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Design, evaluation and optimization of taste masked clarithromycin powder

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Clarithromycin (CLA) is an extremely bitter macrolide antibiotic used to treat paediatric and adult infections. The bitter taste affects patient adherence and may compromise therapy. This research developed a taste masked CLA resinate using Indion® 234, a weak acidic cation exchange resin. The factors affecting formation of the CLA-resin complex were assessed. Design of experiments was used to optimize response while evaluating input variables such as temperature, CLA-resin ratio, stirring time and pH. CLA loading efficiency was determined spectrophotometrically and CLA release using USP Apparatus II. Differential Scanning Calorimetry (DSC), Scanning Electron Microscop (SEM), Fourier Transform Infrared (FT-IR) Spectroscopy and X-ray Diffraction (XRD) were used to confirm complex formation. A spectrophotometric method was used to assess taste evaluation. The optimum CLA-resin ratio, temperature, and stirring time were 1:4, 80 °C, 3 hours, respectively, at pH 8. Characterization techniques revealed that CLA was crystalline and the complex amorphous in nature. FT-IR spectra of resinate revealed the absence of resonance due to the tertiary amine functional group that is responsible for the bitter taste of CLA. CLA was stable in simulated salivary fluid and was released within 3 hours in gastric fluid. All CLA-resin batches revealed complete taste masking. Taste analysis highlighted the improvement of taste masking properties of the resinate as the CLA to resin ratio, increased.

1. Introduction

Clarithromycin (CLA) is a second generation (Zuckerman 2004), extremely bitter macrolide antibiotic (Tripath 2003; Yajima et al. 2002) used for the treatment of different paediatric and adult infections, including but not limited to, lower and upper respiratory tract infections (Portier et al. 2002). CLA is also used to treat *Mycobacterium avium* complex infections in HIV/AIDS patients (Populaire 1998) and *Helicobacter pylori* infections in gastric and duodenal ulcer patients (Suerbaum and Michetti 2002). Patient acceptability of a pharmaceutical product is a key aspect for the development of medicines. In particular, children and older adults differ in many aspects of taste, when compared to other age subsets of the population and require particular consideration in respect of taste of medication (Liu et al. 2014). Non-adherence of patients towards intolerably bitter drugs is an on-going challenge to the pharmaceutical industry (Rahman et al. 2012). A number of orally administered medicationes such as antibiotics (Akre et al. 2012; Yadav et al. 2014), analgesics (Sohi et al. 2004; Ezzatabadipour et al. 2011) and vitamins (Roy 1997; Behera et al. 2007) are bitter in taste leading to patient reluctance, particularly paediatric patients, to use administered medications thus compromising pharmacotherapy (Yajima et al. 2002; Katsuragi and Kurihara 1993).

Scientifically, taste masking is defined as an observed decline of bitter taste of medicines that would otherwise exist (Sohi et al. 2004). To conceal the obnoxious taste of some medicines different techniques have been used. Shen (1996) used coating to mask the taste of ibuprofen and Ndesendo et al. (1996) and Zgoulli et al. (1999) used microencapsulation to mask the unbearable taste of chloroquine diphosphate and erythromycin. The taste of CLA has been masked using microencapsulation (Zgoulli et al. 1999) and use of ion-exchange resins (IER) (Kumar et al. 2014).

The use of IER is a reliable approach in masking the taste of extremely bitter molecules *viz*. levamisole (Cotterill et al. 2006), ciprofloxacin (Pisal et al. 2004), bromhexine (Bajaji and Sayed 2000), chloroquine phosphate (Agarwal et al. 2000), fexofenadine hydrochloride (Pandya et al. 2011) and levofloxacin hemihydrate (Bilandi and Mishra 2015). IER are insoluble solid, pharmacologically inert, high molecular weight cross-linked polymers. They bind to compounds that exchange mobile ions and ultimately the formation of a tasteless drug- resin complex or resinate (Agarwal et al. 2000; Bajaji and Sayed 2000). The ion exchangers are polymeric in nature (Patravale and Prabhu 2005; Punit et al. 2008) and carry an electric charge that is neutralized by the charges of counter ions as reflected in Eqs. (1) and (2). Ideally, cationic and anionic exchange resins are used for reactions with a drug (Guo et al. 2009).

$$Re\text{-}COO^- H^+ + \text{basic drug} \longrightarrow Re\text{-}COO^- Drug^+ + H^+ \quad (1)$$

$$Re\text{-}N(CH_3)_3{}^+Cl^- + \text{acidic drug}^- \longrightarrow Re\text{-}N(CH_3)_3{}^+Drug^- + Cl^- \quad (2)$$

where Re represents the polystrenic matrix which is the backbone of all synthetic resins in existence (Bilandi and Mishra 2014).

