World Journal of Pharmaceutical Science and Research
www.wjpsronline.com
Research Article
ISSN: 2583-6579
SJIF Impact Factor: 3.454
Year - 2024
Volume: 3; Issue: 4
Page: 292-315

DEVELOPMENT OF SOLID ORAL DOSAGE FORM CONTAINING OSELTAMIVIR FOR USE IN THE TREATMENT OF INFLUENZA ILLNESS FOR ALL PATIENT GROUPS

Canberk Yılmaz[1*], Cuneyt Toprak[1], Gokay Gun[1] and Erdınc Babuc[1]

[1]Research and Development Center, World Medicine İlaç San. ve Ticaret A.Ş., Istanbul, Turkiye.

Article Received: 30 June 2024 | | Article Revised: 21 July 2024 | | Article Accepted: 14 August 2024

***Corresponding Author: Canberk Yılmaz**
Research and Development Center, World Medicine İlaç San. ve Ticaret A.Ş., Istanbul, Turkiye.
DOI: https://doi.org/10.5281/zenodo.13624643

How to cite this Article: Canberk Yılmaz*, Cuneyt Toprak, Gokay Gun and Erdınc Babuc. (2024). DEVELOPMENT OF SOLID ORAL DOSAGE FORM CONTAINING OSELTAMIVIR FOR USE IN THE TREATMENT OF INFLUENZA ILLNESS FOR ALL PATIENT GROUPS. World Journal of Pharmaceutical Science and Research, 3(4). https://doi.org/10.5281/zenodo.13624643

ABSTRACT

Oseltamivir is administered orally for the treatment and prevention of acute, uncomplicated seasonal influenza infections. The white used is a neuraminidase inhibitor available by prescription. Although there are 3 different types (A, B, C) Oseltamivir shows activity against A and B influenza viruses. The main purpose of this study is to develop a generic product that can be used by patient populations of all ages in the treatment and prevention of seasonal flu infections, which have been very common in recent years. After various trial productions, the designed unit formula was implemented by ensuring homogeneity with the dry mix geometric dilution production method due to its low dose of preservative (Sodium Benzoate). The suitability of the study was evaluated by taking into account the physical and chemical analysis features in the European Pharmacopoeia standards.

KEYWORDS: Oseltamivir Phosphate Powder For Preparing Oral Suspension, Geometric Dilution Method, Turbiscan Tower, Formulaction, Zeta Potential, Pre Development, Product Development.

INTRODUCTION

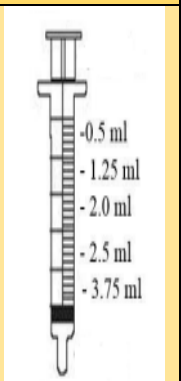
Oseltamivir is an antiviral drug used to treat and prevent the influenza A and influenza B viruses that cause influenza.[1] Oseltamivir reduces the recovery time of patients by 1-2 days by helping to reduce symptoms caused by the flu virus (Influenza), such as nasal congestion, sore throat, fever, chills, and severe fatigue. In addition, it can be used to prevent the flu if there is someone who has not been infected with the disease or has influenza disease nearby. In general, Oseltamivir has an effect by stopping the growth of the flu virus. But it is not a substitute for the flu vaccine used.[2]

Oseltamvir Phosphate is a raw material in the BCS III class. (High Solubility, Low Permeability).[3] Oseltamivir was used as an active ingredient in the developed product by applying a phosphate conversion factor. (One bottle (30 g) of powder for suspension contains 1.182 g of Oseltamivir Phosphate, equivalent to 900 mg of Oseltamivir.). Oseltamivir

Suspension Powder, designed for the use of all patient groups, contains 12 mg/ml of oseltamivir at a concentration of 1.2% when diluted.[4]

Oseltamivir 12 mg/ml Oral Suspension Preparation Powder, whose development process has been completed, is a disabled drug that can be used by all patient populations. Below are the recommended daily intake doses for use by all patients.

Table 1: Oseltamivir Recommended Daily Intake Doses.[3]

Patient Age Population	Mass Index	Daily Recommended Treatment Dosage	Amount To Be Taken In Syringe Or Measuring Cup	Syringe (5ml)	Measuring Cup (20 ml)
0-1 Month Babies	2-4 kg	6 mg	0.50 ml		
1-3 Month Babies	4-7 kg	15 mg	1.25 ml		
3-6 Month Babies	7-10 kg	24 mg	2.00 ml		
-	7-10 kg	30 mg	2.50 ml		
-	15-23 kg	45 mg	3.75 ml		
-	23-40 kg	60 mg	5.00 ml		
-	> 40 kg	75 mg	6.25 ml		

For patients to fully receive their recommended daily intake doses, our product is placed in a box as the primary packaging material; Studies have been carried out to present 30 g of powder in a 75 cc striped bottle, along with a plastic measuring cup and a sensitive syringe set for babies to use. The main packaging materials used in our Oseltamivir 12 mg/ml Powder for Preparation of Oral Suspension product are given for visual purposes.

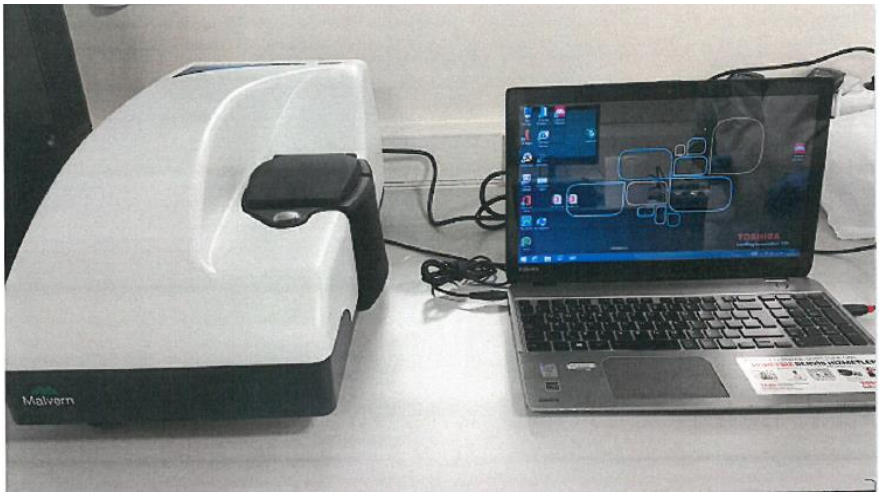
Picture 1: Oseltamivir Phosphate Primer Packaging Materials.

To prepare Oseltamivir Suspension, pre-development devices such as Turbiscan Tower and Zeta Potential were used during the preliminary development studies of our powder product. To obtain a homogeneous mixture during manufacturing and pilot study using different unit formulas and manufacturing methods, the physical behavior under stress conditions was observed using pre-feasibility devices (Turbiscan Tower and Zeta Potential) of the samples. All these studies are described in detail in the following stages.

Zeta Potential General Information

Zeta potential is the electrical potential at the slipping plane. This plane is the interface that separates mobile fluid from the fluid that remains attached to the surface. The zeta potential is an important and readily measurable indicator of the stability of colloidal dispersions.[2] The magnitude of the zeta potential indicates the degree of electrostatic repulsion between adjacent, similarly charged particles in a dispersion. For molecules and particles that are small enough, a high zeta potential will confer stability, and the solution or dispersion will resist aggregation.

