

**FORMULATION AND EVALUATION OF STABILIZED BETA-CAROTENE 7.5%  
DISPERSION IN MULTIVITAMIN SYRUP****M. Rajesh\*<sup>1</sup>, Nadar Antonprisca Jeyapaul<sup>1</sup> and P. Ramkumar<sup>2</sup>**<sup>1</sup>Professor & Head, Department of Pharmaceutics, Sankaralingam Bhuvaneshwari College of Pharmacy, Sivakasi, Tamil Nadu, India.<sup>2</sup>Research and Development Department, Fourrts (India) Laboratories Pvt. Ltd, Kelambakkam, Chennai, Tamil Nadu, India.**Corresponding Author: Dr. M. Rajesh**

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**ABSTRACT**

In most of the multivitamin oral syrups, there are instability problems of vitamin A with vitamin D and E. Beta-carotene (precursor to vitamin A) has poor stability and several studies had reported that Beta-carotene 7.5% dispersion was not stable in multivitamin syrup formulations. So the main objective of the study was to formulate and stabilize Beta-carotene 7.5% dispersion in multivitamin (Vitamin D and E) syrup formulations. Two formulations (B1 and B2) of Beta-carotene 7.5% dispersion syrups were developed. The formulated syrups were evaluated for appearance, colour, taste, pH, wt/ml, viscosity and drug content. Formulation B2 showed good results in terms of general, physical and chemical parameters evaluated compared to formulation B1. Hence, formulation B2 was considered as an optimized formulation. Multivitamins (Vitamin D & E) was incorporated in the optimized formulation (B3) and the stability of formulation B3 was evaluated in terms of general, physical and chemical parameters. The stability reports of formulation B3 revealed that Beta-carotene 7.5% dispersion was stable even in presence of multivitamins. The study thus concludes that stable formulations of multivitamin syrup with Beta-carotene 7.5% dispersion could be successfully developed.

**KEYWORDS:** Beta-carotene, Multivitamins, Optimized formulation, Syrup.**INTRODUCTION**

Syrup is a thick, viscous liquid consisting primarily of a solution of sugar in water, containing a large amount of dissolved sugars but showing little tendency to deposit crystals.<sup>[1]</sup> Beta-Carotene is an organic, strongly colored red-orange pigment found abundant in plants and fruits. Beta-carotene is found in many foods and is sold as a dietary supplement. Beta-carotene is considered as an antioxidant and is also a precursor to vitamin A. Beta-carotene maintains healthy skin and also plays a vital role in eye health. As much as 50 percent of vitamin A in a typical diet is provided by beta-carotene and other carotenoids. Once ingested, beta-carotene is either converted into vitamin A (retinol), which the body can use in a variety of ways, or it acts as an antioxidant and protect cells from the damaging effects of harmful free radicals.<sup>[2]</sup> Beta-carotene 7.5% dispersion is a fine droplets of the beta-carotene oil dispersion encapsulated as a free-flowing powder. The recommended dietary allowance of Beta-carotene is 3 to 6 mg/day.<sup>[3]</sup>

Beta-carotene is prone to oxidation and has poor stability.<sup>[4,5]</sup> Several studies had reported that Beta-carotene 7.5% dispersion is not stable in multivitamin syrup formulations. In this work, two different trial

batches B1 and B2 of Beta-carotene 7.5% dispersion syrups were formulated. Formulation B1 contains Beta-carotene 7.5% dispersion without any antioxidants, stabilizers and buffering agents. Formulation B2 contains Beta-carotene 7.5% dispersion with antioxidants, stabilizers and buffering agents. Formulation B3 is the multivitamin syrup consisting of Beta-carotene 7.5% dispersion, Vitamin D and E with antioxidants, stabilizers and buffering agents.

**MATERIALS AND METHODS****MATERIALS**

Beta-carotene 7.5% dispersion was obtained from Bio-Gen Extracts Pvt. Ltd., Bangalore. Vitamin D3 was procured from Fermenta Biotech Pvt. Ltd., Himachal Pradesh. Vitamin E acetate was purchased from BASF Chemicals Company, Germany. Vitamin C was obtained from HeBei Welcome Pharmaceutical Co., Ltd., China. Sucrose was obtained from E.I.D. Parry, Cuddalore. Disodium edetate was procured from Canton Laboratories Pvt. Ltd., Vadodara. All other chemicals used in the study were of analytical grades.