The resinate is stable in a salivary environment but undergoes degradation in certain regions of the GIT (reflected in equations 3, 4, 5 and 6) due to the availability of competing ions resident in gastric fluids (Korkisch 1988; Guo et al. 2009; Patra et al. 2010).

In the stomach

$$Re\text{-}COO^- drug^+ + HCl \longrightarrow Re\text{-}COOH + \text{drug hydrochloride} \quad (3)$$

$$Re\text{-}N(CH_3)_3{}^+ drug^- + HCl \longrightarrow Re\text{-}N(CH_3)_3Cl + \text{acidic drug} \quad (4)$$

In the intestine

$$Re\text{-}COO^- drug^+ + NaCl \longrightarrow Re\text{-}COONa + \text{drug hydrochloride} \quad (5)$$

$$Re\text{-}N(CH_3)_3{}^+ drug^- + NaCl \longrightarrow Re\text{-}N(CH_3)_3Cl + \text{sodium salt of drug} \quad (6)$$

Consequently, taste masking is achieved with limited or no impact on the bioavailability of a drug bound to the resin (Kumar et al. 2012).CLA possesses a tertiary amine functional group (Fig. 1) that imparts a bitter taste and this functionality forms a complex with cationic exchange resins (Kumar et al. 2014). The objective of this study was to evaluate taste masked CLA powder prepared using a carboxylic acid functionalized crosslinked polyacrylic IER.

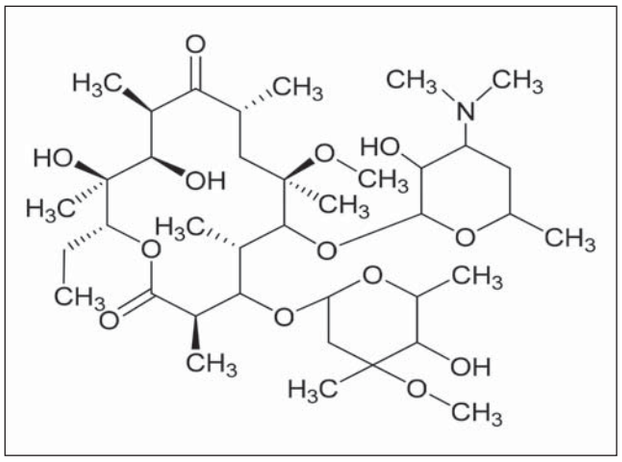

Fig. 1: Molecular structure of CLA. MW = 747.96 g/mol

2. Investigations, results and discussion

2.1. Characterization of CLA and resinate

Characterization studies extensively illustrate the formation of resinate produced due to a reaction between the resin and CLA. DSC analysis revealed a difference in the melting point of CLA and the resinate *viz*. 228 °C and 63 °C, respectively. Physically, the crystalline nature of CLA, indicated by a sharp characteristic endothermic peak (Fig.2) was transformed into an amorphous resinate, reflected as a broad thermogram with an area under curve > 1000mJ (Fig. 3). FT-IR spectroscopy revealed that the tertiary amine functional group responsible for the bitter taste of CLA observed at a wavenumber 1086 cm^{-1} (Fig. 4) was absent in the spectrum for the resinate (Fig. 5). All other characteristic functional groups for CLA and Indion® 234 *viz*. hydroxyl (OH), carboxylic (COO-), ether (C-O) stretching, C-H stretching of the methyl (CH_3) groups and C-C simple bonds were observed. Electron microscopy revealed rectangular shaped particles of CLA (Fig. 6) whereas the resinate particles were irregular in shape (Fig. 7). The X-ray diffractogram for CLA exhibited sharp peaks with high intensities reflecting the crystalline nature (Fig.8) of the compound whilst undefined peaks with low intensity were observed in the diffractogram of the resinate (Fig. 9) suggesting it was amorphous in nature.

Resins activated using 0.1M HCl exhibited the highest loading efficiency for CLA (Table 1) due to the fact that Indion® 234 is composed of potassium salts of carboxylic acid. Consequently, during the activation process, potassium ions are replaced by hydrogen ions to form a pure yet weak acidic cation exchange resin.