Knowing the potential of zeta potential in new product formulations helps us to learn about the physical stability of the product before exposure to the stability conditions of the product.[5]



Picture 2: Malvern Zetasizer Device.[6]

For samples diluted according to the viscosity values of the product such as 1/10,1/20, 1/30, 1/50 with saline solution to be considered stable under stability conditions, the potential value of zeta must necessarily be greater than the values of -31 and -40 MV.[7]

Table 2: Zeta Potential Stability Characteristics Index.[8]

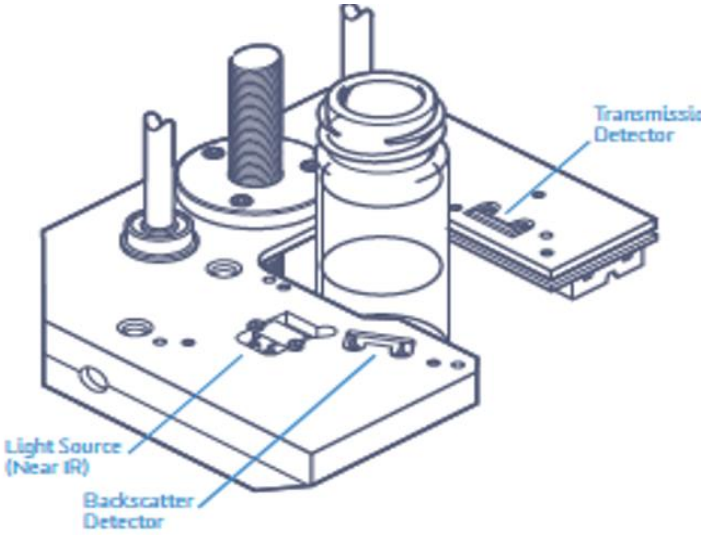
Stability Characteristics Of Zeta Potential	Avg. Zeta Potential In Milivolts
Maximum Agglomeration and Precipitation	0 to +3
Range of Strong Agglomeration and Precipitation	+ 5 to - 5
Threshold of Agglomeration	- 10 to -15
Threshold of Delicate Dispersion	- 16 to -30
Moderate Stability	-31 to -40
Fairly Good Stability	-41 to -60
Very Good Stability	-61 to -80
Extremely Good Stability	-81 to -100

Turbiscan Tower General Information

Turbiscan is a reference technology for direct physical stability analysis. It allows you to accelerate the measurement time and observe the imbalance under stability conditions set in temperature control from 4 °C to 80 °C. 6 stability cabinets can be used at the same or different times, but a single temperature can be set for all cabinets.[9]

Picture 3: Formulaction Turbiscan Tower.

Static multiple light scattering concentrated liquid distributions in their natural state is the most optical method to directly characterize. It works on the principle that photons send 800 nm light sources to the sample. These photons are removed from samples after being repeatedly scattered by particles (or droplets) in dispersions, and 2 simultaneous detectors Detection is provided by (Backscatter and Transmission detector).



Picture 4: Turbiscan Tower Studying Principle.

Evaluation of Turbiscan Analysis Results

Turbiscan Tower analysis results (TSI Global, Bottom, Middle, and Top) Our samples below 3.0 are stable under Set stability conditions showing that they remain in a structure.

TSI (Top)

It is the evaluation part in which the creamy tendency of the sample is interpreted. Migration Rate and Particle Size (mm)in products with a tendency to creamy the particle sizes of raw materials used in the formulation should be reviewed by observing the change of particle sizes of the product over time by making the test.

TSI (Middle)

It is the evaluation of particles in terms of density. The granularity of particles, surface interference, and emulsified state. The formulation gives information about whether surfactant constriction is sufficient.

TSI (Bottom)

Values that control the tendency of the sample to collapse (sedimentation) under stability conditions.

TSI (Global)

In solutions and suspensions, Oswalt represents Ripeng's law.

Oswalt Ripeng Law

A non-homogeneous structure changes over time, that is, small particles describe its precipitation by dissolving over time and merging with large particles law.

Visual equivalent TSI analysis measurements of TSI values corresponding to a particular state of instability are evaluated using the TSI scale associated with the states. The results obtained are evaluated based on the results in the table below to get an idea of the behavior of the product instability conditions.

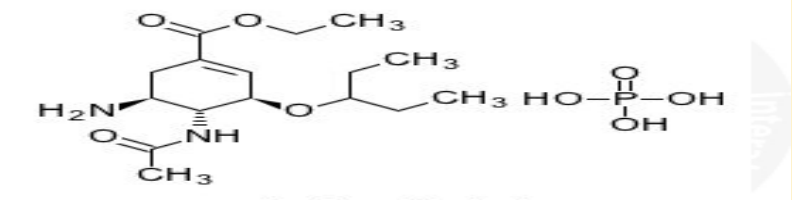
Table 3: Turbiscan Stability Index Value.[8]

A+	Visually Perfect **No significant destabilization is observed and the specimen remains visually stable. A + ranking is the best sign of stability.**
A	**Visually Good** Destabilization has been identified but is at a very early stage (transition or size change). In order a, no visual destabilization is observed at this stage.
B	**Visually At The Transition Stage** The variations detected by Turbiscan are higher than the "early" stage (A) and correspond to the onset of destabilization, however, destabilization is not visual in most cases (>90%).
C	**Visually At The Transition Stage** The variations detected by Turbiscan are higher than the "early" stage (A) and correspond to the onset of destabilization, however, destabilization is not visual in most cases (>90%).
D	**Visual Failure** Extreme and significant variation and destabilization likely appear, corresponding to large sedimentation or cremation, phase separation, and large changes in particle size or color.

Chemical Characteristics of Oseltamivir Phosphate

The characteristic features of Oseltamivir Phosphate raw material, which is supplied from ARENA LIFESCIENCES source in all product development processes, are as follows.

Table 4: Physical, Chemical, and Characteristic Properties of Oseltamivir Phosphate.

Physical, Chemical, And Characteristics Of Oseltamivir Phosphate	
Appearance	White to Whitish colored powder.
Solubility	Freely soluble in Water, soluble in Mehhanol in Dimethyl Sulfoxide and propylene glycol, Sparingly soluble in dimethylformamide, slightly soluble in Alcohol, very slightly soluble in Isopropyl alcohol and polyethylene glycol 400, practically insoluble in acetonitrile.
Structural Formula	
BCS Class	It is in the Class III Drugs Category. (High Solubility, Low Permeability)
Molecular Weight	410.40 g/mol
Monecular Formula	C16H28N2O4. H3PO4
Melting Point	200-210 ° C
Storage Conditions	It should be stored at room temperature between 15-30 °C and in tightly closed airtight containers.
CAS Number	204255-11-8
Hygroscopicity	0.14 % (Non-Hygroscopic)
Optical Rotation	Between -30.7 and -32.6
Isomerism	There are eight possible isomers due to three asymmetric carbons in the molecule. As per the manufacturing process adopted, the resulting substance from the process is Ethyl (3R,4R,5S)-4- acetamido-5-amino-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylate, phosphate (1:1).
Polymorphism	It is known from the literature that the drug substance Oseltamivir phosphate exhibits polymorphism.
ATC Group	JO5A ----> Direct Acting Antivirals JO5AH ----> Neuraminidase Inhibitors JO5AH02 ----> Oseltamivir Phosphate
Therapeutic Category	Anti-Viral

MATERIAL AND METHOD

Material

Oseltamivir Phosphate active substance was procured by (ARENA LIFESCIENCES) The excipients which are used as respectively; Sorbitol P100 T (ROQUETTE), Sodium Benzoate (EASTMAN), Mono Sodium Citrate (JUNGBUNZLAUER), Sodium Saccharin Dihydrate (KAFEING), Titanium Dioxide (HUNTSMAN/SENSIENT), Xanthan Gum ((HUNTSMAN/SENSIENT) Tutti Frutti Flavour (AROMSA) supplied. All raw materials used are suitable for European Pharmacopoeia.

Method

Formulation Trial and Scale-Up Studies

Before developing the Oseltamivir 12 mg/ml Oral Suspension Powder product, the following trial studies were carried out to determine the taste, odor, pH, and Viscosity Agent amounts to be used in the formulation.

The Study of Determining the Amount of Sweetener

To develop a generic product with a taste and smell similar to Powder to prepare Tamiflu 12 mg/ml Oral Suspension, which is the reference product, taste, and smell test studies were conducted in different raw material quantities as follows.

Table 5: Determining the Amount of Sweetener.

Trial Number	Sodium Saccharin Dihydrate (mg/gr)	Tutti Frutti Flavour (mg/gr)
Trial-1	0.25	2,50
Trial-2	0.50	5.00
Trial-3	1.00	10.00
Trial-4	1.25	15,00
Trial-5	1.50	20.00
Trial-6	1.75	25.00
Trial-7	2.00	30.00
Trial-8	2.50	35.00
Trial-9	3.00	40.00
Trial-10	4.00	45.00
Trial-11	5.00	50,00

At the end of the trial studies, it was understood that the closest taste and odor result to the reference product among the samples prepared was the amounts used in Trial 3. In light of this information, it was decided to use 1.00 mg Sodium Saccharin Dihydrate and 10 mg Tutti Fruitti Flavour for 1000 mg in the unit formula.

The Study of Determining the Amount of Opacifier

To develop a generic product with an opacifier similar to Powder to prepare Tamiflu 12 mg/ml Oral Suspension, which is the reference product, taste, and smell test studies were conducted in different raw material quantities as follows.

