API) is one of the significant issues of the pharmaceutical industry during the formulation of dosage form, thereby leading to poor patient compliance. A majority of drugs are bitter due to the presence of amine functional groups, thereby rendering unpleasant taste to the formulation [1]. Hence, it becomes a challenge to the formulator to ensure that the bitterness and obnoxious taste of drugs is masked particularly in pediatric and geriatric formulations dosage form thereby ensuring that the formulation is patient compliant and has product value [2].

Ion-exchange resins are economical and can be incorporated in the development of a basic, rapid, and profitable method of taste masking [3]. Ion-exchange resins are polymeric cross-linkage chains containing salt forming groups in repeating position, which have an affinity for oppositely charged counter ions, thus adsorbing and binding the ions into the polymer matrix in an equilibrium process. The bound drug is desorbed or eluted from the drug-resin complex during the process of absorption into the body [4,5]. The versatility of IER as drug delivery vehicles has attracted pharmaceutical research [6]. Ion-exchange resins are used for masking of taste, sustained release, targeted drug delivery, and drug stabilization [7]. Weak cationic exchange resin of carboxylic acid is used for masking bitter cationic drugs to form a non-bitter complex [8].

Clarithromycin is a macrolide antibiotic used in the treatment of common pediatric infections of the middle ear and upper respiratory tract as well as certain forms of pneumonia that affect the elderly [9]. However, the drug is very bitter making oral administration of the drug [10]. It is a practically water-insoluble drug and shows polymorphism and the problem of stability by hydrolysis when it is in a liquid formulation for a long time [10]. Commercially, it is available as a tablet and suspensions but these formulations possess a problem of drug release in the saliva. Hence, it is an objective of the present research to provide an oral reconstituted suspension of clarithromycin which can deliver pharmaceutically acceptable and stable dosage form of API and provides the public with a useful and economic formulation.

MATERIALS AND METHODS

Materials

Clarithromycin was obtained as a gift sample from Ind-Swift Laboratories Limited, Punjab. Indion 204 and Indion 234 were gifted by Ion Exchange India Ltd., Mumbai. Tulsion-335 was gifted by Thermax Ltd., Pune. Xanthan gum was obtained from HiMedia, Mumbai. Sodium Benzoate, sucrose, sodium citrate, and flavor were purchased from S.D Fine-Chem. Ltd., Mumbai. Aspartame was purchased from NutraSweet Company and all the chemicals were used of either pharma or analytical grade.

Taste evaluation of formulation was performed by volunteers within the age group of 21–25 years. Prior explanation of the study protocol and written consent was obtained from the volunteers [11].

Methods

Standard calibration curve of clarithromycin

The samples of different concentrations of range 20–120 µg/mL were prepared with chloroform. To 10 mL of each dilution taken in separating funnel, 5 mL concentrated hydrochloric acid was added followed by 10 mL of acetone and reaction mixture was shaken gently for 5 min for the formation of a stable orange-colored complex [12]. The upper orange-red colored layer was separated and the absorbance measured at 486 nm against reagent blank [12].

Complexation with ion-exchange resin

Optimization of drug-resin complexation

The loading of the drug onto the resin was optimized for various parameters during processing, including activation conditions, swelling time, stirring time, pH, temperature, and drug:resin ratio [13].

Effect of activation conditions on resin drug loading capacity

Activation of Indion 204, Indion 234, and Tulsion 335 was done by washing the individual resins with deionized water, 1N HCl and 1N NaOH in separate processes. The resin was further subjected to repeated washing with water until neutral pH was reached. Drug-resin complexes (DRC) were prepared by adding 100 mg of activated resin that was swollen for 45 min into a beaker containing 50 mL of distilled water and 100 mg of the drug. The mixture was prepared as a slurry with the aid of magnetic stirrer for 6 h at 60°C. The residue of the mixture was washed with 100 mL of chloroform and filtered. From this solution, 0.5 mL was taken and diluted to 10 mL with chloroform. The unbound amount drug in the filtrate was estimated spectrophotometrically at λ_{\max} 486 nm [12,13].

Optimization of resin concentration for maximum drug loading

Acid activated swollen resins and drugs were added in the ratio of 1:1, 1:1.5, and 1:2–100 mL of deionized water in separate beakers and stirred using a magnetic stirrer for 6 h at 60°C. The mixture residues were filtered and were washed with chloroform. The drug-loading efficiency of the resin was estimated [12,13].

The optimized resin concentration for the maximum loading of the drug was estimated spectrophotometrically (Table 1).