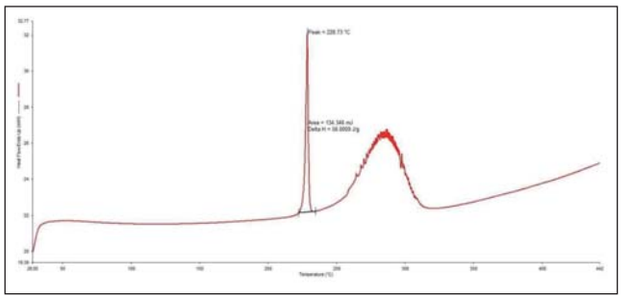

Fig. 2: DSC Thermogram for CLA generated at a heating rate of 10 °C/min

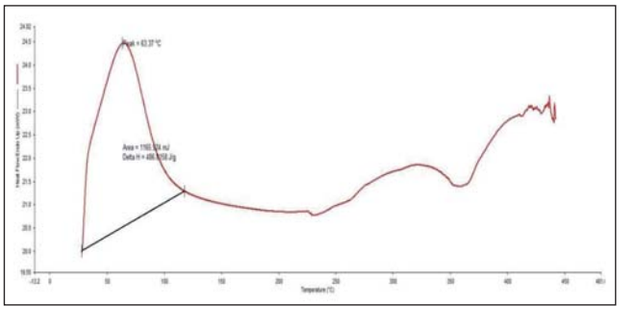

Fig. 3: DSC thermogram for resinate generated at a heating rate of 10 °C/min

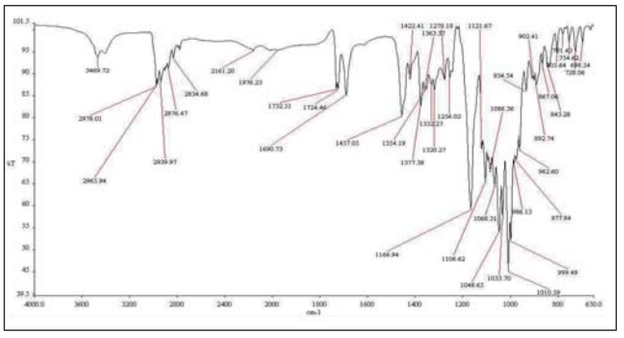

Fig. 4: FTIR absorption spectrum for CLA

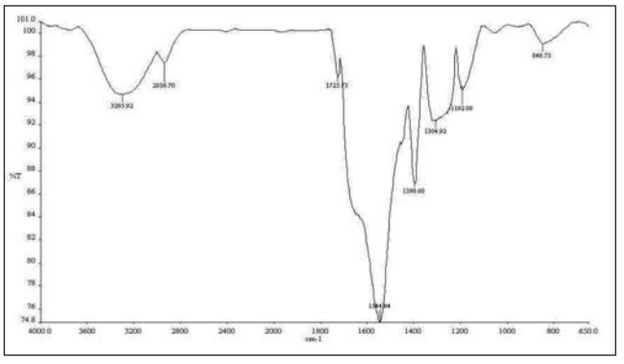

Fig. 5: FTIR absorption spectrum for resinate

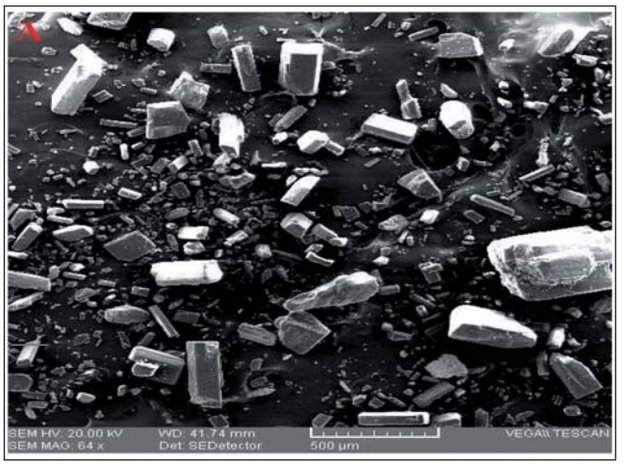

Fig. 6: Scanning electron microscope image of CLA

Activation of resin with alkaline solution resulted in a change only in the salts of carboxylic acid viz., from potassium to a sodium salt and exhibited similar CLA loading results as the inactivated

