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ORAL CONTROLLED RELEASE AND TASTE MASKED SUSPENSION OF CEPHALEXIN USING ION EXCHANGE RESIN

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ABSTRACT

Ion exchange resins are versatile drug carriers capable of different functions like taste masking and controlled drug release. Objective of the study was to use ion exchange resins for masking the taste of Cephalexin and to provide controlled release in the form of reconstitutable suspension. Cephalexin is first generation antibiotic with bitter taste and short half-life. Polymer-coated resins were evaluated for percent drug release and taste masking and compared with microparticles of plain drug coated with polymers. The coating process was optimized by 3^2 factorial design using polymer concentration and pump speed as independent variables and percent drug release as dependent variable. Optimized batch was used to prepare the suspension which was evaluated for drug leaching, sedimentation, dispersibility and percent release. Tulsion A-23 was showed maximum drug binding (83.23%) and maximum Cephalexin loading was (83.16%). The percent complexation at 1:1 drug: resin ratio was found to be 83.68%. Percent drug release of Cephalexin suspension, coated microparticles and uncoated resin was found to be 99.16% in 12 h, 90% drug in 8 h and 96% within 5 h respectively. Coating with retarding polymers gave an extended release up to 12 h. Increase in pump speed and polymer concentration led to decrease in percent release. Leaching of coated drug resin complex suspension and microparticle was observed to be 0.5 % and 2.1% respectively. Negligible leaching was observed in coated drug resin complex suspension hence it was concluded that Tulsion A-23 resinate complex reduces the bitterness as well as taste masking of cephalexin successfully. We may conclude that this technology can be explored for other similar drugs for taste masking purpose.

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INTRODUCTION

Globally research efforts in developing novel drug delivery systems have focussed on oral controlled release dosage forms. Among them, multiple-unit dosage forms, such as beads or microparticles, have gained popularity when compared to non-disintegrating single-unit dosage forms. They distribute more uniformly in the gastrointestinal tract, resulting in reproducible release profiles, better predictable gastric emptying, uniform drug absorption, reduced local irritation, minimized risk of dose dumping and avoidance of unwanted intestinal retention of the polymeric material [1].

Different taste masking approaches are available for bitter tasting drugs such as sweeteners, flavouring agents, complexation, polymer coating using spray drying and ion exchange resins [2]. Low substituted hydroxyl propyl cellulose and ethyl cellulose were used to prepare taste-masked microparticles of sparfloxacin [3]. β -cyclodextrin was studied for masking the taste of terfenadine [4]. Complexation with Tulsion 335, an ion exchange resin was found to be effective for taste masking Tramadol HCL [5]. Ion exchange resins (IER's) have also been used for taste masking of Risperidone[6], Leuprolide[7], Ciprofloxacin[8].

Cephalosporins are broad spectrum antibiotics with a distinct metallic taste, thus necessitating use of appropriate taste masking approaches [9]. Cefuroxime axetil dry suspension was prepared using Lubritab as a taste masking agent [10]. The resin, Kyron T-114 was used to prepare drug resin complex (DRC) for taste masking of cefpodoxime proxetil [11].

Ion exchange resins (IER) are crosslinked, water insoluble, polymers carrying ionizable functional groups. Drugs can be loaded onto the resins by an exchange reaction to form a drug-resin complex (DRC) [12,13]. The use of IER has occupied an important place in the development of controlled release systems because of their better drug retaining properties and prevention of dose dumping. The characteristics of IER, such as their physicochemical stability, inert nature, uniform size, spherical shape, easier coating and reproducible drug release in ionic environment, have encouraged their use in oral drug delivery. Moreover, IERs impart flexibility in designing a variety of delivery systems such as liquids, beads [14], microparticles and simple matrices [15].

An oral suspension could be a suitable dosage form for paediatric and geriatric patients, because of ease of swallowing and flexibility in the dosage administration [16]. The advantages also include improvement of rate and extent of drug absorption, higher patient compliance, reduction of side effects and taste masking for bitter drug [17]. The ease of drug administration strongly justifies the use of liquid orals particularly for patients suffering from Parkinsonism and infants and children who have difficulty in swallowing solid dosage forms [18]. Cephalixin (CEP) is an orally administered first generation, extended spectrum, semisynthetic antibiotic of cephalosporin class. It has a short plasma half-life (80 min) and bioavailability of 50%. It is useful for combating microbial infections including: otitis media, streptococcal pharyngitis, bone and joint infections, pneumonia, cellulitis upper respiratory infection, urinary tract infection, skin infection, vaginal infection [19].