Optimization of swelling time of resin for maximum drug loading

Various batches of acid-activated resins were soaked in 100 mL quantity of deionized water for 10, 20, 30, 40, 50, 60, and 70 min at 60°C temperature in separate beakers. To each beaker drug and resin were added at 1:2 ratio and mixtures were stirred for 6 h at 60°C. Resin drug-loading efficiency was estimated [12,13]. The optimized swelling time of resin required for maximum drug loading was estimated spectrophotometrically (Table 2).

Optimization of stirring time for maximum drug loading

1:2 ratio of drug-resin complexes of separate batches was slurred in 100 mL of deionized water for 30, 60, 120, 180, 240, 300, and 360 min with the aid of magnetic stirrer at 60°C. Resin drug-loading efficiency was estimated [12,13]. The optimized stirring time required for maximum drug loading was estimated spectrophotometrically (Table 2).

Optimization of processing temperature for maximum drug loading

1:2 ratio of drug-resin complexes of separate batches was slurred in 100 mL of deionized water at different temperatures, namely, 25°, 30°, 40°, 50°, 60°, and 70°C using temperature controlled magnetic stirrer for 6 h. The amount of resin drug-loading efficiency was estimated spectrophotometrically from the bound drug. The optimized processing temperature was obtained [12,13] (Table 3).

Optimization of pH for maximum drug loading

1:2 ratio of drug-resin complexes of separate batches were slurred in 100 mL of standard solutions of hydrochloric acid and sodium hydroxide having pH 1.2, 2, 5, 6, 7, and 8 and stirred using a magnetic stirrer for 6 h at 60°C. The drug-loading efficiency was estimated and pH was optimized for maximum drug loading [12,13] (Table 3).

Preparation of drug-resin complexes

Based on optimization study results, batches of drug-resin complexes at 1:1, 1:1.5, and 1:2 ratio were prepared at optimized conditions for maximum loading capacity and subjected to further evaluation [13].

Evaluation of the optimized drug-resin complexes for drug content

The drug content was determined by eluting the 250 mg of DRC with continuous stirring in 100 mL 1N HCl for 1 h to ensure complete elution [13]. The solution was filtered. After suitable dilution, the drug content was determined spectrophotometrically at λ_{\max} 486 nm and the readings were taken in triplicate.

Table 1: Effect of activation conditions and resin concentration for maximum drug loading

Resins	Percentage of drug bound to resin in various activation conditions (%)			Percentage of drug bound to various resins (%)		
	Inactivated	Acid	Base	1:1	1:1.5	1:2
Indion 204	45.26±0.68	66.92±0.83	52.16±0.34	67.15±0.28	75.01±0.40	86.67±0.26
Indion 234	44.59±0.77	66.30±0.72	50.54±0.64	67.87±0.56	75.01±0.29	86.81±0.36
Tulsion 335	44.30±0.48	67.06±0.39	50.73±0.65	70.01±0.63	77.39±0.58	87.14±0.45

Results are mean±standard deviation (n=3)

Table 2: Optimization of swelling time and stirring time for maximum drug loading

Swelling time (min)	Percentage of drug bound to various resins (%)			Stirring time (min)	Percentage of drug bound to various resins (%)		
	Indion 204	Indion 234	Tulsion 335		Indion 204	Indion 234	Tulsion 335
10	70.72±0.32	65.49±0.17	66.20±0.69	30	60.73±0.62	58.58±0.89	60.25±0.88
20	79.29±0.94	75.86±0.75	70.96±0.64	60	65.96±0.36	65.49±0.98	66.20±0.35
30	80.19±0.17	79.81±0.98	78.43±0.76	120	71.20±0.55	70.82±0.79	70.96±0.48
40	83.67±0.70	83.05±0.37	83.14±0.47	180	76.91±0.88	74.86±0.97	75.01±0.68
50	85.91±0.67	85.29±0.87	86.62±0.39	240	80.72±0.69	79.62±0.78	79.29±0.46
60	86.91±0.46	85.29±0.62	87.86±0.63	300	84.76±0.46	83.43±0.69	82.62±0.73
70	86.91±0.59	85.29±0.69	88.1±0.78	360	86.67±0.78	85.81±0.87	86.19±0.61

Results are mean±standard deviation (n=3)

Evaluation of the prepared drug-resin complexes for drug release

The drug release studies were performed by the USP Type XXIII tablet dissolution apparatus. DRC equivalent to 250 mg of clarithromycin was taken in 900 mL of 0.1 N HCl. The temperature and speed of the apparatus were maintained at $37 \pm 0.5^\circ\text{C}$ and 75 rpm, respectively. Aliquots were withdrawn after every 2 min for 30 min and were filtered with Whatman filter paper no. 41 and were analyzed spectrophotometrically at λ_{max} 486 nm. Triplicate readings were taken [13,14].