Table 6: Determining the Amount of Oppacifier.

Trial Number	Titanium Dioxide (mg/gr)
Trial-1	1,00
Trial-2	2,00
Trial-3	3,00
Trial-4	5,00
Trial-5	10,00
Trial-6	12,50
Trial-7	15,00
Trial-8	17,50
Trial-9	20,00
Trial-10	22,50
Trial-11	25,00
Trial-12	27,50
Trial-13	30,00

It was understood that the closest visual result to the reference product among the samples prepared as a result of the trial studies was the amount used in Trial 5. In light of this information, it was decided to use 10 mg of Titanium Dioxide for 1000 mg in the unit formulation.

The Study of Determining the Amount of pH Agent

When the Powder product was diluted and the pH measurement was performed to prepare the Tamiflu 12 mg/ml Oral Suspension, which is the reference product, it was found to be 3.90 for a 75 cc product. Studies have been carried out to determine the closest amount to the reference product by using different amounts of pH Agent in the formulations prepared below.

Table 7: Determining the Amount of pH Agent.

Trial Number	Monosodium Citrate (mg/gr)	The Measured pH Value
Trial-1	5,00	7,53
Trial-2	10,00	7,05
Trial-3	15,00	6,74
Trial-4	20,00	6,55
Trial-5	30,00	6,17
Trial-6	40,00	5,69
Trial-7	45,00	5,01
Trial-8	50,00	4,57
Trial-9	51,00	4,45
Trial-10	52,00	4,38
Trial-11	53,00	4,19
Trial-12	54,00	4,05
Trial-13	55,00	3,95
Trial-14	56,00	3,80
Trial-15	57,00	3,72

As a result of trial studies, it was understood that the closest similar result to the reference product among the samples prepared was the amount of pH agent number 13. In light of this information, it was decided to use 55 mg of Monosodium Citrate for 1000 mg in the unit formulation.

The Study of Determining the Amount of Viscosity Agent

When the Powder was diluted to Prepare the reference product Tamiflu 12 mg/ml Oral Suspension, the following density and viscosity information were obtained.

Table 8: Reference Product Viscosity Value.

Tamiflu 12 mg/ml Oral Suspension Viscosity Value			
Spindle Type	**rpm**	**Tork**	**Results**
SC-4 Spindle	10,00	% 40	196 cP
SC-4 Spindle	20,00	% 50	100 cP
SC-4 Spindle	30,00	% 60	90 cP

Table 9: Reference Product Density Value.

Tamiflu 12 mg/ml Oral Suspension Density Value	
Density	1,07 g/ml

To develop products with values close to the reference product viscosity and density values, studies have been conducted using 3 different viscosity agents, the names and quantities of which are given in the following table.

Table 10: Determining the Amount of Viscosity Agent.

Trial Number	Xanthan Gum (mg/gr)	Sodium Carboxymethylcellulose (Blanose) (mg/gr)	Polyacrylic Acid (Carbomer) (mg/gr)
Trial-1	1,00	1,00	1,00
Trial-2	2,00	2,00	2,00
Trial-3	3,00	3,00	3,00
Trial-4	5,00	5,00	5,00
Trial-5	10,00	10,00	7,50
Trial-6	15,00	15,00	10,00
Trial-6	20,00	20,00	15,00

Based on the results of the 6 tests performed, the following results were obtained as a viscosity value close to the reference product.

Table 11: Viscosity Analysis Results of Trials.

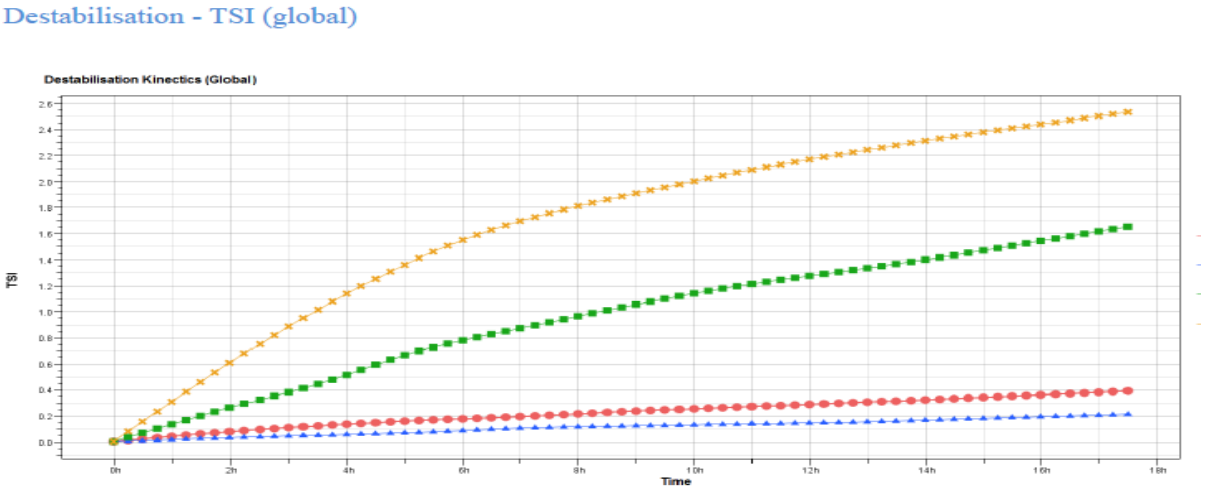
Raw Material Name	Amount (mg/gr)	Viscosity Value (SC-4 Spindle) (rpm)	Results (cP)
Xanthan Gum	10,00	**10.00**	218.00
		20.00	132.00
		30.00	110.00
Sodium Carboxymethylcellulose (Blanose)	20,00	**10.00**	250.00
		20.00	175.00
		30.00	139.00
Polyacrylic Acid (Carbomer)	7,50	**10.00**	151.00
		20.00	85.00
		30.00	59.00

Three different results with similar properties to the reference product were obtained. It was decided to prepare test products in small sizes with 3 different raw materials and subject them to turbiscan and zeta potential analyses to observe their behavior under stress conditions. Formulation development studies will begin with the raw material and amount that behaves closest to the reference product under stress conditions.

Comparative Turbiscan Analysis Results

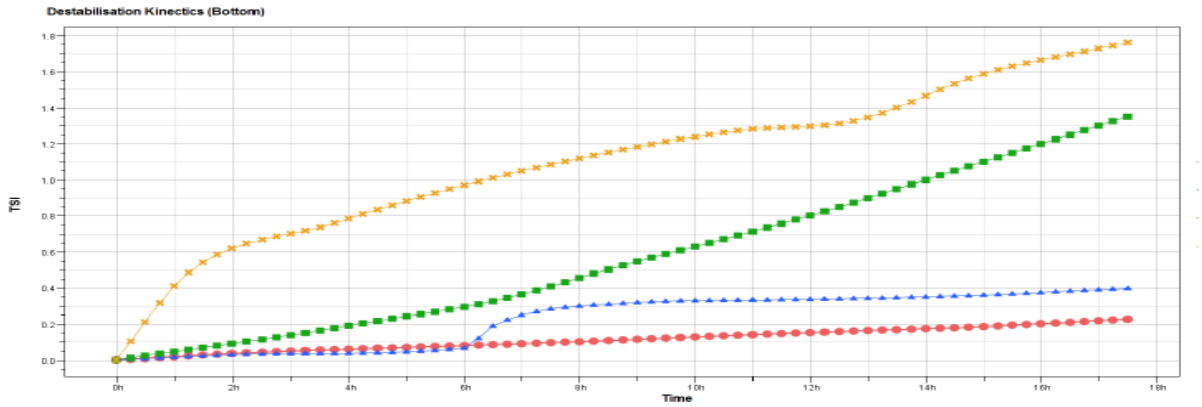
Table 12: Turbiscan Analysis Preliminary Information.