The objective of this study was to mask the bitter taste of CEP using IERs. The drug resin complexes were coated with rate retarding polymers to achieve controlled release of drug. The target patients for this preparation are paediatric and geriatric patients. In the present work, ion exchange resins of CEP was prepared using Tulsion A-23. The resins were further coated with ethyl cellulose and cellulose acetate butyrate to provide controlled release profile and formulated into suspension using xanthum gum as suspending agent.

MATERIAL AND METHOD

Materials:

CEP was obtained as gift sample from Maxim Pharmaceuticals, Pune. Tulsion A-23 was obtained from Thermax Pvt. Ltd. Pune. Cellulose acetate butyrate was purchased from Otto Chemicals Pvt Ltd. Ethyl cellulose was procured from Loba Chemicals Pvt Ltd., Mumbai and HPMC from Colorcon Asia Pvt. Ltd. All reagents used were of analytical reagent grade.

Preliminary evaluations:

Preparation of drug resin complex (DRC):

Resins are selected on the basis of nature of drug and requirement of formulation. Various resins like Amberlite IRP204, Tulsion A-23, Indion 254, Indion 204, Indion 454 and Amberlite IR 400 were investigated for complexation with CEP. The complexes were initially prepared keeping drug-resin ratio constant (1:1). The drug and resin were subjected to stirring for 1h, 2h, 3h, 4h, 5h and 6h and analysed for drug content after each time. Different drug-resin ratios like 1:2, 1:3 and 1:4 was also investigated. Resinates obtained were separated by filtration and drug content was determined by UV spectrophotometry at 257nm in distilled water and 261nm in 0.1 N HCl. DRC was further characterized in terms of spectral analysis by FTIR and threshold bitterness concentration.

Fourier Transforms Infra-Red spectroscopy of DRC

FT-IR spectral studies of CEP, Tulsion A-23, and DRC were carried on FT-IR 460 PLUS by JASCO series II instrument using DRIFT method (JASCO Analytical Instruments, Madison, WI). Scanning was done from 4000 to 400 cm^{-1} . FTIR of CEP, Tulsion A-23 and drug resin complex was obtained.

Threshold bitterness concentration

A panel of ten healthy human volunteers was selected for the study. Each volunteer held a quantity of DRC equivalent to 50 mg of CEP in oral cavity for 30 seconds. The taste of the DRC was reported by them immediately, then and after 30, 60, 120, 180 and 300 seconds on the scale described in the Table 1[20].

Table 1: Ranking scheme for bitterness.

Taste	Rank
No bitterness	0
Threshold bitterness	1
Bitter	2
Moderate bitter	3
Strong bitter	4

Coating of Drug Resin Complex (DRC):

The DRC was subjected to coating with different concentrations of cellulose acetate butyrate and ethyl cellulose at 1:1 ratio using chloroform as solvent in R and D pan coater (Make: Pharmatech). The coating solution was sprayed with help of spray gun at a pressure of 1.5 N/m² and from a distance of 25 cm from coating pan. The coating process was optimized using 3² factorial designs using Design Expert V7.1.4.3. Pump speed and polymer concentration were selected as independent variables and percent drug release as dependent variables (Table 2). The optimized coated DRC was evaluated in terms of particle size, surface morphology, *in vitro* dissolution and taste evaluation by threshold bitterness concentration and micromeritic properties [21]. Microparticles of CEP were prepared by wet granulation and coated using similar polymers and procedure as above. The optimized DRC was further used to prepare reconstitutable suspension and compared with coated microparticles of drug prepared using same conditions as for optimized DRC.

Table 2: Factorial designs 3² for preparation of Coated DRC.

Sr. No.	Batch No. for DRC	Polymer Concentration Quantity of EC and CAB in (mg)	Pump speed (RPM)
1.	F1	1500	7
2.	F2	1500	1
3.	F3	500	7
4.	F4	1500	4
5.	F5	1000	7
6.	F6	500	4
7.	F7	500	1
8.	F8	1000	1
9.	F9	1000	4

Evaluation of Coated DRC***In vitro* drug release studies of coated DRC:**

In vitro dissolution studies of nine factorial batches (F1-F9), optimized coated DRC and coated microparticles was carried out using USP type II dissolution apparatus with 1000 ml dissolution medium (750 ml of 0.1 N HCl for first 2 h, followed by 250 ml phosphate buffer pH 6.8). The paddle speed was set at 100 rpm at 37°C and test time was 12 h. Aliquots of 5 ml were withdrawn every hour, filtered and absorbance was measured by UV spectroscopy at 261nm. The medium was replaced with equal volume of fresh dissolution fluid.