Differential scanning calorimetry (DSC) was carried out for the characterization of the complex formed. All the DRCs were subjected to DSC and the thermograms were studied for drug-polymer complex formation [13-15].

Micromeritics: The DRCs were evaluated for the angle of repose, Carr's index, tapped and bulk density, and Hausner's ratio [13].

Formulation of the prepared drug-resin complexes into dry powder suspension

Accurately weighed amounts of the prepared complexes of clarithromycin resinates (Indion 204, Indion 234, and Tulsion 335) at 1:1, 1:1.5, and 1:2 drug:resin ratios equivalent to 250 mg of clarithromycin were mixed with other excipients such as suspending agents, sweetener, flavoring agent, preservative, anti-caking agent, and buffer by conventional technique [16,17]. All the ingredients were passed through 44# and mixed. The dry suspension is reconstituted up to 100 ml with distilled water before use. The formulations S1-S9 represented with DRC and S10 represented without DRC (Table 4).

Evaluation parameters

The angle of repose, Carr's index, as well as the Hausner's ratio for drug powder and dry powder suspension, were determined and compared [13].

Evaluation of the prepared oral reconstituted suspensions

100 mL of a reconstituted oral suspension of clarithromycin was prepared and fully evaluated for color and odor, viscosity, pH, sedimentation rate, redispersibility, and particle size [16-18].

Furthermore, drug content, drug leaching into the suspension, and *in vitro* dissolution studies of the drug from the prepared suspensions were determined and compared [17-19].

Assessment of the bitter taste of drug (bitterness threshold)

The bitter taste threshold value of clarithromycin was determined based on the bitter taste recognized by six volunteers. Before measurement, informed written consent was taken from each volunteer [20].

Various concentrations (10–100 $\mu\text{g/mL}$) of the drug were prepared in phosphate buffer pH 6.7. The buffer solution was used for rinsing the mouth and then, 10 mL of the most dilute solution was swirled in the mouth near the base of the tongue for 30 s and tasted. After 30 s, if the bitter sensation was no longer felt in the mouth, the solution was spat out and wait for 1 min to ascertain whether this is due to delayed sensitivity. Then rinse with safe drinking water. The recording was.

"–" = Did not detect any difference in taste

"+" = Detected some difference but was not able to specify about the taste and

"++" = Detected a bitter taste.

The next highest concentration should not be tasted until at least 10 min have passed. The threshold of the bitterness of the drug is defined as the concentration at which more than half of the volunteers detected bitterness when holding the drug in their mouth. The threshold value was correspondingly selected from the different drug concentrations as the lowest concentration that had a bitter taste [21] (Table 5).

In vivo evaluation of the bitter taste of the formulations

Gustatory sensation tests of prepared suspensions were done using the equivalent density examination method [21]. The pure drug formulation was kept as control during the study. Before the experiment, the study protocol was explained and written consent was obtained from volunteers (n=6; three males and three females). Prepared formulae were kept in the mouth by each volunteer and the bitterness level was recorded against a standard using a numerical scale. The standard quinine hydrochloride concentrations used were 0.01, 0.03, 0.10, 0.30,

Table 3: Optimization of processing temperature and pH for maximum drug loading

Temperature ($^\circ\text{C}$)	Percentage of drug bound to various resins (%)			pH	Percentage of drug bound to various resins (%)		
	Indion 204	Indion 234	Tulsion 335		Indion 204	Indion 234	Tulsion 335
25	74.25 \pm 0.69	72.82 \pm 0.58	74.25 \pm 0.53	1.2	49.26 \pm 0.86	48.07 \pm 0.38	54.74 \pm 0.57
30	76.87 \pm 0.47	74.9 \pm 0.46	74.97 \pm 0.58	2	54.50 \pm 0.35	51.17 \pm 0.55	59.26 \pm 0.78
40	79.73 \pm 0.53	78.06 \pm 0.73	80.44 \pm 0.33	5	68.30 \pm 0.35	68.30 \pm 0.59	75.92 \pm 0.77
50	82.34 \pm 0.98	82.87 \pm 0.59	83.06 \pm 0.98	6	76.63 \pm 0.65	75.20 \pm 0.87	79.25 \pm 0.46
60	86.39 \pm 0.53	85.77 \pm 0.28	86.39 \pm 0.46	7	86.15 \pm 0.69	84.01 \pm 0.59	85.44 \pm 0.68
70	89.48 \pm 0.27	87.72 \pm 0.85	88.77 \pm 0.92	8	88.53 \pm 0.58	86.39 \pm 0.66	87.58 \pm 0.35

Results are mean \pm standard deviation (n=3)

