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Formulation Designing of Taste masked Dry Syrup of Ciprofloxacin HCL

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ABSTRACT

Taste masking and development of palatable dosage forms of bitter drugs constitutes the objective of many a research project in the field of pharmaceutical technology. Taste is an important factor in the development of dosage form. The problem of bitter and obnoxious taste of drug in pediatric patient can create a bad psychological effect on mind. The purpose of this research was to mask the intensely bitter taste of Ciprofloxacin is a broad spectrum antibiotic. It is extremely bitter taste resulting in poor patient's compliance. The aim of present work was to prepare drug resin complex (DRC) using ion exchange resin (Kyron T114) for taste masking and formulate oral reconstituable dry syrup. Formulated ciprofloxacin reconstituable dry syrup has acceptable Drug Dissolution properties. In evaluating period of 7 days no significant change was observed in pH, sedimentation volume, specific gravityand drug content.From the results it concluded that effective taste masking of ciprofloxacin was achieve using Kyron T114 and successfully evaluated in reconstituable dry syrup.

Keywords: Ciprofloxacin, Sedimentation Volume, Ion exchange resin, Kyron T114, Drug Resin Complex (DRC),

INTRODUCTION

In the pharmaceutical industry, taste-masking science broadly covers physiological and physiochemical approaches to prevent Active Pharmaceutical Ingredient (API) or drugs from interacting with taste buds; thereby eliminating or reducing negative sensory response. Physiological approaches consist of inhibiting or modifying an API-mediated bitterness response by incorporating agents into a pharmaceutical formulation. Agents like sodium chloride, phosphatidic acid and peppermint flavor are known to inhibit bitterness by selected API molecules via a mechanism that takes place at the bitterness receptors in the taste buds.[1,2]

Further, majority of the orally administered drug substances are of very to extremely bitter taste. In most cases, the solid formulations are coated with advice not to chew but to swallow the intact tablet.[3] However, for small children the administration of the dose of a whole tablet is frequently not recommended and to administer tablets in general is not recommended. Only liquid formulations should be given or if these are not available, the tablet should be crushed to a suspension and administered by a spoon. The bitter taste in such cases is frequently a serious problem[4,5].

Various taste masking techniques such as the addition of sweeteners and flavors, coating with polymers, adsorption to ion-exchange resin, and chemicai modifications such as the use of insoluble prodrugs have been reported. Each technique

has its own disadvantages. Addition of sweeteners and flavors is not very successful for extremely bitter and water soluble drugs. Ion-exchange resins are functional group specific (amino group) and sometimes cause delayed drug release while coating with polymer requires sophisticated instruments. Chemical modification may alter the pharmacokinetic of drug substance[6,7].

Oral administration of bitter drugs with an acceptable degree of palatability is a key issue for health care providers, especially for pediatric patients. Several oral pharmaceuticals, numerous food and beverage products, and bulking agents have unpleasant, bitter-tasting components. So, any pharmaceutical formulation with a pleasing taste would definitely be preferred over a competitor's product and would translate into better compliance and therapeutic value for the patient and more business and profits for the company. The desire of improved palatability in these products has prompted the development of numerous formulations with improved performance and acceptability[8,9].

MATERIALS AND METHODS

Materials

Ciprofloxacin HCl was obtained as a gift sample from Cipla private Laboratories Ltd. Ion exchange resins (Kyron T114) obtained from Corel PharmaLimited as a gift sample.

Preparation of standard curve of Ciprofloxacin HCl10

100 mg of Ciprofloxacin HCl was dissolved in 0.1 N HCl in 100 ml of volumetric flask and the solution was made upto volume with 0.1 N HCl.

The standard solution of Ciprofloxacin was subsequently diluted with 0.1 N HCl to obtain a series of dilutions containing 1, 2, 3, 4 and 5 µg of Ciprofloxacin in 1 ml solution. The absorbance of these solutions was measured at 276 nm using UV-VIS spectrophotometer (Electrolab, Model SL 1500) against blank.