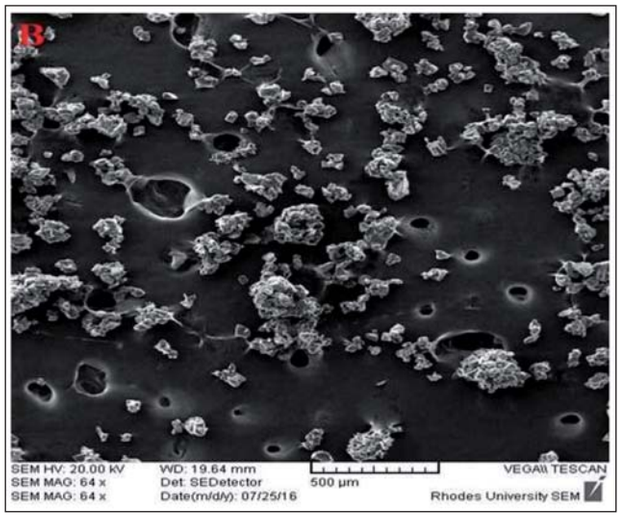

Fig. 7: Scanning electron microscope image of resinate

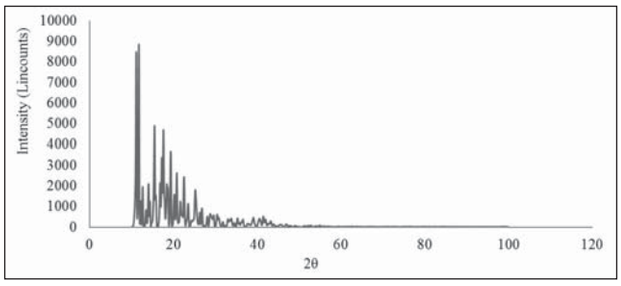

Fig. 8: X-ray diffraction pattern for CLA

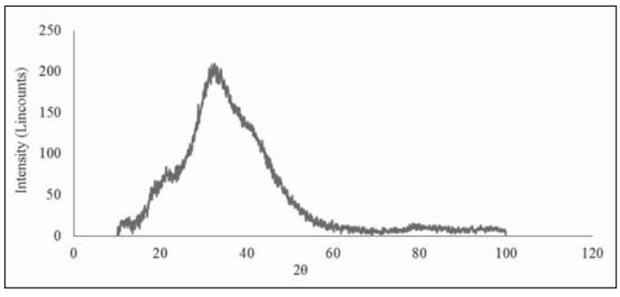

Fig. 9: X-ray diffraction pattern for the resinate

Table 1: Effect of activation process on CLA loading efficiency

Type of activated resin	CLA:resin	DLE (%)
Acid-activated Indion® 234	1:2	48.4
Alkaline-activated Indion® 234	1:2	19.6
Inactivated Indion®234	1:2	14.5

resin. Therefore acidic activation was considered a prerequisite to successful formulation design activities.

From screening studies (Table 2) it is evident that swelling time and stirring speed have a limited impact on CLA drug loading efficiency (DLE) and that may be attributed to the possibility that the optimum stirring speed and swelling time for IER activation to reach equilibrium is 30 min and 350 rpm. Screening studies confirmed that temperature, CLA: resin ratio, stirring time and pH had significant impact on DLE and consequentially were investigated extensively during optimization studies.

An increase in temperature tends to increase the diffusion rate of ions by decreasing the thickness of the exhaustive exchange zone (Dasankoppa et al. 2016; Dahima and Sharma 2010) and the retarding force acting on adsorption ions (Fil et al. 2012). CLA loading decreased at low pH since in an acidic environment the resin exists as a free acid in non-ionic state (Dasankoppa et al. 2016) and excess H^+ ions which have higher binding affinity to COO^- of the resin competed with CLA for the binding sites of Indion 234® (Wani et al. 2010). CLA loading increased as the pH increased above the pKa of CLA, due to ionization of both the CLA and resin, in accordance with the Henderson-Hasselbalch equation expressed in equation 7.

$$pH = pKa + \log {}^{A}/_{HA} \quad (7)$$

where Ka is the dissociation constant of the weak acid, pKa = -log Ka, and HA and A are the molarities of the weak acid and its conjugate base respectively.

The stirring time affected CLA loading as the ion exchange in solution occurs stoichiometrically (Dahima and Sharma 2010). The amount of resin used during the reaction with respect to the drug is important since ion exchange density decreases with an increase in amount of resin used. This phenomenon is due to unsaturation of exchange active sites. Similarly an increase in the amount of resin results in an increase in the number of active sites leading to higher drug loading (Alyuz and Veli 2009).

2.2. Optimization studies

2.2.1. Central composite design (CCD)

In general, resinates demonstrated good DLE (Table 3) and six batches exhibited a DLE of > 90%. Batches with high CLA: resin ratios exhibited higher loading efficiencies. The batch with a 1:1

Table 2: Screening studies results for CLA-Indion 234® complex

Batch Number	CLA (1): Resin	Swelling time (h)	Stirring time (h)	Stirring speed (rpm)	Temperature (°C)	pH	DLE (%)
DRC001	2	30	3	350	60	8	48.4
DRC002	4	30	3	350	60	8	75.8
DRC003	2	30	3	350	60	8	48.4
DRC004	2	90	3	350	60	8	49.0
DRC005	2	30	3	350	60	8	48.4
DRC006	2	30	5	350	60	8	59.7
DRC007	2	30	3	450	60	8	48.7
DRC008	2	30	3	350	60	8	48.4
DRC009	2	30	3	350	80	8	60.6
DRC010	2	30	3	350	60	10	49.6

