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Original Article

Formulation and evaluation of an Anti-pyretic (Paracetamol) syrup for Paediatric

Pawan Singh*, Prevesh Kumar and Neelkant Prasad

Pharmacy Academy, IFTM University, Lodhipur Rajput, Moradabad, India

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ABSTRACT: Background: Studies suggested that fever may have a beneficial for safe drug delivery. The use of paracetamol in therapeutic doses generally is safe, although hepatotoxicity has occurred with recommended dosages in children. **Material and Method:** home storage conditions at a temperature ranging from (2-8 °C) representing refrigerator and accelerated condition. Prepare a solvent mixture consisting of 0.4 volumes of formic acid, 15 volumes of methanol and 85 volumes of water. **Result:** Evaluated prepared 4 formulations the physical description (Color, odor, and taste) were found colorless, none and sweet. The pH of F1, F2, F3, and F4 was found 5.39,5.16,5.09 and 5.04. In these four formulations, we were selected F1 on the behalf of best pH. The F1 formulation weight per ml was found 1.0312 gm/ml. the assay of paracetamol syrup F1 formulation was found 99.88%. The stability of four formulations was found 5.36,5.16,5.08 and 5.03 **Conclusion:** It was concluded that F1 formulation was good and stabilized formulation. Like syrup formulations made by use of a combination of physiologically compatible mixed solubilizes. The proposed mixed solubilizes are known to be safe; hence, toxicities/safety related issues may not raise concern, suggesting the adaptability for large-scale manufacturing i.e. industrial feasibility.

⇑ Corresponding author at:
Pawan Singh, Assistant Professor, Pharmacy Academy, IFTM University, Lodhipur Rajput, Moradabad, India
E-mail: pawansingh690@gmail.com

INTRODUCTION

Fever is defined as temperature above the normal range, rectal temperature above 38.8°C, oral temperature above 37.8°C and an axillary temperature above 37.2°C all are considered abnormal. Fever in children is one of the most common clinical symptoms managed by pediatricians and other healthcare providers [1]. Fever is not the primary illness. the syrup is primarily composed of a mixture of sugars, water, and minerals. In addition to these three components, maple syrup will contain minor amounts of various other organic compounds such as organic acids, amino acids, proteins, phenol compounds and even a few vitamins. Variation in the levels of these various components gives syrup the broad spectrum of flavors experienced with syrup from different producers and from different sap runs at the same location [2]. When making any syrup has a good flavor as most of the flavors will only be further concentrated resulting in poor tasting products.

Once you have selected syrups with excellent flavor, selecting the syrups based on correct chemistry for the desired confection is second in importance [3].

Antipyretic syrup

Paracetamol is one of the most popular and most commonly used analgesic and antipyretic drugs around the world, available without a prescription, both in mono- and multi-component preparations [4]. It is the drug of choice in patients that cannot be treated with non-steroidal anti-inflammatory drugs (NSAID), such as people with bronchial asthma, peptic ulcer disease, hemophilia, salicylate-sensitized people, children under 12 years of age, pregnant or breastfeeding women. It is recommended as a first-line treatment of pain associated with osteoarthritis. The mechanism of action is complex and includes the effects of both the peripheral (COX inhibition) and central COX [5].

Paracetamol is well tolerated produces few side effects from the gastrointestinal tract, however, despite that, every year, has seen a steadily increasing number of registered cases of Paracetamol-induced liver intoxication all over the world [6].

Given the growing problem of the safety of acetaminophen is questioned the validity of the sale of the drug without a prescription.

This work, in conjunction with the latest reports on the mechanism of action of Paracetamol, trying to point out that it is not a panacea devoid of side effects, and indeed, especially when is taken regularly and in large doses (> 4 g/day), there is a risk of serious side effects [7].

Problems with Antipyretic syrup in children cause

1. Many formulations used the higher amount of sweetener that causes mostly children diabetes
2. Mostly formulation used the higher amount of preservatives that cause cancer.