Determination of the particle size and surface morphology of coated and uncoated DRC

Particle size of coated and uncoated DRC was determined by optical microscopy (Make-Almicro) by dispersing sufficient amount of the resins in water. A drop of the suspension was mounted on the glass slide. The mean globular diameter of the particles was calculated by Edmundson's equation [22]. Scanning Electron Microscopy (SEM) was done to investigate the topography of the DRCs (Jeol Scanning electron microscope). The particles were fixed on a Jeol brass stub using double-sided adhesive tape and then were made electrically conductive by coating in a vacuum, with a thin layer of platinum (3–5 nm) for 100 s and at 30 W.

Preparation of oral controlled release suspension of CEP:

Required quantity of sugar was dissolved in specified quantity of purified water and was filtered. Weighed quantities of sorbitol, glycerine, xanthan gum, tween80, methyl paraben and propyl paraben were added to the sugar solution with continuous stirring at 50 rpm. The coated DRC/ microparticle was added to the syrup under mechanical stirring at 25 rpm and 37°C (Table3). Required quantities (quantity sufficient) of strawberry flavour was added to above suspension and stirred for 10 min. The volume of suspension was made up to required quantity using purified water.

Table 3: Formulation of oral controlled release suspension.

Sr. No.	Ingredients	Quantity
1	Coated DRC/Coated microparticles equivalent to	375 mg drug
2	Sucrose	48%
3	Sorbitol solution 70%	9.16 %
4	Xanthan gum	0.4%
5	Glycerine	9.96%
6	Tween 80	0.04%
7	Propyl Paraben	0.1%
8	Flavours (Strawberry)	q. s.
9	Deionised water	q.s. to 5ml

Evaluation of controlled release suspension:

The suspensions were characterized by sedimentation, redispersibility, taste evaluation, *in vitro* release and drug leaching.

Sedimentation characteristics and redispersibility

The suspensions were evaluated for physical stability by determining the sedimentation volume. The suspensions (30ml) were taken in 100 ml graduated measuring cylinder and dispersed thoroughly. The suspension was then allowed to settle and volume of sediment was noted after 3 minutes. This is the original volume of sediment (H_o). The cylinder was kept undisturbed for 14 days. The volume of sediment read on the 14th day and was considered as final volume of sediment (H_u) [14].

$$\text{Separation ratio} = H_s/H_o$$

Where,

H_s = Height of upper clear layer in mm and

H_o = Original height of sample column in mm.

The sedimentation volume should have values less than 1. The ultimate height of the solid phase after settling depends on the concentration of solid and the particle size.

The dispersibility of the suspensions was checked by subjecting 10 ml of each suspension to vibrations in vortex mixer (Remi) at 5 vibrations per second. The sedimented suspensions were subjected to vibrations until there was no sediment at the bottom of the cylinder. The time required for redispersing was measured in seconds.

Drug leaching into the suspensions

Leaching studies were performed using orbital shaker wherein the suspension was stirred at 100 rpm at 25°C for 24h. Samples were withdrawn and diluted suitably for further estimation of drug content using UV spectrophotometer. The study was performed to determine amount of drug released during storage or shelf life [23].

Stability studies

CEP suspension was packed in 60 ml amber colour glass bottle. The packed bottles were placed in stability chamber maintained at $40 \pm 2^\circ\text{C}$ and $75 \pm 5\%$ RH for 1 month. The samples were withdrawn after one month and were observed for changes on the physical parameter (i.e., change in colour, assay, viscosity, any bad odour & pH, leaching).