Table 3: Responses for resinate batches observed during CCD experiments

Experiment No.	Batch No.	Dependent variables				Independent variable
		CLA(1):resin	Temperature (°C)	Stirring time (h)	pH	DLE (%)
1	DRC011	4	80	3	10	94.0
2	DRC012	2	80	5	8	64.1
3	DRC013	3	70	4	9	70.0
4	DRC014	4	70	4	9	86.5
5	DRC015	2	70	4	9	62.4
6	DRC016	3	70	4	9	70.0
7	DRC017	4	60	3	8	75.8
8	DRC018	4	80	5	10	99.5
9	DRC019	3	70	6	9	80.4
10	DRC020	4	60	5	8	92.0
11	DRC021	4	80	3	8	93.3
12	DRC022	3	90	4	9	80.1
13	DRC023	3	70	4	11	72.6
14	DRC024	3	70	4	9	70.0
15	DRC025	5	70	4	9	96.4
16	DRC026	1	70	4	9	46.1
17	DRC027	3	70	4	7	68.8
18	DRC028	3	70	4	9	70.0
19	DRC029	2	80	3	10	61.2
20	DRC030	2	60	5	8	59.7
21	DRC031	2	80	3	8	60.6
22	DRC032	4	60	3	10	77.4
23	DRC033	3	70	4	9	70.0
24	DRC034	2	80	5	10	65.3
25	DRC035	2	60	5	10	60.5
26	DRC036	4	70	3	8	82.5
27	DRC037	4	80	5	8	98.9
28	DRC038	3	50	4	9	60.6
29	DRC039	3	70	2	9	62.6
30	DRC040	3	70	4	9	70.0

Table 4: Summary of analysis of coefficients of correlation

		Model			
Response	**Parameter**	**Linear**	**2FI**	**Quadratic**	**Cubic**
DLE	R^2	0.9496	0.9661	0.9723	0.9950
	Ra^2	0.9415	0.9483	0.9465	0.9757
	PRESS	406.06	862.96	1020.99	+
		Lack of fit			
Prob > F		0.789	0.422	0.556	0.138

+ = case (s) with leverage of 1.0000: PRESS statistic not defined, red = significant parameters.

CLA: resin ratio was the only batch to exhibit a DLE of < 50 % whereas the batch with 1:5 ratio exhibited the highest loading efficiency of 99.5%. Batches with 1:4 CLA: resin ratios exhibited high loading efficiencies when crucial factors such as solvent temperature and stirring time were increased. Increasing the time of contact between the resin and CLA, from 3 h to 5 h resulted to a 5% increase in CLA loading and this marginal increase is not worth the added energy consumption. Therefore to reduce production costs, the stirring time was maintained at 3 h.

Statistical parameters such as regression coefficient (R^2), adjusted regression coefficient (Ra^2), predicted residual error sum of squares (PRESS) and lack of fit were used to identify the best regression model for these data. The regression models investigated included a 2FI, cubic, linear and quadratic model. The linear model was selected for optimisation as it exhibited an acceptable lack of fit (highest p-value), the lowest PRESS and the lowest difference between R^2 and Ra^2 (Table 4).

Analysis of variance (ANOVA) elucidated that CLA loading was dependent on CLA: resin ratio, solvent temperature and stirring time. In contrast the pH was not significant in respect of DLE based on the pH ranges analyzed (Table 5). At higher pH, the solution becomes basic, thereby saturating the weak cationic resin that consequently impedes CLA binding (Dasankoppa et al. 2016).

2.2.2. Response surface model plot for DLE response

Contour plots and 3D plots (Fig. 10 a-f) revealed that temperature, CLA: resin ratio and stirring time exhibit direct proportionality with DLE. The factors were also independent of each other. An increase

Table 5: ANOVA analysis for the linear model for DLE of the resinates

Source	Sum of squares	Degrees of freedom (df)	Mean square	F value	Prob > F	Comment
Model	5167.00	4	1291.75	117.75	< 0.0001	Significant
Drug:resin	4717.97	1	4717.97	430.08	< 0.0001	Significant
Temperature	573.63	1	573.63	52.29	< 0.0001	Significant
Stirring time	383.96	1	383.96	35.00	< 0.0001	Significant
pH	2.31	1	2.31	0.21	0.6506	Not significant
Residual	274.25	25	10.97			
Lack of Fit	274.25	20	13.71			
Pure Error	0.000	5	0.000			

in temperature led to the increase in CLA loading (Fig. 10a, 10b and 10f) even when the other variables were kept constant. The same effect is seen with increase in CLA: resin ratio (10a and 10e) and stirring time (10b, 10d and 10e). CLA loading increased by > 15% (10c) when the CLA: resin ratio was changed from 1:3 to 1:4 while other factors were maintained. Fig. 10c, 10d and 10f asserts the insignificance of increasing pH above 8.