## METHODS

### PREFORMULATION STUDIES

#### Description

It is the initial evaluation during preformulation study which assess the colour and taste of the substance. The colour and taste of Beta-carotene 7.5% dispersion was evaluated visually.

#### Solubility

Solubility was determined as per I.P specification. Beta-carotene 7.5% dispersion was dissolved in purified water by using Ultrasonicator.

#### Drug-excipients Compatibility Study

Drug-excipients compatibility studies were performed by preparing Drug-excipient blends with different excipients. The blends were kept in the room temperature. The ratio of drug-excipients blend was 1:1. The samples were evaluated for any changes in the physical characterization with references to its controlled sample kept in room temperature for a period of 30 days.<sup>[6]</sup>

### FORMULATION OF BETA-CAROTENE 7.5% DISPERSION SYRUP

Three formulations (B1, B2 and B3) containing Beta-carotene 7.5% dispersion syrups were developed with 100% overage. The formulation B1 consists of only Beta-carotene 7.5% dispersion without any stabilizers, antioxidants and buffering agents. The formulation B2

consists of Beta-carotene 7.5% dispersion with stabilizers, antioxidants and buffering agents. The formulation B3 consists of Beta-carotene 7.5% dispersion along with vitamin D, E, stabilizers, antioxidants and buffering agents.

#### Formulation of Beta-carotene 7.5% dispersion Syrup (B2)

Dissolve sucrose in boiling purified water under constant stirring. Dissolve separately sodium benzoate, disodium edetate, citric acid, sodium citrate, ascorbic acid and saccharin sodium in purified water and add to the syrup solution. Disperse xanthan gum in propylene glycol and add to the syrup under constant stirring. Add glycerin and sorbitol to the syrup. Separately warm polysorbate 80 and dissolve butylated hydroxy toluene and add to the syrup. Separately dissolve Beta-carotene 7.5% dispersion in purified water and add to the syrup. Then add orange flavor to the syrup. Make up the volume using purified water. Filter the syrup using 200 mesh nylon cloth and check the pH of syrup (pH limit: 4.0 - 5.5).<sup>[7]</sup>

Procedure of formulation B1 is same as formulation B2 except addition of ascorbic acid, disodium edetate, citric acid, sodium citrate and butylated hydroxy toluene. Procedure of formulation B3 is same as formulation B2 along with the addition of Vitamin D3 and Vitamin E acetate. The composition of Beta-carotene 7.5% dispersion syrups were presented in table1.

**Table 1: Composition of Beta-carotene 7.5% Dispersion Syrups.**

Syrup Formulations For 1000ml(%)				
S. No.	Materials	Formulation Code		
		B1*	B2*	B3*
1	Beta-carotene 7.5% dispersion	0.128	0.128	0.128
2	Vitamin D <sub>3</sub>	~	~	0.0002
3	Vitamin E acetate	~	~	0.15
4	Ascorbic acid	~	0.25	0.25
5	Sucrose	25	25	25
6	Sodium benzoate	0.2	0.2	0.2
7	Disodium edetate	~	0.01	0.01
8	Citric acid	~	0.02	0.02
9	Sodium citrate	~	0.1	0.1
10	Glycerin	3	3	3
11	Sorbitol 70% solution	3	3	3
12	Xanthan gum	0.2	0.2	0.2
13	Propylene glycol	5	5	5
14	Polysorbate 80	1	1	1
15	Butylated hydroxy toluene	~	0.001	0.001
16	Saccharin sodium	0.05	0.05	0.05
17	Orange flavor	0.8	0.8	0.8
18	Purified water	QS	QS	QS

\*B1-Syrup containing Beta-carotene 7.5% dispersion without stabilizers, antioxidants and buffering agents.

\*B2- Syrup containing Beta-carotene 7.5% dispersion with stabilizers, antioxidants and buffering agents.

\*B3-Syrup containing Beta-carotene 7.5% dispersion, with Vitamin D, E, stabilizers, antioxidants and buffering agents.

## EVALUATION OF BETA-CAROTENE 7.5% DISPERSION SYRUPS

The evaluation of syrups such as General parameters (Appearance, colour and taste), Physical parameters (pH, Wt/ml and Viscosity) and Chemical parameter (Assay of Beta-carotene 7.5% dispersion) was carried out. All the formulations were filled in two separate 100ml amber colored PET bottles and placed in stability chamber maintained at  $30\pm 2^{\circ}\text{C}/65\pm 5\% \text{RH}$  and at  $40\pm 2^{\circ}\text{C}/75\pm 5\% \text{RH}$  for 2 months and the above tests were carried out at every 1 month interval.

