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FORMULATION& EVALUATION OF CEFUROXIME ORALSUSPENSION FOR PEDIATRICS

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Abstract

In the present study we have formulated the cefuroxime oral suspension for pediatrics by masking the taste of the drug which is bitter in taste in the studies we have carried seven trails in the process of masking the taste by change in the concentration of Indion-204 from 2.5gms to 30gms out of all the trails of formulations the final trail S-7 was given the best result in the taste masking of the drug from bitterness of taste. The evaluation parameters carried for all the trails from S-1 to S-7 such, as Solubility, viscosity, Taste, PH, Sedimentation Volume in these entire parameters trail S-7 given the best output result in all the conditions. Finally the bitter taste of the drug was masked by the Drug Resin Complexation method using 30gms of Indion-204 used in the formulation trail S-7.

Keywords: *Solubility, viscosity, Taste, PH, Sedimentation Volume.*

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INTRODUCTION

SUSPENSION

It may be defined as a coarse dispersion of finely subdivided insolublesolid drug particles suspended in a suitable liquid (usually aqueous) medium.It is a heterogeneous system consisting of a solid disperses in a solid,liquid or gas.It is a biphasic preparations particle of one or more solids basically itmay be flocculated or deflocculated.

PHARMACEUTICALAPPLICATIONS OFSUSPENSION

- For Oral Use
- For External Use
- For Injections

ORAL SUSPENSION

It contains one or more active ingredients suspended in a suitable vehicle. Suspended solids may slowly separate on keeping but are easily redispersed. It should be packed in wide mouth bottles.

ADVANTAGES OF ORALSUSPENSIONS

- It is a better means of administration than of solid dosage forms such as tablet, capsules especially when swallowing is difficult.
- It is an ideal dosage form for infants and old patients because of easy administration.
- It contains sub-divided solid particles; surface area is large and this is taken advantage of drugs which are adsorptive.
- Suspensions are chemically more stable than solutions.

DESIRABLE PROPERTIES OF SUSPENSIONS

- It should not be rapid settling of suspended particles.

- The particles do settle they must not form a hard cake at the bottom of thecontainer.
- It should be redispersal into uniform mixture when shaken.
- A suspension should be easily pourable.
- The colour and odour should be acceptable and pleasing for oral and externaluses.
- Appropriate preservatives should be incorporated in order to minimize the microbial contamination.

PROBLEMS OF SUSPENSIONS

- Wetting of disperse phase.
- Settling of disperse phase and resuspendibility of settled matter.
- Particle – particle interactions lead to particle size growth or caking. To formulate a suspension the above problems, have to be overcome.

FORMULATION OF SUSPENSIONS

In designing a suspension formula, a number of factors must be kept in sight. First of all, a decision has to be taken whether a flocculated or non-flocculated system has to be evolved. Secondly, it's important to ensure that the disperse phase particles are well dispersing in the continuous phase. Then finally the decision has to be taken about suspending agents, dispersants, organoleptic additives and preservatives is required to produce satisfactory suspension. The choice of an appropriate suspending agent depends upon the use ofproducts, facilities for preparation and the duration of product storage.

EVALUATION OF SUSPENSIONS

A number of procedures have been suggested in the past for evaluating the physical stability of suspensions. Some of these are empirical in the sense that they have no mathematical base. Some methods currently being used are so drastic that they destroy the structure of suspension. The methods used may be categorized as

- Sedimentation methods
- Rheological methods
- Electro kinetic methods
- Micrometric methods

TASTE MASKING

Many drugs containing amine or amide groups or salts there of often have a strong bitter taste. Taste masking techniques using various sweeteners, amino acids, flavours & adsorbents have been unsuccessful in masking the taste. In most coating techniques don't have an acceptable in-vivo drug releasing mechanism. Cation exchange resins have been used to adsorb amine drugs for sustained release action & taste masking. The widely used cation – exchange resins are poly sulfonic acid &

polycarboxylic acid polymers.

The two methods were followed for the formulation of mouth disintegrating tablets.

1. By addition of sweeteners and disintegrants.
2. Mass extrusion technique.

In these formulations, PH range is about 4.5 to 6.5 preferably 5.5 is maintained.

Suitable thickening agents are used in these taste masking

Formulations that is xanthan gum, Guargum, gelatin, gum, tragacanth gum and many others.12

In this taste masking formulations, to prevent microbial contamination, preservatives like sodium benzoate (0.1 to 0.2%) or benzoic acid is used.