Symbol	Measurements	Ref Scan.	Duration	No Scans	T (C°)	Bottom Of The Cell	Meniscus
	Original Product	0 s.	17 hours 30 min.	71	39.98	6.14	46.74
	Xanthan Gum	0 s.	17 hours 30 min.	71	39.98	6.10	47.22
	Blanose	0 s.	17hours 30 min.	71	39.98	6.20	46.60
	Carbomer	0 s.	17hours 30 min.	71	39.98	6.16	46.56



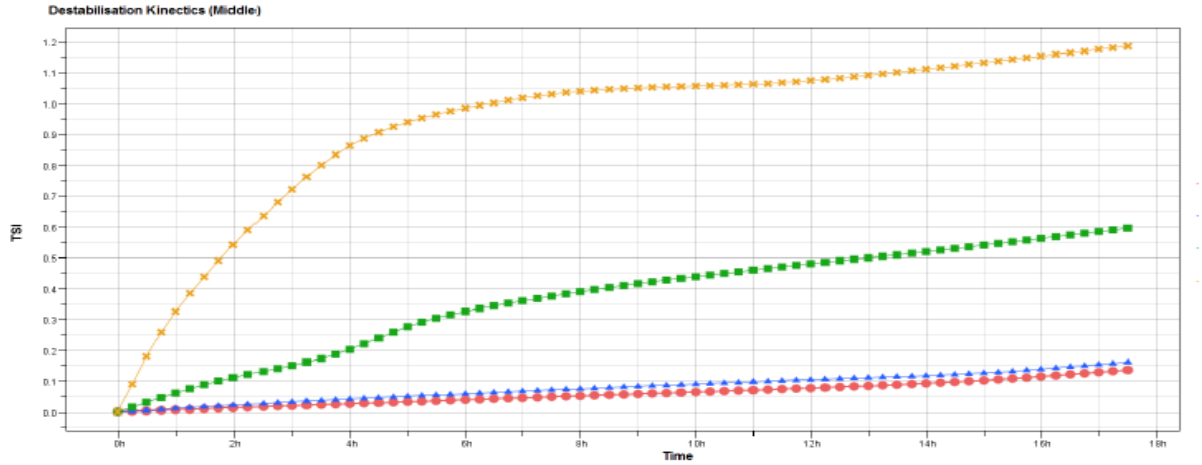
Picture 5: Turbiscan TSI (Global) Analysis Chart.

Destabilisation - TSI (bottom)



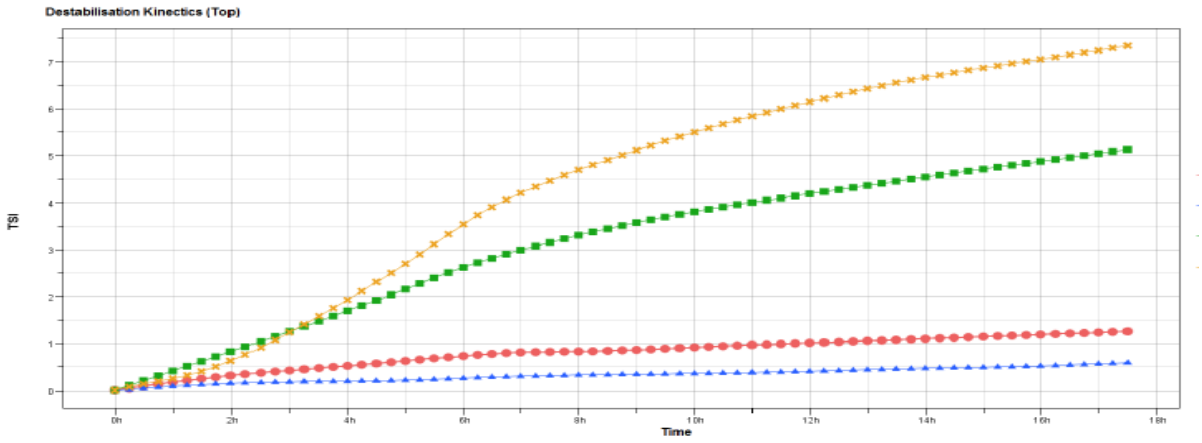
Picture 6: Turbiscan TSI (Bottom) Analysis Chart.

Destabilisation - TSI (middle)



Picture 7: Turbiscan TSI (Middle) Analysis Chart.

Destabilisation - TSI (top)



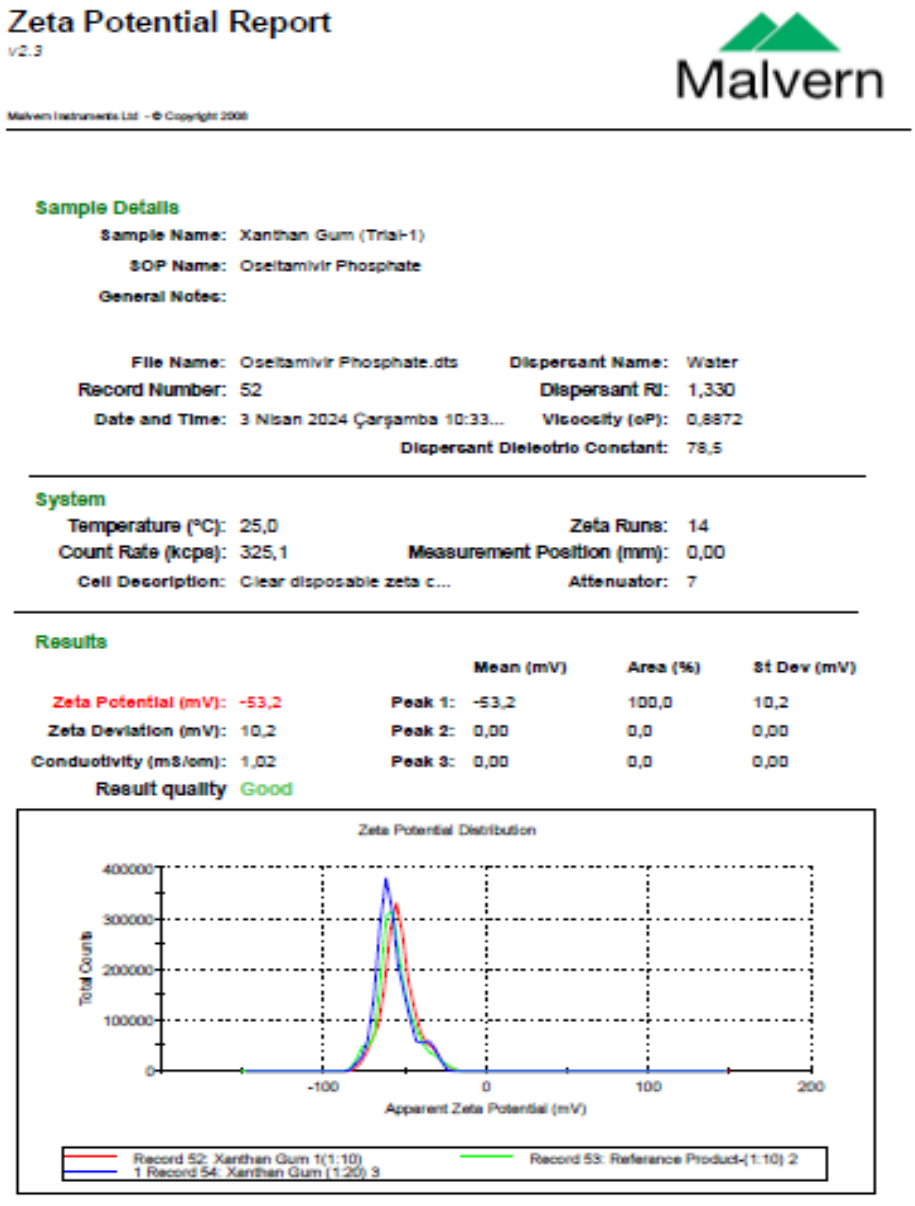
Picture 8: Turbiscan TSI (Top) Analysis Chart.

Table 13: Turbiscan Analysis Results.

Symbol	Measurements	TSI (Global) 17 hours	TSI (Bottom) 17 hours	TSI (Middle) 17 hours	TSI (Top) 17 hours
	Original Product	0.4	0.2	0.1	1.2
	Xanthan Gum	0.2	0.4	0.2	0.6
	Blanose	1.6	1.3	0.6	6.0
	Carbomer	2.6	1.7	1.2	7.2

It was decided to continue formulation studies with Xanthan Gum raw material, which exhibits similar stable behavior to the reference product under stress conditions. In this regard, comparative Zeta potential analyses were carried out between the reference product and the trial with Xanthan Gum.

Comparative Zeta Potential Results (Trial-1 and Reference Product)



Picture 9: Zeta Potential Analysis Results.

Evaluation of Turbiscan and Zeta Potential Analysis Results

The evaluation of the analysis results obtained is as follows.

