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FORMULATION, DEVELOPMENT AND EVALUATION OF ORAL RECONSTITUTABLE DRY SYRUP.

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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 (Indion 234) for taste masking and formulate oral reconstituable dry syrup of DRC. DRC was evaluated for effect of variables like drug resin ratio, pH, temperature, soaking time of resin and stirring time reconstituable dry syrup was prepared by using xanthan gum and microcrystalline cellulose as suspending agent formulated recostituable dry syrup was evaluated for before reconstitution parameters like flow properties, particle size and drug content and after reconstitution parameter like sedimentation rate redispercibility particle size, viscosity, pH and drug content. Formulated ciprofloxacin reconstituable dry syrup has acceptable sedimentation properties. In evaluating period of 14 days no significant change was observed in pH, viscosity, particle size and drug content.From the results it concluded that effective taste masking of ciprofloxacin was achieve using indion 234 and successfully evaluated in reconstituable dry syrup.

Key Words: *Sedimentation rate, Ion exchange resin, Stability, Ciprofloxacin, Indion 234, Acacia, Tragacanth, Sodium carboxy methyl cellulose.*

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INTRODUCTION:

A number of patients, especially pediatric and geriatric patients, have difficulty in swallowing solid dosage forms hence liquid dosage forms are needed**1**. So drugs which are slightly soluble in water hence formulation of a suspension will be most suitable but product may not be physically and chemically stable. in the present work, attention is paid to develop a Reconstitutable suspension dosage form as dry syrup [1,2]. Dry syrups are commercial dry mixtures that require the addition of water at the time of dispensing. The dry syrup is prepared commercially using drug, colorants, flavors, sweeteners, stabilizing agents and preserving agents that may be need to enhance the stability of the formulation. A number of official and commercial preparations are available as dry powder mixtures or granules that are intended to be suspended in water or some other vehicle prior to oral administration [1-3]. Most of the drugs prepared as a dry suspension for oral suspension are antibiotics. The dry mix of oral suspension is prepared commercially to contain the drug, colorants, flavors, sweeteners, stabilizing agents, suspending agents and preserving agents that may be need to enhance the stability of the formulation. The granules in the sachets must be taken as a suspension in a glass containing prescribed amount of ingestible liquid, mostly water. Although studies have demonstrated that the dry oral suspension after constitution in a liquid is stable for 24 hours after preparation, it is recommended that the suspension should be consumed immediately after preparation [4,5]. Taste is one of the most important parameters governing patient compliance. Undesirable taste is one of several important formulation problems that are encountered with certain drugs [8]. 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 [9-12].

MATERIALS AND METHODS:

Following drug substance, resin, excipients and chemicals were used for the formulation and evaluation studies. Ciprofloxacin, Indion 234, Acacia, Tragacanth, Sodium carboxy methyl cellulose, Mannitol, Magnesium Stearate, Sodium Benzoate, Sucrose, Acetone

Process Development

a) Powder blends
b) Granulated products
c) Combination products

a) Powder blends: Powder blends sometimes called powder mixtures are prepared by mixing the excipients of the dry mixture in powder form. Excipients present in small quantities may require a two stage mixing operation. Such excipients can be mixed with a portion of a major excipient to aid in their dispersion. For example, milled sucrose provides a large surface area for the adsorption of the small quantities of flavor oils. The second stage comprises the mixing of the remaining excipients. The selection of the appropriate mixer involves several considerations, the most significant of which is that the mixer should rapidly and reliably produce a homogenous mixture.

b) Granulated products: All the excipients in granulated products are processed by granulation.Wet granulation is the usual process and the granulating fluid is water or an aqueous binder solution. There are two methods of incorporating the drug. The drug can be dry blended with the other excipients or it can be dissolved or suspended in the granulating fluid. Wet granulation usually consists of the following steps. The solid excipients are blended and massed with the granulating fluid in a planetary mixer. The wet mass is formed into granules in one of the following before drying: vibratory sieve, oscillating granulator, grater or mill. For drugs subject to hydrolysis, non aqueous granulating fluids can be used. Most often wet massing and screening is used. The formed granules are dried in a tray oven or fluid bed drier. The dried granules are then screened in a vibratory sieve or oscillating granulator to break up or remove aggregates of granules.

c) Combination product: Powdered and granulated excipients can be combined to overcome some disadvantages of granulated products. Less energy and equipment for granulation may be required if the majority of the diluents can be added after granulation. Also heat sensitive excipients such as flavors can be added after drying of the granulation to avoid exposure to elevated temperatures. The general method is first to granulate some of the excipients , then blend the remaining excipients with the dried granules before filling the container. The presence of the diluents helps to improve flow and reduces both segregation and dust formation.

