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Development of taste masked levofloxacin oral suspension using ion exchange resinates

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ABTRSACT

In the present work, taste masked resinates of levofloxacin using Tulsion-335, an acidic cation ion exchange resins were used to develop its oral suspension formulations. The drug resin complexes were prepared by batch process by taking drug to resin ratios of 1:1, 1:2, 1:3 and 1:4. The techniques of differential scanning calorimetry (DSC), X-ray diffraction (XRD) and Fourier transform infrared spectroscopy (FTIR) were used to characterize the drug resinates. The ratio of 1:4 was found to be effective for masking the bitter taste of the drug as confirmed by the taste studies. Dissolution rate studies of the taste masked drug resin complexes were carried out in Phosphate buffer pH 6.8 (Salivary pH). Dissolution rate studies in phosphate buffer pH 6.8 showed that more than 90% of pure drug was dissolved in 5 minutes, while in the same period the dissolution of levofloxacin from drug resin complex in 1:4 ratio was below 40%. This was the possible reason for reduction of bitter taste of drug. Finally the resins were used for the preparation and evaluation of oral suspension of the bitter drug. The developed oral suspension was found to be better in taste when compared with marketed suspension of levofloxacin.

Keywords: Levofloxacin, Acidic Cation Exchange Resin, Taste Masking, DSC, FTIR, X-ray Diffraction, Tulsion-335 (Polacrilex resin)

INTRODUCTION

The oral route of drug administration is popular, convenient and widely accepted method of administering the drugs. Oral route of drug administration have wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain avoidance and most importantly patient compliance [1]. However, taste is an important factor in the success of oral dosage form; the bitter taste drugs often present formulation problems and affect the patient compliance.

Physiologically, taste is a sensory response resulting from a chemical stimulation of taste buds on the tongue. The sense of taste is conducted to the brain by a process called taste transduction. This process begins with the interaction of tastant (i.e., food or medicine) with taste receptor cells in the taste buds.

Numerous techniques have been described in academic and patent literature for masking of bitter or undesirable taste of drugs like addition of flavors, sweetener and amino acids, microencapsulation, inclusion complexation with cyclodextrin, complexation with ion exchange resin, salt preparation, group alteration and prodrug approach [2-6].

Complexation with ion exchange resin is a simple, efficient and proven technique for taste masking of a number of bitter tasting drugs. In this technique, the bitter tasting drugs can be attached to the oppositely charged resin substrate, forming insoluble adsorbates or resinates through weak ionic bonding [7]. Saliva, with an average pH of 6.8 and a cation concentration of 40 meq/l would only elute a limited percentage of drugs from adsorbate or the dissociation of the drug-resin complex does not occur. This suitably masks the unpleasant taste and odor of drugs.

Immediately after ingestion, ions in the body (especially in the lower pH of the stomach) cause rapid elution from or disintegration of ion exchange resin drug complex and dissolve the drug in the gastric content. The free drug is now bioavailable, which can be easily absorbed from the GIT. Thus in this technique taste masking is achieved without affecting the bioavailability of drug [8-9].

Levofloxacin, a fluoroquinolone antibiotic is extremely bitter in taste. This drug is marketed as a film coated tablet, dispersible tablet, dry syrup and suspension. Most of marketed formulation does not provide sufficient taste masking and are not palatable. It was therefore considered worthwhile to develop a taste masked levofloxacin formulation especially for children for whom swallowing of tablet may be difficult. However, the designing of taste masked preparation for drug with unpleasant taste is difficult because of usual need to incorporate two contradictory characteristics in the product, i.e., masking of unpleasant taste for patient compliance and complete releasing of the drug from preparation to avoid lowering of bioavailability.

Complexation with ion exchange resin is a simple, efficient and proven technique for taste masking of a number of bitter tasting drugs [10-12]. Thus the objective of the present study was to utilize this technique to mask the bitter taste of levofloxacin (weakly basic drug), using Tulsion-335 which is a weak acid cation exchange resin.

EXPERIMENTAL SECTION

Levofloxacin was received as gift sample Vishal Pharma., Kurukshetra; Acidic cation exchange resin Tulsion-335 was a kind gift from Thermax Limited, Chemical Division, Pune, India and aspartame was a kind gift sample from Martin and Brown Pharma., Hisar. All other chemicals were of analytical reagent grade and used as received.

Purification of resin

Tulsion 335 was purified by washing with distilled water. The wet resin was activated by 0.1M HCl 300 ml followed by washing with distilled water. The resin was then dried in vacuum oven at 60^{o}C till the moisture content came below 5% which was checked by Karl Fisher titrator. The purified resin was stored in an air tight glass vial.