### 1. General parameters

The formulated syrups were stored at  $30\pm 2^{\circ}\text{C}/65\pm 5\% \text{RH}$  and  $40\pm 2^{\circ}\text{C}/75\pm 5\% \text{RH}$  for 2 months. The appearance, colour and taste of the syrups were evaluated visually at every 1 month interval.

### 2. Physical parameters

All the formulated syrups were stored at  $30\pm 2^{\circ}\text{C}/65\pm 5\% \text{RH}$  and  $40\pm 2^{\circ}\text{C}/75\pm 5\% \text{RH}$  for 2 months. The pH, wt/ml and viscosity of the syrups were evaluated at every 1 month interval.

#### Determination of pH

The determination of pH was carried out by immersing the electrodes in the formulated syrups using Digital pH meter.

#### Determination of Weight/milliliter

The weight/milliliter of a liquid is the weight, in gram, of 1ml of liquid when weighed in air at  $25^{\circ}\text{C}$ , unless otherwise specified. A pre weighed volumetric flask was taken and the syrup was added up to the mark. The net volume was noted. Then the volumetric flask was weighed and weight/milliliter was calculated accordingly.

#### Determination of viscosity

Viscosity is measured using Ostwald-type viscometer. Fill the viscometer, previously washed and completely dried, with the liquid under examination through tube L to slightly above the mark G, using a long pipette. Place the tube vertically in a water-bath maintained at the temperature indicated in the monograph and allow to stand for not less than 30 min to allow the temperature to reach equilibrium. Adjust the volume of the liquid so that the bottom of the meniscus settles at the mark G. Suck or blow the liquid to a point above 5 mm above the mark E. After releasing pressure or suction, measure the time taken for the bottom of the meniscus to fall from the top edge of mark E to the top edge of mark F.<sup>[8]</sup>

### 3. Chemical parameter

This includes assay of Beta-carotene 7.5% dispersion by UV-VIS spectrophotometer at 455 nm. Accurately weighed quantity of Beta-carotene 7.5% dispersion was suitably diluted in purified water in amber colored standard measuring flask and make up to the volume

using purified water. Then filtered through Whatman filter paper (Standard). Accurately weighed quantity of formulated syrup was suitably diluted in purified water in amber colored standard measuring flask and make up the volume to the mark. (Sample). The assay of Beta-carotene 7.5% dispersion was calculated using the formula.

$$\text{Percentage Assay} = \frac{\text{Drug content}}{\text{Label claim}} \times 100$$

## RESULTS AND DISCUSSIONS

### PREFORMULATION STUDIES

#### Description

The colour of Beta-carotene 7.5% dispersion was found to be reddish-orange. Beta-carotene 7.5% dispersion showed oily taste.

#### Solubility Test

The solubility study revealed that Beta-carotene 7.5% dispersion was soluble in purified water (1 in 10 parts).

#### Drug-Excipients Compatibility Study

The drug-excipients compatibility study revealed that there was no change or interaction between drug and excipients on storage at room temperature for 30 days. Thus it was concluded that the excipients selected for the formulation were compatible with Beta-carotene 7.5% dispersion and suitable for formulation development. The results are shown in table 2.