Formulation of dry syrup using drug- resin complex:

The oral reconstitutable suspension of Ciprofloxacin was prepared from the optimized DRC (drug resin ratio 1:3). The formula is presented in Table 1. All the ingredients for suspension were passed through mesh no. 40 to make uniform particle size dispersion. The DRC equivalent to 250 mg was mixed with the excipients. The prepared suspension was evaluated for before and after reconstitution parameters.

Table 1: Formulation of dry syrup using drug- resin complex

Ingredients	F3 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)
Ciprofloxacin	250	-	-	-	-	-	-	-
DRC equivalent To dose	-	250	250	250	250	250	250	250
Acacia	3	1.5	-	-	3	1.5	-	-
Tragacanth	1.5	0.75	1.5	0.75	1.5	0.75	1.5	0.75
Sodium Carboxy Methyl Cellulose	-	-	1.8	0.9	-	-	1.8	0.9
Mannitol	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Magnesium Stearate	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Sodium benzoate	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06
Sucrose	13.74	15.99	14.94	16.59	14.04	16.29	15.24	16.89
Orange flavor	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Acetone	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Purified water q.s.	30	30	30	30	30	30	30	30
Total	271	271	271	271	271	271	271	271

RESULT AND DISCUSSION:

IR Study of Ciprofloxacin:

Ciprofloxacin was identified by FT-IR study and the prominent peaks are obtained at 3335.394 cm-1(O-H stretching), 1700.643 cm-1 (C=O stretching), 1023.647 cm-1 (C-F stretching)

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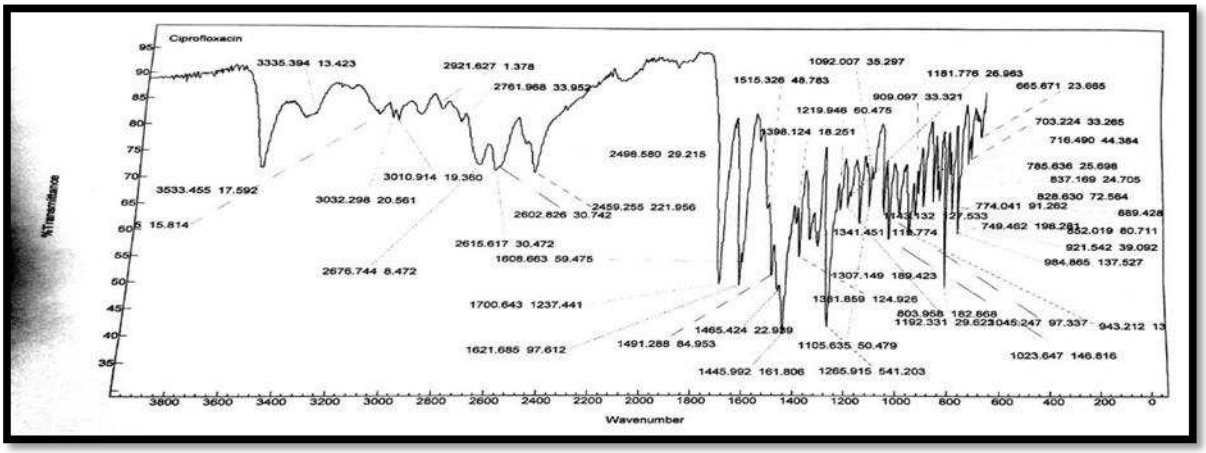

Fig.1: IR of Ciprofloxacin

Table 2:Tabular values of IR spectrum of Indion 234 complex

Sr no.	IR Peak cm^{-1}	Groups
1	3629	OH Stretch
2	3046	Aliphatic CH Stretch
3	1686	C=O

