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Formulation and evaluation of dry syrup containing bitter drug

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ABSTRACT

Dosage forms are designed both for improving the physical and mechanical properties of materials, oral suspensions which requires mixing prior to administration is more acceptable and stable. They preferred when drug stability is a major concern. In present study solid dispersion technique was used for taste masking and dissolution enhancement. It has been defined as dispersion of one or more active ingredients in an inert carrier with solvent evaporation method used. In present study taste masking is most important phenomenon under study, as drug is bitter which is important issue for health care providers especially with paediatrics and geriatric patient. Taste masking generally achieved with solid dispersion technique. In which the taste of the final formulation were evaluated from human volunteers and grades were given according to the taste of the final formulation. The study concludes the dissolution enhanced as well as taste was masked of Cefpodoxime proxetil using Eudragit EPO and Stearic Acid Polymer in 1:1 ratio.

Keywords: Taste Masking, Dissolution Enhancement, Sensory Analysis, Solid Dispersion Technique, Cefpodoxime proxetil, Dry syrup.

INTRODUCTION

Drug are most important part which have to be developed in to an acceptable dosage form. Nearly 70 % preparation available in market are solid from composed of tablet, capsule and powder i.e. dry syrup, effervescent powder, powder for topical use, powder for injection etc. Oral route offer convenience and ease of administration, greater flexibility in dosage form design. These dosage forms are designed either for improving the physical and mechanical properties of materials during manufacture. The oral solutions and suspensions requires mixing prior to administration is more acceptable and stable. The reconstituted system is the formulation of choice when the drug stability is a major concern. After reconstitution, these systems have a short but acceptable life.

Oral administration of bitter drugs is important issue for health care providers especially with paediatrics and geriatric patient. The Factors which Affects Selection of Taste Masking Technology are Extent of Bitter Taste, Dose of Active Pharmaceuticals, Drug Particle Shape and Size Distribution, Dosage Forms, Drug Solubility, Ionic Characteristics of the Drug.

The methods of Taste Maskings are classified as below-
1. Sensory Approaches:
I. Using Flavoring and Sweetening Agents
II. Numbing of Taste Buds
2. Complexation and Adsorption:
I. Complexation with Ion Exchange Resins
II. Formation of Inclusion Complexes with β-Cyclodextrin Derivative
III. Wax Embedding of Drugs
3. Chemical Approaches:

I. Formation of Prodrug
II. Formation of Different Salts
4. Barrier Approaches:
I. Using Viscosity Modifier
II. Using Emulsions
III. Using Liposome
IV. Using Microspheres or Microcapsules

Other approaches in taste masking of the drug base on the formulation of the drug in the dosage form are as follows: Coating, Granulation, Sweeteners, Microencapsulation, Taste Suppressants and Potentiators, Solid Dispersions etc. while Solid dispersion is most efficient and commonly used due to its ease of formulation. It has been defined as dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by melting (fusion) solvent or melting solvent method.

The solid dispersion mostly formulated with Solvent evaporation method. In which both drug and carrier are dissolved inorganic solvent. After entire dissolution, the solvent is evaporated. The solid mass is ground, sieved and dried.

Evaluation of Taste Masking[1,2,3]

Ranking Test OR Panel Testing OR Sensory Analysis Taste evaluation was performed by tasting the samples on human volunteers. Classifying bitter taste into following five classes Very strong bitter taste, Strong bitter taste, Moderately bitter taste, Slightly bitter taste, No bitter taste.

MATERIALS AND METHODS

Materials

The Formulation Drug and Excipients used are Cefpodoxime Proxetil generous gift sample by Ozone International Ltd. Mumbai., Eudragit EPO gifted by Evonik Degussa India Pvt. Ltd. Mumbai., Methyl Cellulose by Ozone International Ltd. Mumbai., Ethyl Cellulose by Ozone International Ltd. Mumbai, β-cyclodextrin Jay Chem Marketing, Mumbai. Steric Acid by Ozone International Ltd. Mumbai.

