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DEVELOPMENT SODIUM ALGINATE SODIUM BICARBONATE CALCIUM CARBONATE ORAL SUSPENSION USING TURBISCAN TOWER AND ZETA POTANTIAL

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Introduction:

Sodium Alginate

Sodium Alginate is a natural polysaccharide product that was first described in a patent application by the British chemist Edward C C Stanford in 1881. To this day brown algae are still the main source used to extract sodium alginate from. This group includes many of the seaweeds, like kelps, found in chilly northern seas. In addition to the food industry, the gelling properties of Sodium Alginate have been used in medical, dental and cosmetic applications for years. Sodium Alginate is the sodium form of alginate. Alginate is a linear, anionic polysaccharide consisting of two form of 1, 4-linked hexuronic acid residues, β-d-mannuronopyranosyl (M) and α-l-guluronopyranosyl (G) residues. It can be arranged in the form of blocks of repeating M residues (MM blocks), blocks of repeating G residues (GG blocks), and blocks of mixed M and G residues (MG blocks). [1] Commercially available alginate currently originates from algae. Alginate has wide applications. For example, one of its most important role is being used as wound dressing materials for the treatment of acute or chronic wounds. The use of alginate crosslinking to make hydrogels for cell encapsulation is also quite valuable. The emergence of various kinds of its derivatives recently has further extended its application. Sodium Alginate occurs as an odorless and tasteless, white to pale yellowish-brown colored powder. Colorless or slightly yellow solid occur- ring in filamentous, granular, and powdered forms. Sodium Alginate BCS is the raw material with 2 solubility [2] Forms a viscous colloidal solution with water; insoluble in Alcohol, Ether, and Chloroform. Com-bustible. Sodium Alginate can be used as a flavorless gum. It is used by the foods industry to increase viscosity and as an emulsifier. It is also used in indigestion tablets and the preparation of dental impressions.

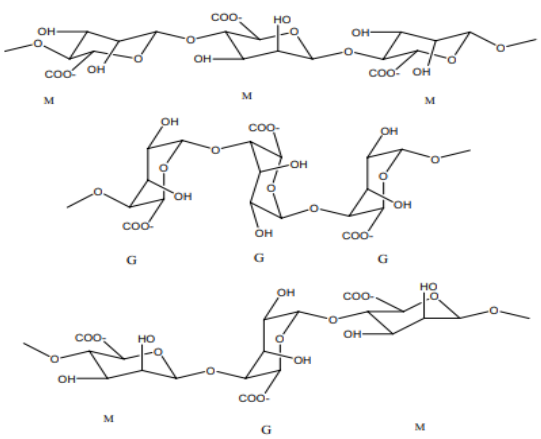


Figure 1 : The molecular Structure Of Sodium Alginate [3]

Sodium Alginate (NaAlg) and its modified forms have been widely used as membranes in pervaporation (PV) separation of aqueous-organic solutions because of the hydrophilic nature and versatility to modify/tune their structures to achieve the desired separation.

Sodium alginate is a polymer which can be extracted from brown seaweed and kelps. It is one of the structural polymers that help to build the cell walls of these plants. It has some unusual properties and a wide variety of uses [4]

Sodium Bicarbonate

Sodium Bicarbonate severe renal disease, uncontrolled diabetes, severe dehydration or shock, circulatory failure, extracorporeal circulation of blood, cardiac arrest and severe primary lactic acidosis is used to treat metabolic acidosis may occur. It is also indicated in severe diarrhea, often accompanied by a significant loss of bicarbonate. It is also indicated for the treatment of certain drug poisonings, including barbiturates (where decomposition of the barbituratprotein complex is desired), salicylates or methyl alcohol poisoning, and hemolytic reactions that require alkalinization of urine to reduce the nephrotoxicity of blood pigments. [5]

Sodium Bicarbonate is a compound used in the treatment of metabolic acidosis associated with conditions such as sequential kidney disease and shock-induced circulatory failure, as well as symptomatic treatment of acid supplementation, acid preparation and acid convenience. In addition, Sodium Carbonate is a white, crystalline powder used as a release in pH buffering agent, electrolyte regenerator, systemic and topical treatment solutions. [6] Soluble in water, practically insoluble in Ethanol (96%). When heated in the dry state or in solution, it gradually converts to Sodium Carbonate. [7]