TECHNIQUES EMPLOYED FOR TASTE MASKING

- Use of Flavor Enhancers
- Applying Polymer Coatings
- Complexation and Adsorption Approaches
- Formulation of Inclusion Complex with Beta Cyclodextrin Derivatives
- Wax Embedding of Drugs

Materials & Methods

S. No	Name of the Material	Category
1	Cefuroxime IP	Active Ingredient

2	Indion-204	Cation Exchange Resin
3	Sucrose	Sweetener
4	Sorbitol Solutions (70%)	Sweetener
5	Xanthan gum	Suspending Agent
6	Propylene glycol IP	Solvent for Preservative
7	Sodium Benzoate IP	Preservative
8	Methyl paraben IP	Preservative
9	Propyl Paraben IP	Preservative
10	Citric Acid monohydrate	Acidulant
11	Sodium Citrate IP	Buffering agent
12	Sodium chloride	Electrolyte
13	Glycerin	Viscosity builder
14	Sunset Yellow FCF	Colouring agent
15	Tween-80	Wetting agent
16	Masking Flavour 2521	Flavouring agent
17	Orange oil Flavour	Flavouring agent

FORMULATION OF SUSPENSION

S. No	Ingredients	S-1	S-2	S-3	S-4	S-5	S-6	S-7
1	Cefuroxime (g)	10	10	10	10	10	10	10
2	Indion-204 (g)	2.5	5	7.5	10	20	25	30
3	Sucrose (g)	300	300	300	300	300	300	300
4	Xanthan gum (g)	1.5	1.5	1.5	1.5	1.5	1.5	1.5
5	Tween 80 (g)	0.5	0.5	0.5	0.5	0.5	0.5	0.5
6	Sorbitol (g)	100	100	100	100	100	100	100
7	Propylene glycol(g)	50	50	50	50	50	50	50
8	Methyl paraben (g)	1	1	1	1	1	1	1
9	Propyl paraben (g)	0.5	0.5	0.5	0.5	0.5	0.5	0.5
10	Sodium citrate (g)	1.5	1.5	1.5	1.5	1.5	1.5	1.5
11	Citric acid (g)	1	1	1	1	1	1	1
12	Sodium chloride (mg)	1.25	1.25	1.25	1.25	1.25	1.25	1.25
13	Glycerin (g)	50	50	50	50	50	50	50
14	Mint flavour (ml)	10	10	10	10	10	10	10
15	Orange oil flavour (ml)	5	5	5	5	5	5	5
16	Sunset yellow FCF (mg)	25	50	50	50	50	50	50
17	DM Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s

FORMULATION DEVELOPEMENT

Following ingredients were selected to develop the desired formulation.

FORMULATION OF SUSPENSION

Step -1: Drug and ion exchange resins were weighed accurately. Then the resin was poured into DM water. The drug was added in to the resinate with continuous stirring to get drug resinate.

Step -2: Sucrose was added to 150 ml of DM water and boiled for complete dissolving of sucrose. Then the sorbitol was mixed with the sugar solution.

Step -3: Xanthan gum was poured in to glycerin and mixed to dissolve the gum completely.

Step-4: Tween 80 was added in to the drug resinate. The sugar, sorbitol solution and xanthan gum solution were added in to the drug resinate formulation.

Step -5:Methyl paraben and propyl paraben were added separately into propylene glycol and dissolved completely. This was added to the drug resinate formulation.

Step-6: Sodium citrate, citric acid and sodium chloride were dissolved in DM water and poured in to the drug resinate formulation.

Step-7: The flavors and colour were added into the drug resinate formulation. Finally, suspension was made up to 1000 ml with DM water and mixed for 30 minutes.

EVALUATION OF SUSPENSIONS

Taste evaluation of optimized formulation

The taste evaluation was performed with 10 volunteers. The Formulation (S-7) was held in the mouth for 15 seconds by each volunteer and the bitterness level was recorded against pure drug using a numerical scale.pH

pH is be defined as the negative logarithm of hydrogen ion concentration.

Mathematically it is written as:pH = log 1/ [H3O+] Since the logarithm of 1 is zero.