Experimental

The **preformulation** studies were performed as follows,

Excipient compatibility study To study the compatibility of the excipients with drug by IR spectroscopy & DSC.

A. Fourier Transform Infrared Spectrophotometeric analysis (FTIR):

Infrared spectrum of Cefpodoxime proxetil, Eudragit EPO, Formulation of dry syrup and Cefpodoxime proxetil and Eudragit EPO complex were determined on Fourier Transform Infrared Spectrophotometer (IRAffinity-1S, Shimadzu) using KBr dispersion method. The spectra were scanned over a frequency range 4000- 400 cm^{-1}.

B. Differential scanning colorimetry (DSC):

The sample (2 mg) was analysed with DSC at a constant heating rate of 5˚C/min in atmosphere of nitrogen. The exact peak temperatures, melting point and heat of fusion, Glass transition temperature were determined. The temperature range for the scan was 30°C to 450°C for all the samples.

Determination of λ_{max}:

λmax determined of cefpodoxime proxetil with glycine buffer pH 3.0. The concentration to obtain 20 µg/ml with glycin buffer. The UV spectrum was recorded in the range 200-400 nm. The wavelength of maximum absorption (λ_{max}) was found from the scan using double beam (UV- 1601 Shimadzu) UV visible spectrophotometer.

Phase solubility Studies[4,5]

Solubility measurements were performed in triplicate using the method reported by Higuchi and Connors. In this excess amount of drug of about (100 mg) was added to 25 ml glycine buffer pH 3.0 containing increasing concentrations of the Polymer (i.e., 1%, 2%, 3%, 4%, 5%, 6% w/v). They were sealed and shaken at room temperature after filtered through whatman filter paper filtrate was suitably diluted and analyzed at UV-Visible spectrophotometrically (1601, Shimadzu, Japan) at specified wavelength.

Preparation of standard curve of Cefpodoxime Proxetil
Calibration curve was plotted with 3.0 pH glycine buffer at λ_{max} 233.0 nm using UV- visible spectrophotometer (Shimadzu). The serial dilution of 5, 10, 20, 30, 40µg/ml were prepared in buffer. The absorbance taken in triplicate its averages taken as values for standard calibration curve.

Taste masking by using ion exchange resins[6]
Pre-treatment of the resin:
The resin treated with deionised water and alcohol to remove the impurities. The resultant resin was dried and further used as excipient.
Preparation of Drug: Resin complex:

The drug-polymer complex was prepared with the help of phase solubility study. The polymers were used are Eudragit EPO, methyl cellulose, ethyl cellulose & β-cyclodextrin. The drug and polymer concentration in complex determined with the help of phase solubility study. The solid dispersion prepared with solvent evaporation method. The drug and polymer ratio fixed as 1:1 with that of phase solubility study for all polymers. The complex in which polymeric 1 part divided with stearic acid and polymer equally. Which further designed with a ratio that is 1:0.5, 1:1, 1:1.5 by keeping polymer concentration constant and stearic acid concentration varied. This blend dissolved in acetone with constant stirring and allow to evaporate on aluminium foil covered petri plate upto complete dryness. The dried powder complex was stored in air tight container.

Evaluation of complex
Pre-formulation studies of powder blend[7]:
The prepared powder blend was subjected to preformulation studies like angle of repose, bulk density, tapped density, carr's index and hausner ratio.

Drug content:
This was carried out to determine actual drug content per unit weight of the drug polymer complex (DPC). The specific weight of complex was evaluated with pH 3.0 glycine buffer. And analysed at 233.0 nm on UV Visible Spectrophotometer.

Development of Dry Syrup Formulation Blend: All the ingredients were accurately weighed. Accurately weighed complex sifted through #40 mesh with other excipients excluding flavour. Flavour was sifted separately. All mixtures were loaded for blending for 10 minute to ensure complete mixing. After mixing of all the ingredients were filled in to the HDPE bottle as primary storing container and sealed.