Preparation of drug-resin complex11

Drug resin complexes (DRC) were prepared by using batch process. Accurately weighed amount of Kyron T 114 dispersed in a beaker containing deionized water and allowed to swell for 45 minutes. Swelled resin slurry was filtered on what man filter paper. Then it was washed with deionized water. Drug resin complex (DRC) was prepared, by placing acid activated resin in a beaker containing deionized water. Accurately weighed amount of Ciprofloxacin was added slowly to the resin slurry and stirred for 3hours in magnetic stirrer. During stirring, pH of the drug resin slurry was measured frequently and adjusts to 6.5 by using 0.1 M KOH. After three hours of stirring, the DRC was separated from dispersion by filtration and washed with deionized water. DRC was dried at 55°C until it was dry. The dried mass was powdered and sieved through 40-mesh sieve. Complex was evaluated for drug loading efficiency.

Evaluation of DRC :[12]

Effect of drug-resin ratio on complex formation

Ratio of the resin to drug can greatly impact the complex formation and ultimately affects the taste masking ability. It was necessary to find out the optimum drug to resin ratio. In each case drug resin complexes (DRC) of Ciprofloxacin and Kyron T 114 were prepared in 1:1, 1:2 and 1:3 ratios.

Drug loading efficiency for DRC

DRC equivalent to 100 mg of Ciprofloxacin was weighed accurately and was transferred into 100 ml of volumetric flask. 100 ml of 0.1 N HCl was added to this volumetric flask and was stirred continuously for 1 hour on a magnetic stirrer. After stirring, this solution was filtered through whattman filter paper. Filtered sample solution was suitably diluted with 0.1 N HCl and the amount of drug dissolved were determined by UV spectrophotometer, by measuring the absorbance of the sample at 276 nm.

Differential Scanning Calorimetry

Differential scanning calorimetry (DSC) thermo grams of the Ciprofloxacin, Resins and drug resin complexes were recorded on NETZSCH DSC 204 (Germany). Samples (2-7 mg) were sealed into aluminum pans and scanned at a heating rate of 10°C/min over a temperature range of 20-360°C under a nitrogen gas stream.

Fourier Transform Infrared (FT-IR) Studies

FT-IR spectra of Ciprofloxacin, Resins and drug resin complexes were recorded in the range of 400 to 4,000 cm−1 using a FTIR spectrophotometer (Bruker, Germany) by the KBr disc method.

Dissolution profiles of Ciprofloxacin- Resin complex in 0.1 N HCl

The dissolution rate of Ciprofloxacin from its DRC (1:3 ratio) was performed by using DISSO 2000, Lab India 8-Station Dissolution Rate Test Apparatus with a paddle stirrer (USP type II) at 50 rpm. 900 ml of 0.1 N HCl was used as dissolution medium which was maintained at 37±0.5ºC. DRC equivalent to 100 mg of Ciprofloxacin was transferred to the each dissolution vessel. Aliquots of dissolution medium (5 ml) were withdrawn through 0.45 µ nylon disc filter at different time intervals of 5, 10, 15, 20, 25, and 30 minutes. The sample of dissolution fluid withdrawn at each time was replaced with fresh dissolution fluid. Filtered sample solution was suitably diluted with 0.1 N HCl and the amount of drug dissolved were determined by UV spectrophotometer, by measuring the absorbance of the sample at 276 nm.

Formulation of Syrup

DRC (422 mg) equivalent to 100 mg of Ciprofloxacin and other ingredients were passed through 60-mesh sieve and collected individually. According to the formula given in Table 1, all ingredients were accurately weighed and blended homogeneously. This homogeneous dry syrup was filled in to an amber colored bottle and stored in a dry place at room temperature.