The equation may also be written:pH = - log(H3O+)

Viscosity

Viscosity of suspension is a great importance for stability and palatability of suspensions. Suspensions have least physical stability amongst all dosage forms due to sedimentation and cake formation.78 Sedimentation is governed by stoke's law,

$V = d2(\varrho s - \varrho l)\ g / 18\ n$

Sedimentation Volume

Sedimentation volume F is the ratio of equilibrium volume of sediment (Vu) to the total volume of suspension (Vo).

$F = Vu / Vo$

Vu - Volume of sediment

Vo - total volume of suspension

The sedimentation volume F normally ranges from less than 1 to 1. When F=1, the sediment volume and the total volume are equal and such a suspension is pharmaceutically acceptable.

Assay

Accurately measured volume (5ml) of suspension was transferred to a 50ml volumetric flask, the volume was made up with 0.1N HCl to break the complex and sonicated for 30min. To the above solution 0.2ml of potassium permanganate was added and heated for 10 mins at 37^{0}C. The excess of potassium permanganate was neutralized with oxalic acid. To the resulting mixture, 2ml of reagent solution was added and heated at 37^{0}C for 1 min. The absorbance of the resulting solution was measured at 412nm taking a reagent blank.

In vitro Dissolution study

Dissolution profile of Cefuroxime suspension was determined using the USP (type II) paddle apparatus with a speed of 50 rpm. Dissolution was tested in acidic buffer 0.1N HCl of 900ml at 37 ±0.5˚C. Aliquot volume was withdrawn at 10, 20, 30 and 60 min and filtered through 0.45µ membrane filter. To that 0.2ml of potassium permanganate was added and heated for 10 min at 37^{0}C. The excess of potassium permanganate was neutralized with oxalic acid. To the resulting mixture, 2ml of reagent solution was added and heated at 37^{0}C for 1 min. The absorbance of the resulting solution was measured at 412nm taking a reagent blank.

STABILITY STUDIES OF THE FINISHED PRODUCT

Stability of a drug can be defined as the time from date of manufacture and packaging of the formulation until its chemical or biological activity is not less than a predetermined level of labeled potency and its physical characteristics

have not changed appreciably or deleteriously. Although there are exceptions, 90% of labeled potency is recognized as the minimum acceptable potency level.