Formulation and preparation of Dry Syrup:

Batches of Dry Syrup Formulation

Batches Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Cefpodoximeproxetil	50	50	50	50	50	50	50	50	50	50	50	50
Eudragit EPO	25	25	25	_	_	_	_	_	_	_	_	_
Methyl cellulose	_	_	_	25	25	25		_	_	_	_	_
Ethyl cellulose	_	_	_	_	_	_	25	25	25	_	_	_
β-cyclodextrin	_	_	_	_	_	_	_	_	_	25	25	25
Steric acid	12.5	25	37.5	12.5	25	37.5	12.5	25	37.5	12.5	25	37.5
Sodium Benzoate	50	50	50	50	50	50	50	50	50	50	50	50
Sodium Saccharin	400	400	400	400	400	400	400	400	400	400	400	400
Xanthum gum	100	100	100	100	100	100	100	100	100	100	100	100
Aerosil	40	40	40	40	40	40	40	40	40	40	40	40
Talc	50	50	50	50	50	50	50	50	50	50	50	50
Flavor	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Lactose	450	450	450	450	450	450	450	450	450	450	450	450
Pharma Grade Sugar	900	900	900	900	900	900	900	900	900	900	900	900

Evaluation of Dry Syrup
In vitro dissolution studies[8]
Single dose of reconstituted syrup were studied for in vitro dissolution using USP type II dissolution testing apparatus. The media used were glycine buffer ph 3.0 (900ml) with speed 75 rpm and at 37±0.5^{0}C.duration of study was 60 min. absorbance was measured at 233 nm by UV spectrophotometer[57].

Sedimentation Volume (F)[9][9]

Sedimentation volume (F) is a ratio of the final or ultimate volume of sediment (Vu) to the original volume of sediment (Vo) before settling. It can be calculated by following equation.

F = V u / Vo---------- (1)

Where, Vu = final or ultimate volume of sediment
Vo = original volume of suspension before settling.

Taste Evaluation (Pannel method or sensory method)[10]

The optimized formulation and Cefpodoxime Proxetil were subjected to taste evaluation on human volunteers. Classifying bitter taste into following five classes. Class 5: Very strong bitter taste, Class 4:Strong bitter taste, Class 3: Moderately bitter taste, Class 2: Slightly bitter taste, Class 1:No bitter taste. The pure drug was used as a standard control with an average bitter taste of class 5.0. A written consent of the members of the panel was taken and were explained the procedure involved in testing the taste of complexes.

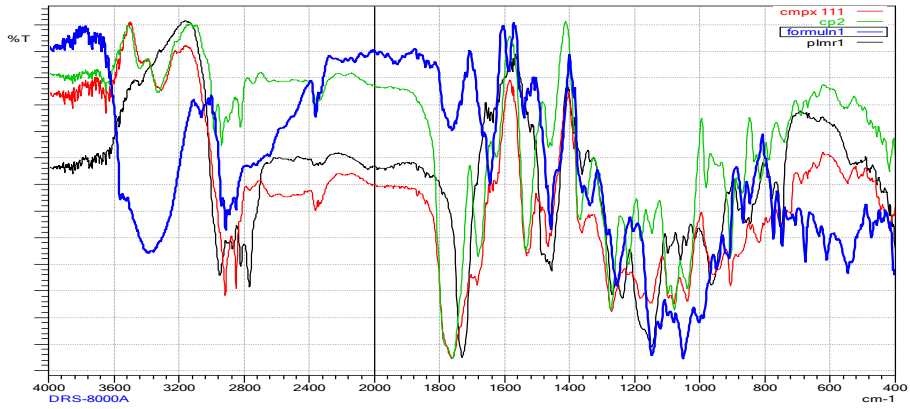
RESULTS AND DISCUSSION

Pre-formulation Studies:

Compatibility Study

9.2.1 Fourier Transform Infrared Spectrophotometeric analysis:

The IR absorption spectra of the Cefpodoxime Proxetil were taken in the range of 4000-400 cm^{-1} using DRS method with KBr as a background, The overlay graph of the Drug, Polymer, Complex, Formulation is as follows.