Table 1: Formulation of Ciprofloxacin Kyron T 114 Dry Syrup

Ingredients/ 5 ml	Formulation			
	CRDS02 (mg)	CRDS03 (mg)	CRDS04 (mg)	CRDS05 (mg)
DRC	422	422	422	422
Sodium citrate	72	70	74	74
Citric Acid	72	70	74	74
Lutrol F 68	30	30	30	30
Sorbitol	2200	---	---	---
Erythroitol	---	2200	2200	2200
Aspartame	---	55	65	65
Sodium benzoate	0.4	0.4	0.4	0.4
Xanthan gum	150	120	100	---
Sodium CMC	---	---	---	100
Orange flavour	qs	qs	qs	qs

Evaluation of dry syrup[13]

Sedimentation volume (%)

The sedimentation volume was determined by keeping reconstituted dry syrup in 100 ml of measuring cylinder and kept aside for 7 days without any disturbance at room temperature. The separation of clear liquid was noticed on 1st and 7th day. The sedimentation volume (F %) was calculated using the formula F%=100Vu/Vo, where Vu is the volume of sediment and Vo is the original height of the sample.

pH and specific gravity measurements

Change in pH of the reconstituted syrup was measured using a digital pH meter on 1st and 7th day at 25ºC.

The specific gravity of the reconstituted syrup was determined on 1st and 7th day in a specific gravity bottle at 25ºC by using following formula.

Specific gravity = weight of the liquid syrup formulation/weight of an equal volume of water.

Drug content determination from reconstituted syrup

Reconstituted dry syrup equivalent to 100 mg of Ciprofloxacin was measured accurately and was transferred into 100 ml of volumetric flask. 100 ml of 0.1 N HCl was added to this volumetric flask and was stirred continuously for 1 hour on a magnetic stirrer. After stirring, this solution was filtered through whattman filter paper. Filtered sample solution was suitably diluted with 0.1 N HCl and the amount of drug dissolved was determined by UV spectrophotometer, by measuring the absorbance of the sample at 276 nm.

In vitro dissolution studies

An in vitro dissolution rate of Ciprofloxacin from its reconstituted syrup on 1st and 7th day was performed by using DISSO 2000, Lab India 8-Station Dissolution Rate Test Apparatus with a paddle stirrer (USP type II) at 50 rpm. 900 ml of 0.1 N HCl was used as dissolution medium which was maintained at 37±0.5ºC. The reconstituted syrup equivalent to 100 mg of Ciprofloxacin was transferred to each dissolution vessel. Aliquots of dissolution medium (5 ml) were withdrawn through 0.45 µ nylon disc filter at different time intervals of 5, 10, 15, 20, 25 and 30 minutes. The sample of dissolution fluid withdrawn at each time was replaced with fresh dissolution fluid. Filtered sample solution was suitably diluted with 0.1 N HCl and the amount of drug dissolved was determined by UV spectrophotometer by measuring the absorbance of the sample at 276 nm.

RESULTS AND DISCUSSION

Standard Graph of Ciprofloxacin HCl

Table 2: Standard graph of Ciprofloxacin HCl in 0.1N HCl

Concentration (µg/ml)	Absorbance
1	0.085
2	0.181
3	0.280
4	0.363
5	0.463

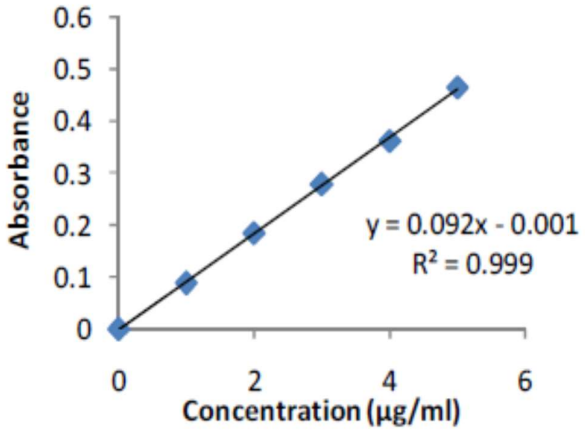

Fig. 1: Calibration curve of CiprofloxacinHCl in 0.1 N HCl

Evaluation of Ciprofloxacin HCl- Kyron T114 Complex

Effect of drug-resin ratio on complex formation

Table 3: Effect of Drug Resin Ratio on complex formation

Drug-resin ratio	Time (hrs)	Percent ciprofloxacin HCl loading
1:1	3	70.31
1:2		87.46
1:3		96.25