Table 14: All Trials Turbiscan Analysis Results.

Turbiscan Tower Analysis Results						
Measurement	**TSI (Top)**	**TSI (Middle)**	**TSI (Bottom)**	**TSI (Global)**	**TSI Index Classification**	**General Assessment**
Original Product	1.2	0.1	0.2	0.4	A+	Visually Perfect
Xanthan Gum	0.6	0.2	0.4	0.2	A+	Visually Perfect
Blanose	6.0	0.6	1.3	1.6	C	Visually At The Transition Stage
Carbomer	7.2	1.2	1.7	2.6	C	Visually At The Transition Stage

Table 15: Xanthan Gum Zeta Potential Results.

Zeta Potential Analysis Results		
Measurement	**Zeta Potential**	**General Assessment**
Xanthan Gum	-53.2 MV	Fairly Good Stability

As a result of all trials, the quantities of raw materials planned to be used were determined. Since Oseltamivir Phosphate is a BCS III class raw material (High solubility, Low Permeability) and its amount in the formulation is considered to be suitable for dry mixture, it was decided to choose Sorbitol P100 T, which has high filler fluidity. If the preservative amounts are distributed homogeneously, it is planned to finalize our product and move on to the analysis and stability phase. The final unit formula obtained as a result of all experiments is as follows.

Table 16: Final Formulation.

Ingredients	Function	Amount (mg/gr)
Oseltamivir Phosphate	Active Substance	39.40
Sodium Benzoate	Antimicrobial Preservative	2.50
Sorbitol P 100 T	Filler	872.10
Monosodium Citrate	pH Agent	55.00
Sodium Saccharin Dihydrate	Sweetener	1.00
Titanium Dioxide	Opacifier	10.00
Xanthan Gum	Viscosity Agent	10.00
Tutti Frutti Flavour	Aromatizan	10.00
TOTAL		**1000.00**

Trial-1 Manufacturing Method

Batch Size: 3 kg / 30 Bottle

1st Stage: Weighing

Raw materials are weighed by the manufacturing formula.

2nd Stage: Mixing

Oseltamivir Phosphate, Sodium Benzoate, Monosodium Citrate, Sodium Saccharin Dihydrate, Titanium Dioxide, Xanthan Gum, and Tutti Frutti Flavor are mixed in a cubic mixer.

3rd Stage: Final Mixing

The final mixture is made by adding Sorbitol P100 T to the resulting mixture.

The flow characteristics of the final mixture obtained during product development studies are evaluated by the Carr Index and Hausner Ratio. The flow characteristics for Trial-1 are evaluated below.

$$Carr's\ Index = \frac{\rho bulk}{\rho tab} \times 100 \quad Hausner\ Rate = \frac{\rho tab}{\rho bulk}$$

Table 17: Carr Index and Hausner Ratio Results Evaluation Table.

Flow Properties	Carr's Index (%)	Hausner Rate
Excellent	5-15	1,05-1,18
Good	12-16	1,14-1,19
Appropriate	18-21	1,22-1,27
Weak	23-35	1,30-1,54
Very Weak	33-38	1,49-1,61
Extremely Weak	>40	>1,67

Bulk Density (ρ_{bulk}): 0.50 (g/ml) Tapped Density ($\rho_{tab.}$): 0.58 (g/ml)

Carr's Index: $\frac{0.58 - 0.50}{0.58} * 100 = 13.79$ Hausner Ratio (HR): $\frac{0.58}{0.50} = 1.16$

As indicated in the above formula and tables, both Carr's index value is between 5-15 (13.79) and the Hausner Ratio (HR) is between 1.05 -1.18 (1.16) indicating that the dust flow is good.

4th Stage: Filling

The final mixture is filled into a 75 cc lined bottle of 30 ± 3 %. (29.10 gr -30.90 gr)

Trial-1 Result

To control the homogeneity of the final product filled with the filling process; The dosage units were subjected to homogeneity analysis. Due to the reason for seeing out-of-limit results in the amount of Sodium Benzoate, it was decided to conduct Trial 2 with the Geometric dilution manufacturing method.

Table 18: Trial-1 Uniformity of Dosage Unit Results (Sodium Benzoate).

Test	Specifications	Sample Information	Result
Uniformity of Dosage Unit **Sodium Benzoate**	2.5 ± % 5 mg/gr (2,375 mg/tb -2,625 mg/gr) Acceptance value (AV) should meet the requirements. Not more than 2 of the individual masses deviate from the average mass by more than 5.00 % and none deviates by more than 10.00 %	**1. Sample**	1.387 mg/gr (55.48 %)
		2. Sample	2.547 mg/gr (101.88 %)
		3. Sample	1.232 mg/gr (49.28 %)
		4. Sample	0.356 mg/gr (14.24 %)
		5. Sample	3.050 mg/gr (122.00 %)
		6. Sample	2.480 mg/gr (99.20 %)
		7. Sample	2.632 mg/gr (105.28 %)
		8. Sample	1.853 mg/gr (74.12)
		9. Sample	1.672 mg/gr (66.88 %)
		10. Sample	1.997 mg/gr (79.88 %)
Standard Deviation			**30.37**
Average Weight			**1.921 mg/gr**
AV (Average Value)			**72.90**

Trial-2 Manufacturing Method

Batch Size: 3 kg / 100 Bottle

1st Stage: Weighing

Raw materials are weighed by the manufacturing formula.

2nd Stage: Sieving and Mixing

Oseltamivir Phosphate, Sodium Benzoate, Monosodium Citrate, and Titanium Dioxide are sieved through a 0.3 mm sieve and Sodium Saccharine Dihydrate, Xanthan Gum, Tutti Frutti Flavor are mixed in a cubic mixer.

3rd Stage: Mixing

The resulting mixture is mixed with 1/3 Sorbitol P100 T in a cubic mixer.

4th Stage: Mixing

The resulting mixture is mixed with 1/3 Sorbitol P100 T in a cubic mixer.

5th Stage: Final Mixing

The final mixture is made by adding 1/3 Sorbitol P100 T to the resulting mixture.

The flow characteristics of the final mixture obtained during product development studies are evaluated by the Carr Index and Hausner Ratio. The flow characteristics for Trial-1 are evaluated below.

$$Carr's\ Index = \frac{\rho bulk}{\rho tab}\ x\ 100\ Hausner\ Rate = \frac{\rho tab}{\rho bulk}$$

Table 19: Carr Index and Hausner Ratio Results Evaluation Table.

Flow Properties	Carr's Index (%)	Hausner Rate
Excellent	5-15	1,05-1,18
Good	12-16	1,14-1,19
Appropriate	18-21	1,22-1,27
Weak	23-35	1,30-1,54
Very Weak	33-38	1,49-1,61
Extremely Weak	>40	>1,67

Bulk Density (**ρbulk**): 0.50 (g/ml) Tapped Density ($\mathbf{p}_{tap.}$): 0.58 (g/ml)

Carr's Index: $\frac{0.57 - 0.51}{0.57} * 100 = 10.53$ Hausner Ratio (HR): $\frac{0.57}{0.51} = 1.12$

As indicated in the above formula and tables, both Carr's index value is between 5-15 (10.53) and the Hausner Ratio (HR) is between 1.05 -1.18 (1.12) indicating that the dust flow is excellent.

4th Stage: Filling

The final mixture is filled into a 75 cc lined bottle of 30 ± 3 %. (29.10 gr -30.90 gr)

Trial-2 Result

A homogeneous mixture was obtained in experiment 2, which was prepared by the geometric observation method. After the results were found to be appropriate, it was decided to subject the Trial-2 samples to chemical analysis. The content uniformity analysis results of Trial 2 are as follows.

Table 20: Trial-2 Uniformity Of Dosage Unit Results(Sodium Benzoate).

Test	Specifications	Sample Information	Result
Uniformity of Dosage Unit **Sodium Benzoate**	2.5 ± % 5 mg/gr (2,375 mg/tb -2,625 mg/gr) Acceptance value (AV) should meet the requirements. Not more than 2 of the individual masses deviate from the average mass by more than 5.00 % and none deviates by more than 10.00 %	**1. Sample**	2,524 mg/gr (100.96 %)
		2. Sample	2.536 mg/gr (101.44 %)
		3. Sample	2.450 mg/gr (98.00%)
		4. Sample	2.389 mg/gr (95.56 %)
		5. Sample	2.501 mg/gr (100.01 %)
		6. Sample	2.581 mg/gr (103.24 %)
		7. Sample	2.605 mg/gr (104.20 %)
		8. Sample	2.498 mg/gr (99.92)
		9. Sample	2.438 mg/gr (97.52 %)
		10. Sample	2.590 mg/gr (103.60 %)
Standard Deviation			**0.067**
Average Weight			**2.511 mg/gr**
AV (Average Value)			**0.161**

When the results of the content uniformity analyses of Sodium Benzoate, which has the smallest amount (2%) in the formulation, were evaluated, it was clearly understood that our product was homogeneous. For this reason, it was decided to subject the samples to finished product analysis.