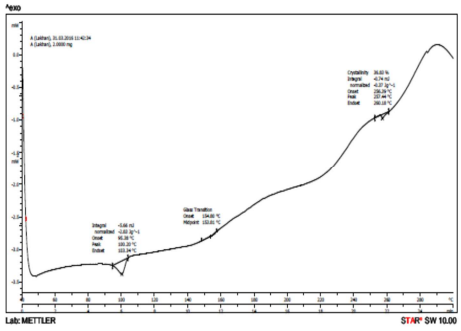


Overlay graph of IR spectrum

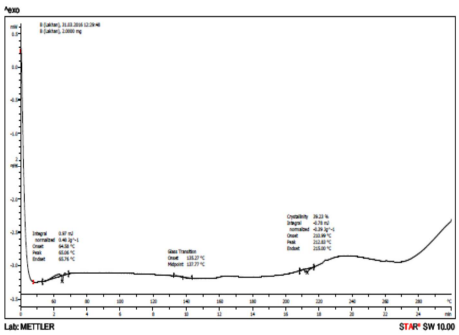
In Above overlay graph there can be observed there is no change in structure of the drug due to addition of the excipient and polymer .and remain stable after addition and no interaction between excipient with the drug was performed.

Differential scanning colorimetry:

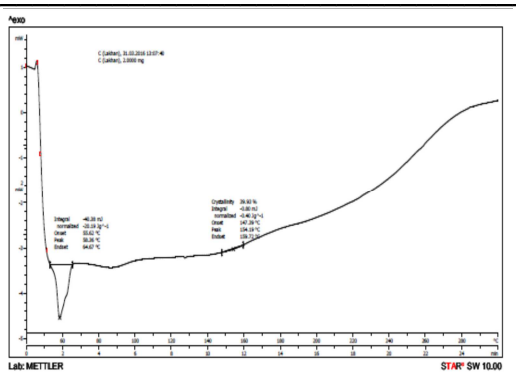
The thermograms of Cefpodoxime Proxetil, Eudragit EPO and Drug Polymer Complex are as follows



DSC Thermogram of Cefpodoxime Proxetil



DSC Thermogram of Eudragit EPO

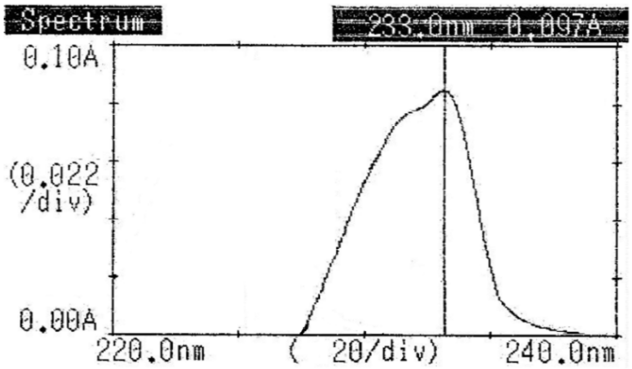


DSC Thermogram of Cepodoxime Proxetil and Eudragit EPO complex

from this study it was conclude that the drug is stable with polymer and not cause any structural change if temperature rises also the polymer forms a matrix in which drug is embedded hence can be suggest the drug is complexed in polymer matrix.

Determination of λ max:

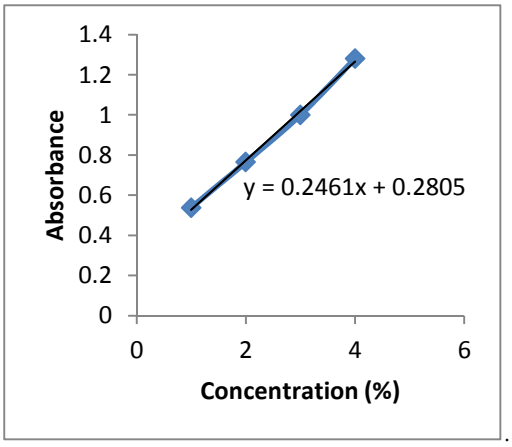
Absorption maxima (λ max) of Cefpodoxime Proxetil in glycine buffer pH3.0 were estimated in UV spectrophotometer was found to be 233.0 nm.