Table 4: Formulation table for oral reconstituted suspension

S. No.	Ingredients	Gram per tablet									
		S1	S2	S3	S4	S5	S6	S7	S8	S9	S10
1.	Drug*	-	-	-	-	-	-	-	-	-	250 mg
2.	DRC Indion 204	6.41 g	7.62	8.15	-	-	-	-	-	-	-
3.	DRC Indion 234	-	-	-	6.94	7.91	8.42	-	-	-	-
4.	DRC Tulsion 335	-	-	-	-	-	-	6.66	7.81	8.42	-
5.	Xanthan gum	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
6.	Sodium benzoate	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
7.	Aspartame	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25
8.	Aerosil	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
9.	Sodium citrate	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
10.	Sucrose	2.13	1.42	0.60	1.60	0.63	0.12	1.89	0.74	0.12	6.05
11.	Total weight*	11	11	11	11	11	11	11	11	11	11
12.	Lake sunset yellow	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
13.	Flavor	1 ml	1 m	1 ml							

Dose of clarithromycin* - 125 mg/5 mL. DRC: Drug-resin complex. *Reconstituted with 100 mL of water at the time of use

and 1.00 mM and the corresponding bitterness scores were defined as 0, 1, 2, 3, and 4, respectively. Before testing, the volunteers are given the standard quinine solutions and asked to swirl in their mouths and were told the concentrations and bitterness scores of each solution [22]. After tasting a test formulation suspended in water, they were asked to give the sample a bitterness score in comparison to the standard. All samples were kept in the mouth for 15 s. After testing the sample, the volunteers rinsed their mouths well and waited for at least 20 min before tasting the next sample. The average scores for bitterness, flavor, mouthfeel, and overall acceptability for each formulation were calculated and also the standard deviation was arrived (Table 6).

Statistical analysis

The scores were then interpreted by one-way ANOVA [23] using GraphPad Prism Version 5.0 Software. Dunnett’s multiple comparison test was used for comparing all the formulations (S1-S9) with the control formulation (S10). The statistical significance was then interpreted. Tukey’s multiple comparison tests are used for comparing the scores within the groups with different ratios of the same resins, and then the formulations having the highest significance levels from each group were compared [24].

RESULTS AND DISCUSSION

Optimization of drug-resin complexation and resin concentration for maximum drug loading is presented in Table 1. Optimization of swelling time and stirring time of resin for maximum drug loading is shown in Table 2. Optimization of processing temperature and pH for maximum drug loading is presented in Table 3. The loading capacity of the resin for clarithromycin was higher in the acid-activated condition when compared to alkaline conditions. This could be explained by the stoichiometric exchange nature reaction between drug and resin in solution. All resins displayed an increase in drug loading capacity with an increase in swelling time. It was found that as the time of stirring of the solution increased, the drug loading also increased and maximum drug loading was achieved within 6 h.

The effect of temperature for optimization is necessary, as, at higher temperatures, the ion diffusion increased. The percent drug-loaded increased with the rise in pH, which was due to the nature of the used resins and drug where the ionization was favored at pH 8. DRC

comprising Indion 204, Indion 234, and Tulsion 335 at maximum drug-resin ratio (1:2) exhibited drug content in a range of 92.10±0.59%, 89.01±0.55%, and 89.01±0.46%, respectively, and faster dissolution when compared to the pure drug (Fig. 1).

DSC thermograms of drug, resin, and DRC are depicted in Fig. 2.

DRC displayed good micromeritic properties with the angle of repose ranging from 26° 12±0.57 to 29° 38±0.47, bulk density values of 0.419±0.01–0.472±0.01 g/cm³, tapped density of 0.505±0.07–0.575±0.07 g/cm³, percent compressibility index of 13.461±0.89–17.913±0.73, and Hausner’s ratio of 1.155±0.08–1.218±0.07. Dry powder suspension parameters were evaluated. The powder displayed angle of repose from 22° 59±0.88 to 25° 69±0.73, bulk density of 0.442±0.01–0.479±0.04 g/cm³, tapped density of 0.52±0.06–0.541±0.07 g/cm³, percent compressibility index values from 10.800±0.69 to 15.163±0.55, and Hausner’s ratio ranging from 1.121±0.06 to 1.78±0.07. The dry powder displayed good micromeritic properties with the angle of repose ranging from 22° 59±0.88 to 25° 69±0.73, bulk density values of 0.442±0.01–0.479±0.04 g/cm³, tapped density of 0.520±0.06–0.543±0.08 g/cm³, percent compressibility index of 10.800±0.69–15.163±0.55, and Hausner’s ratio of 1.121±0.06–1.160±0.08.