Solution of syrup related

1. The sweetener is used as per the guideline for manufacturing related to the country.
2. In cause of preservative, must be follow as per requirement in suitable concentration as per guideline U.S.P.

MATERIALS

Paracetamol was received as a gift sample from CDH. Other excipients namely Polyethylene glycol 6000 (PEG 6000), Glycerin, D.M Water, Sucrose, Propylene glycol, Citric acid monohydrate was purchased from S.D. Fine chemicals limited, Mumbai. All the chemicals used were of analytical grades.

FORMULATION (F1) of Paracetamol SYRUP (250 mg /10 ml)

Table 1: Batch size 50.0 ml Paracetamol syrup

Ingredients	Weight	Function
Part I		
Paracetamol	1.25g	Active ingredient
Polyethylene glycol 6000 (PEG 6000)	5.0 g	Solubilizer
Glycerin	1.25 g	Diluent and sweetener
D.M. Water	15.0 ml	Diluent
Part II		
Sucrose	15.0 g	Sweetening agent
D.M Water	10.0 g	Diluent
Propylene glycol	.002 g	Preservative
Citric acid monohydrate	0.030 g	pH modifier

FORMULATION (F2) of Paracetamol SYRUP (250 mg /10 ml)

Table 2: Batch size 50.0 ml Paracetamol syrup

Ingredients	Weight	Function
Part I		
Paracetamol	1.25g	Active ingredient
Polyethylene glycol 6000 (PEG 6000)	5.0 g	Solubilizer
Glycerin	1.25 g	Diluent and sweetener
D.M. Water	15.0 ml	Diluent
Part II		
Sucrose	15.0 g	Sweetening agent
D.M. Water	10.0 g	Diluent
Propylene glycol	.004 gm	Preservative
Citric acid monohydrate	0.030 g	pH modifier

FORMULATION (F3) of Paracetamol Syrup (250 mg /10 ml)

Table 3: Batch size 50.0 ml Paracetamol syrup

Ingredients	Weight	Function
Part I		
Paracetamol	1.25g	Active ingredient
Polyethylene glycol 6000 (PEG 6000)	5.0 g	Solubilizer
Glycerin	1.25 g	Diluent and sweetener
D.M. Water	15.0 ml	Diluent
Part II		
Sucrose	15.0 g	Sweetening agent
D.M. Water	10.0 g	Diluent
Propylene glycol	.002g	Preservative
Citric acid monohydrate	0.035 g	pH modifier

FORMULATION (F4) of Paracetamol SYRUP (250 mg /10 ml)

Table 4: Batch size 50.0 ml Paracetamol syrup

Ingredients	Weight	Function
Part I		
Paracetamol	1.25g	Active ingredient
Polyethylene glycol 6000 (PEG 6000)	5.0 g	Solubilizer
Glycerin	1.25 g	Diluent and sweetener
D.M.Water	15.0 ml	Diluent
Part II		
Sucrose	15.0 g	Sweetening agent
D.M. Water	10.0 g	Diluent
Propylene glycol	0.004 g	Preservative
Citric acid monohydrate	0.035 g	pH modifier

Method of preparation (In-house procedure)

Procedure and Manufacturing of Paracetamol Syrup

Part I

1. Heat (PEG 6000) at 50 °C and add Paracetamol in it. Stir the solution for 30 minutes.
2. Heat Glycerin at 50 °C and then add in step 1 solution ((PEG 6000)-+Paracetamol) under continuous stirring. Stir the solution for 20 minutes. Transparent solution will be obtained
3. Heat water at 50 °C and put it under continuous stirring.
4. Add step 1 solution ((PEG 6000) + Paracetamol+ Glycerin) slowly into D.M. Water under continuous stirring. The transparent solution will be obtained.

Part II

5. Weigh accurately sucrose. Add sucrose in hot (65°C) D.M. Water under continuous stirring till it dissolved.
6. Filter above solution through a filter press. Keep filtrate under stirring.
7. Added Preservative, Sweetener in it with continuous stirring for 10 minutes.