RESULTS AND DISCUSSION:**Selection of resin for DRC:**

Depending on the nature of the drug, anion and cation exchange resins are selected. A number of resins were subjected for binding CEP viz. Amberlite IRP204, TulsionA-23, Indion 254, Indion 204, Indion 454 and Amberlite IR 400 (Fig.1). Of these, TulsionA-23 was selected as it showed maximum drug binding (83.23%). CEP is 3-methyl-7-(α -D-phenylglycylamino)-3-cephem-4-carboxylic acid. The carboxylate anion in CEP is presumed to be involved in binding with anion exchange resins. Tulsion A-23 was selected as it has quaternary ammonium group with a replaceable chloride ion. A coordinate bond is formed between carboxylate ion and ammonium ion by donation of lone pair of electrons. The strength of interaction between the resin and drug molecule influences its applicability. Tulsion A-23 is a strong anion exchange resin and can be used for controlling the release and for masking bitterness of drug [24]. As strong anion exchange resins have stronger basic groups as well as higher percentage of cross linking these can retard the drug release for longer time.

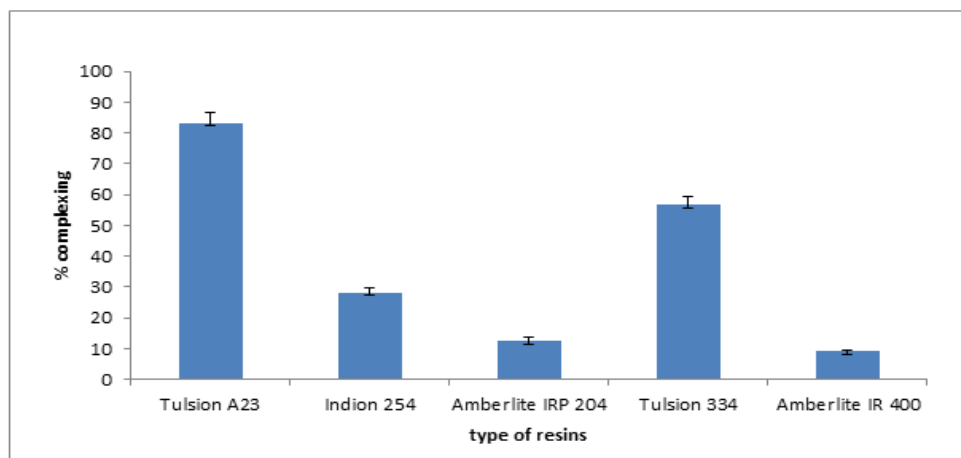


Fig. 1: Percent drug Complexation with different resins.

Drug resin complex:

CEP was loaded on TulsionA-23 by batch process using different drug-resin ratios as 1:1, 1:2, 1:3 and 1:4. Batch process is simpler and quicker than column process as interaction between resin and drug is greater in case of batch process. In batch process resin particles are stirred with large volume of concentrated drug solution. Subsequently the resin is washed to remove adhering free and un-associated drug and air dried. In case of column process a highly concentrated drug solution is eluted through a bed or column of the resin, until equilibrium is established [25]. In present study higher drug loading was evident with 1:1 drug-resin ratio. Complexation between the drug and resin is essentially a process of diffusion of ions between the resin and surrounding drug solution. As the reaction is an equilibrium phenomenon, maximum efficacy is best achieved in batch process wherein the anionic group of resin is replaced with drug possessing carboxylate anion. Additionally, batch process provides greater surface area for ion exchange due to higher swelling efficiency [20]. The percent complexation after 6h at 1:1 ratio was found to be 83.68% and 86.98% at 1:2 proportion whereas it was 89 and 95% at 1:3 and 1:4 ratios, respectively. As there was an insignificant increase in percent complexation with higher drug-resin ratio, further studies were conducted using 1:1 drug-resin ratio. Another consideration for selecting this ratio was problems associated with suspendability of larger amount of DRC.

Effect of swelling of resin on loading of CEP was studied at different swelling times of 30, 60, 90, 180 and 360 minutes. The swelling and hydrating properties of TulsionA-23 affect the rate of ion exchange, which in turn affects the percentage drug loading. Maximum CEP loading of 83.16% was observed after 90 min swelling time. Increase in swelling time beyond 90 min did not lead to a significant increase in drug loading.

The percent drug loading on resin without activation, resin treated with acid, resin treated with alkali and resin treated with both acid and alkali was found to be 73.13%, 81.05%, 81.98% and 83.16% w/w respectively. A 10 % increase in drug loading was seen when resin was activated with both acid and alkali.