2.2. *In vitro release studies*

In vitro release studies confirmed the hypothesis that CLA release from the resinate complex is highly dependent on physiological pH (Korkisch 1988; Kumar et al. 2014) and the influence of the amount of resin used on the release of CLA from resinate (Fig. 11) was confirmed. In gastric pH 1.2, all batches released >99% CLA within 3 h. In the initial 2 h of the study, the batch prepared using

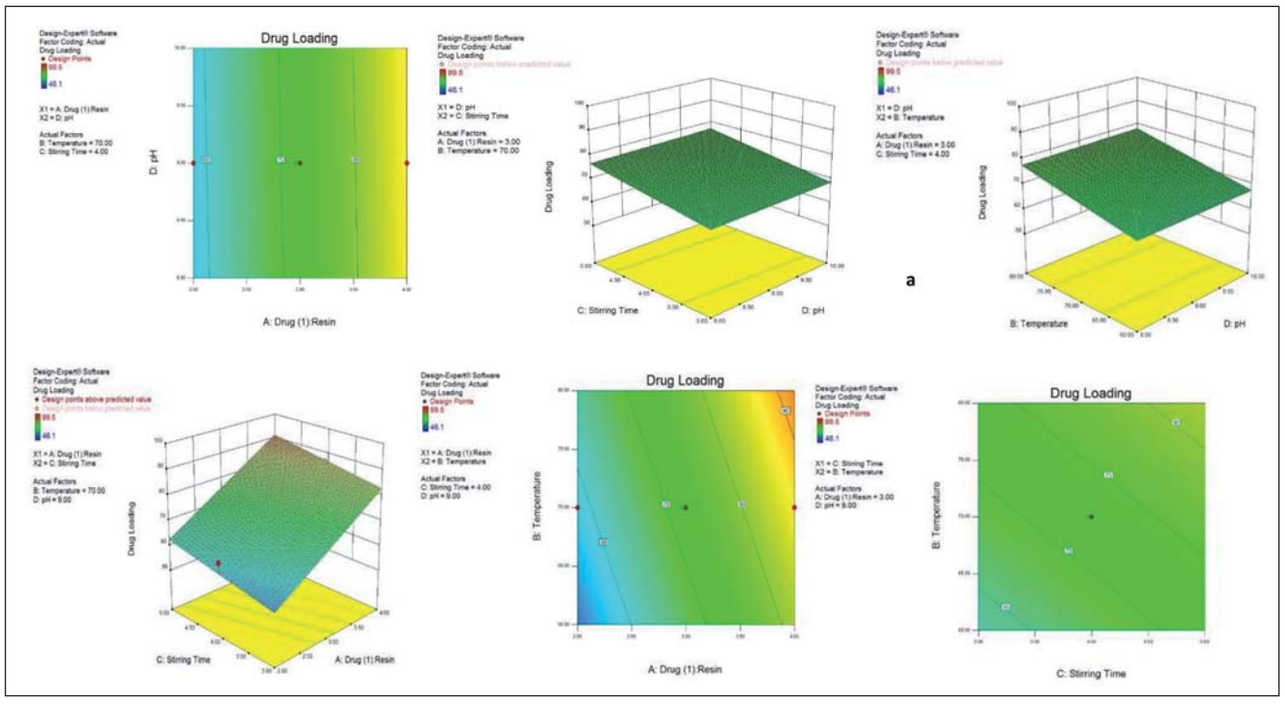

Fig. 10. Contour and 3D plots depicting the relationship between CLA: resin ratio and temperature (a), stirring time and temperature (b), CLA: resin ratio and pH (c), stirring time and pH (d), CLA: resin ratio and stirring time (e) and temperature and pH (f) with respect to CLA loading in the resinates.

a 1:5 CLA: resin ratio released < 70%, and that with a 1:3 ratio released< 85% and the 1:1 ratio released > 95%. The complex was stable in salivary fluids releasing < 5% CLA over 3 hours.

2.3. *Taste analysis*

The concentration of CLA in all batches were below the threshold taste concentration of CLA (Yajima et al. 2002). Taste masking properties increased with an increase in amount of resin used. Batch DRC025 in which a 1:5 CLA: resin ratio was used revealed the best masking properties with concentrations of 22µg/mL observed (Table 6). Batches with CLA: resin ratios of 1:4 exhibited excellent taste masking properties as CLA concentrations were < 40 µg/mL. Batch DRC026 in which the CLA: resin ratio used was 1:1, exhibited the highest CLA concentration.

2.4. *Conclusions*

The use of an ion exchange resin to conceal the bitter taste of drug molecules for orally disposable dosage forms is an affordable and reliable approach to improving taste of medicines. Adequate time of contact between resins and drug in addition to an increase in drug to resin ratio and solvent temperature are vital in achieving an optimum drug loading. The results of these studies reveal the feasibility of using Indion® 234 to reduce the bitter taste of CLA.