Mixing of Part I and Part II

8. Slowly add part I in Part II under continuous stirring. Stir it till clear solution is obtained
9. Check pH above solution. If pH is not between 3.80-6. Then add accordingly Citric acid solution to adjust Ph.
10. Add color solution in above solution under stirring. Now, add flavor under continuous stirring
11. Make volume 100 ml of D.M. water if required.
12. Clear transparent Paracetamol syrup is obtained
13. 0.18 ml NaOH for maintaining the pH

Evaluation of Paracetamol Syrup

Physical property [8]

Appearance: Clear and transparent

Determination of pH [9]

The pH value conventionally represents the acidity or alkalinity of an aqueous solution. The pH value of a solution was determined potentiometrically by means of the glass electrode. A digital pH meter was allowed to stabilize. Then the pH meter was standardized using buffer tablets. The suspension formulation was placed in the pH meter. The reading was noted when there is no fluctuation in the pH meter.

Determination of Weight per ml [10]

A pre-weighed 50 ml volumetric flask was taken, and the oral syrup was added up to the mark. The net volume was noted. Then weighed the above volumetric flask to evaluate weight per ml.

Freeze and thaw studies [11]

The Freeze and Thaw studies were done by exposing the final formulation (F1) alternately at 8 °C.

Accelerated stability study [12]

The F1 syrup was packed in 100 ml Pet bottle. The packed bottles were placed in stability chamber maintained at 2-8°C and 25°C for 2 weeks.

The analyses comprised chemical testing of quantifiable parameters, which could possibly change during storage, such as pH.

Assay of paracetamol Syrup [13]

System condition

High-performance liquid chromatography, using a stainless-steel column (25 cm x 4.6 mm), packed with octa silyl silica gel for chromatography (5 µm).

Method of preparation of Mobile phase

Prepare a solvent mixture consisting of 0.4 volumes of formic acid, 15 volumes of methanol and 85 volumes of water.

As the mobile phase use a filtered and degassed solution of 0.01 M sodium butane sulfonate in the above solvent mixture.

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 243 nm.

Prepare the Assay solutions

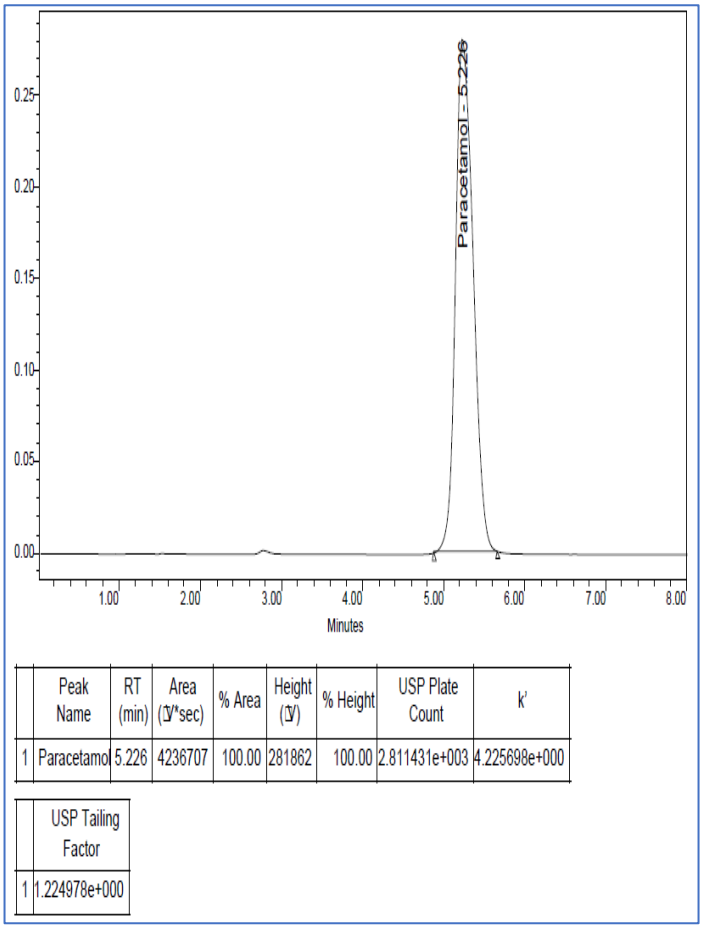
1. Shake the container of oral suspension to resuspend any settled material. Shake an accurately weighed quantity of the oral syrup containing the equivalent of about Filter a portion of this solution through a 0.45 µm filter, discarding the first few ml of the filtrate.