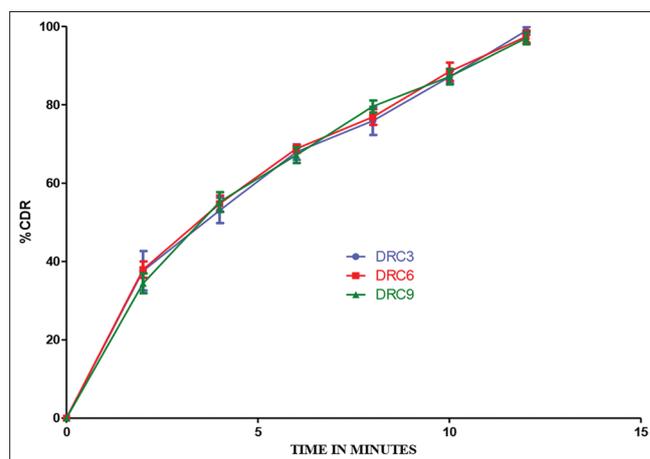


Fig. 1: *In vitro* dissolution release profiles of resin complex exhibiting maximum drug release. Errors bars represent the standard deviation of n=3, DRC3 (drug-resin complex 3-Indion 204) (—●—); DRC6 (drug-resin complex 6-Indion 234) (—■—); DRC9 (drug-resin complex 9-Tulsion 255) (—▲—)

Table 5: Determination of bitterness threshold of clarithromycin

Concentration (µg/ml)	Volunteers					
	1	2	3	4	5	6
10	-	-	-	-	-	-
20	-	-	-	-	-	-
30	-	-	-	-	-	-
40	-	-	-	-	-	-
50	-	-	-	-	+	+
60	+	+	-	-	+	+
70	+	+	-	+	+	+
80	+	+	+	+	+	+
90	+	++	+	+	++	+
100	++	++	++	++	++	++

-Non bitter, +bitter, ++threshold bitterness

Table 6: Preference points for standard bitterness and palatability

Score	Mouthfeel	Flavor	Overall acceptability
0	No	No	No
1	Gritty	Poor	Poor
2	Smooth	Acceptable	Acceptable
3	Creamy	Good	Good
4	Very creamy	Very good	Very good

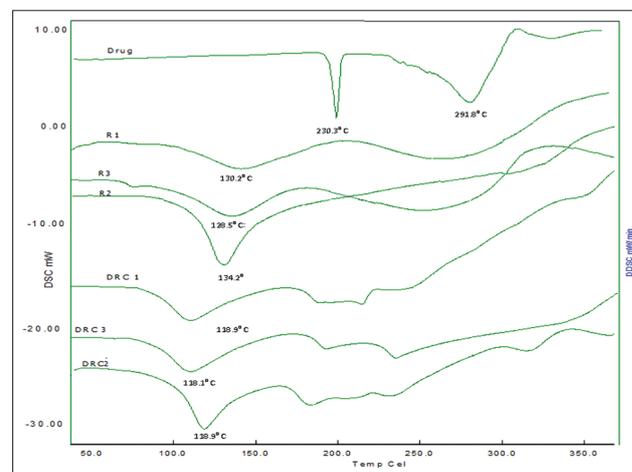


Fig. 2: The DSC thermograms of clarithromycin and thermograms of the drug-resinate mixtures. Drug-clarithromycin; R1-Indion; R2-Indion; R3-Tulsion; DRC3-Drug:resin Indion 204 (1:2); DRC6-Drug:resin Indion 234 (1:2); DRC9-Drug:resin Tulsion 255 (1:2)

All the prepared oral reconstituted suspensions (S1-S10) were subjected to evaluation. The ranges of viscosity was found to be 225.6 ± 0.76 – 273.2 ± 0.44 cps, pH was found to be 7.1 ± 0.04 – 7.4 ± 0.06 , sedimentation rate was found to be 0.95–0.99 on 0th day and 0.93–0.98 on 7th day, redispersibility was found to be + on 0th day and + on 7th day, and drug content was found to be 97.57 ± 0.69 – $98.99 \pm 0.66\%$, and particle size was found to be 97.89 ± 0.57 – 168.97 ± 0.97 μm .

All the formulations comprising DRC displayed rapid drug release when compared to S10 formulations. S3, S6, and S9 formulations exhibited a release $98.64 \pm 0.356\%$, $99.05 \pm 0.239\%$, and $98.85 \pm 0.303\%$ in 14 min, respectively, other formulations exhibited release within 16–24 min. S10 formulations displayed a release of $98.02 \pm 0.432\%$ after 24 min (Fig. 3). Thus, from the release studies, it was evident that the ion-exchange resins can also act as dissolution enhancers apart from taste masking.

The threshold for the bitterness of clarithromycin was detected by varying its concentration, and threshold value was obtained from volunteers (n=6) (Table 5). The reference points for standard bitterness and palatability are shown in Table 6.