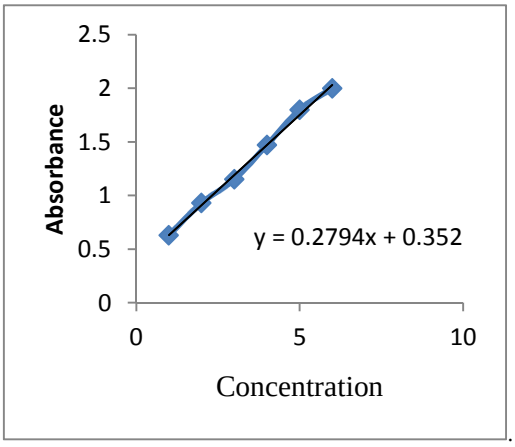
UV spectra of Cefpodoxime Proxetil

Phase solubility Studies

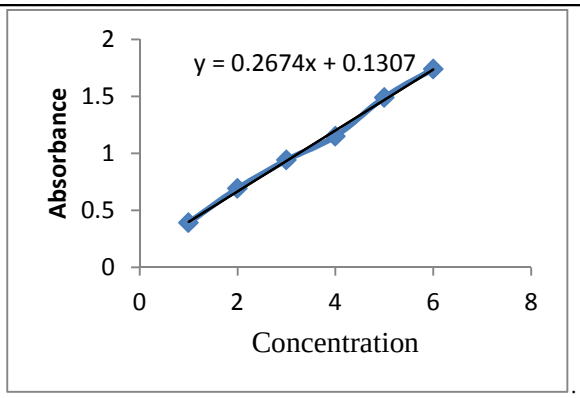
The phase solubility study of drug as follow



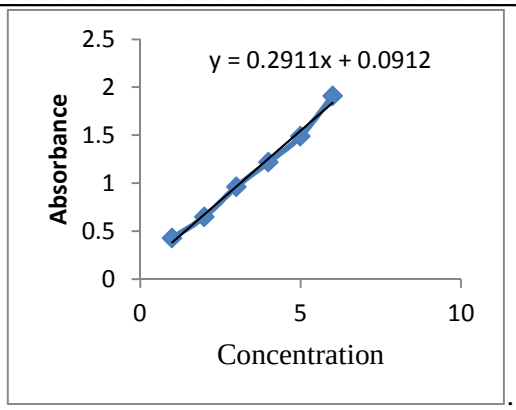
Phase Solubility Study of Eudragit EPO and Cefpodoxime Proxetil



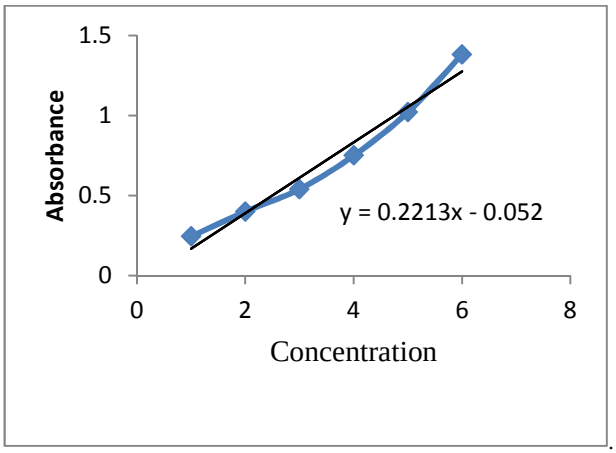
Phase Solubility Study of β- cyclodextrin and Cefpodoxime Proxetil