2. Accurately weigh about 250 mg of paracetamol and dissolve in about of solvent mixture. Dilute this solution to 5 ml of the solvent mixture 100 ml. Dilute 10 ml of the resulting solution to 50 ml of the solvent mixture Filter a portion of this solution through a 0.45 µm filter, discarding the first few ml of the filtrate.

3. Dissolve 10.1812 gm of paracetamol syrup solution in about 5 ml of the solvent mixture, and

1000 ml of the solvent mixture. And 5 ml of resulting solution to 100 ml solvent mixture. Filter a portion of this solution through a 0.45 µm filter, discarding the first few ml of the filtrate. Inject separately 20 µl each of solutions (1), (2) (3), (4) and (5) and record the chromatograms of standard paracetamol and taken two chromatograms of paracetamol syrup preparade in the lab.

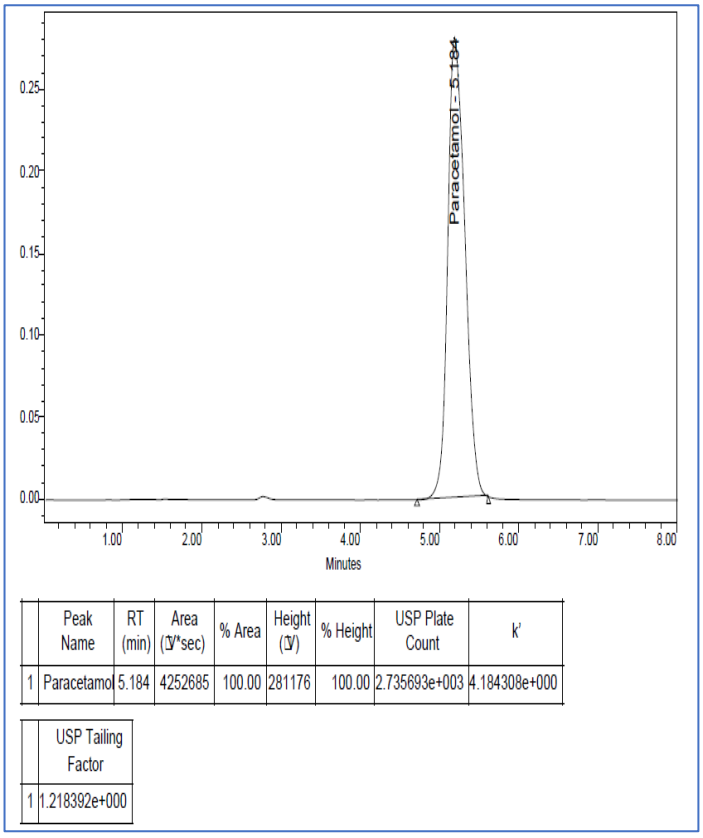
In the chromatogram obtained with a solution the following peak is eluted at the following relative retention, with reference to paracetamol. Measure the areas of the peak responses in the chromatograms obtained with solutions.