Characterization of DRC:

Taste evaluation:

Two approaches are commonly utilized to overcome unpleasant taste of the drug: 1. Reduction of drug solubility in saliva, where a balance between reduced solubility and bioavailability must be achieved. 2. Alter the ability of the drug to interact with taste receptor [26]. Molecule interacts with taste receptor on the tongue to give bitter, sweet or other taste sensation, when they dissolve in saliva. This sensation is the result of signal transduction from the receptor organs for taste, commonly known as taste buds. These taste buds contain very sensitive nerve endings, which produce and transmit electrical impulses via the seventh, ninth and tenth cranial nerves to those areas of the brain, which are devoted to the perception of taste [27]. The glossopharyngeal nerve is responsible for taste on the back side of the tongue. Saliva is not able to break the drug resin complex but the complex is weak enough to be broken down by hydrochloric acid present in the stomach [28].

Based on preliminary results, DRC prepared using 1:1 ratio of resin and drug with stirring time of 6 h was evaluated for taste. In the present study, the taste of DRC (equivalent to 50µg/ml) was compared with taste of pure drug solution (CEP). The volunteers were asked to hold 10 ml of each solution in oral cavity for 30s. No bitterness was reported for DRC throughout the study. From the outcomes of taste evaluations, it was concluded that the taste masking of CEP by making an ion exchange complex with Tulsion A-23 was complete and satisfactory (Table 4). Hence the aforementioned DRC was used for preparing controlled release beads using rate-retarding polymers.

Table 4: *In vivo* taste evaluation of Drug Resin Complex.

No. of Volunteers	1	2	3	4	5	6	7	8	9	10
Pure Drug	3	2	3	2	3	3	3	3	4	4
DRC	0	0	0	0	0	0	0	0	0	0

0: No bitterness, 1: Threshold bitterness, 2: Bitter, 3: Moderate bitter, 4: Strong bitter

Fourier transforms infra-red spectroscopy (FT-IR)

The graph was obtained for drug resin complex and resin only. The graph in shows peaks of unbound sites or sites available for exchange in the resin After drug resin complex has been formed the peaks for these sites do not appear in graph for drug resin complex indicating that the free sites or the sites available for binding are bound with the drug as seen in Fig. 2.

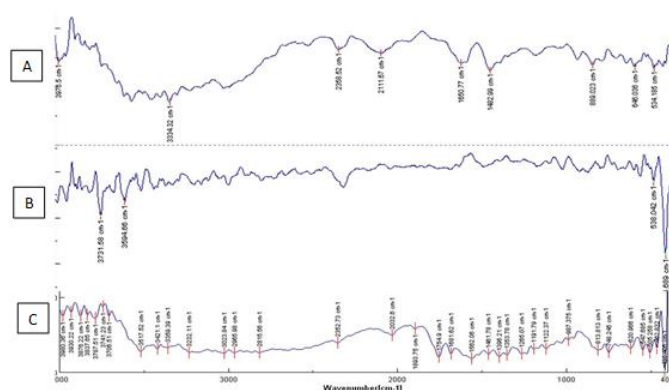


Fig. 2: FT- IR graph for A) Tulsion A-23 resin, B) Drug resin complex, C) Pure Drug.

Optimization:

The formulations were prepared according to protocol of 3² factorial design. Three levels were selected as high, medium and low of 2 independent variable factors i.e., pump speed and concentration of polymer. The prepared formulations were analysed on the basis of experimental results obtained from *in vitro* release of drug. The data obtained was subjected to Design Expert software V7.1.4.3. Quadratic model was suggested to run the design. F-values, P-value and model F-value for *in vitro* drug release was obtained from ANOVA. The selection of model and polynomial equation is listed in (Table5).

Table 5: Summary of results of regression analysis for response for *in vitro* drug release and quadratic equation obtained.

<i>In vitro</i> drug release					
Model	Model F value	p value	R ²	Adequate Precision	Standard deviation
Quadratic	16.05	0.0225	0.9640	12.119	3.18
Drug release = +87.14 - 9.92 * A - 5.83 * B -1.43 * A * B - 1.18 * A ² - 2.01 * B ²					

For *in vitro* drug release, the Model F-value of 16.05 implied the model was significant. There was only a 2.25% chance that a "Model F-Value" this large could occur due to noise. P values were found to be 0.0225, less than 0.0500 indicate model terms are significant.