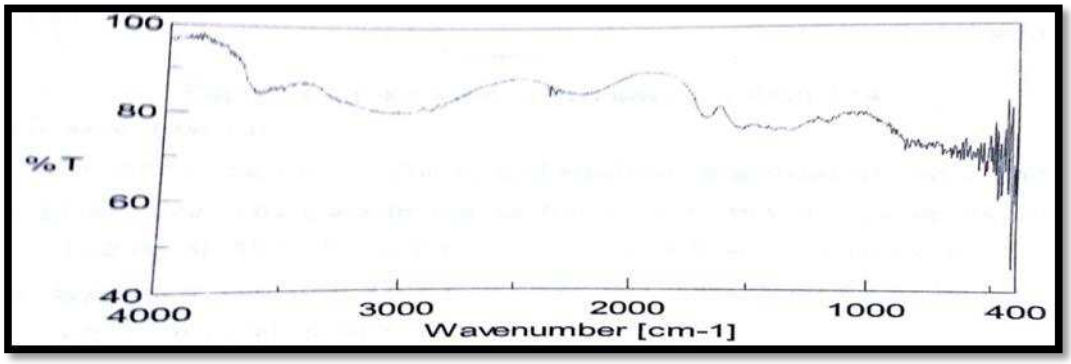

Fig.2: Infrared Specrum of Indion 234

Table 3: Tabular values of IR spectrum of Ciprofloxacin-Indion 234 complex

Sr no.	IR Peak cm^{-1}	Groups
1	1710	C=O
2	1368	C-N
3	2857	C-H Alkane Stretch
4	1439	C-H Alkanes Bend

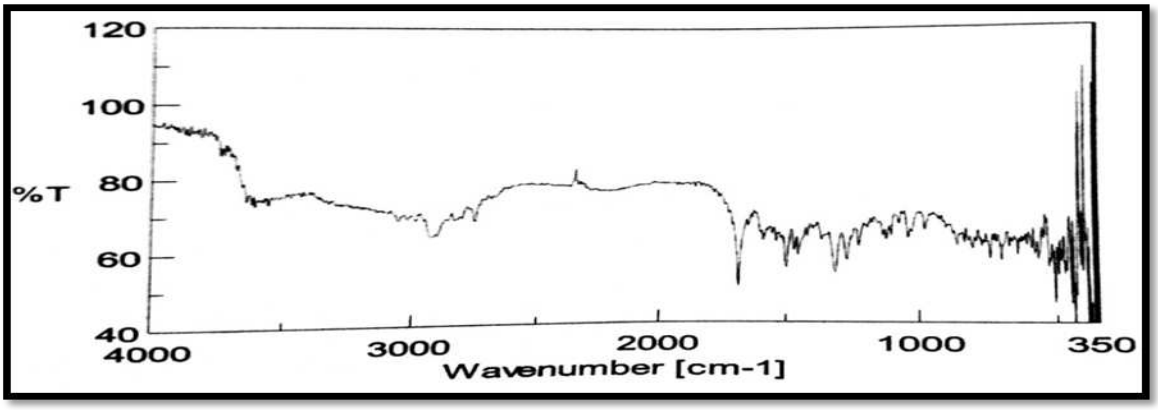

Fig.3: IR of Drug Resin Complex

Construction of Calibration curve by UV spectrometer:

Calibration curve of Ciprofloxacin by UV spectrophotometer was prepared in 0.1 N HCI at λmax 279nm.

Calibration curve of Ciprofloxacin in 0.1 N HCL:

Table 4: Construction of Calibration curve of Ciprofloxacin in 0.1N HCI

Sr no.	Concentration (µg/ml)	Absorbance	Standard Deviation
	0	0	0
1	5	0.2034	±0.0034
2	10	0.3258	±0.0070
3	15	0.4479	±0.0079
4	20	0.5648	±0.0018
5	25	0.7753	±0.0016