	Peak Name	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height	USP Plate Count	k'
1	Paracetamol	5.226	4236707	100.00	281862	100.00	2.811431e+003	4.225698e+000

	USP Tailing Factor
1	1.224978e+000

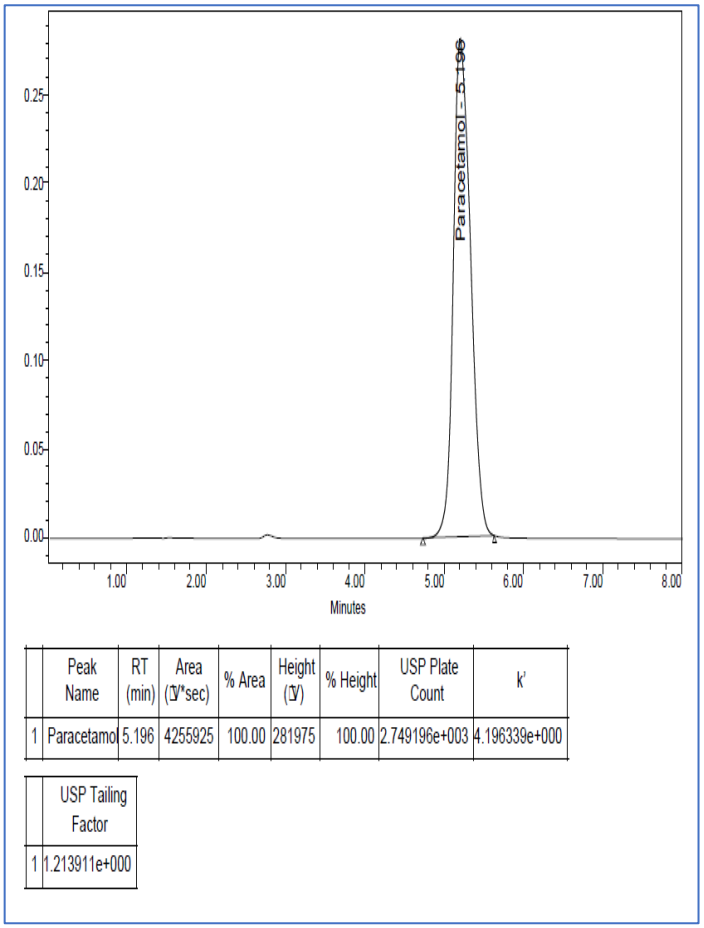
Fig. 1: First Chromatogram of Standard paracetamol



	Peak Name	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height	USP Plate Count	k'
1	Paracetamol	5.184	4252685	100.00	281176	100.00	2.735693e+003	4.184308e+000

	USP Tailing Factor
1	1.218392e+000

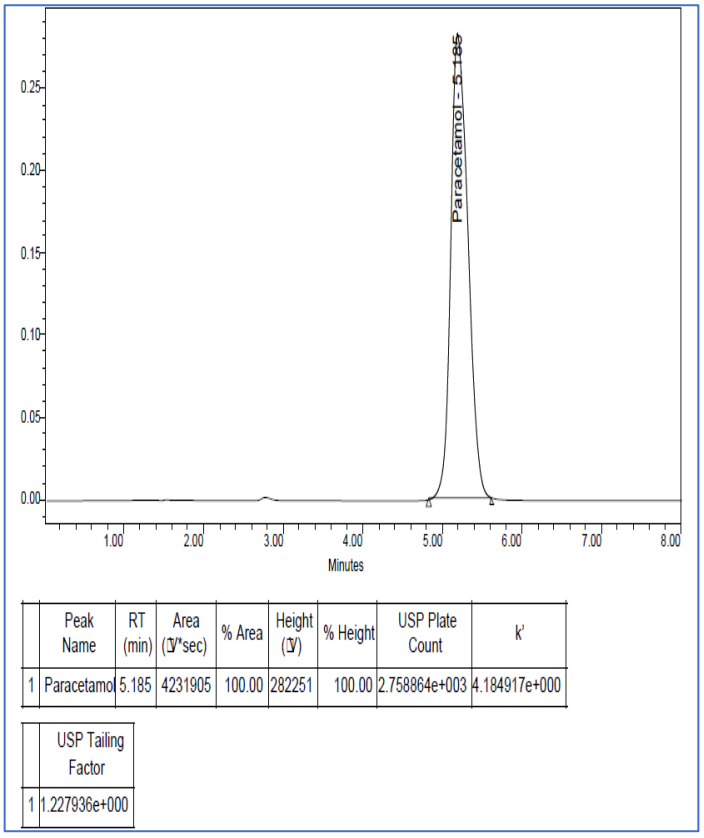
Fig 2: Second Chromatogram of Standard paracetamol