Preparation of drug resin complex

In the present study, the drug resin complex was prepared as follows. In this method, 2% slurry of resin Tulsion T-335 was prepared in distilled water. The slurry was stirred using magnetic stirrer at 300 rpm. After half an hour of stirring required amount of drug was added slowly. Then stirring was continued for 4 hours. The slurry so obtained after 4 hour was filtered, washed with distilled water and dried at 60^{o}C to a constant weight to obtained desired complex. The Drug-Resin complexes (DRC) so obtained were filtered and washed with distilled water and dried at 60 ^{0}C in hot air oven to a constant weight.

Optimization of conditions for complexation

Mixing time: For optimization of mixing time the stirring of drug resin mixture was carried out for 1h, 2h, 3h, 4h and 5h at room temperature on a mechanical shaker to allow maximum possible loading. The sample was then evaluated for drug loading after each time interval.

Effect of pH**:** Buffer solutions of different pH ranging from 4 to 9 were prepared as per USP specifications. The drug resin mixing was carried out at different pH to study the effect of pH on drug loading.

Differential Scanning Calorimetry (DSC) characterization of samples

The thermal behavior of each drug resin complex was examined by differential scanning calorimeter (DSC Q10, TA Instruments). Sample 3-4 mg was run at a scanning rate of 10°C/min over a temperature range of 45 to 250°C in a nitrogen environment.

Fourier transform Infrared Spectral (FTIR) study

Drug resin complex was crushed to make KBr Pellets (0.5%, w/w) and then their IR (IR 200 Spectrometer, Thermo Electron Corporation) spectra were recorded over the region 400–4000 cm−1

X-ray Diffraction (XRD) characterization of samples

An X-ray diffractometer (Xpert Pro's Pan Analytical Instrument, Model Philips PW 3040/60) was employed to study the crystalline form of the drug in the complex. The X-ray copper target tube K_{α} (λ=1.5465980 A°) was operated at Crystal monochromator voltage of 45mV and current 30 mA. The scanning was carried out over 2θ range of 8° to 60.

***In-Vitro* Dissolution Rate Studies**

Dissolution studies of complexes were performed according to USP XXIII Apparatus II (LabIndia DS 500) in Phosphate Buffer pH 6.8 (simulating salivary pH) by adding complex equivalent to 125 mg of levofloxacin in 900 ml of dissolution media. The temperature was maintained at 37±0.5°C and the rotation speed was 50 rpm. The samples were withdrawn at various time intervals and analyzed by UV (LobaLife). The test was carried out in triplicate.

Taste evaluation study

The bitterness evaluation test was performed with human volunteers according to a previously described method after clearance from human ethical committee [13]. Test was carried out on a trained taste panel of 6 human volunteers (3 males and 3 females, with a mean age of 25 years), from who informed consent was first obtained. The volunteers rinsed their mouths thoroughly before and after the tasting. Each sample was held in the volunteers' mouths for 30s and then expectorated, and the taste was evaluated and assigned a numerical value according to the following scale: 0- Tasteless, 1- Slight bitter, 2- Moderate bitter, 3- Strong bitter. The lower score indicated a greater masking effect.

Preparation of an oral suspension

Accurately weighed amount of Tulsion T335 was added to 25 ml of purified water. The slurry was stirred for half an hour with mechanical stirrer. Then weighed amount of levofloxacin hemihydrate, sodium benzoate and aspartame was added to previously prepared resin slurry under stirred conditions. After complete addition of drug solution, xanthan gum paste and flavor were added. Stirring was continued for 2 hours and finally the volume was adjusted with purified water.

Evaluation of suspension:

Particle size analysis

Particle size measurements of the formulated suspension of drug resin complex were determined by Nanotrac system (Mircotrac, Inc., Montgomeryville, PA) using laser diffraction. Suspension of drug resin complex were dispersed in distilled water by vigorous shaking and analyzed in triplicate with three readings per suspension formulation sample.

Ease of redispersibility

Ease of redispersibility was determined by allowing the suspension to settle in a measuring cylinder. The mouth of the cylinder was closed and was inverted through 180^0 and the number of inversions necessary to restore a homogeneous suspension was determined.

Sedimentation volume

Sedimentation volume was determined by properly shaking and storing the suspensions in 100 ml measuring cylinder. The suspensions were allowed to settle down for 24 hour and sedimentation time as well as sedimentation volumes were determined. The sedimentation volume was calculated using the official formula as follow:

Sedimentation volume (Vs) = Hu/Ho
Where
Vs= sedimentation volume,
Hu= Ultimate height of suspension,
Ho= Original height of the suspension before settling

Dissolution rate study of prepared suspension and marketed product at salivary pH

Drug release was determined by adding suspension and marketed product (L-CIN suspension, Lupin Ltd.) equivalent to 125 mg of drug in 900 ml of dissolution medium in a USP type Lab India DS-8000 Apparatus using a paddle at 50 rpm and temperature was 37±0.5 and paddle depth was 25 mm. USP phosphate buffer of pH 6.8 simulating the salivary pH was used as dissolution media. The samples were withdrawn at suitable time intervals. After suitable dilution the filtrates were analyzed by UV Spectroscopy

Drug release kinetics

In order to understand the mechanism and kinetics of drug release, the results of the *in vitro* drug release study were fitted to various kinetics equations like zero order (percentage cumulative drug release vs. time), first order (log percentage cumulative drug remaining vs. time), Higuchi matrix (percentage cumulative drug release vs. square root of time).