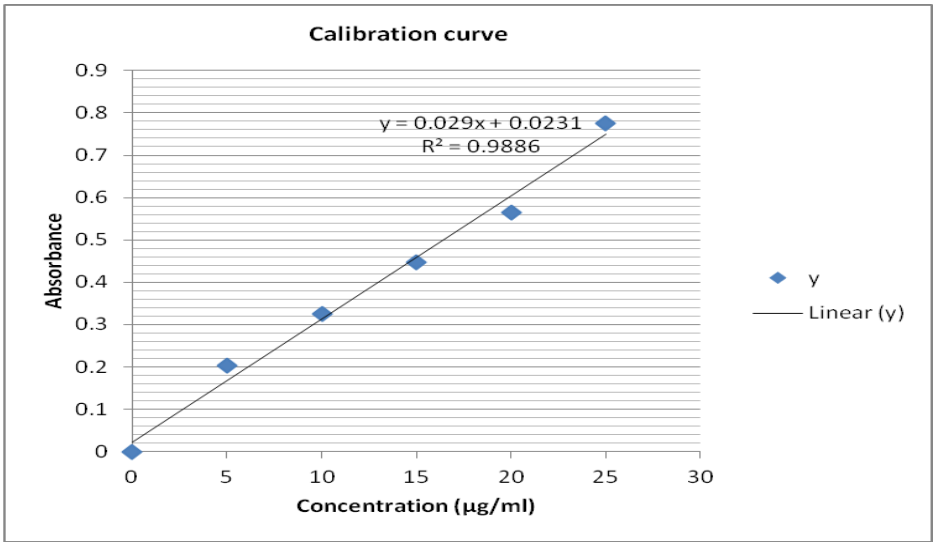

Fig.4: Effect of Swelling of Resin on Drug Loading

The effect of resin swelling on amount of drug loading was determined. The swelling time was optimized by carrying out loading of Ciprofloxacin in five different batches separately, where Indion 234 was allowed to swell for 10, 30, 60, and 120 min results were sown in table 5.

Optimizing Drug loading of stirring time:

The ion exchange process is an equilibrium reaction and the rate, where the exchange between the counter ions in the resin and ions in the solution occurs in stoichiometry. Therefore, it was essential to know the time required for equilibration. For the purpose drug resin complex was prepared for different time periods, where the complex was on a magnetic stirrer and the percent drug loading obtained at different time was calculated. Maximum drug loading occurs in 30 min stirring results were sown in table 6.

Table 5: Effect of Indion 234 swelling on drug loading

Sr No.	State of Indion 234	Percent drug loading
1	Unswollen resin	77.22±0.51
2	10 min swelling	85.76±0.47
3	30 min swelling	96.98±0.72
4	60 min swelling	97.17±0.39
5	120 min swelling	97.54±0.78

Table 6: Effect of stirring time on drug loading

Sr No.	Stirring time (in min)	Percent drug loading
1	5	50.20%
2	10	56.25%
3	15	71.27%
4	20	93.53%
5	30	95.50%
6	240	95.63%

Table 7: Determination of Percentage bound drug from drug resin complex of Ciprofloxacin

Sr no.	Drug resin complex	Percentage bound drug
1	DRC(1:1)	92.34% ± 0.98%
2	DRC(1:2)	96.26% ± 0.88%,
3	DRC(1:3)	96.50% ± 1.10%
4	DRC(1:4)	97.26% ± 0.88%

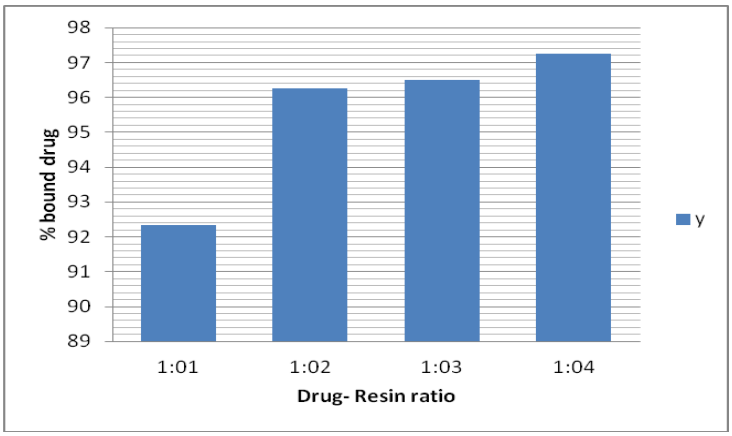

Fig.5: Percentage bound drug

Evaluation of taste masked oral reconstitutable system:

Table 8: Evaluation data on flow properties of Taste masked powder mixture of various formulations

Formulation	Bulk density(gm/ml)	Tap density(gm/ml)	Angle of repose(º)
F1	0.4875	0.5623	27.12
F2	0.523	0.5806	27.56
F3	0.505	0.5802	28.09
F4	0.4879	0.5658	27.68
F5	0.4789	0.5610	28.02
F6	0.536	0.5695	28.01
F7	0.526	0.5693	28.10
F8	0.489	0.5804	26.23

Formulation F1 was prepared without resin, which may provide clear distinction between actual taste of drug before masking and taste after masking by making complex with resin with different ratios.