	Peak Name	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height	USP Plate Count	k'
1	Paracetamol	5.196	4255925	100.00	281975	100.00	2.749196e+003	4.196339e+000

	USP Tailing Factor
1	1.213911e+000

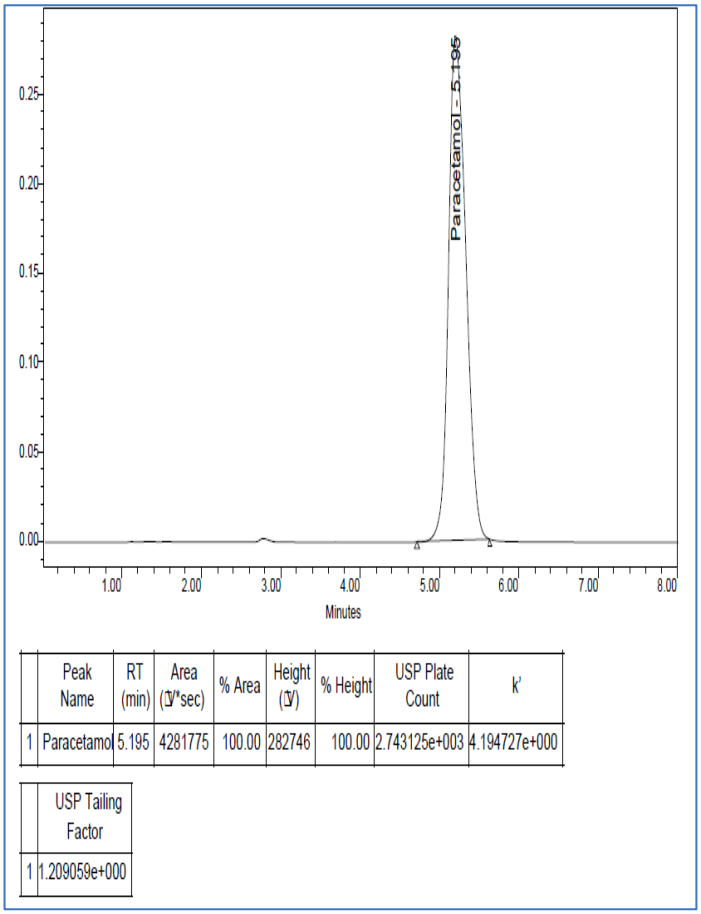
Fig. 3: Third Chromatogram of Standard paracetamol



	Peak Name	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height	USP Plate Count	k'
1	Paracetamol	5.185	4231905	100.00	282251	100.00	2.758864e+003	4.184917e+000