Phase Solubility Study of Ethyl Cellulose and Cefpodoxime Proxetil



Phase Solubility Study of Methyl Cellulose and Cefpodoxime Proxetil



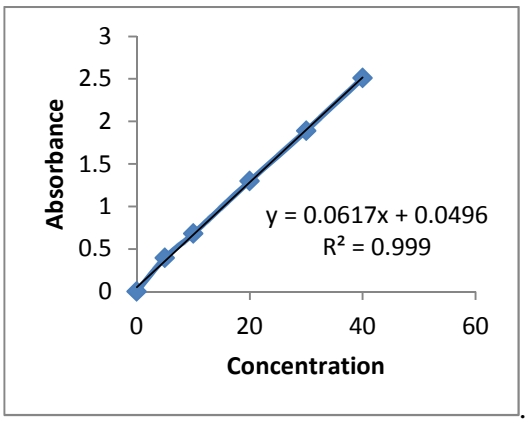
Phase Solubility Study of Steric Acid and Cefpodoxime Proxetil

Standard calibration curve of Cefpodoxime Proxetil:

Standard calibration curve of Cefpodoxime Proxetil were prepared in pH 3.0 glycine buffer were estimated in UV spectrophotometry.

Sr. No.	Concentration (µg/ml)	Absorbance
1	0	0
2	5	0.397
3	10	0.6806
4	20	1.2991
5	30	1.8903
6	40	2.5092

Standard calibration curve in 3.0 glycine buffer.



Calibration curve of Cefpodoxime Proxetil in 3.0 glycine buffer

Evaluation of API & Polymer complex

Pre-formulation study of powder blend

The evaluation of various powder blend was performed with regarding to bulk density, tapped density, Carr's index, Hausner's ratio and Angle of repose was performed for the prepared powder blend of all batches (F1-F12) and results were indicated. The results of all these tests were complied with specification in I.P. standards.

Evaluation of API and excipients blend

Formulations	Angle of repose ±SD* (degree)	Bulk density ±SD (gm/ml)*	Tapped density ±SD (gm/ml)*	Hausner's ratio	Carr's index (%)
F1	28.95±1.5	0.46±0.21	0.54±0.11	1.17	14.81
F2	26.98±0.64	0.56±0.14	0.45±0.15	1.10	11.20
F3	30.18±0.094	0.52±0.28	0.66±0.18	1.26	12.11
F4	35.82±0.25	0.54±0.14	0.65±0.17	1.20	16.92
F5	29.09±0.32	0.42±0.33	0.49±0.14	1.16	14.28
F6	28.98±0.14	0.40±0.11	0.55±0.22	1.14	21.21
F7	37.21±0.54	0.46±0.015	0.57±0.02	1.23	19.29
F8	34.44±0.28	0.48±0.12	0.59±0.39	1.22	18.64
F9	33.24±0.41	0.51±0.26	0.64±0.46	1.25	20.31
F10	30.55±0.018	0.49±0.45	0.58±0.61	1.18	15.51
F11	32.22±1.25	0.61±0.33	0.52±1.35	1.23	22.30
F12	35.47±1.34	0.64±1.2	0.47±1.48	1.16	16.45

*****Mean±SD for n=3*

Drug content

The drug-polymer complexes prepared by solvent evaporation method in ratio of 1:0.5, 1:1 & 1:1.5 were subjected to content uniformity. The percent of drug present in each ratio. This indicated that, the drug contents are within limit of official compendia.

Evaluation of drug content

Resin	Resin to Drug Ratio	Drug content (%)
Eudragit EPO	1:0.5	89.57
	1:1	99.93
	1:1.5	97.54
β-cyclodextrin	1:0.5	87.22
	1:1	77.48
	1:1.5	88.78
Methyl cellulose	1:0.5	76.23
	1:1	96.35
	1:1.5	82.69
Ethyl cellulose	1:0.5	79.20
	1:1	93.87
	1:1.5	90.98