In this case A, B are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model. "Adequate Precision" measures the signal to noise ratio, a ratio greater than 4 is desirable. The obtained ratio of 12.119 indicates an adequate signal. Thus, the proposed model can be used to navigate the design space.

Since the values of R² are quite high, that is 0.9640; the polynomial equations form excellent fits to the experimental data and are highly statistically valid. Factor A is concentration of polymer and factor B is pump speed. From the equation it is clear that as the concentration of polymer and pump speed increases the release decreases. Decrease in release on increase in pump speed could be due to faster volumetric discharge of polymeric solution leading to denser polymer films on the DRC surface. The reason for decrease in release on increase in polymer concentration may be formation of stronger network (polymer crosslink) through which drug diffusion becomes slower. Both factors promote slower diffusion of drug through coated film. The above findings are supported by the coefficients of the polynomial equations.

***In vitro* release: coated DRC (optimization)**

The *in vitro* dissolution studies are the benchmark tools for studying release profile of drug from formulations. The drug release from coated DRC is retarded. The retarding effect is attributed to drug bound to strong ion exchange resin. This effect is further enhanced by coating with pH independent polymers like ethyl cellulose and cellulose acetate butyrate. *In -Vitro* drug release from DRC is given in Table 6. The release from uncoated resin was above 96% within 5h. Therefore, to extend the release up to 12h the DRC were coated with a mixture of ethyl cellulose and cellulose acetate butyrate. The mechanism of release from coated DRC is by diffusion through intact polymeric membranes [29], hence a significantly slower release is obtained after coating of DRC. Release of drug from F3, F6, F7 and F8 was found to be above 90 % within 10 h. This is attributed to low polymer concentration whereas batch F1 recorded maximum retardation of release of drug among all batches i.e., 66% at 10h as both the variable factors, pump speed and polymer concentration were high. Drug release from F2, F4, and F5 was just below 80% at 10 h. Formulation F2 exhibited 92% release in 12 h (Fig.3). Further, this data was subjected to Design Expert software V7.1.4.3. The release retarding effect is mainly due to coating of polymer which is water insoluble. Ethyl cellulose and cellulose acetate butyrate are used as coating polymers which are pH independent materials thus the release occurs by diffusion process and would not be affected by pH of medium.

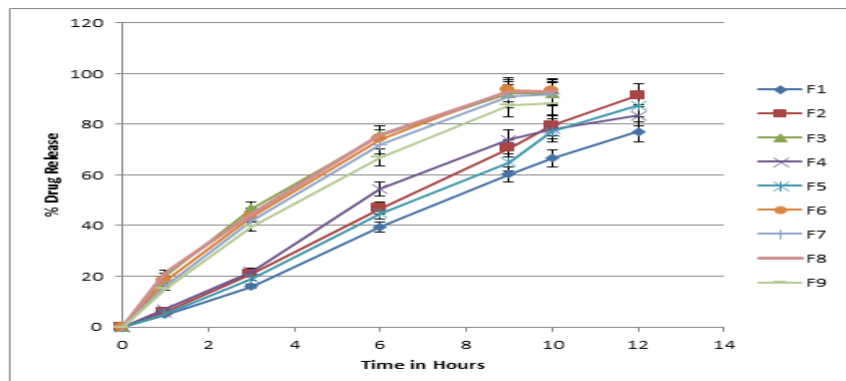


Fig. 3: *In- vitro* % drug release from DRC of formulation.

Dissolution study showed that increase in concentration of ethyl cellulose and cellulose acetate butyrate, decreased the release which may be attributed to the slower rate of diffusion medium into the coated DRC due to greater polymer concentration (which results in a greater crosslinking mesh) as also greater thickness of films. Increase in pump speed led to slower drug release. This could be attributed to faster rate of volumetric discharge of the polymeric solution leading to thicker coats on the DRCs.

Table 6: *In -Vitro* drug release from DRC.

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
H	% Release	% Release	% Release	% Release	% Release	% Release	% Release	% Release	% Release
1	4.94	5.83	20.19	6.98	5.26	18.28	16.32	21.2	15.22
2	15.88	20.97	46.79	21.91	19.21	43.44	41.89	44.7	39.76
3	39.42	46.81	75.72	54.58	44.86	74.08	72.04	75.73	66.98
4	60.26	70.49	92.16	73.93	64.98	93.56	91.18	92.86	87.48
5	66.64	79.42	92.16	78.06	77.06	93.2	91.86	92.86	88.14
6	77.08	91.39	-	83.49	87.42	-	-	-	-

Response surface plots:

The relationship between the variables at different levels and response was further elucidated by constructing 3-D response surface plots. The effects of X_1 and X_2 on response variable are shown in (Fig.4).