**Table 2: Drug (Beta-Carotene 7.5% Dispersion) – Excipients Compatibility Study.**

S.No.	Composition	Storage Condition: Room Temperature	
		Initial Period	After 30 Days
1	Beta-carotene 7.5% dispersion	Reddish-orange colour powder	NCC
2	Beta-carotene 7.5% dispersion + Sucrose	Reddish-orange white colour powder	NCC
3	Beta-carotene 7.5% dispersion + Sodium benzoate	Reddish-orange white colour powder	NCC
4	Beta-carotene 7.5% dispersion + Disodium edetate	Reddish-orange white colour powder	NCC
5	Beta-carotene 7.5% dispersion + Citric acid	Reddish-orange white colour powder	NCC
6	Beta-carotene 7.5% dispersion + Sodium citrate	Reddish-orange white colour powder	NCC
7	Beta-carotene 7.5% dispersion + Glycerin	Viscous liquid with reddish-orange solids	NCC
8	Beta-carotene 7.5% dispersion + Ascorbic acid	Reddish-orange white colour powder	NCC
9	Beta-carotene 7.5% dispersion + Sorbitol 70% solution	Viscous liquid with reddish-orange solids	NCC
10	Beta-carotene 7.5% dispersion + Xanthan gum	Reddish-orange white colour powder	NCC
11	Beta-carotene 7.5% dispersion + Propylene glycol	Viscous liquid with reddish-orange solids	NCC
12	Beta-carotene 7.5% dispersion + Polysorbate 80	Viscous liquid with reddish-orange solids	NCC
13	Beta-carotene 7.5% dispersion + Butylated hydroxy toluene	Reddish-orange white colour powder	NCC
14	Beta-carotene 7.5% dispersion + Vitamin D3	Reddish-orange white colour powder	NCC
15	Beta-carotene 7.5% dispersion + Vitamin E acetate	Viscous liquid with reddish-orange solids	NCC
16	Beta-carotene 7.5% dispersion + Saccharin sodium	Reddish-orange white colour powder	NCC
17	Beta-carotene 7.5% dispersion + Orange flavor	Viscous liquid with reddish-orange solids	NCC
18	Beta-carotene 7.5% dispersion + Purified water	Orange colour solution	NCC

\* NCC – No Characteristic Change.

## EVALUATION OF BETA-CAROTENE 7.5% DISPERSION SYRUP

### General Parameters

There was no change observed in the appearance, colour and taste in formulation B2 and B3 after 1<sup>st</sup> and 2<sup>nd</sup> month even after stored at 30±2°C/65±5% RH and 40±2°C/75±5% RH. But formulation B1 showed colour change from orange to light orange when stored at 40±2°C/75±5% RH. This may be due to the absence of stabilizers, antioxidants and buffering agents in formulation B1 which affected its stability. The results of general parameters of formulated syrups are shown in table 3.

**Table 3: Evaluation of General Parameters of Beta-Carotene 7.5% Dispersion Syrups.**

Formulation Code	Parameters	Initial Period	Storage Temperature			
			30±2°C/65±5% RH		40±2°C/75±5% RH	
			1 <sup>st</sup> Month	2 <sup>nd</sup> Month	1 <sup>st</sup> Month	2 <sup>nd</sup> Month
B1	Appearance	Orange viscous liquid	NCC	NCC	NCC	NCC
	Colour	Orange colour	NCC	NCC	Light orange colour	Light orange colour
	Taste	Sweet oily taste	NCC	NCC	NCC	NCC
B2	Appearance	Orange viscous liquid	NCC	NCC	NCC	NCC
	Colour	Orange colour	NCC	NCC	NCC	NCC
	Taste	Sweet oily taste	NCC	NCC	NCC	NCC
B3	Appearance	Orange viscous liquid	NCC	NCC	NCC	NCC
	Colour	Orange colour	NCC	NCC	NCC	NCC
	Taste	Sweet oily taste	NCC	NCC	NCC	NCC

\*NCC – No Characteristic Change.

### Physical Parameters

In Physical parameters (pH, wt/ml and viscosity) evaluation the viscosity and pH of formulation B1 were not within the limit when stored at 30±2°C/65±5% RH and 40±2°C/75±5% RH as this syrup does not contain any stabilizer and buffering agent. In formulation B2 and

B3 all the parameters were within the limit and both the formulation were stable at 30±2°C/65±5% RH and 40±2°C/75±5% RH. The results of physical parameters of formulated syrup are shown in table 4.

**Table 4: Evaluation of Physical Parameters of Beta-Carotene 7.5% Dispersion Syrups.**

Formulation Code	Parameters	Limit	Initial Period	Storage Temperature			
				30±2°C/65±5%RH		40±2°C/75±5%RH	
				1 <sup>st</sup> Month	2 <sup>nd</sup> Month	1 <sup>st</sup> Month	2 <sup>nd</sup> Month
B1	pH	4.0 - 5.5	5.97	5.88	5.86	6.40	6.33
	Weight/milliliter (g/ml)	1.0-1.25	1.1071	1.102	1.101	1.099	1.097
	Viscosity (mm <sup>2</sup> s <sup>-1</sup> )	18-30	16.33	15.33	15.23	19.54	19.50
B2	pH	4.0 - 5.5	4.42	4.56	4.55	4.51	4.50
	Weight/milliliter (g/ml)	1.0-1.25	1.135	1.131	1.126	1.110	1.095
	Viscosity (mm <sup>2</sup> s <sup>-1</sup> )	18 - 30	19.67	19.33	19.24	27.33	27.26
B3	pH	4.0 - 5.5	4.54	4.54	4.52	4.50	4.49
	Weight/milliliter (g/ml)	1.0-1.25	1.105	1.103	1.098	1.064	1.062
	Viscosity (mm <sup>2</sup> s <sup>-1</sup> )	18 - 30	19.65	19.61	19.60	18.33	18.31