RESULTS AND DISCUSSION

Selection of resin

The selection of an ion exchange resin for a particular drug delivery application is generally based upon its functional group characteristics. In the present work the drug levofloxacin is a free base for which a weak acid cation exchange resin is useful for taste masking. From the different variety of the cation exchange resins available in the market, Tulsion, a reputed brand of ion exchange resins of Thermax India Ltd. was used for taste masking. Tulsion-335 grade chemically known as Polacrilex resin which is a weakly acidic polyacrylic copolymer was chosen as a cation exchange resin for taste masking of levofloxacin. Tulsion-335 uses the hydrogen ion as an exchange ion which helps it in adsorbing the drug in its base form. On exposure of acidic pH of stomach desorption of drug takes place due to high affinity of the resin for the hydrogen ion. In acidic environment, Tulsion-335 is in nonionic state and exists as the free acid. Hence drug loading onto this cation exchange resin is carried out at higher pH. Since the physiochemical properties of Tulsion -335 grade were best suited for the needs of present formulation and hence it was selected as the ion exchange resin for the present work. The drug resin complex thus prepared was optimized with respect to drug to polymer ratio, effect of drug to resin ratio on drug loading, effect of pH for drug resin complexation and mixing time on drug resin complexation.

Selection of drug to resin ratio

Complexation of drug with Tulsion was studied for optimum drug to resin ratio for maximum loading. The values for percentage drug complexed for the drug to rein ration of 1:1, 1:2, 1:3 and 1:4 was found to be 62.48, 74.06, 82.56 and 83.14 respectively. The values of percentage drug bound to resin showed an increasing trend with the increase in resin content which is attributed to the increased interaction between the drug molecules and the resin particles. One way ANOVA was applied to compare the effect of different drug to resin ratios on drug loading. In case of ratios 1:1 and 1:2 drug bound was less than, 1:3 and 1:4 as shown by the result of one way ANOVA where the *p* value ($p< 0.05$) indicated significant difference. The ratio of 1:3 and 1:4 did not indicate significant difference ($p>0.05$).

Differential Scanning Calorimetry Evaluation

Complex prepared using different drug to polymer ratios were also subjected to thermal characterization and taste evaluation**.** Figure 1 shows the DSC scan of complexes prepared with different ratios of drug to resin. From the figure it is evident that drug has been partially complexed in case of 1:1 ratio because their DSC pattern contains feeble peak characteristics of levofloxacin. But in case of 1:2, 1:3 and 1:4 no peak related to levofloxacin has been observed which shows drug has undergone physical changes from crystalline to amorphous which confirm the formation of complexes.

Taste Evaluation study

From the results of taste evaluation as shown in Table 1, it is evident that there is very little or no bitterness imparted with 1:2, 1:3, and 1:4 drug resin complex with reference to pure drug since a person is not able to keep the pure drug in the mouth in 30 sec. One way ANOVA was applied for comparing the results of taste study for different drug to resin ratios. Out of these three taste masking complex 1:4 showed better taste masking ability than 1:2 and 1:3 ($p< 0.05$ indicating significant difference). Hence the ratio of 1:4 was found to be the optimized ratio and was further taken up form formulation of an oral suspension of the drug.

Characterization of drug resin complexes

FTIR Spectra and X-ray diffraction was employed to study the interaction between Levofloxacin and Tulsion 335. The FTIR spectrum of physical mixture was similar to synthetic spectra produced by addition of Levofloxacin and Tulsion 335. This indicated that there was no interaction between Levofloxacin and Tulsion 335. The spectra of complex was different from that of physical mixture and exhibited marked variation in some bands (broadening and intensity reduction) which can be interpreted assuming change in hydrogen bonds of drug due to interaction with Tulsion 335 . Interaction between Levofloxacin and Tulsion 335 would be inhibitory and/or retardatory factor in the crystallization and cause Levofloxacin to be precipitated out in an amorphous form. Powder X-ray diffraction pattern of Levofloxacin, Tulsion 335, Physical mixture of Levofloxacin and Tulsion 335 and Taste masked complex (1:4) are shown in Figure 2. The result of X-ray diffraction showed that the pure drug exhibited crystalline property, while Tulsion 335 exhibited amorphous pattern. Physical mixture of Levofloxacin with Tulsion 335 exhibited crystalline property of levofloxacin indicated that drug has not undergone any physical change while the complex displayed amorphous pattern. All the peaks of levofloxacin were absent in case of the complex. It proved the drug was changed into amorphous form after the preparation process of complex.