This establishes the molecular formula of the product as $NaHCO_3$, the molecular weight as 84.0 and structure of the same as given as below [8]

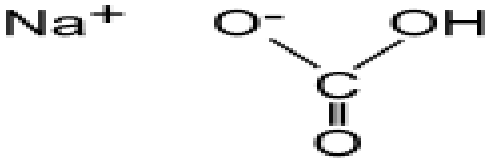


Figure 2 : The Molecular Structure Of Sodium Bicarbonate [9]

Sodium Bicarbonate is a systemic alkalizer that increases plasma bicarbonate, buffering excess hydrogen ion concentration and raising blood pH, thereby reversing the clinical manifestations of acidosis. It is also a urine alkalizer

that increases the excretion of free bicarbonate ions in the urine, thereby effectively raising the pH of the urine. The actual dissolution of uric acid stones can be achieved by maintaining an alkaline urine. Sodium Bicarbonate acts as an antacid and reacts chemically to neutralize stomach acid amounts or buffer existing, but has no direct effect on output. This effect causes the pH value of stomach contents to increase, thus relieving the symptoms of hyperacidity. [10]

Calcium Carbonate

Calcium Carbonate is the carbonic salt of calcium (CaCO3). Calcium Carbonate is used therapeutically as a phosphate buffer in hemodialysis, as an antacid in gastric hyperacidity for temporary relief of indigestion and heartburn, and as a calcium supplement for preventing and treating osteoporosis.

Ground Calcium Carbonate results directly from the mining of limestone. The extraction process keeps the carbonate very close to its original state of purity and delivers a finely ground product either in dry or slurry form. Precipitated Calcium Carbonate (CAS: 471-34-1) is produced industrially by the decomposition of limestone to calcium oxide followed by subsequent recarbonization or as a by-product of the Solvay process (which is used to make sodium carbonate). Precipitated Calcium Carbonate is purer than ground Calcium Carbonate and has different (and tailorable) handling properties. [11]

Calcium Carbonate is an abundant mineral with several advantages to be a successful carrier to improve oral bioavailability of poorly water-soluble drugs, such as praziquantel. Praziquantel is an antiparasitic drug classified in group II of the Biopharmaceutical Classification System hence characterized by high-permeability and low-solubility. Therefore, the dissolution rate is the limiting factor for the gastrointestinal absorption that contributes to the low bioavailability. [12]

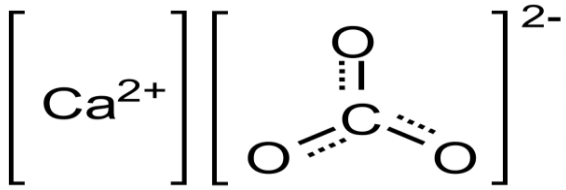


Figure 3 : The Molecular Structure Of Calcium Carbonate [13]

Since Calcium Carbonate is a raw material with BCS Class 2, which has little water dissolution, Sodium Alginate Sodium Bicarbonate Calcium Carbonate was used as a raw material to be D90 < 20 microns (micronized) in the oral suspension formulation.

Sodium Alginate Sodium Bicarbonate Calcium Carbonate combination is a combination of two antacids (Calcium Carbonate and Sodium Bicarbonate) and Sodium Alginate, and pharmacotherapeutically A02BX is in the other class of drugs for peptic ulcer and gastroesophageal reflux disease. [13]

Rapidly react to the combination of Sodium Alginate, Sodium Bicarbonate, Calcium Carbonate with stomach acid, creating alginic acid gel with a near neutral pH, when ingested, and studies have shown that by the release of free stomach acid, the pocket interacts with and closes, reduce exposure to esophageal acid. The combination floats over stomach contents, effectively blocks gastro-esophageal reflux for up to 4 hours and protects the esophagus from acid, pepsin and bile. In severe cases, the release itself can be emptied back into the esophagus, depending on the contents of the stomach, and can have a sedative effect. Also in vitro evidence has shown that it has a secondary effect on its release and is able to capture bile and pepsin in its structure, protecting the esophagus more than these gastric components. [14]

Calcium Carbonate neutralizes stomach acid, allowing rapid removal of indigestion and heartburn. This effect is enhanced by the addition of sodium bicarbonate, which also has a neutralizing effect. For this reason, the combination was formulated in 2 different containers as carbomer gel and active substance parts and achieved success in development studies.