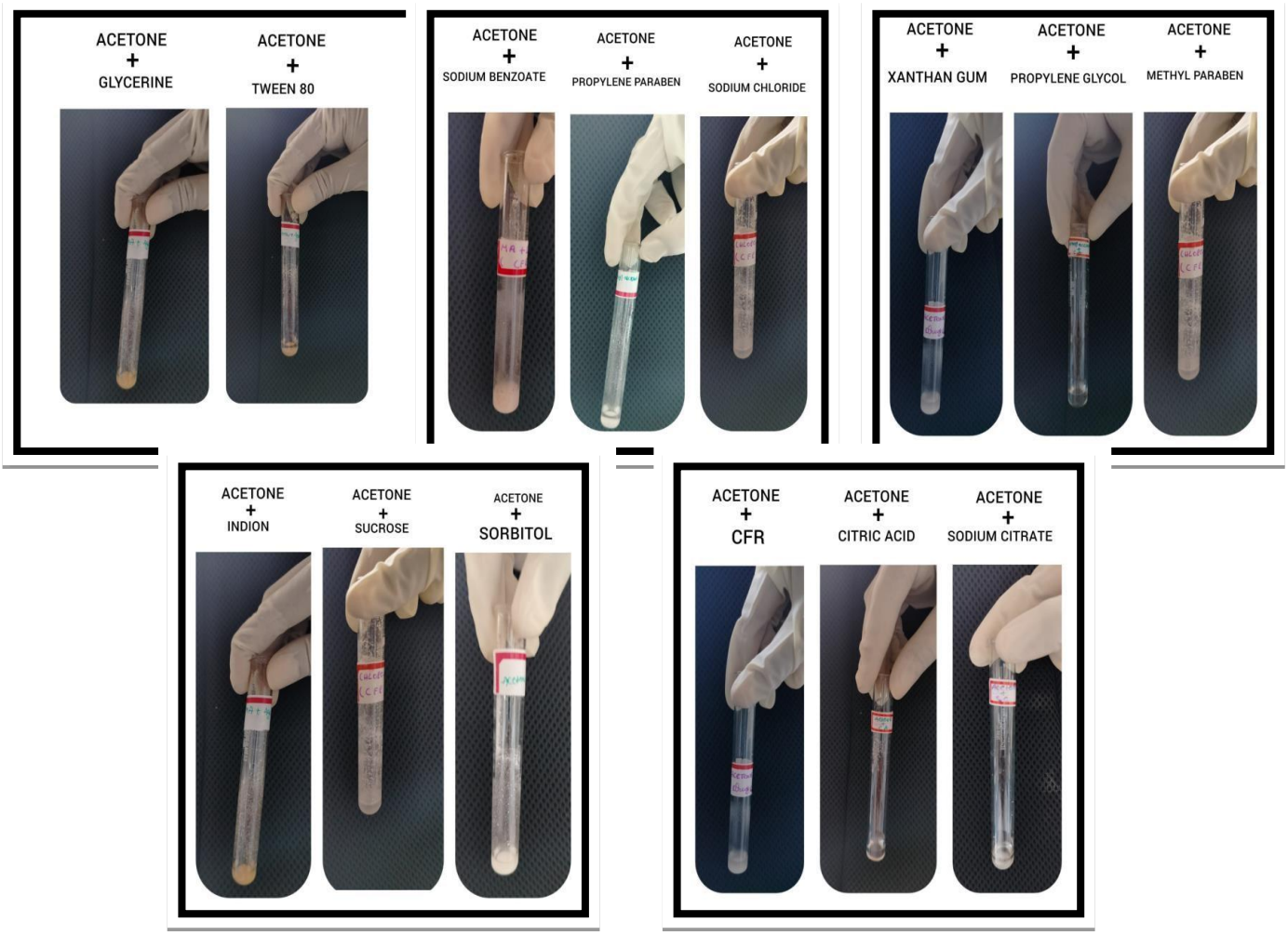
METHOD

The selected formulations were packed in wide mouth bottle. They were stored at 25°± 2°C /60%± 5% RH and 40° ± 2°C /75%± 5% RH for 15 days in humidity chamber and evaluated for their physical appearance and drug content at specified intervals of time.

Results & Discussion

Solubility Studies: Solubility studies were done for candidate drug and excipients as per requirement of development.

S. NO	SOLUTE	SOLVENTS				
	SOLUTE	ETHANOL	ETHER	WATER	ACETONE	CHLOROFORM
1	API	Freely soluble	ND	In soluble	Freely soluble	ND
2	Sucrose	ND	ND	Very soluble	ND	In soluble
3	Xanthan gum	In soluble	In soluble	soluble	ND	ND
4	Tween80	Soluble	In soluble	soluble	ND	ND
5	Sorbitol	Slightly soluble	In soluble	Very soluble	ND	In soluble
6	Sodium citrate	In soluble	ND	Freely Soluble	ND	ND
7	Citricacid monohydrate	Freely Soluble	Sparingly soluble	Very soluble	ND	ND
8	Sodium chloride	Slightly soluble	ND	Freely Soluble	ND	ND
9	Sodium benzoate	Sparingly soluble	ND	Freely Soluble	ND	ND
10	Glycerin	Miscible	ND	Miscible	Slightly soluble	In soluble
11	Propylene glycol	Miscible	Soluble	Miscible	Miscible	Miscible
12	Methyl paraben	Freely Soluble	ND	Slightly soluble	ND	ND
13	Propyl paraben	Freely Soluble	Freely Soluble	Slightly soluble	ND	ND



SOLUBILITY OF DURG & SOLUBILITY OF EXCEPIENTS WITH DRUG SOLUBLE SOLVENTS

EVALUATION OF CEFUROXIME SUSPENSION

S. No	Test for Evaluation	Observation						
		S -1	S - 2	S- 3	S- 4	S -5	S – 6	S - 7
1	Taste	Bitter	Bitter	Bitter	Bitter	Bitter	Slightly Bitter	Not Bitter
2	pH	3.54	3.58	3.61	3.67	3.70	3.64	3.66
3	Viscosity (Cps)	576	589	632	648	644	652	665
4	Sedimentation volume (F)	0.94	0.95	0.96	0.97	0.97	0.99	0.99

Inference

- Oral suspensions were formulated in different combinations S-1, S-2, S-3, S-4,S-5,S-6,S-7
- From the above formulations, it was found that the bitter taste was not masked for formulations S-1,S-2, S-3, S-4 & S-5.
- Slightly bitter taste was observed in the formulation, S-6.
- The taste was completely masked in formulation S-7.
- The pH of formulations S-1 to S-7 ranged from 3.54 to 3.70 and the viscosity ranged from 576 to 665 Cps&The sedimentation volume (F) ranged from 0.94 to 0.99.