Formulation F1 and the taste masked powder mixture of all the formulations F2-F8 were tested by various studies including bulk density(ranging from 0.48 to 0.50 gm/ml), tap density (ranging from 0.5610 to 5806 gm/ml) & angle of repose (ranging from 26.23º to 28.10º). All the results showed good flow properties.

Table 9: Evaluation of taste masked oral reconstitutable suspension

Formulation	Average particle size	Viscocity (cps)	Flowrate (ml/s)	pH	Redispersibility (no.of strokes)	Sedimentation Volume	
						F	β
F1	20.5	600±0.12	0.55	5..3	10	0.1	1
F2	22.5	553±0.11	0.52	5.2	10	0.2	1
F3	21.8	502±0.10	0.52	5..3	10	0.2	1
F4	22.3	412±0.15	0.55	5.2	10	0.1	1
F5	21.3	500±0.24	0.52	5..3	10	0.2	1
F6	23.0	400±0.12	0.55	5.2	10	0.1	1
F7	21.1	600±0.02	0.55	5..3	10	0.2	1
F8	22.3	505±0.14	0.55	5.3	10	0.2	1

Drug content Uniformity

Table 10: Drug content Uniformity Test

Formulation	% Drug Content
	Ciprofloxacin(λmax 279nm)
F1	98%
F2	92%
F3	87%
F4	90%
F5	91%
F6	92%
F7	90%
F8	97%

The result showed that the sedimentation volume was good for all the formulations. Between flocculated and deflocculated systems, the flocculated systems are considered to be most preferable one. The results showed that the average particle size of taste masked of the reconstituted dry syrup was from (20.5 to 23.0) , viscocity of the taste masked reconstituted dry syrup was from (412 to 600 cps). The flow rate taste masked of the reconstituted dry syrup was from (0.52-0.55 ml/s) for all the formulations. The pH of all the formulations was in the range (5.2 to 5.3). Thus this pH is acidic. The results obtained for drug content uniformity test showed that the drug content in all formulation was in the range of (92.41 to 99.79).

***In-vitro* drug release study:**

The study was carried out in 0.1 N HCI using USP II apparatus at 100 rpm. The formulation showed 95% drug release within 35 min. The drug resin complex was stable in salivary pH for a period of administration. It also shows that the resin does not retard the release of drug from suspension results were sown in table11.

***In-vitro* drug release for Ciprofloxacin at λmax-279nm**

Table 11: Cumulative Percentage of drug released

Times in min.	F1	F2	F3	F4	F5	F6	F7	F8
5	27.00	22.00	22.02	21.00	20.02	20.00	21.00	20.02
10	35.00	33.01	35.03	28.10	32.09	30.20	32.00	28.00
15	50.05	44.03	47.05	45.03	46.05	48.05	43.05	48.03
20	57.67	54.61	57.63	53.64	54.63	55.67	54.67	55.67
25	69.43	64.42	66.45	65.45	63.45	65.45	66.45	63.45
30	80.84	79.84	80.84	78.84	80.84	79.84	80.82	80.80
35	99.79	93.42	93.42	92.40	92.42	92.41	95.43	96.82