Drug Release Study

The dissolution rate study was designed to assess whether the dissolution rate is retarded during the initial period in order to suppress the bitterness. The dissolution rate studies in phosphate buffer pH 6.8 showed that more than 90 % of drug was dissolved in 5 minutes, while in the same period the dissolution of levofloxacin from drug resin complex in 1:4 ratio was below 40% (Figure 3). The dissolution of levofloxacin is thus reduced at salivary pH from the complex. The reduction in drug release in the initial period clearly suggests that upon development of taste masked complex into some stable dosage formulations such as rapidly disintegrating tablets or suspensions, where the contact time of drug with taste buds will be very less, this retardation of drug release will be very significant. Hence this reduction of dissolution rate of levofloxacin from the complex is responsible for reduction of the bitterness of the drug which is further proved by the taste masking studies. However, the resin complex was found to be released completely (97.17%) in simulated gastric fluid as shown in Figure 4.

Formulation and evaluation of suspension:

Oral Suspension was formulated using Tulsion T-335 resin and drug in optimized 1:4 ratio, other additive like flavoring agent, sweetening agent, and xanthan gum as suspending agent as shown in Table 2. The formulated suspensions were evaluated for different parameters as shown in Table 3. The sedimentation volume and sedimentation time was found to be 0.7 to 0.82, value of redispersibility was found to 95%. and particle size was found to be in range of 66.98 to 67.21µm.

Table 1: Bitterness evaluation by taste panel

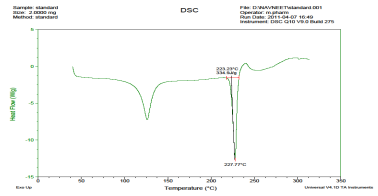
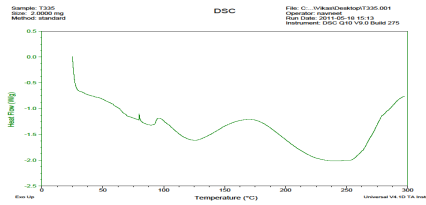
Type of Product		Volunteers Score					
		I	II	III	IV	V	VI
Pure Drug	30 s	4+	4+	4+	4+	4+	4+
DRC1(1:1)	30 s	2	2	2	2	1	1
DRC1(1:2)	30 s	1	1	1	1	1	1
DRC1(1:3)	30 s	0	1	0	1	0	0
DRC(1:4)	30 s	0	0	1	0	0	0

Table 2. Formulation of taste masked suspensions

Ingredients (gms)	**Formulation Code**			
	LFS 1	**LFS 2**	**LFS 3**	**LFS 4**
Levofloxacin hemihydrate	2.5	2.5	2.5	2.5
Tulsion T335	5.0	10.0	15.0	20.0
Aspartame	0.250	0.500	0.750	1.00
Xanthan gum	0.500	0.500	0.500	0.500
Sodium benzoate	0.200	0.200	0.200	0.200
Peppermint flavor	0.025	0.05	0.075	0.1

Table 3. Evaluation of taste masked suspensions

Parameters Evaluated	**LFS 1**	**LFS 2**	**LFS 3**	**LFS 4**
Appearance	Pale Yellow	Pale Yellow	Pale yellow	Pale yellow
Taste	Moderately Bitter	Sweet	Bitter after taste	Bitter after taste
Sedimentation Volume (After 24 hrs)	0.7	0.73	0.8	0.82
Redispersability (%)	92.0	95.0	94.0	95.0
Particle size range (µm)	66.35	65.98	67.21	66.67
Drug content (%)	95.46	96.12	98.68	97.58
In-vitro % drug release (after 60 min.)	95.99	97.55	97.19	97.00