Dunnett's test was performed to evaluate bitterness and overall acceptability of S1-S9 in comparison to S10 formulation without DRC (Table 7). Tukey's test was performed to evaluate bitterness and overall acceptability by selecting one formulation which was significantly different from each of the three groups, i.e., S3 (from group of S1, S2, and S3), S6 (from group of S4, S5, and S6), and S9 (from group of S7, S8, and S9), as shown in Table 8. The drug loading capacity of the resin was increased in acidic activated conditions than in alkaline activated conditions and this is due to the cationic nature of the used resin (Indion 204) since the COO- group of the Indion is loaded by H+ of the acid but not OH- of the base. As the polymer concentration increased, the amount of drug-loaded onto all the resins also increased due to the stoichiometric exchange nature of the reaction in solution between drug and resin.

All the resins displayed an increase in drug loading capacity with an increase in swelling time; therefore, the time of swelling has to be established. The rate and extent of the ion-exchange process are increased if the resin is swollen and hydrated. In the unswollen resin matrix, the exchangeable groups are latent and remain coiled toward their backbone. Swelling increases the surface area and these groups are oriented toward outside. It was found that maximum drug loading was achieved within 6 h with an increase in the time of stirring the solution.

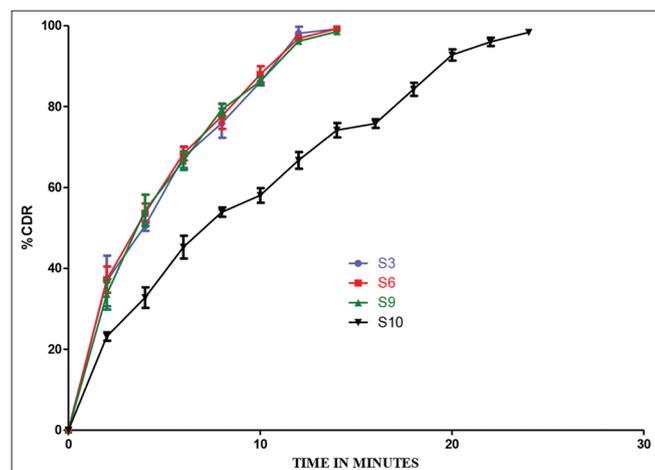


Fig. 3: *In vitro* cumulative percentage drug released from suspensions versus time. Optimized formulations versus control. Errors bars represent the standard deviation of n=3, S3 (—●—); S6 (—■—); S9 (—▲—); S10 (—▼—)

The effect of temperature on the exchange reactions showed that as the temperature rises, the exhaustive exchange zone is markedly shrunk, through which there is an increase in the ion diffusion rate. The percentage drug-loaded increased with increased pH; this is due to the nature of the used resin and drugs where the ionization was favored at pH 8. The decreased complexation at higher pH is because at higher pH, the solution becomes basic and cationic ion of resin gets saturated with the basic solution, thereby hindering the drug attachment. The decreased complexation at lower pH is because of an acidic environment the resin existed as a free acid in a non-ionic state and all the drug is released in the filtrate. The evaluated parameters were within the acceptable range. The *in vitro* dissolution studies were carried out for all the 9 DRC formulations and found to be excellent. The percentage drug released from 1:2 ratios of all the DRC was higher. The percentage of drug released from 1:2 ratio DRC6 of Indion 234

Table 7: Dunnett's test for bitterness, mouthfeel, and overall acceptability evaluation for all the formulations statistical data analysis

Dunnett's test for bitterness	Mean score of S10±SD	Mean scores S1-S9±SD	Summary
S10 versus S1	3.83±0.4082	2.16±0.408	***
S10 versus S2		1.5±0.547	***
S10 versus S3		0.33±0.516	***
S10 versus S4		2.33±0.516	***
S10 versus S5		1.33±0.516	***
S10 versus S6		0.16±0.408	***
S10 versus S7		2.16±0.408	***
S10 versus S8		1.33±0.516	***
S10 versus S9		0.16±0.408	***

Dunnett's test for mouthfeel	Mean score of S10±SD	Mean scores S1-S9±SD	Summary
S10 versus S1	2.00±0.6325	2.00±0.632	ns
S10 versus S2		1.66±0.516	ns
S10 versus S3		2.00±0.894	ns
S10 versus S4		2.16±0.752	ns
S10 versus S5		1.83±0.752	ns
S10 versus S6		1.66±0.516	ns
S10 versus S7		1.83±0.752	ns
S10 versus S8		2.00±0.632	ns
S10 versus S9		1.83±0.752	ns