Table 20: Trial-2 Finished Product Analysis Results.

Finished Product Analysis Results (Trial-2)		
Test	**Specification**	**Results**
Appearance	White to Whitish colored powder.	Complies
Identification **Oseltamivir Phosphate**	Retention times of main peaks which are obtained from sample and standard solutions chromatograms should be similar.	Complies
Water Content	NMT 4.00 %	0.52 %
Uniformity of Dosage Units **Oseltamivir Phosphate Sodium Benzoate**	Acceptance value (AV) should meet the requirements. Not more than 2 of the individual masses deviate from the average mass by more than 5.0% and none deviates by more than 10.0%	Complies
Assay **Oseltamivir** **Sodium Benzoate** **(mg/gr)**	30 mg/gr ± 5.0% (28.50– 31.50 mg/gr) 2.5 mg/gr ± 5.0% (2.25– 2.625 mg/gr)	30.09 2.51
Diluted Assay **Oseltamivir** **Sodium Benzoate** **(mg/ml)**	6.0 mg/ml ± 5.0% (5.82– 6.30 mg/ml) 0.5 mg/gr ± 5.0% (0.485– 0.525 mg/ml)	5.90 0.50
Viscosity **SC-4 Spindle** **10 rpm** **20 rpm** **30 rpm**	For Information.	 205 cP 121 cP 105 cP
Density	For Information.	1.07 g/ml
Dissolution **Oseltamivir Phosphate**	At least 85% of the label value after 15 minutes Q = (% 75)	91.96 %
Related Substances **Impurity A** **Impurity B** **Impurity C** **Unknown Impuritiy** **Total Impurities**	 NMT 2.0% NMT 0.3% NMT 0.5% NMT 0.5% NMT 3.0%	 0.18 % 0.06 % 0.05 % 0.03 % 0.35 %

Table 21: Trial-2 Long-Term Stability Result.

Trial-2 Long Term Stability Stability Test Condition : 25°C ± 2°C – 60 % RH ± 5								
Tests	**Specifications**	**The Beginning of Stability**	**3rd Month**	**6th Month**	**9th Month**	**12th Month**	**18th Month**	**24th Month**
Appearance	White to Whitish colored powder.	Complies	Complies	Complies	Complies	Complies	Complies	Complies
Identification Oseltamivir Phosphate	Retention times of main peaks which are obtained from sample and standard solutions chromatograms should be similar.	Complies	Complies	Complies	Complies	Complies	Complies	Complies
Water Content	NMT 4.00 %	0.52 %	0.78 %	1.25 %	1.48 %	1.77 %	2.15 %	2.49 %
Assay Oseltamivir Sodium Benzoate (mg/gr)	30 mg/gr ± 10.0% (27.00– 33.00 mg/gr) 2.5 mg/gr ± 10.0% (2.25– 2.75 mg/gr)	30.09 2.51	30.53 2.49	30.02 2.48	29.66 2.45	28.60 2.42	28.14 2.40	27.88 2.36
Diluted Assay Oseltamivir Sodium Benzoate (mg/ml)	6.0 mg/ml ± 10.0% (5.40– 6.60 mg/ml) 0.5 mg/gr ± 75.0%-%115 (0.375– 0.575 mg/ml)	5.90 0.50	5.89 0.49	5.87 0.48	5.83 0.47	5.79 0.47	5.67 0.46	5.66 0.46
Dissolution Oseltamivir Phosphate	At least 85% of the label value after 15 minutes. Q = (% 75)	91.96 %	92.85 %	92.96 %	91.37 %	90.43 %	89.85 %	88.49 %
Related Substances **Impurity A** **Impurity B** **Impurity C** **Unknown Impuritiy** **Total Impurities**	 NMT 2.0% NMT 0.3% NMT 0.5% NMT 0.5% NMT 3.0%	 0.18 % 0.06 % 0.06 % 0.03 % 0.33 %	 0.21 % 0.07 % 0.05 % 0.10 % 0.43 %	 0.25 % 0.07 % 0.07 % 0.17 % 0.58 %	 0.34 % 0.07 % 0.07 % 0.19 % 0.67 %	 0.39 % 0.08 % 0.09 % 0.21 % 0.77 %	 0.44 % 0.08 % 0.11 % 0.27 % 0.90 %	 0.51 % 0.10 % 0.16 % 0.34 % 1.11 %

Table 22: Trial-2 Accelerated Term Stability Results.

Trial-2 Accelerated Stability 40°C ± 2°C – 75 % RH ± 5				
Tests	**Specifications**	**The Beginning of Stability**	**3rd Month**	**6th Month**
Appearance	White to Whitish colored powder.	Complies	Complies	Complies
Identification Oseltamivir Phosphate	Retention times of main peaks which are obtained from sample and standard solutions chromatograms should be similar.	Complies	Complies	Complies
Water Content	NMT 4.00 %	0.52 %	0.85 %	1.57 %
Assay Oseltamivir Sodium Benzoate (mg/gr)	30 mg/gr ± 10.0% (27.00– 33.00 mg/gr) 2.5 mg/gr ± 10.0% (2.25– 2.75 mg/gr)	30.09 2.51	29.59 2.43	28.31 2.35
Diluted Assay Oseltamivir Sodium Benzoate (mg/ml)	6.0 mg/ml ± 10.0% (5.40– 6.60 mg/ml) 0.5 mg/gr ± 75.0%-%115 (0.375– 0.575 mg/ml)	5.90 0.50	5.70 0.48	5.63 0.46
Dissolution Oseltamivir Phosphate	At least 85% of the label value after 15 minutes. Q = (% 75)	91.96 %	88.34 %	85.46 %
Related Substances **Impurity A** **Impurity B** **Impurity C** **Unknown Impuritiy** **Total Impurities**	 NMT 2.0% NMT 0.3% NMT 0.5% NMT 0.5% NMT 3.0%	 0.18 % 0.06 % 0.06 % 0.03 % 0.33 %	 0.54 % 0.10 % 0.15 % 0.31 % 1.10 %	 0.79 % 0.24 % 0.27 % 0.49 % 1.79 %

Scale-Up Study Manufacturing Method

Batch Size: 30 kg / 1000 Bottle

The Scale-Up study is planned to be 10 times larger than laboratory-scale manufacturing. The obtained samples were placed in long-term stability (25°C ± 2°C/60 ± 5% RH) and accelerated stability (40°C ± 2°C/75 ± 5% RH) and monitored.

1st Stage: Weighing

Raw materials are weighed by the manufacturing formula.

2nd Stage: Sieving and Mixing

Oseltamivir Phosphate, Sodium Benzoate, Monosodium Citrate, and Titanium Dioxide are sieved through a 0.3 mm Russell vibrating sieve, and Sodium Saccharine Dihydrate, Xanthan Gum, Tutti Frutti Flavor are mixed in a steel container.

3rd Stage: Mixing

The resulting mixture is mixed with 1/3 Sorbitol P100 T in a steel container.

4th Stage: Mixing

The resulting mixture is mixed with 1/3 Sorbitol P100 T in a steel container.

5th Stage: Final Mixing

The final mixture is made by adding 1/3 Sorbitol P100 T to the resulting mixture.

The flow characteristics, Carr Index, and Hausner Ratio of the final bulk obtained during scale-up studies are as follows.

$$Carr's\ Index = \frac{\rho bulk}{\rho tab}\ x\ 100 \quad Hausner\ Rate = \frac{\rho tab}{\rho bulk}$$

Table 23: Carr Index and Hausner Ratio Results Evaluation Table.