(a)	***(b)***
	

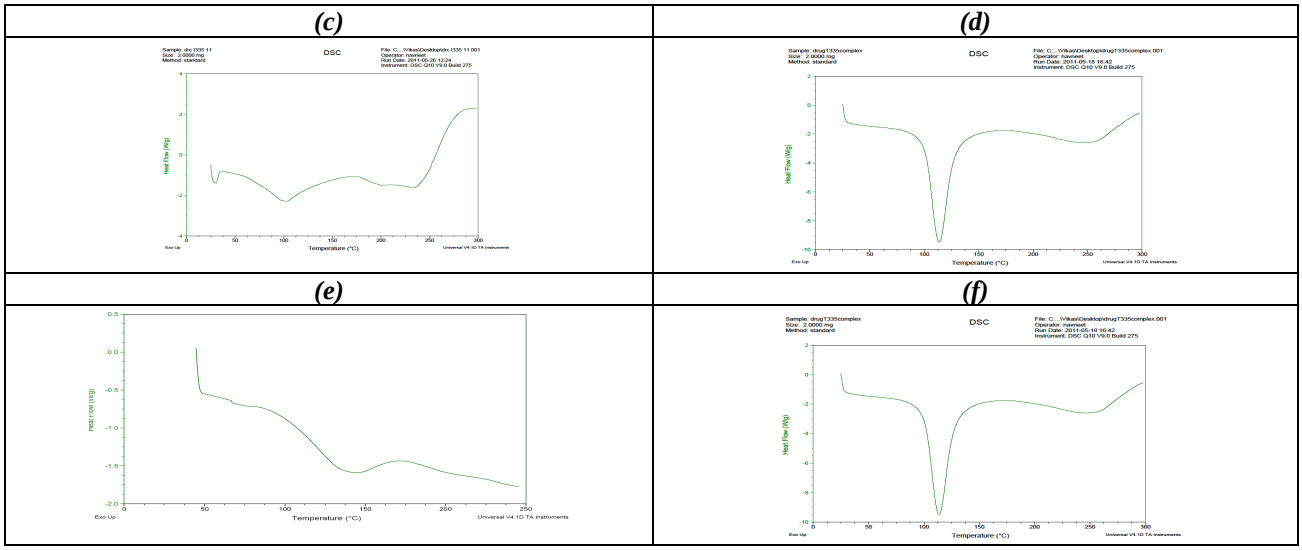


Figure 1: DSC thermograms of (a)Levofloxacin, (b)Tulsion Ion Exchange resin 335, (c) complex of levofloxacin with Tulsion 335 in (1:1), (d) complex of levofloxacin with Tulsion 335 in (1:2): (e) complex of levofloxacin with Tulsion 335 in (1:3) and (f) complex of levofloxacin with Tulsion 335 in (1:4)

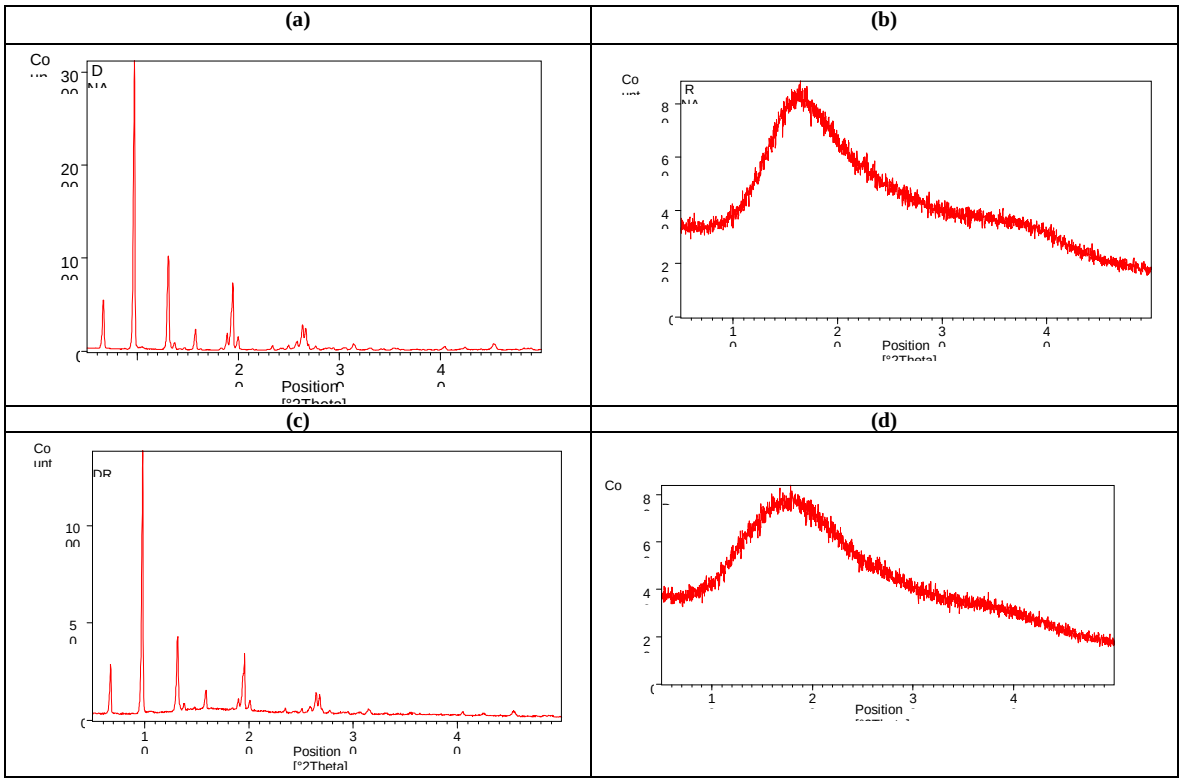


Figure 2: Powder X-Ray Diffraction Pattern of (a) levofloxacin, (b) Tulsion 335, (c) physical mixture of Levofloxacin and Tulsion 335, (d) taste masked drug resin complex (1:4)