Dunnett's test for flavor	Mean score of S10±SD	Mean scores S1-S9±SD	Summary
S10 versus S1	3.00±0.000	0.408	ns
S10 versus S2		3.33±0.516	ns
S10 versus S3		3.50±0.547	*
S10 versus S4		3.66±0.516	**
S10 versus S5		4.00±0.000	*
S10 versus S6		3.83±0.408	ns
S10 versus S7		2.83±0.752	ns
S10 versus S8		3.00±0.000	ns
S10 versus S9		3.00±0.000	ns
S10 versus S1		3.00±0.000	ns

Dunnett's test for acceptability	Mean score of S10±SD	Mean scores S1-S9±SD	Summary
S10 versus S1	0.16±0.4082	1.16±0.408	**
S10 versus S2		1.66±0.514	***
S10 versus S3		3.50±0.547	***
S10 versus S4		1.50±0.547	***
S10 versus S5		2.16±0.400	***
S10 versus S6		4.00±0.000	***
S10 versus S7		1.16±0.408	**
S10 versus S8		1.33±0.516	***
S10 versus S9		3.33±0.516	***
S10 versus S1		1.16±0.408	**

***p<0.001, **p<0.01, *p<0.05, ns=non-significant results are mean±standard deviation (n=3). SD: Standard deviation

Table 8: Tukey's test for bitterness, mouthfeel, and overall acceptability evaluation for all the formulations statistical data analysis

Tukey's test for bitterness		Summary
S1 versus S2	2.16±0.408 versus 1.50±0.547	ns
S1 versus S3	2.16±0.408 versus 0.33±0.516	***
S2 versus S3	1.50±0.547 versus 0.33±0.516	**
S4 versus S5	2.33±0.516 versus 1.33±0.516	**
S4 versus S6	2.33±0.516 versus 0.16±0.408	***
S5 versus S6	1.33±0.516 versus 0.16±0.408	**
S7 versus S8	2.16±0.408 versus 1.33±0.516	*
S7 versus S9	2.16±0.408 versus 0.16±0.408	***
S8 versus S9	1.33±0.516 versus 0.16±0.408	**

Tukey's test for mouthfeel		Summary
S1 versus S2	1.66±0.516 versus 2.00±0.894	ns
S1 versus S3	1.66±0.516 versus 2.16±0.752	ns
S2 versus S3	2.00±0.894 versus 2.16±0.752	ns
S4 versus S5	1.83±0.752 versus 1.66±0.516	ns
S4 versus S6	1.83±0.752 versus 1.83±0.752	ns
S5 versus S6	1.66±0.516 versus 1.83±0.752	ns
S7 versus S8	2.00±0.632 versus 1.83±0.752	ns
S7 versus S9	2.00±0.632 versus 2.00±0.894	ns
S8 versus S9	1.83±0.752 versus 2.00±0.894	ns

Tukey's test for flavor		Summary
S1 versus S2	3.16±0.408 versus 3.33±0.516	ns
S1 versus S3	3.16±0.408 versus 3.50±0.547	ns
S2 versus S3	3.33±0.516 versus 3.50±0.547	ns
S4 versus S5	3.66±0.516 versus 4.00±0.000	ns
S4 versus S6	3.66±0.516 versus 3.83±0.408	ns
S5 versus S6	4.00±0.000 versus 3.83±0.408	ns
S7 versus S8	2.83±0.752 versus 3.00±0.000	ns
S7 versus S9	2.83±0.752 versus 3.00±0.000	ns
S8 versus S9	3.00±0.000 versus 3.00±0.000	ns

Tukey's test for acceptability		Summary
S1 versus S2	1.16±0.408 versus 1.66±0.514	ns
S1 versus S3	1.16±0.408 versus 3.50±0.547	***
S2 versus S3	1.66±0.514 versus 3.50±0.547	***
S4 versus S5	1.50±0.547 versus 2.16±0.408	*
S4 versus S6	1.50±0.547 versus 4.00±0.000	***
S5 versus S6	2.16±0.408 versus 4.00±0.000	***
S7 versus S8	1.16±0.408 versus 1.33±0.516	ns
S7 versus S9	1.16±0.408 versus 3.33±0.516	***
S8 versus S9	1.33±0.516 versus 3.33±0.516	***