	USP Tailing Factor
1	1.227936e+000

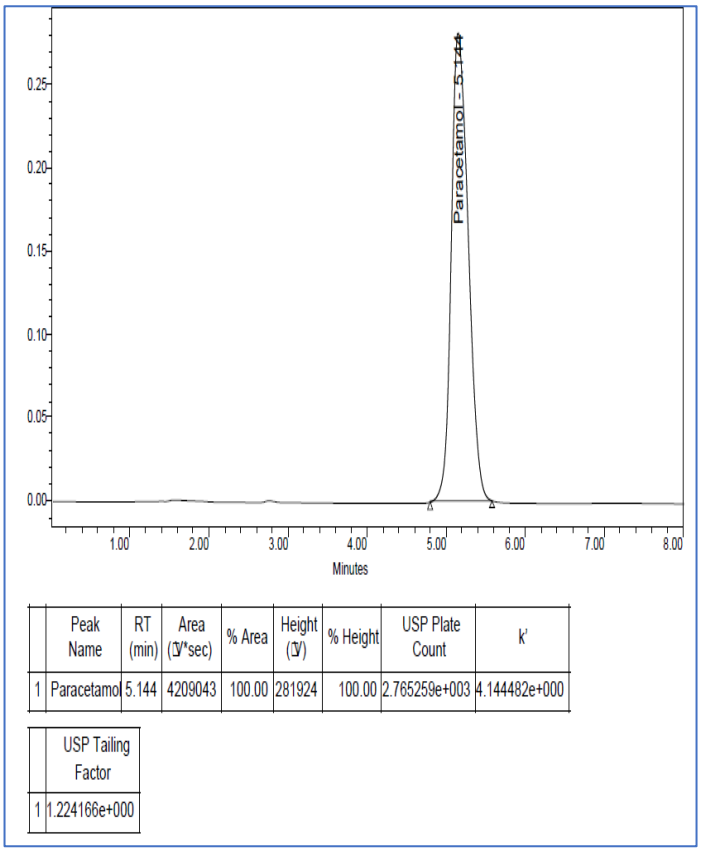
Fig. 4: Fourth Chromatogram of Standard paracetamol



	Peak Name	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height	USP Plate Count	k'
1	Paracetamol	5.195	4281775	100.00	282746	100.00	2.743125e+003	4.194727e+000

	USP Tailing Factor
1	1.209059e+000

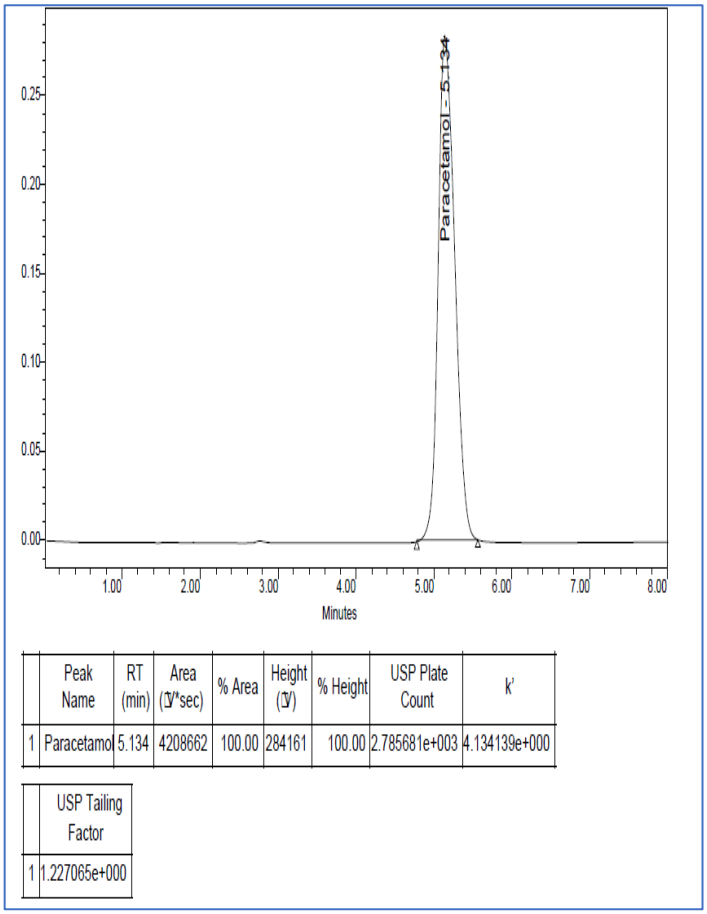
Fig. 5: Fifth Chromatogram of Standard paracetamol