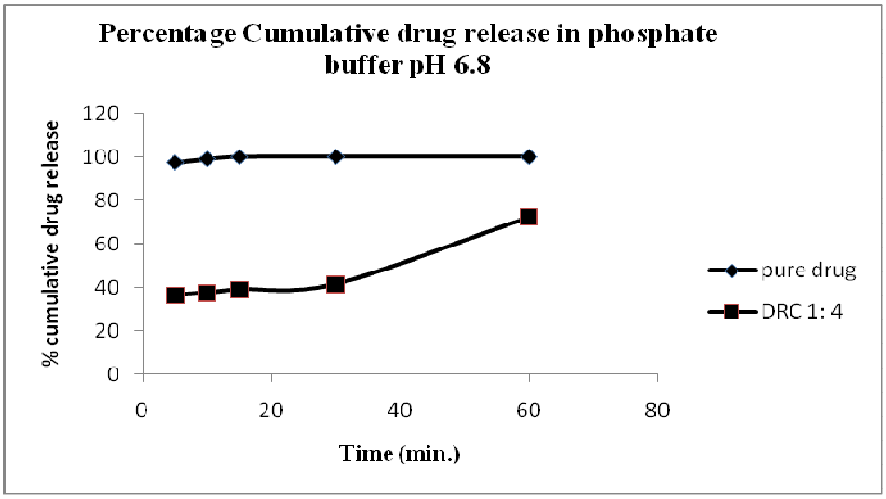


Figure 3: ***In vitro*** **drug release from drug resin complex in phosphate buffer pH 6.8**

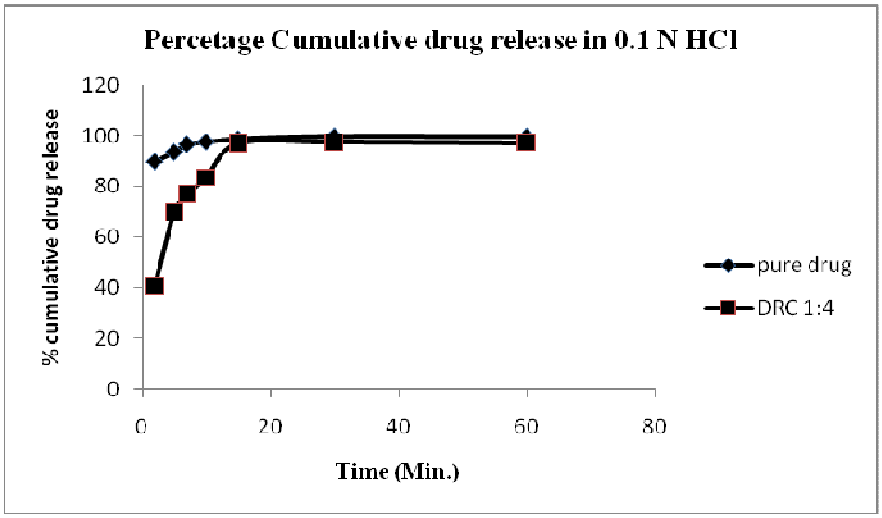


Figure 4: ***In vitro*** **drug release from drug resin complex in simulated gastric fluid**