The response surface diagrams are known to facilitate an understanding of the contribution of the variables and their interactions at all levels are shown in Fig. 4. The 3D response surface plots are shown in Fig. 4. A decrease in drug release with increase in concentration of polymer was observed. Similar effect was seen with increase in pump speed. Formulation of optimized batch obtained by Design Expert.

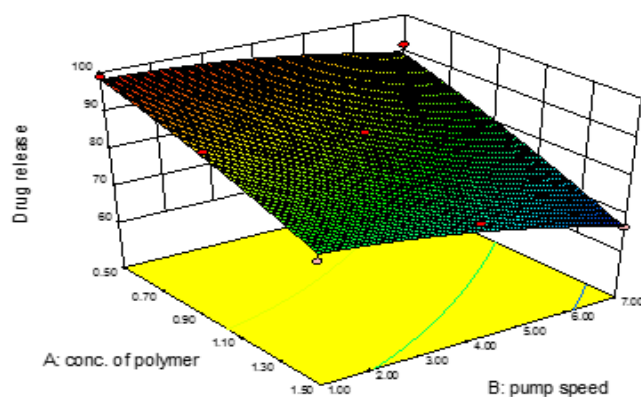


Fig. 4: Influence of concentration of polymer and pump speed on the *in vitro* drug release showing the 3-D Response surface plot .

Based on the constraints and target inputs provided, the software provided the formula for the optimized batch as 1.3 % polymer concentration and pump speed of 5 rpm. The predicted and observed response of percent drug release for the optimized batch were found to be 100 % and 99.16% respectively as shown in Table 7, indicating their consonance. The optimized batch F2 was used for preparing the suspension.

Table 7: Preparation of optimized formulation.

Sr. No.	Optimized formula obtained	Response	Observed value
1.	X1 = 1.31% X2 = 5RPM	% Drug release	99.16%

Micromeritics properties of coated and uncoated DRC

The particle size differed before coating and after coating. The particle size of the Tulsion A-23 resins was found to be between 550 to 750 μm and they exhibited good flow properties. The average particle size of the uncoated resin was found to be 698.12 μm . The coated resin particles were found to have an average particle size of 713.12 μm . The particle size was revealed to increase by an average of 15 μm indicating that polymer coating solution was deposited on the DRC and increase in particle size is the thickness of polymer coat on DRC.

The surface morphology studied with help of SEM revealed a smooth surface with minimal aberration and spherical shape as shown in (Fig.5).

Micromeritic properties of coated drug resin complex was evaluated such as bulk density, angle of repose, compressibility (Carr's index %), Hausner's ratio, shape and size particle. Bulk density was found that the 0.675 ± 0.64 , angle of repose were found as 25.81 ± 0.44 , Carr's index was found to be 13.57 ± 0.20 , Hausner's ratio was 1.157 ± 0.2 . The resins exhibited satisfactory flow and compressibility characteristics.

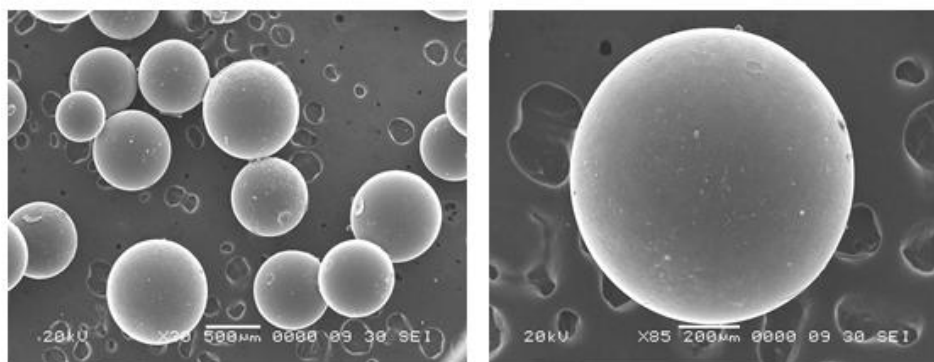


Fig. 5: Scanning Electron Micrograph (SEM) of DRC.