Table 4.0: Drug loading efficiency forDrug – Kyron T114 complex

Drug resin ratio	Time (hrs)	Percent Ciprofloxacin HCl Loading
1:3	3	96.25

Differential Scanning Calorimetry

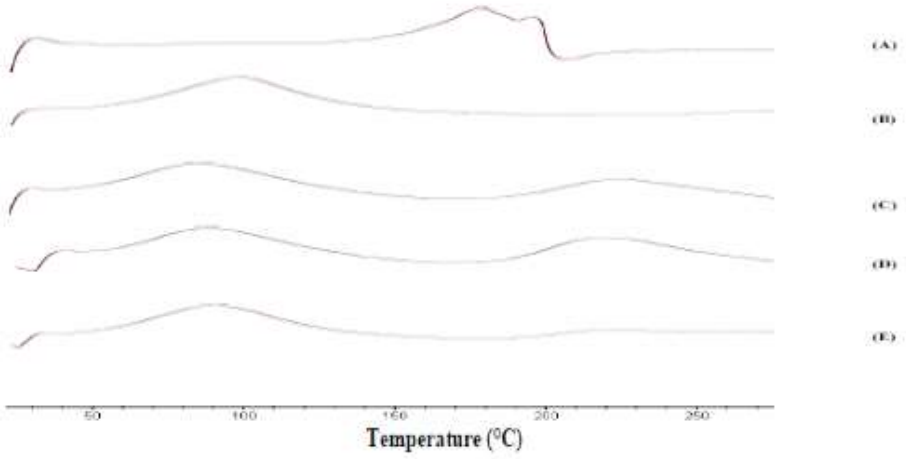

Fig. 2: DSC Thermograms of (A) Ciprofloxacin, (B) Kyron T114, (C) Cipro- KyronT114 (1:1), (D) Cipro- KyronT114 (1:2), (E) Cipro- KyronT114 (1:3)

Table 5.0:DSC Studies of ciprofloxacin HCl – Kyron T114 complex systems

Product	DSC (°C)	
	T_{peak} (°C)	ΔH_{fusion} (J/g)
Ciprofloxacin HCl	152.1	162.9
C-I 114 (1:1)	219.6	133.7
C-I 114 (1:2)	210.9	129.7
C-I 114 (1:3)	220.6	22.9

Fourier Transform Infrared (FT-IR) Studies

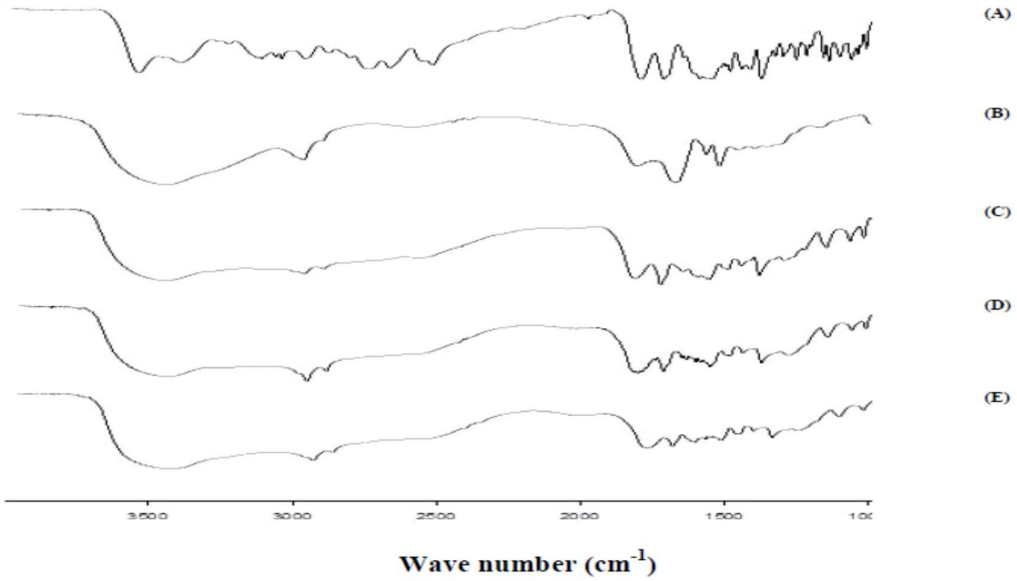

Fig. 3: FTIR Spectras of (A) Ciprofloxacin, (B) Kyron T114, (C) Cipro- KyronT114 (1:1), (D) Cipro- KyronT114 (1:2), (E) Cipro- KyronT114 (1:3)