### Chemical Parameter

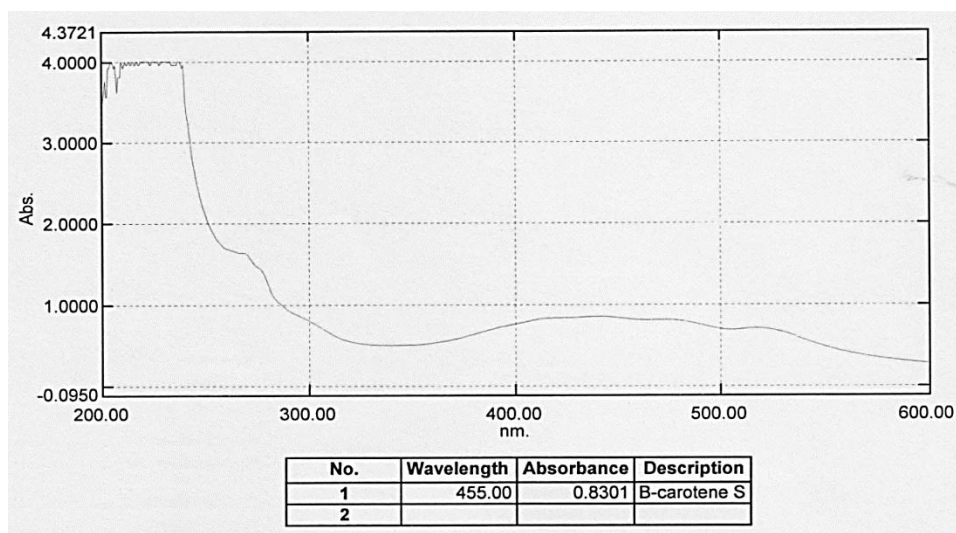
In Chemical parameter evaluation it was observed that the drug content of formulation B1 decreased when stored at both 30±2°C/65±5% RH and 40±2°C/75±5% RH for 2 months. The reason for decline in drug content in formulation B1 may be that the syrup was formulated

without antioxidants, stabilizers and buffering agents. The drug content of formulation B2 and B3 were found to be stable at 30±2°C/65±5% RH and 40±2°C/75±5% RH. The results were presented in table 5 and the UV spectrum of Beta-carotene 7.5% dispersion syrups are shown in figure 1 to 3.

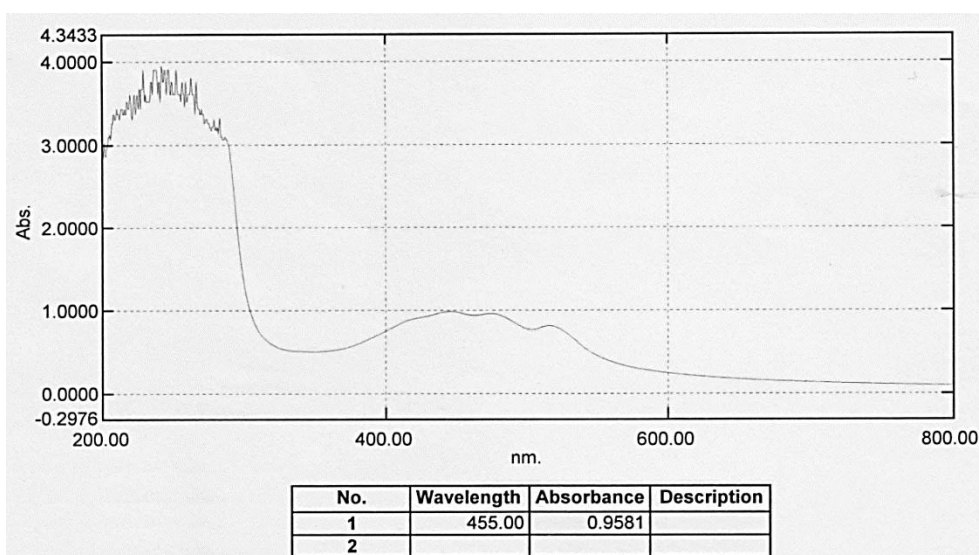
**Table 5: Evaluation of Chemical Parameter of Beta-Carotene 7.5% Dispersion Syrups.**