Evaluation of oral controlled release suspension

The optimized batch of coated DRC was used to prepare CEP suspension which was evaluated for colour, flavour and taste. The suspension was found to be pleasant in appearance and acceptable as far as taste was concerned and possessed excellent redispersibility property with optimum particle size distribution. The pH of the coated DRC suspension was found to be 5.3 and coated microparticle suspension was 4.8, which is slightly acidic and is suitable for oral formulations. Sedimentation volume of the coated DRC suspension was found to be 1 and coated microparticle suspension was found to be 0.8. This indicated that the suspension was optimum and acceptable. The suspension was easily redispersible. The percentage drug content of coated DRC and coated microparticles was found to be 97.85% and 95.88% respectively. The biggest challenge for controlled release liquid preparations is leaching of drug in suspension during shelf life or storage. In the present study, leaching from coated DRC suspension was observed to be 0.5% and from suspension of coated microparticles, it was found to be about 2.1%. An obvious inference that we can draw from this is that the drug is in complexed form with the resin and is further coated with polymers thus reducing any tendency of drug to leach out. Moreover, this is observed as the drug does not release from the resin until it does not receive counter ions. The bitterness level of both suspensions was compared with threshold bitterness of drug. All volunteers for suspension of coated DRC whereas 50 % of volunteers reported bitterness score 0 to 5 for the suspension coated microparticles. Resuspendability of coated DRC and coated microparticles were required 5 and 3 shakes for resuspension. Both the suspensions were found to be easily redispersible on gentle shaking,

The percent drug release of CEP suspension prepared according to the optimized batch generated by using Design Expert was found to be 99.16% in 12h whereas the suspension containing coated microparticles was found to release nearly 90% drug in a span of 8 h.

Stability Studies

CEP Suspension was subjected at $40 \pm 2^\circ\text{C}$ and $75 \pm 5\%$ RH for 1 month in stability chamber. After a period of one month, the samples were observed for any change in physical parameters. It was observed that no change in colour. It was also noted that suspension was free of any kind of bad odour. Results obtained from the evaluation after stability studies are shown in (Table 8).

The sedimentation studies showed that the sedimentation volume of all formulations was below 1, which indicated that the formulations were forming loosely bound sediments and were readily resuspendable. The density of vehicle and the coated DRC should have similar values. If density of coated DRC is less than density of suspending vehicle, the DRC float on vehicle. If density is more than vehicle then DRC settle down quickly. The redispersibility of suspension was checked using vortex mixer, and was found to redisperse within 120 sec. The biggest problem for controlled release liquids is leaching of drug in suspension during shelf life or storage. If the drug is released in suspension itself, it makes the suspension bitter and does not allow controlled release hence the objective of formulation is not achieved. The leaching obtained was below 1% as DRC releases drug only in presence of counter ions.

Table 8: Evaluation parameter of prepared DRC suspension.

Evaluation Parameters	Initial	After 1 Month
Sedimentation Volume	1	1
Resuspendability	06	06
Assay %	97.85%	97.12%
Taste	Not Bitter	Not Bitter
Leaching	0.5%	0.8%
Redispersibility	112 sec	119sec

CONCLUSION

Taste masking of cephalexin was successfully achieved using Tulsion A-23, a strong anion exchange resin. Controlled release suspension was prepared by coating the drug resin complex with release retarding polymers. The metallic taste of the drug was successfully masked. Coating the resinate with cellulose acetate butyrate and ethyl cellulose was found to extend the release of drug upto 12 h. Leaching of drug was found to be negligible in case of coated drug resin complex as compared to coated microparticles and storage at 40°C and 75% RH led to a marginal increase in leaching in case of coated resins. Thus, we may conclude that complexation with ion exchange resins and further coating the resins with rate retarding polymers can be employed for taste masking and achieving controlled release of the drug. Future research may be directed towards using same technology for improving the stability of active ingredients.

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CONFLICT OF INTERESTS

The authors report no conflict of interest.

LIST OF ABBREVIATIONS–

IER: Ion Exchange Resins

DRC: Drug Resin Complex

CEP: Cephalexin

FTIR: Fourier Transform Infrared Spectroscopy

HPMC: Hydroxy Propyl Methyl Cellulose

SEM: Scanning Electron Microscopy

ANOVA: Analysis of Variants

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