ASSAY

Assay of formulated Cefuroxime suspension

1	Taste	No change	No change
2	Colour	No change	No change
3	pH	3.74	3.67
4	Viscosity (Cps)	660	665
5	Sedimentation volume (F)	0.99	0.99
6	Drug content (%)*	98.06±0.0236	98.97±0.0423

S. No	Formulation	Drug content (%) *
1	S -1	98.9 ± 0.0031
2	S -2	97.85 ± 0.1021
3	S -3	99.70 ± 0.187
4	S -4	98.34 ± 0.1542
5	S -5	99.16 ± 0.0021
6	S -6	99.89 ± 0.078
7	S -7	99.78 0.0245

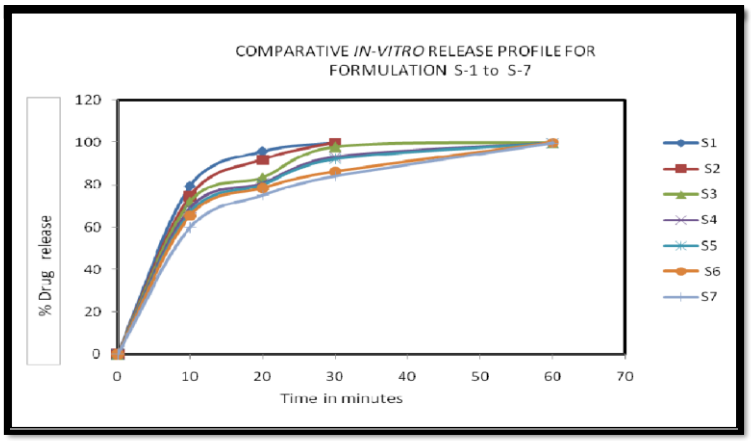
INFERENCE

- The drug content of the suspension ranged from 97.85% to 99.85%.
- The drug content of the formulation was within the limits.
- In vitro drug release of formulated Cefuroxime suspension.

Time (min)	CUMULATIVE % DRUG RELEASE*						
	S-1	S-2	S-3	S-4	S-5	S-6	S-7
10	79.44± 0.02	74.62± 0.0500	72.05± 0.0360	69.05± 0.0150	67.02± 0.0458	65.44± 0.0321	59.82± 0.0568
20	95.81± 0.0057	91.86± 0.0206	83.43± 0.0264	80.89± 0.0046	80.12± 0.0251	78-47± 0.0300	75.02± 0.0512
30	99.79± 0.010	99.88± 0.0152	97.92± 0.0125	93.25± 0.0600	92.22± 0.0642	86.19± 0.0808	84.02± 0.0611
60	-	-	99.82± 0.0264	99.72± 0.0400	99.72± 0.0305	99.86± 0.0360	99.62± 0.0850

COMPARATIVE IN-VITRO RELEASE PROFILE OFS-1 to S-7

- In comparative stive with all the profiles of drug release in dissolution studies S-7 formulation shows the best % of drug release
- The Comparative studies of all the profiles the trail S-& was shown very accurate and efficient formulative studies



FORMULATION TRAILS FROM S1 TO S7

STABILITY TESTING

- Stability Studies of formulated Cefuroxime Suspension (Formulation S-7)
- Stability studies of S-7 were carried out by placing the samples at different temperature and relative humidity (40 ±2°C/ 75±5% RH, 25±2°C/ 60±5% RH, 5±3°C) for 15 days in humidity chamber and evaluated. There is no significant change in release characteristics and other evaluation parameters. Based on the results it can be concluded that the formulated oral suspension was stable at room temperature over a period of 15 days. Even though stability is assured for 15 days, further studies at different temperature and humidity conditions are needed to establish its shelf life.

Summary & Conclusion

- Several formulations were carried out by Drug-resin complexation method.
- It was concluded that the formulation S-7 was satisfactory than other formulations of S-1, S-2, S-3, S-4, S-5 & S-6.
- The formulations S-7 is found to be accurate for all the parameters in all aspects.
- The bitter taste was masked in formulations S-7 better.

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