Formulation Code	Parameter	Initial Period	Storage Temperature			
			30±2°C/65±5%RH		40±2°C/75±5%RH	
			1 <sup>st</sup> Month	2 <sup>nd</sup> Month	1 <sup>st</sup> Month	2 <sup>nd</sup> Month
B1	Assay (%)	181.43	147.86	109.02	130.68	106.25
B2		191.80	190.02	188.65	189.83	185.63
B3		199.67	198.98	190.54	190.46	185.76

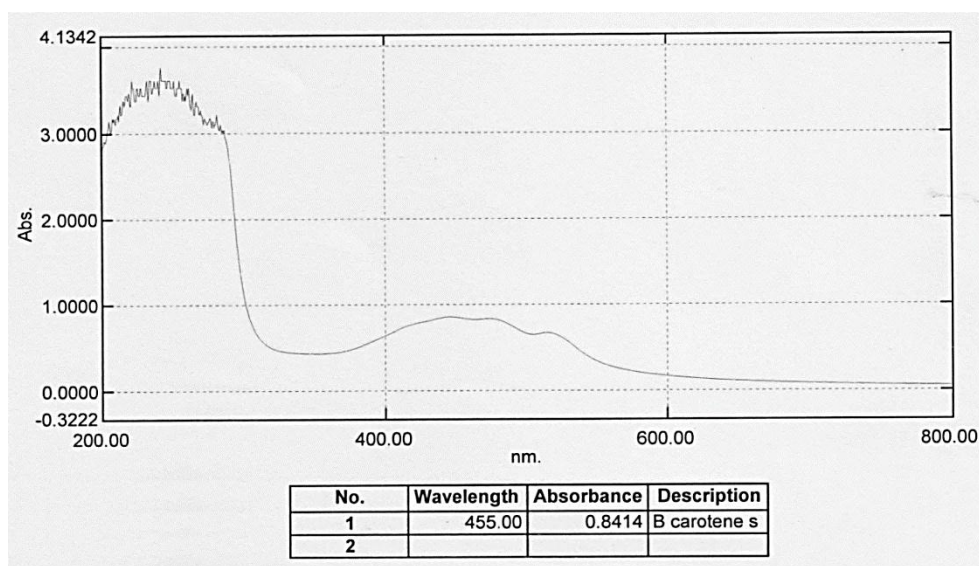




**Fig. 1: UV Spectrum of Beta-Carotene 7.5% Dispersion Syrup (Formulation B1).**



**Fig 2: UV Spectrum of Beta-Carotene 7.5% Dispersion Syrup (Formulation B2).**



**Fig 3: UV Spectrum of Beta-Carotene 7.5% Dispersion Syrup (Formulation B3).**

## CONCLUSION

From the results, it can be concluded that the stability report of the formulation B1 was not good. The absence of stabilizers, antioxidants and buffering agents in the formulation B1 could be a reason behind the decline in drug content of Beta-carotene 7.5% dispersion. Whereas, the formulation B2 showed good stability of Beta-carotene 7.5% dispersion as it contains stabilizers, antioxidants and buffering agents. Formulation B2 also showed good stability in terms of General, Physical and Chemical parameters and was selected as optimized formulation. Multivitamins (Vitamin D and E) were incorporated in the optimized formulation and the formulation was termed as B3. The stability of formulation B3 was evaluated in terms of General, Physical and Chemical parameters. The stability report of formulation B3 revealed that Beta-carotene 7.5% dispersion was stable even in presence of Vitamin E and Vitamin D (Multivitamins).

The study concludes that stable formulation of multivitamin syrup (Vitamin A and E) with Beta-carotene 7.5% dispersion (B3) could be successfully developed as the stability results showed that the developed formulations were found to be stable in terms of General, Physical and Chemical parameters evaluated at  $30\pm 2^{\circ}\text{C}/65\pm 5\%$  RH and  $40\pm 2^{\circ}\text{C}/75\pm 5\%$  RH for 2 months.

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