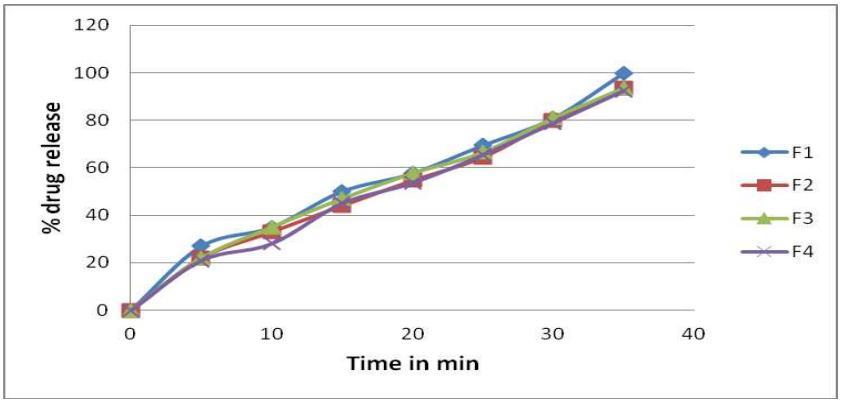

Fig.6: Drug release profile of Formulation F1-F4 in 0.1N HCI

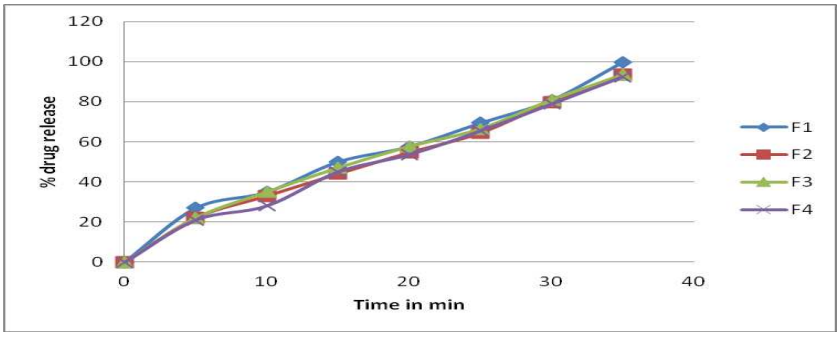

Fig.7: Drug release profile of formulation F5-F8 in 0.1N HCI

Stability study of formulation F8

The accelerated stability study did not show any significant drug loss or changes in the viscosity , pH, sedimentation ratio and resuspendability of the taste masked suspension of resinate.

Suspension of F8 was kept for accelarated study at 40±2°c and 75± RH for 15 days. The taste masking oral reconstituted suspension evaluated after reconstitution 7th and 15th day of reconstitution. The samples were observed for any change in physical parameters results were sown in table 12.

Table 12: Evaluation Parameter after Stability study of ciprofloxacin F8 .

Formulation F8						
		Day 1	**Day 6**	**Day 12**	**Day 24**	**Day 36**
Sedimentation Rate	**F**	0.1	0.1	0.1	0.1	0.1
	β	1	0.8	0.7	0.6	0.5
Viscosity		505±0.14	486±0.15	440±0.11	412±0.12	350±0.15
Colour		Pale yellow	Pale yellow	Pale yellow	Pale yellow	Pale yellow
Taste		Palatable	Palatable	Palatable	Palatable	Palatable
pH		5.3	5.2	5.0	4.9	4.5
% Drug Release		96.21				
% Drug Content		97.00				
Assay of Ciprofloxacin		99.97				

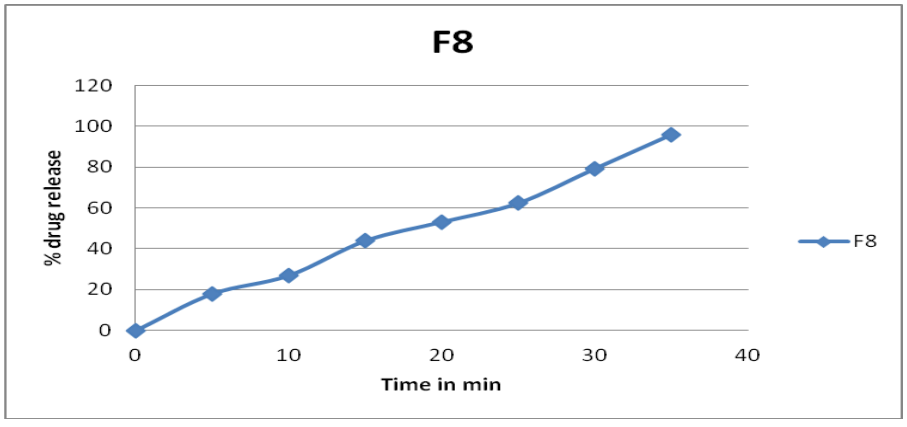

Fig.8: Drug release after Stability study of ciprofloxacin F8 .

CONCLUSION:

Thus, from the study we can conclude that the objective to mask the unpleasant taste of the drug i.e. Ciprofloxacin for paediatric patients is achieved which enhances the palatability of the formulation. Also, by giving the drug the dry syrup form the stability problem of the drug can also be resolved. Hence, the objective of the project work is achieved by the successful development of dry syrup of the drug Ciprofloxacin by using weak cation resin Indion 234 for the highly palatable pediatric formulation.

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