3. Experimental

3.1. *Materials*

Bulk CLA was purchased from Skyrun Industrial Co. Limited, Taizhou, China. Indion 234®, a weak cationic ion exchange resin was selected for this study due to an ability of exchanging mobile ions with weakly basic drugs, was purchased from Ion

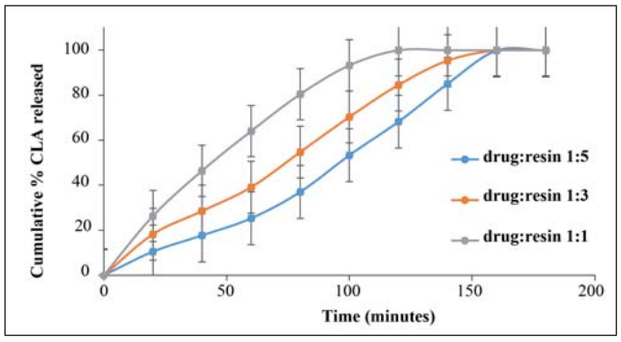

Fig. 11: In vitro release of CLA from resonates in a solution of pH 1.2

Exchange (India) Ltd, Mumbai, India. All other reagents were of analytical grade and were used without further purification.

3.2. Purification and activation of the resin

Indion® 234 is a crosslinked acrylic polymer with a carboxylic acid functional group existing in potassium ionic form. Activation of resins using acids is crucial since it results in exchange counter ions, and when exposed in the solution it leads to rapid ion exchange (Kadliya et al. 2003; Guo et al. 2009) as the H^+ ions are easily protonated compared to K^+ ions. Purification of Indion® 234 was undertaken to ensure the removal of potential impurities, and was then activated using 0.1M HCl and 0.1M NaOH as reflected in Fig. 12.

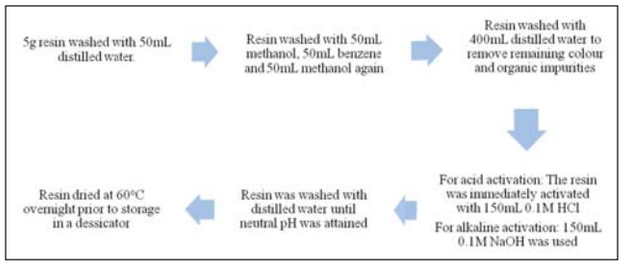

Fig. 12: Purification and activation process used for Indion® 234 (Kumar et al. 2014).

3.3. Screening studies

Screening studies were undertaken to determine the factors that may influence CLA loading during complexation and included the type of ion exchange resin, CLA used or external conditions. The ion exchange dependent factors include but are not limited to ion exchange capacity that affects binding affinity and drug release (Jaskari et al. 2001; Uchida et al. 2003), particle size, adsorption efficiency, drug release (Abdekhodaie and Wu 2006; Irwin et al. 1990) and degree of crosslinking that affects drug diffusion (Sawaya et al. 1987). The factors dependent on the drug include lipophilicity (Jaskari et al. 2001; Vuorio et al. 2004; Ramirez et al. 2002), molecular size (Irwin and Belaid 1987) and steric properties (Kril and Fung 1990) that are crucial for binding affinity between drug and resin. However, the formation of resinate is also affected and is dependent on the external conditions set for a reaction. The conditions include but are not limited to stirring speed (Chen et al. 1996, Irwin et al. 1990), pH (Kankkunen et al. 2002), stirring time (Bilandi and Mishra 2015), temperature (Chen et al. 1996; Irwin et al. 1990), swelling time (Patel et al. 2010) and drug:resin ratio (Abdekhodaie and Wu 2006; Sawaya et al. 1987). Swelling and hydration of a resin prior to commencing the ion exchange reaction is a prerequisite as it increases the surface area in addition to the rate and extent of the reaction (Dasankoppa et al. 2016). Agitation facilitates contact between the ions in solution and exchange sites ensuring effective transfer of ions at the binding sites (Ahalya et al. 2005). The pH of the solution affects both the solubility and degree of ionization of both the drug and resin (Bhoyar and Amgaonkar 2011). The ionization of the drug and resin is governed by their dissociation constants (pKa) (Vuorio et al. 2004) and is paramount as ion exchange reactions are limited below their pKa (Sohi et al. 2004; Singh et al. 2007). For this study pH range selected was 8 to 10 as the pKa of weak acidic resin is below 6 (Sohi et al. 2004; Cheremisinoff 2002) and CLA is 8.9 (Mandell et al. 2011). The weak acidic resins are able to retain cations in the COO^- form, which exist above their pKa as ionization of weakly acidic cationic exchange resins occurs to an appreciable extent only in alkaline solution (Sharma and Lewis 2010; William 2006). To establish the impact of external factors on performance, screening studies were undertaken using a "change one factor at a time" approach.