Table 6.0: Dissolution profiles of Ciprofloxacin – Kyron T114 complex in 0.1 N HCl

Time (min)	% Ciprofloxacin dissolved
0	0
5	70.05
10	78.45
15	84.67
20	92.59
25	96.45
30	99.12

Evaluation of Syrup of Ciprofloxacin – Kyron T114 Complex

Table 7.0: Evaluation of physical properties of dry syrups

Formulation	Sedimentation volume (%)		pH of the formulation		Specific gravity		Drug content (%)	
	Day- 1	Day- 7	Day- 1	Day- 7	Day- 1	Day- 7	Day- 1	Day- 7
CRDSO2	99.4	99.4	4.50	4.32	1.15	1.17	96.03	95.34
CRDSO3	91.8	90.3	4.48	4.53	1.14	1.16	97.74	96.23
CRDSO4	79.5	77.8	4.42	4.52	1.13	1.15	98.67	97.31

CRDSO5	71.2	66.7	5.54	5.52	1.13	1.16	98.82	97.32

Table 8.0: Dissolution studies of Ciprofloxacin Dry syrups on day 1

Time (min)	Cumulative % of drug release			
	CRDS02	CRDS03	CRDS04	CRDS05
0	0	0	0	0
5	74.13	78.43	82.56	83.04
10	78.42	86.32	90.05	90.89
15	86.85	93.13	97.18	98.32
20	93.29	97.71	99.39	99.64
25	97.65	99.23	---	---
30	99.12	---	---	---

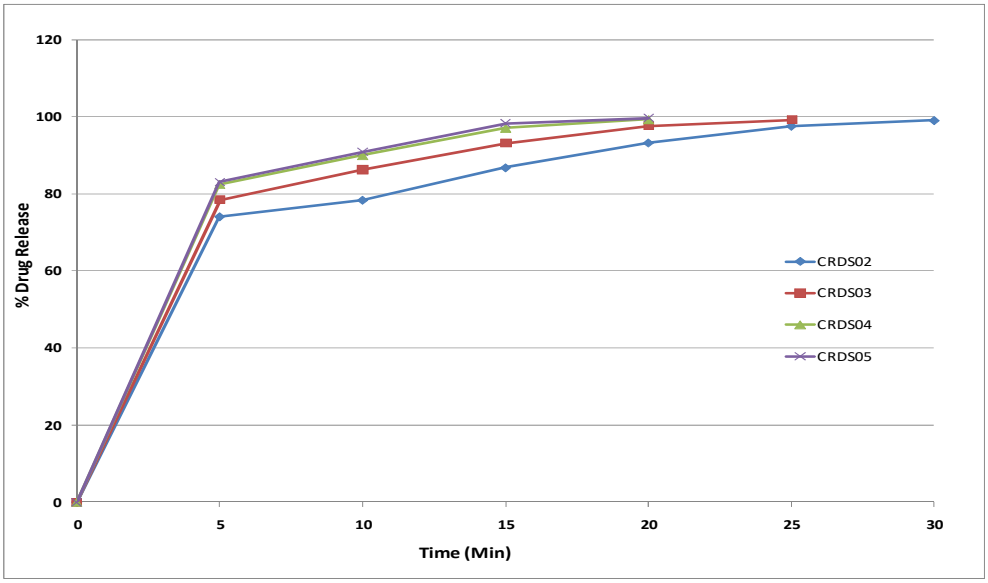

Fig.4: Dissolution studies of Ciprofloxacin Dry syrups on day 1

Table 9.0: Dissolution studies of Ciprofloxacin dry syrups on day 7

Time (min)	Cumulative % of drug release			
	CRDS02	CRDS03	CRDS04	CRDS05
0	0	0	0	0
5	73.05	76.247	80.41	81.75
10	77.34	84.75	87.87	88.96
15	84.78	91.39	95.45	96.58
20	91.63	96.17	97.43	97.64
25	95.08	97.06	---	---
30	97.04	---	---	---