Evaluation of Dry Syrup

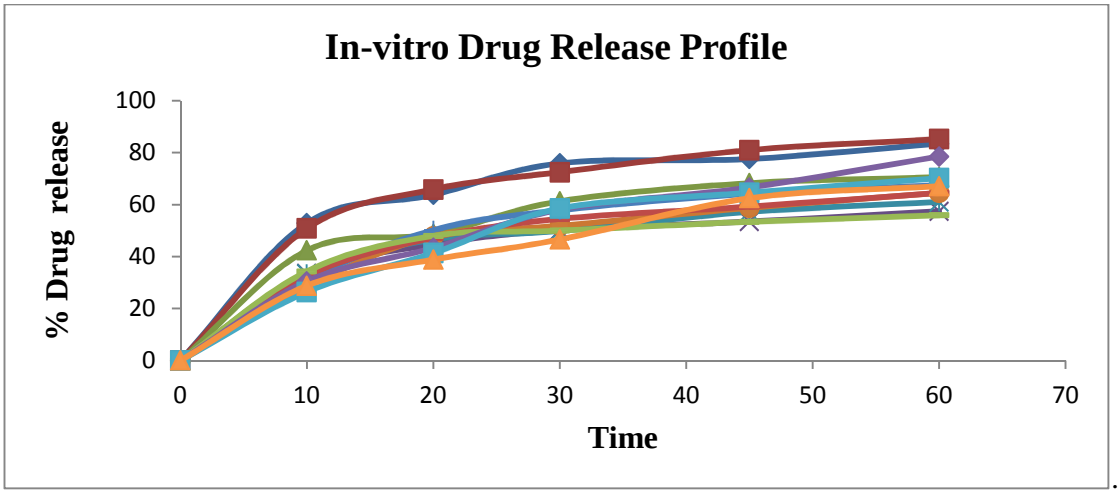
In vitro dissolution studies

Dissolution testing of each of the complex was carried out to observe the release pattern of the drug from the complex. Dissolution of drug was also carried out to compare with release pattern of the drug with the complex. The dissolution studies were carried out in glycine buffer pH3.0.

Cumulative % In-vitro Drug release profile of Formulation

Time min.	Cumulative % drug release											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
10	42.35± 0.14	50.85± 0.48	52.86± 1.09	28.63± 0.61	33.43± 0.05	33.47± 0.24	34.31± 0.41	32.43± 0.87	30.92± 0.09	28.78± 0.13	26.43± 1.07	30.48± 0.12
20	48.66± 0.26	65.84± 0.36	63.76± 0.24	47.86± 0.45	46.55± 0.41	44.69± 0.51	47.96± 0.54	47.25± 0.38	50.16± 0.49	38.84± 0.58	41.35± 0.76	43.33± 0.37
30	61.28± 0.48	72.48± 0.49	75.87± 0.47	51.84± 1.28	49.88± 0.14	50.15± 0.81	50± 0.93	54.48± 0.67	57.82± 0.69	46.57± 0.30	58.48± 0.08	58.06± 0.53
45	68.24± 1.28	80.94± 1.4	77.56± 0.94	58.75± 1.73	57.2± 0.67	53.48± 1.15	53.38± 0.21	59.22± 0.98	64.14± 0.22	62.46± 0.74	64.56± 0.52	66.58± 1.22
60	70.54± 0.61	85.22± 0.28	83.45± 0.77	64.54± 0.72	61± 0.55	57.45± 1.38	55.88± 0.17	64.48± 0.40	67.44± 1.42	67.08± 0.84	70.21± 1.36	78.52± 1.38

*****Mean±SD for n=3*



In-vitro Drug Release Profile Graph

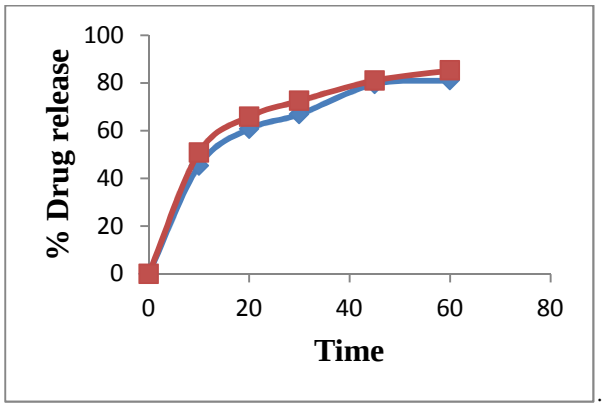
From the above study, it was found that drug with complex of Eudragit EPO in ratio of 1:1 with drug show better release and drug loading. Hence, 1:1 batch was selected for optimized batch for formulation of Dry syrup.