Flow Properties	Carr's Index (%)	Hausner Rate
Excellent	5-15	1,05-1,18
Good	12-16	1,14-1,19
Appropriate	18-21	1,22-1,27
Weak	23-35	1,30-1,54
Very Weak	33-38	1,49-1,61
Extremely Weak	>40	>1,67

Bulk Density (**ρbulk**): 0.51 (g/ml) Tapped Density ($\mathbf{p}_{tap.}$): 0.60 (g/ml)

Carr's Index: $\frac{(0.60 - 0.51)}{0.60} * 100 = 15.00$ Hausner Ratio (HR): $\frac{0.60}{0.51} = 1.18$

As indicated in the above formula and tables, both Carr's index value is between 12-16 (15.00) and the Hausner Ratio (HR) is between 1.14 -1.19 (1.18) indicating that the dust flow is good.

4th Stage: Filling

The final mixture is filled into a 75 cc lined bottle of 30 ± 3 %. (29.10 gr -30.90 gr)

Scale-Up Study Results

After the scale-up study, the samples were subjected to physical and chemical tests. The finished product results of the scale-up study are as follows.

Table 24: Scale-Up Study Finished Product Analysis Results.

Finished Product Analysis Results (Trial-2)		
Test	**Specification**	**Results**
Appearance	White to Whitish colored powder.	Complies
Identification Oseltamivir Phosphate	Retention times of main peaks which are obtained from sample and standard solutions chromatograms should be similar.	Complies
Water Content	NMT 4.00 %	0.73 %
Uniformity of Dosage Units Oseltamivir Phosphate Sodium Benzoate	Acceptance value (AV) should meet the requirements. Not more than 2 of the individual masses deviate from the average mass by more than 5.0% and none deviates by more than 10.0%	Complies
Assay Oseltamivir Sodium Benzoate (mg/gr)	30 mg/gr ± 5.0% (28.50– 31.50 mg/gr) 2.5 mg/gr ± 5.0% (2.25– 2.625 mg/gr)	30.32 2.67
Diluted Assay Oseltamivir Sodium Benzoate (mg/ml)	6.0 mg/ml ± 5.0% (5.82– 6.30 mg/ml) 0.5 mg/gr ± 5.0% (0.485– 0.525 mg/ml)	6.10 0.51
Viscosity	For Information.	210 cP

(SC-4 Spindle) **10 rpm** **20 rpm** **30 rpm**		125 cP 107 cP
Density	For Information.	1.07 g/ml
Dissolution **Oseltamivir Phosphate**	At least 85% of the label value after 15 minutes Q = (% 75)	93.95 %
Related Substances **Impurity A** **Impurity B** **Impurity C** **Unknown Impuritiy** **Total Impurities**	 NMT 2.0% NMT 0.3% NMT 0.5% NMT 0.5% NMT 3.0%	 0.24 % 0.07 % 0.05% 0.02 % 0.38 %

The finished product analysis results of the samples obtained from the scale-up study were also found to be appropriate when compared with the reference product. Since the analysis results of the samples obtained from the scale-up study were appropriate, a stability study was carried out on the product. The samples have long-term stability (25°C ± 2°C/60 ± 5% RH), intermediate stability (30°C ± 2°C/65 ± 5% RH) and accelerated stability (40°C ± 2°). C/ 75 ± 5% RH) was removed and monitored. Impurity specifications for the series where stability was monitored were determined by taking, into account the impurity specification "ICH Q3b R2 impurities in new drug products" document. Stability results are included in the tables below.

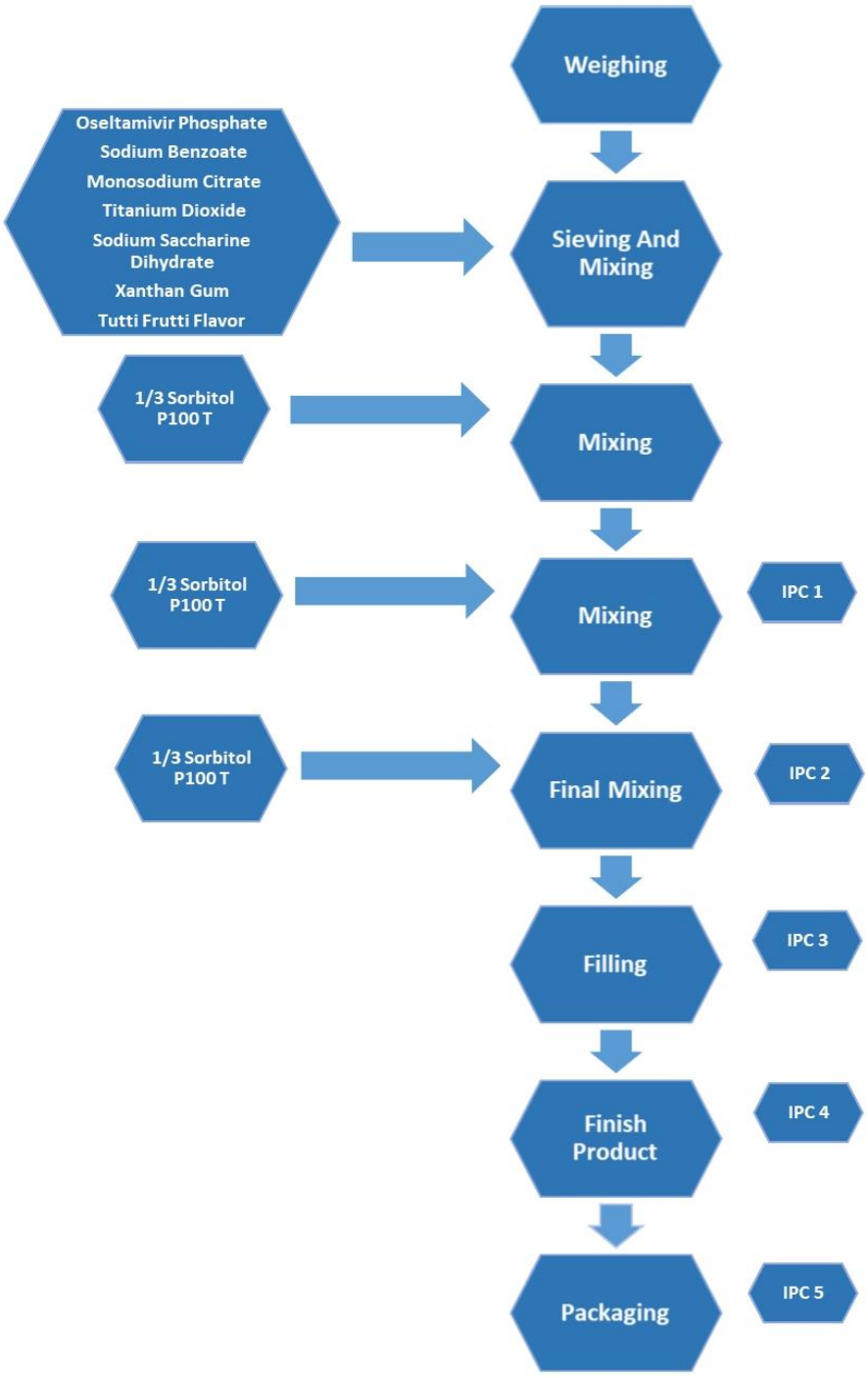
Table 25: Scale-Up Study Long-Term Stability Results.

Scale-Up Study Long-Term Stability **Stability Test Condition : 25°C ± 2°C – 60 % RH ± 5**								
Tests	**Specifications**	**The Beginning Of Stability**	**3rd Month**	**6th Month**	**9th Month**	**12th Month**	**18th Month**	**24th Month**
Appearance	White to Whitish colored powder.	Complies	Complies	Complies	Complies	Complies	Complies	Complies
Identification Oseltamivir Phosphate	Retention times of main peaks which are obtained from sample and standard solutions chromatograms should be similar.	Complies	Complies	Complies	Complies	Complies	Complies	Complies
Water Content	NMT 4.00 %	0.73 %	0.81 %	0.96 %	1.35 %	1.68 %	2.04 %	2.35 %
Assay Oseltamivir Sodium Benzoate **(mg/gr)**	30 mg/gr ± 10.0% (27.00– 33.00 mg/gr) 2.5 mg/gr ± 10.0% (2.25– 2.75 mg/gr)	 30.32 2.67	 31.80 2.58	 31.15 2.52	 30.21 2.49	 29.72 2.47	 29.18 2.43	 28.53 2.39
Diluted Assay Oseltamivir Sodium Benzoate **(mg/ml)**	6.0 mg/ml ± 10.0% (5.40– 6.60 mg/ml) 0.5 mg/gr ± 10.0% (0.450– 0.550 mg/ml)	 6.10 0.51	 6.05 0.51	 6.01 0.49	 5.94 0.48	 5.81 0.48	 5.75 0.47	 5.60 0.47
Dissolution Oseltamivir Phosphate	At least 85% of the label value after 15 minutes. Q = (% 75)	93.95 %	93.72 %	94.05 %	93.33 %	92.18 %	91.90 %	90.41 %
Related Substances Impurity A Impurity B Impurity C Unknown Impuritiy Total Impurities	 NMT 2.0% NMT 0.3% NMT 0.5% NMT 0.5% NMT 3.0%	 0.24 % 0.07 % 0.05 % 0.02 % 0.38 %	 0.26 % 0.08 % 0.06 % 0.05 % 0.45 %	 0.32 % 0.08 % 0.06 % 0.08 % 0.54 %	 0.37 % 0.08 % 0.06 % 0.14 % 0.65 %	 0.41 % 0.07 % 0.08 % 0.19 % 0.75 %	 0.48 % 0.07 % 0.08 % 0.23 % 0.86 %	 0.57 % 0.09 % 0.08 % 0.29 % 1.03 %

Table 26: Scale-Up Study Accelerated Term Stability Results.