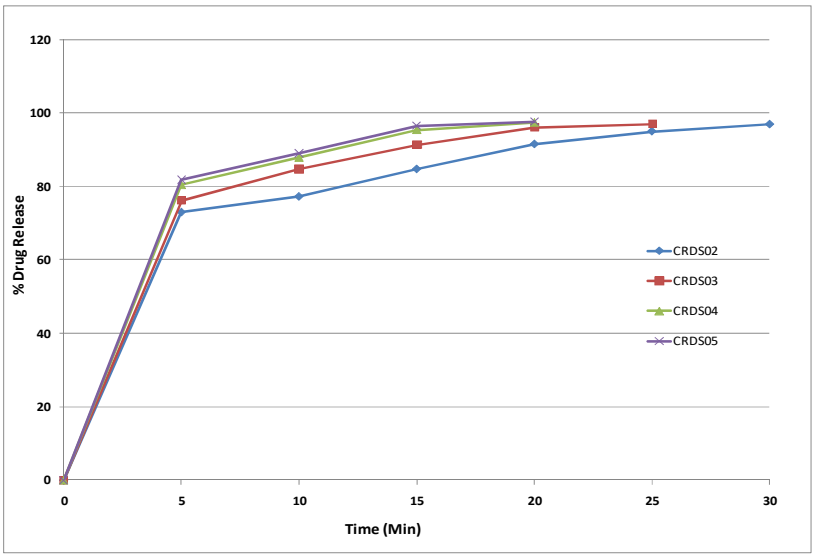

Fig.5: Dissolution studies of Ciprofloxacin dry syrups on day 7

There was no significant loss of drug during the preparation of drug resin complexes in 1:3 ratio when compared to other proportions. Hence 1:3 ratio was used for further studies.

The dissolution rate of Ciprofloxacin from DRC complex system (1:3) was studied using 0.1 N HCl as the dissolution fluid.

The correlation coefficient (r) value is greater than 0.910 indicating that the dissolution of Ciprofloxacin from Ciprofloxacin– Kyron T 114 complex obeyed first order dissolution kinetics.

Various concentrations of suspending agents were added to formulations CRDS02 to CRDS05. After reconstitution, each dry syrup formulation was evaluated for sedimentation volume, pH, specific gravity and drug content on day 1 & day 7. Results are shown in Table 7. Percentage sedimentation volume was found to be between 71.2 to 99.4 on day 1and 66.7 to 99.4 on day 7. Each sample of the formulation had good visual appearance and high sedimentation volume, which indicates that the DRC formed flocs.

There was no drastic change in the pH of reconstituted dry syrup from day 1 to day 7. The pH of the formulation greatly influences the drug release which in turns affects the bitterness of the syrup. All the formulations had the pH of above 4.42 to below 5.54 and 4.32 to 5.52 on day 1 and day 7 respectively. Specific gravity of the reconstituted syrup was found to be in the range of 1.13 to 1.15 & 1.15 to 1.17 on day 1 and day 7 respectively. It influences the degree of sedimentations. As the density of the syrup is high the rate of settlement of particles will tends to low. The percentage drug content of reconstituted syrup was found to be between 96.03 to 98.82 & 95.34 to 97.32 of ciprofloxacin HCl on day 1 and day 7 respectively, which were within the acceptable limits.

All the release profiles showed two different phases of drug release. An initial rapid release phase is followed by a slower release phase. These results could be attributed to the general phenomenon of particle size reduction during dissolution process

CONCLUSION

Complexation of ciprofloxacin HCl with ion exchange resin is a simple and efficient technique for masking the bitterness of the drug.

Ciprofloxacin drug is highly bitter in taste. Thus, from the study we can mask the unpleasant taste of the drug i.e. Ciprofloxacin for paediatric patients and this enhances the palatability of the formulation.

The present investigation was undertaken with an overall objective of studying the drug resin complexation (DRC) to mask the bitter taste of the drug. The resin, namely, Kyron T114 was selected for the study of feasibility of employing drug resin complexation for masking the bitter taste of drug.

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