In vitro Drug Release Study of Marketed Formulation and Optimised batch

Time (minutes)	Cumulative % drug release	
	Opox Dry syrup 50mg	Formulation F2
0	0	0
10	45.39±0.53	50.85±0.48
20	60.77±0.44	65.84±0.36
30	66.85±0.11	72.48±0.49
45	79.95±1.07	80.94±1.4
60	81.06±0.47	85.22±0.28

**Mean±SD for n=3*

In-vitro Drug Release of Marketed Formulation and Optimised batch



In-vitro Drug Release of Marketed Formulation and Optimised batch

The rate of in-vitro drug release of marketed Opox Dry syrup 50mg was lower than optimized batch.

Model fitting of Drug release profile

Model Fitting of Drug release profile

Model / Formulation		Zero Order	First Order	Korse Mayer Peppas	Hickson Crowell	Higuchi
F1	R^2	0.7528	0.3811	0.9983	0.5116	-3.1166
F2	R^2	0.7238	0.3796	0.9982	0.4980	-3.2553
F3	R^2	0.6876	0.3779	0.9981	0.4830	-3.3432
F4	R^2	0.8058	0.3867	0.9988	0.5526	-2.7680
F5	R^2	0.7571	0.3818	0.9984	0.5154	-3.0673
F6	R^2	0.7188	0.3799	0.9983	0.4982	-3.1741
F7	R^2	0.6622	0.3777	0.9981	0.4771	-3.2817
F8	R^2	0.7806	0.3839	0.9986	0.5321	-2.9388
F9	R^2	0.7907	0.3862	0.9988	0.5476	-2.7992
F10	R^2	0.9004	0.3915	0.9991	0.6001	-2.4624
F11	R^2	0.8736	0.3934	0.9993	0.6067	-2.3923
F12	R^2	0.9090	0.3929	0.9992	0.6109	-2.4124

Sedimentation Volume (F)

Sedimentation Volume

Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Sedimentation Volume	0.97	0.98	0.96	0.93	0.87	0.92	0.90	0.86	0.95	0.88	0.97	0.91

Evaluation of Taste by Panel test:

Selected volunteers were given the numerical values for the inferences obtained. It was confirmed that the drug taste was masked. This might be happened due to imbibing effect of Eudragit EPO.

Evaluation of taste by panel test

Resin	Resin to drug ratio (polymer:drug)	Class given by panel
Euragit EPO	1:0.5	3
	1:1	2
	1:1.5	3
β-cyclodextrin	1:0.5	5
	1:1	3
	1:1.5	4
Methyl cellulose	1:0.5	4
	1:1	5
	1:1.5	3
Ethyl cellulose	1:0.5	5
	1:1	4
	1:1.5	3

DISCUSSION

the hypothesis of current investigation is that if the taste masking done by the ion exchange resin (Eudragit EPO, methyl cellulose, ethyl cellulose, β cyclodextrin, staric acid) which concentration with drug optimized by phase solubility diagram was decided. which might leads to dissolution enhancement in. The present research work was an attempt to study systematically, the effect of formulation variables on the release properties and taste masking of Cefpodoxime Proxetil.

The drug found uninteracted with the various polymers, it was evident from the IR spectra. Complex preparation ratio was selected on the phase solubility studies.For selection of formulation ratio, phase solubility studies was carried out in that all polymer with drug gave an linear proportion i.e. 1:1 because they gave A_L type graph. Hence 1:1 drug polymer ratio was considered for taste masking.

CONCLUSION

The drug resin complex show good taste masking property for Cefpodoxime proxetil with Eudragit EPO and steric acid in 1:1 ratio. The prepared dry syrup of Cefpodoxime proxetil(F2) showed good taste. The release profile of optimised formulation (F2) of Cefpodoxime proxetil dry syrup was better as compared to marketed formulation.

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