	Peak Name	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height	USP Plate Count	k'
1	Paracetamol	5.144	4209043	100.00	281924	100.00	2.765259e+003	4.144482e+000

	USP Tailing Factor
1	1.224166e+000

Fig. 6: First Chromatogram of Sample paracetamol syrup



	Peak Name	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height	USP Plate Count	k'
1	Paracetamol	5.134	4208662	100.00	284161	100.00	2.785681e+003	4.134139e+000

	USP Tailing Factor
1	1.227065e+000

Fig. 7: Second Chromatogram of Sample paracetamol syrup

RESULTS AND DISCUSSION-

Physical description

Table 5: Physical description

S. no.	Physical parameter	Result
1	Color (F1, F2, F3, F4)	Colorless
2	Odor (F1, F2, F3, F4)	None
3	Taste (F1, F2, F3, F4)	Sweet

pH

Table 6: pH

S. no.	Formulation No	pH
1	F1	5.39
2	F2	5.16
3	F3	5.09
4	F4	5.04

Weight/ml: **Mass of solute**: 25.78000 gm

Total solution volume: 25 ml

Weight/ml: 1.0312 gm/ml

Freeze and thaw studies

There was no precipitation and turbidity observed in the formulation.

Physical Stability Study

The physical stability studies revealed that two formulated syrups remained clear (no precipitation) during 10 weeks at all temperature conditions. Two formulated syrups were colorless at room temperature up to 2 weeks at least. Two formulated syrups kept at 8°C colorless after 6th or 7th week. Two formulated syrups developed slight color after 4 weeks at 25°C.

There was moderate color development in two formulated syrups at 25°C after 2 weeks.

Table 7: Physical Stability Study

S. no.	Formulation no	Initial pH	Final pH
1	1	5.39	5.36
2	2	5.16	5.16
3	3	5.09	5.08
4	4	5.04	5.03

Assay of paracetamol syrup

Product Name	PARACETAMOL ORAL SOLUTION I.P					
Batch No	IFTM-16025					
Std. wt. of paracetamol	250.6	mg	Potency	99.38	%	
Weight of Sample	10.1812	gm	Wt./ml	1.0312	gm/ml	
Average Weight	10	ml				
	1	**2**	**3**	**4**	**5**	**Mean**
Std Area of Paracetamol	4236707	4252685	4255925	4231905	4281775	4251799
Sample Area of Paracetamol	4209043	4208662				4208853
Assay of paracetamol (in mg) =	Area os sample x weight of standard x			5x100x50xpotency of standard		
	Area of standard x100 x50 x sample weight x 5 x 100					
Assay in %	Obtained in mg x100					
	250					
	in mg	in %				
Assay of paracetamol	249.70	99.88				

CONCLUSION

The four trials were planned to prepare this formulation with excipients in different quantity like Propylene glycol used as solubilizing, sucrose is used as sweetener and base. We found that the first formulation (F1) i.e. final formulation was clear and stabilized. In the second (F2) formulation crystallization was observed due to less quantity of propylene glycol and the third (F3) formulation was not of good taste. So, it was concluded that F1 formulation was good and stabilized formulation. Like syrup formulations made by use of a combination of physiologically compatible mixed solubilizes, there is a good scope for development of syrup formulations of other poorly water-soluble drugs using a combination of mixed solubilizes using their reduced concentrations. The proposed mixed solubilizes are known to be safe; hence, toxicities/safety related issues may not raise concern, suggesting the adaptability for large-scale manufacturing i.e. industrial feasibility. The proposed techniques would be economical, convenient, and safe. Thus, the study opens the chances of preparing such syrup (oral liquid solution) formulations of poorly water-soluble drugs. This may reduce the individual concentration of solubilizes and so reduce their potential for toxicity associated with them. If by combining the solubilizes, synergistic solubility enhancement is achieved, there is a further reduction in the concentrations of solubilizes for the desired solubility and hence a further reduction in toxicities.

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