Scale-Up Study Accelerated Stability 40°C ± 2°C – 75 % RH ± 5				
Tests	**Specifications**	**The Beginning of Stability**	**3rd Month**	**6th Month**
Appearance	White to Whitish colored powder.	Complies	Complies	Complies
Identification Oseltamivir Phosphate	Retention times of main peaks which are obtained from sample and standard solutions chromatograms should be similar.	Complies	Complies	Complies
Water Content	NMT 4.00 %	0.73 %	1.75 %	2.60 %
Assay Oseltamivir Sodium Benzoate **(mg/gr)**	30 mg/gr ± 10.0% (27.00– 33.00 mg/gr) 2.5 mg/gr ± 10.0% (2.25– 2.75 mg/gr)	 30.32 2.67	 29.07 2.39	 28.15 2.33
Diluted Assay Oseltamivir Sodium Benzoate **(mg/ml)**	6.0 mg/ml ± 10.0% (5.40– 6.60 mg/ml) 0.5 mg/gr ± 10.0% (0.450– 0.550 mg/ml)	 6.10 0.51	 5.82 0.47	 5.69 0.46
Dissolution Oseltamivir Phosphate	At least 85% of the label value after 15 minutes. Q = (% 75)	93.95 %	89.27 %	88.04 %
Related Substances Impurity A Impurity B Impurity C Unknown Impuritiy Total Impurities	 NMT 2.0% NMT 0.3% NMT 0.5% NMT 0.5% NMT 3.0%	 0.24 % 0.07 % 0.05 % 0.02 % 0.38 %	 0.51 % 0.10 % 0.11 % 0.25 % 0.97 %	 0.75 % 0.16 % 0.18 % 0.36 % 1.45 %

Manufacturing Flow Chart



RESULTS AND DISCUSSION

Within the scope of the completed R&D studies, a total of 3 trial productions were carried out for Oseltamivir 12 mg/ml Oral Suspension (Trial-1, Trial-2, and Scale Up Study). Physical and chemical analyses were carried out in the trial studies, using the European Pharmacopoeia as a reference.

As a result of the analyses carried out with the previously determined unit formula and the European pharmacopeia as a reference, it was clearly understood that our developed product was developed to be suitable for use in patient populations of all ages in the treatment and prevention of Influenza A and B viruses.

But after the studies, there is a question in everyone's mind;

1- Regarding the selection of different viscosity agents, is the Xanthan Gum raw material, which is thought to be the best choice after Zeta Potential and Turbiscan analysis and developed on a unit formula, really the right choice?

2- Can Carbomer and Blanose viscosity agents give better performance in stability processes or product use despite their low performance in Zeta Potential and Turbiscan analyses?

To seek answers to the above questions, in the light of the information in the reference product prospectus that the dry powder remains stable (Visual and Physical) for 10 days after dilution; With the final formulation and production method, Xanthan Gum, Blanose, and Carbomer samples were prepared, diluted and left to stand for 10 days.

At the end of 10 days, sedimentation was observed in the samples kept other than Xanthan Gum and it was observed that there was no re-disperse when shaken. Below, the analysis results and visuals of the samples kept for 10 days are shared.

Table 27: R&D Trials Physical Stability Data (10 Days).

Oral Suspension Appearance Specification: *White to Whitish colored, Opaque, Viscous Suspension*

	Specifications	***Start***	***3 Month***	***Visual Check***
Carbomer	***Aggregation***	*Complies*	*N.A*	
	Flocculation	*Complies*	*N.A*	
	Coalescence	*Complies*	*N.A*	
	Sedimentation	*Complies*	*N.A*	
	Phase Decomposition	*Complies*	*N.A*	
	Re-dispersibility	*Complies*	*N.A*	
Blanose	***Aggregation***	*Complies*	*N.A*	
	Flocculation	*Complies*	*N.A*	
	Coalescence	*Complies*	*N.A*	
	Sedimentation	*Complies*	*N.A*	
	Phase Decomposition	*Complies*	*N.A*	
	Re-dispersibility	*Complies*	*N.A*	
Xanthan Gum	***Aggregation***	*Complies*	*Complies*	
	Flocculation	*Complies*	*Complies*	
	Coalescence	*Complies*	*Complies*	
	Sedimentation	*Complies*	*Complies*	
	Phase Decomposition	*Complies*	*Complies*	
	Re-dispersibility	*Complies*	*Complies*	
Xanthan Gum Pilot Study	***Aggregation***	*Complies*	*Complies*	
	Flocculation	*Complies*	*Complies*	
	Coalescence	*Complies*	*Complies*	
	Sedimentation	*Complies*	*Complies*	
	Phase Decomposition	*Complies*	*Complies*	
	Re-dispersibility	*Complies*	*Complies*	

ACKNOWLEDGEMENT

This article was sponsored by World Medicine Pharmaceutical Company. The authors are grateful to Rusen KALENDER, the founder and chairman of the World Medicine Pharmaceutical Company. I will not forget to share with you our valuable advisors and teammates in the realization of this study. I would like to thank, Product Development Assistant Manager Cuneyt TOPRAK, Technology Transfer and Product Development Manager Gokay GUN, and R&D Director Erdinc BABUC.

REFERENCES

1. *Wong SS, Yuen KY,* "Avian influenza virus infections in humans" *Chest, January 2006; 129 (1): 156-68.* **Doi*:*** 10.1378/chest.129.1.156. PMC 7094746. PMID 16424427
2. S. Doktorovova, R. Shegokar, P. Martins-Lopes, Silva C.M. Lopes, R.H. Müller, E.B. Souto. Modified Rose Bengal Assay for Surface Hydrophobicity Evaluation of Cationic Solid Lipid Nanoparticles (cSLN). European Journal of Pharmaceutical Sciences, 45(5): 606–612. Doi*:* ttps://doi.org/10.3390/app9204438
3. S. Doktorovova, R. Shegokar, P. Martins-Lopes, Silva C.M. Lopes, R.H. Müller, E.B. Souto..Modified Rose Bengal Assay for Surface Hydrophobicity Evaluation of Cationic Solid Lipid Nanoparticles (cSLN). European Journal of Pharmaceutical Sciences, 45(5): 606–612. Doi : https://doi.org/10.1016/j.ejps.2011.12.016
4. Environmental Fate and Behaviour of Nanomaterials: New knowledge on Important Transformation Processes. Cited [2021 June3] Doi*:* 10.13140/2.1.1943.4240
5. Environmental Fate and Behaviour of Nanomaterials: New knowledge on Important Transformation Processes Cited [2021 June3] Doi: 10.13140/2.1.1943.4240

Monograph on the Internet

6. *European Medicines Agency (EMA) Biowaiver Monograph for Immediate-Release Solid Oral Dosage Forms: Oseltamivir Phosphate – Draft Document*, Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/tamiflu
7. *Food Drug Administration (FDA),* Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021087s062lbl.pdf
8. Malvern ZetaSizer Technology Surface Zeta Potential Cited [2021 July 3] Available from: https://www.malvernpanalytical.com/en/assets/MRK1839_tcm50-17228.pdf
9. Turbiscan Stabilty Index Cited [2021 July 1] Available from: https://www.formulaction.com/en/knowledge-center/turbiscan-stability-index