3.4. Preparation of resinates

The schematic diagram (Fig. 13) depicts the process of resinate formation. Acid-activated resins were permitted to swell in deionized water after which an accurately weighed quantity of CLA was added. The system was stirred at predetermined speeds at a controlled temperature for a specified time as defined for screening and/or design of experiments (DoE) studies using a model H3760-HSE hotplate stirrer (Benchmark Scientific®, Edison, New Jersey, USA). On completion, the residue was washed with acetonitrile (ACN) to separate the complex and unbound CLA. To remove ACN the residue was washed with deionized water. The complex was dried at 60 oC overnight to remove any ACN and the powders were stored in glass vials.

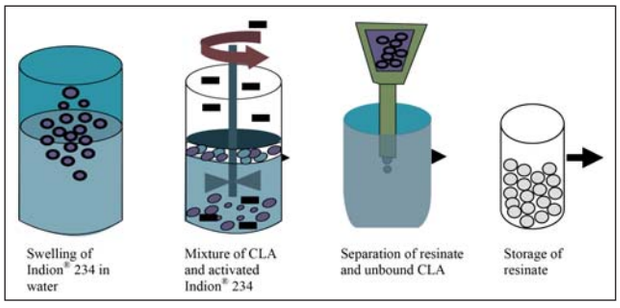

Fig. 13: Complexation procedure for resinates.

3.5. Characterization of bulk CLA and resinate

3.5.1. Differential scanning calorimetry

A model DSC-6000 PerkinElmer Differential Scanning Calorimeter (PerkinElmer® Inc., Massachusetts, USA) was used to generate the thermograms for CLA and the resinate. An accurately weighed 4 mg sample was placed in an aluminium pan. The temperature range was 25–400 ºC and a heating rate of 10 ºC/min was used. An empty aluminium pan was used as a reference. Analysis of all samples was conducted in triplicate under nitrogen purged at a flow rate of 19.8 mL/min.

3.5.2. Scanning electron microscopy

A small amount of sample was dusted onto a graphite card and sputter coated with gold for fifteen minutes under vacuum. The samples were then visualized using a Vega® Scanning Electron Microscope (Tescan®, Brno Czechoslovakia Republic) at an accelerated voltage of 20kV to determine the particle size and shape of CLA and complexes.

3.5.3. X-ray powder diffraction

X-ray powder diffraction patterns were generated using a Bruker D8 Discover X-ray diffractometer (Bruker AXS Advanced X-ray solutions GmbH, Karlsruhe, Germany) equipped with a proportional counter, using Cu-Kα radiation (λ = 1.5405 Å, nickel filter). The general voltage of experiments was 30 kV with a current of 40 mA. Data were collected in the range from 2θ = 10º to 100º, scanning at 1.5º /min-1 with a filter time-constant of 0.38 s per step using a slit width of 6.0 mm. Samples were placed on a silicon wafer slide and diffraction data were analyzed using version 14.0 EVA software (Bruker AXS Advanced x-ray solutions GmbH, Karlsruhe, Germany). Baseline correction was performed on each diffraction pattern by subtracting a spline function fitted to the curved background.

3.6. Design of experiments

Optimization of resinate composition in respect of DLE was undertaken with the aid of a Design Expert®Version 8.0.2 statistical software (Stat-Ease Inc., Minneapolis, USA). The factors identified in screening studies that had a significant impact on DLE were optimized. The low and high levels of CLA: resin ratio were 1:2 and 1:4, respectively, temperature at 60 °C and 80 °C, stirring time at 3 h to 5 h and pH at 8 and 10. Thirty experiments were conducted using a CCD.

3.7. In vitro release studies

A Hanson Research SR8 Plus Dissolution USP Apparatus II (Hanson Research CorporationTM, Chatsworth, California, USA) was used for dissolution testing of all batches of resinate. The temperature of the dissolution medium was 37±0.5 °C. The media used were 900 mL 50 mM phosphate buffer (pH 6.8) and 0.1M HCl (pH 1.2) agitated at 50 rpm. All samples were analyzed at 210 nm using a Lambda 25 PerkinElmer UV/Vis Spectrophotometer (PerkinElmer® Inc., Massachusetts, USA). Sample solutions were withdrawn every 20 min for analysis and replaced immediately following measurement.

3.8. Taste evaluation

A spectrophotometric method was used for taste analysis. Approximately 200 mg of resinate was mixed with 10 mL phosphate buffer (pH 6.8) and the solution vortexed for 60 s after which the solution was filtered. The concentration of CLA in the filtrate was then monitored at 210 nm. The CLA concentration was compared to a threshold concentration. The threshold concentration of bitterness is defined as the concentration at which bitterness is recognized in a sensory test (Yajima et al. 2002). The threshold concentration of CLA has been defined by volunteers to be 135 µg/mL (Yajima et al. 2002).

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