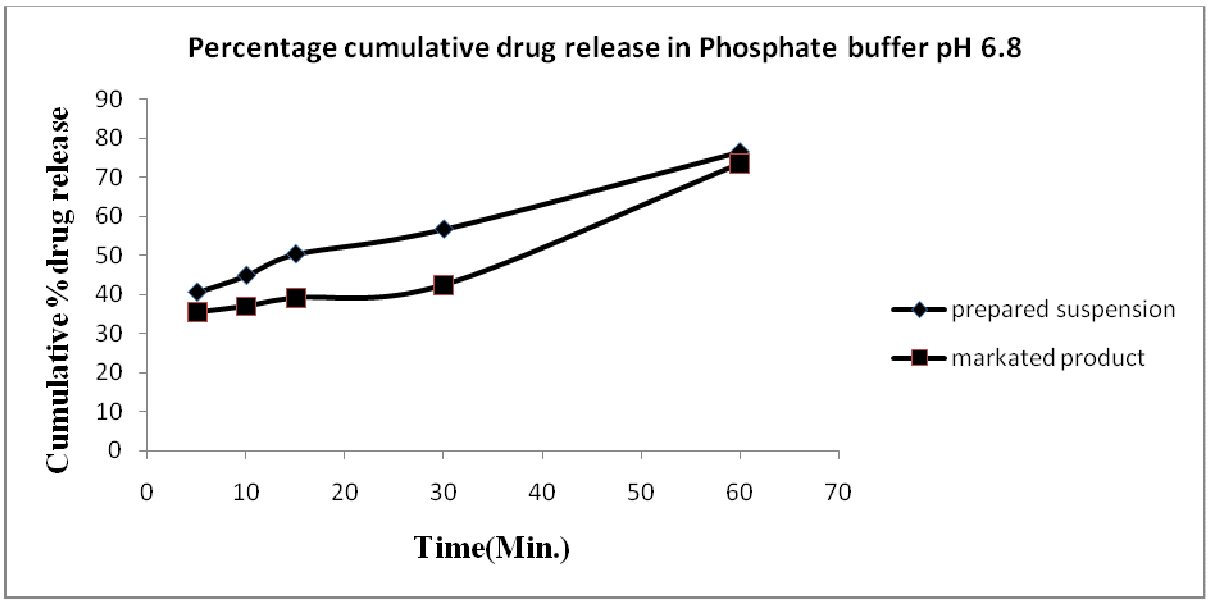


Figure 5. ***In vitro*** **drug release from taste masked suspension in phosphate buffer pH 6.8**

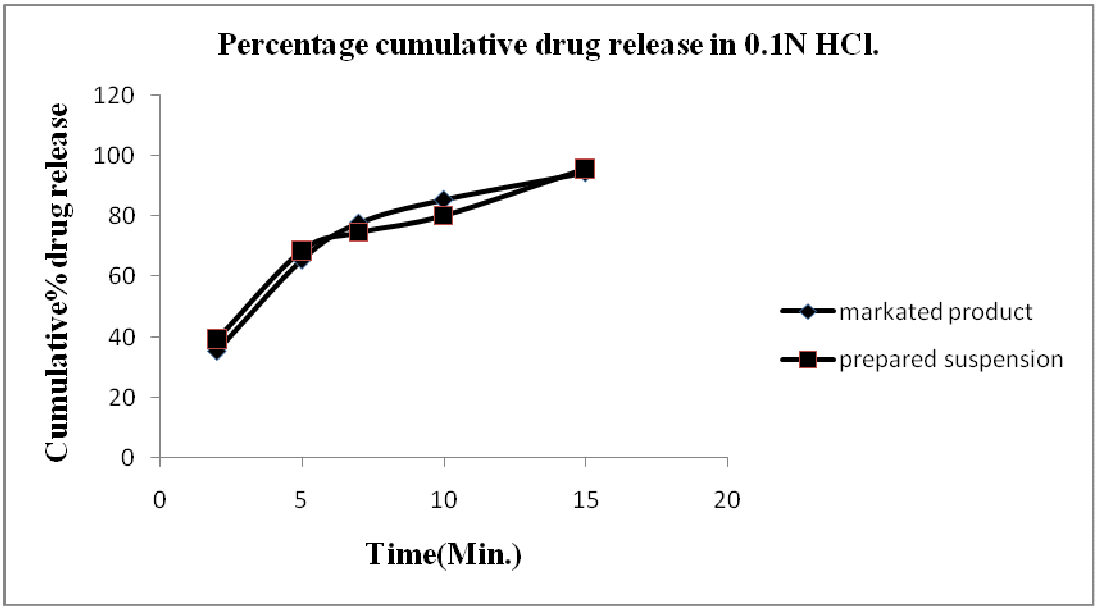
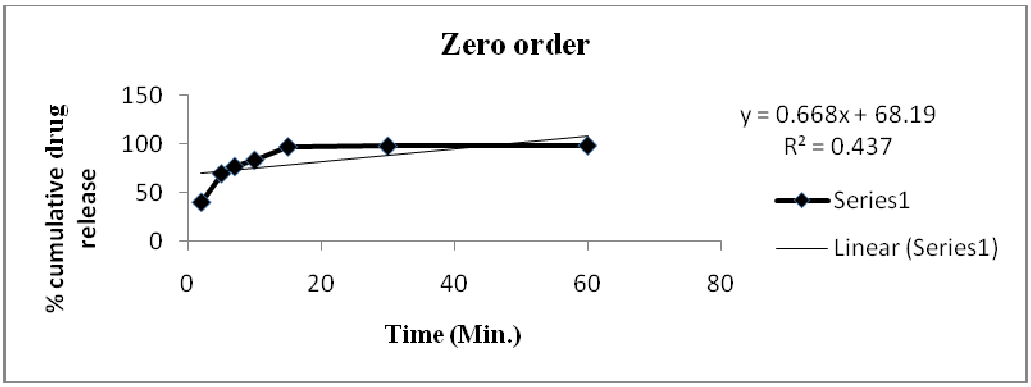