***p<0.001, **p<0.01, *p<0.05, ns=non-significant results are mean±standard deviation (n=3)

(DRC6) was found to be higher. This is due to the presence of more exchangeable H⁺ ions in the stomach causing the rapid exchange of similar ions in DRC thereby releasing the drug. DSC thermograms of clarithromycin showed sharp characteristic endothermic peaks which were not visible in the thermograms of the drug resinate mixtures (DRC3, DRC6, and DRC9), thereby indicating interaction and complex formation. All micrometric properties of the DRC were within the acceptable range. The formulations did display rapid drug release, but enhanced drug dissolution was observed in S3, S6, and S9 formulation due to a higher ratio of drug to resin (1:2). The taste evaluation test showed that the DRC concentration (1:2) of the formulations showed that there was no release in saliva thereby satisfactorily masking the bitter taste. In the case of Dunnett's test for bitterness and overall acceptability evaluation, S1-S9 when compared to S10 gave p<0.001. Hence, all the formulations are significant when compared to S10. In case of Tukey's test for bitterness and overall acceptability, evaluation was carried out by selecting one formulation which was highly statistically significant from each of the three groups, i.e., S3 (from group of S1, S2, and S3), S6 (from group of S4, S5, and S6), and S9 (from group of S7, S8, and S9). Hence, all three formulations possess good taste masking of the drug and good overall acceptability. S6 was widely

accepted by the volunteers. In the case of Dunnett's test and Tukey's test for mouthfeel evaluation, S1-S9 when compared to S10 showed no significant difference. Hence, all the formulations have significantly same mouthfeel when compared to S10. This concludes that the addition of resins to the formulation did not alter the mouthfeel of the suspensions. From the above data, it can be concluded that ion-exchange complexation of clarithromycin with Indion 204, Indion 234, and Tulsion 335 could efficiently mask the bitter taste and achieve palatable taste suitable for pediatric use.

CONCLUSION

Taste masking could be effectively achieved by the use of ion-exchange resins as it was found to be a safe, commercially inexpensive and easy method to achieve taste-masked complex of a bitter drug with a smooth feel. The taste-masked complex was successfully developed as an oral reconstituted suspension that can be considered as the geriatric and pediatric friendly dosage form.

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AUTHORS' CONTRIBUTIONS

All authors contributed equally.

CONFLICTS OF INTEREST

There are no conflicts of interest.

AUTHORS FUNDING

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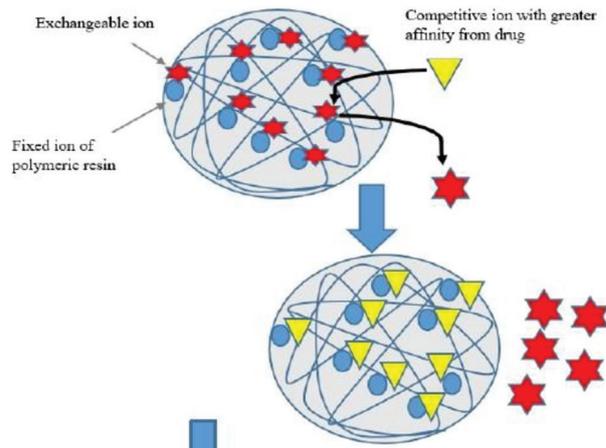
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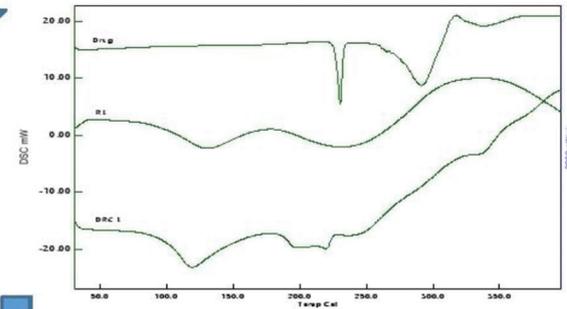
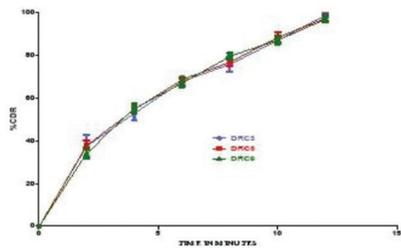
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PICTORIAL ABSTRACT

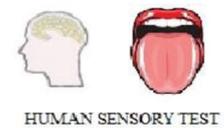
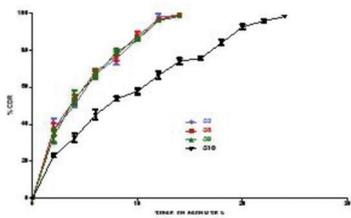
COMPLEXATION



DRC EVALUATION

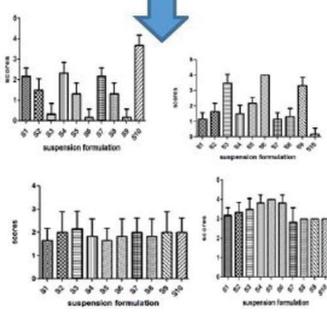


FORMULATION, EVALUATION AND STATISTICAL PREFERENCE OF WIDELY ACCEPTED FORMULATION



HUMAN SENSORY TEST

DRY SUSPENSION



STATISTICAL EVALUATION