Figure 6: ***In vitro*** **drug release from taste masked suspension in simulated gastric fluid**



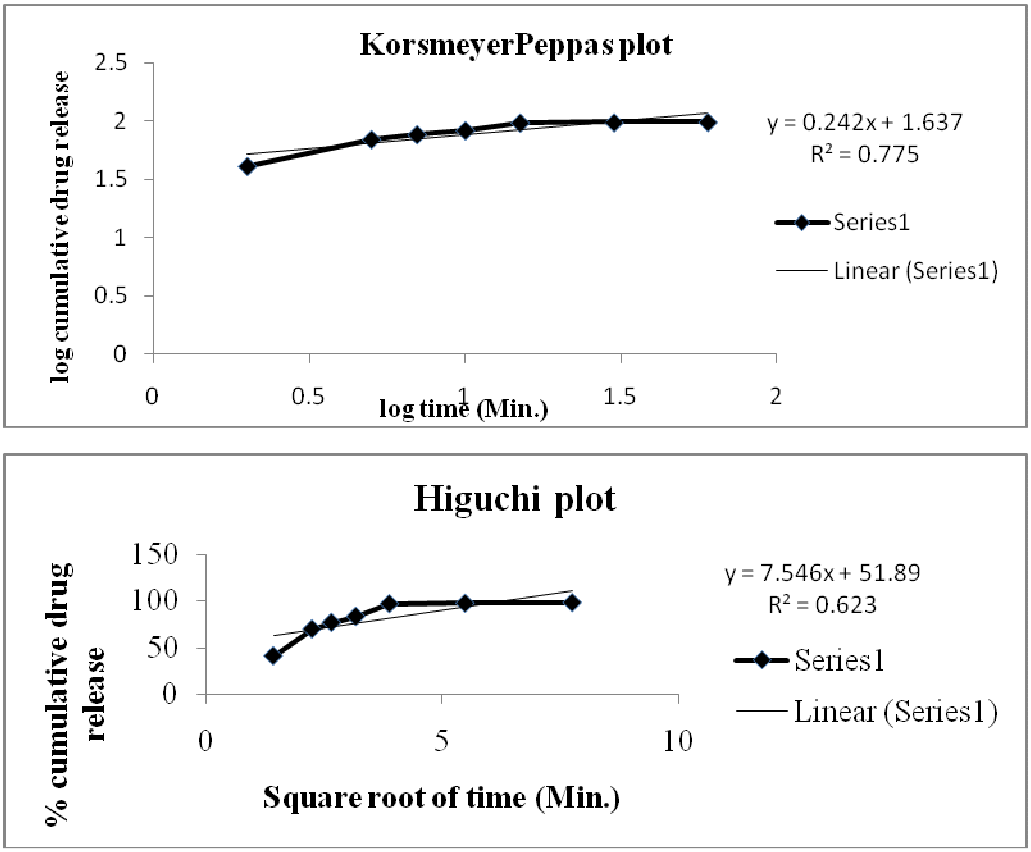


Figure 7: Release kinetics of taste masked suspension

***In vitro* dissolution study**

The cumulative drug release at salivary pH was 42% in 30 minute as shown in Figure 5. The low drug release at salivary pH showed that the taste is effectively masked in the developed formulation and drug was bound to the resin at salivary pH. In case of simulated gastric fluid more than 95% drug was released in 30 minutes from the suspension which revealed that there was no effect on release of drug on complexation with resin in gastric pH. Hence the oral suspension provided a good taste masked properties without affecting the release of drug. The results of dissolution study were found to be comparable to marketed formulation. The results are shown in Figure 6.

Release Kinetics

The *in vitro* release data for levofloxacin hemihydrates suspension was analyzed by various kinetic models as shown in Figure 7. The kinetic models used were zero order, first order, Higuchi and Korsemeyer-Peppas equation. The releases constant were calculated from the slope of the respective plots. Higher correlation was observed in the Koresmeyer-Peppas equation. For planery geometry, the value of n=0.5 indicates a Fickian diffusion mechanism, for 0.5<n<1.0, indicates anomalous (non Fickian) and n=1 implies Class II transport. Both dissolution and diffusion profile of the drug from the suspension showed fitting to Koresmeyer-peppas plot and indicated Fickian diffusion mechanism for the release of the drug from the suspension.

CONCLUSION

From the in-vitro dissolution and taste evaluation studies it was concluded that effective taste masking was achieved for levofloxacin using the technique of complexation with ion exchange resin without affecting the bioavailability of drug. Ion Exchange resin complex can be formulated as granules, dry syrup or suspension and can be taken for scale up after carrying out requisite studies.

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