The excipients used in the formulation are : Sodium Hydroxide (Gelling Agent), Carbomer 974 NF (Viscosity Agent), Methyl Paraben (Antimicrobial Preservative), Propyl Paraben (Antimicrobial Preservative), Sodium Saccharin (Flavoring Agent), Peppermint Oil (Aromatizane) ,Xanthan Gum (Viscosity Agent) and Pure Water (Solvent).

In this study, we summarized the combination formulation of Sodium Alginate Sodium Bicarbonate Calcium Carbonate produced by double cap method using pre-development devices Turbiscan Tower and Zeta Potential devices.

MATERIALS AND METHODS

Materials

The active ingredients in the formulation were supplied Sodium Alginate (FMC-NORWAY), Sodium Bicarbonate (CANTON LAB - INDIA) Calcium Carbonate (SHANGAI NUOCHENG-CHINA).The excipient which are used as respectively; Sodium Hydroxide (MERCK, GERMANY), Carbomer 974 NF (LUBRIZOL,GERMANY), Methyl Paraben (CLARIANT, GERMANY), Propyl Paraben (CLARIANT, GERMANY), Sodium Saccharin (KAIFENG XINGHUA, CHINA) Peppermint Oil (AROMSA-TURKEY) and Xanthan Gum (JUNGBUNZLAUER – SWITZERLAND) supplied. All raw materials used are suitable for European Pharmacopoeia.

Methods

Trial studies indicated in Table 1 were performed using the homogeneous mixing method. In addition, after trial 4, a non-destructive mixer head was used to prevent Sodium Alginate from breaking down.

Ingredients

Ingredients	Function	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5
Sodium Alginate	Active Substance	500,00	500,00	500,00	500,00	500,00
Sodium Bicarbonate	Active Substance	213,00				
Calcium Carbonate	Active Substance	325,00				
Carbomer	Viscosity Agent	-				
Xanthan Gum	Viscosity Agent	-				
Methyl Paraben	Antimicrobial Preservative	-				
Propyl Paraben	Antimicrobial Preservative	-				
Sodium Saccharin	Flavoring Agent	-				
Peppermint Oil	Aromatizane	-				
Sodium Hydroxide	Gelling Agent	-				
Pure Water	Solvent	to 10 ml				

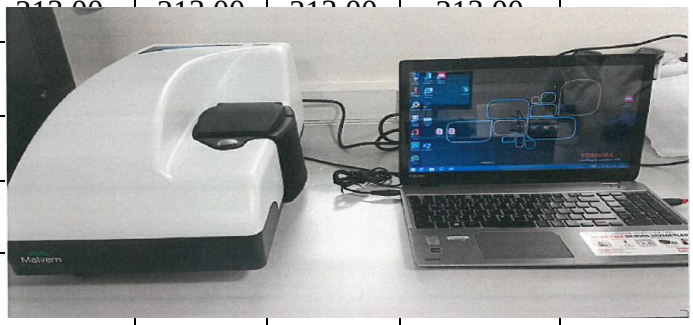
Table 1 : R&D Trial Formulations

Degradation in suspension formulations physical (Sedimentation, Flocculation, Coalescence, Phase Separation, Phase Transformation) suspension selection should be made correctly to prevent antimicrobial agents and preservatives observed in the surfactant used in the formulation.The zeta potential is a measurement of the thrust or deceleration value of particles between them.It gives information about the accuracy and stability of surfactant concentration in samples diluted using brine solution without waiting time.Particle size increase in Turbiscan Tower (Flocculation, Coalescence), particle migration (Sedimentation, such as visual perception of movement, which is 50 times faster cremation instability can be determined as an objective and reproducible results preformulation studies, formulation and process optimization, quality control and streamline their processes that helps improve the stability of device.

Zeta Potential General Information

Zeta potential is the electrical potential at the slipping plane. This plane is the interface which separates mobile fluid from fluid that remains attached to the surface. The zeta potential is an important and readily measurable indicator of the stability of colloidal dispersions. 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, 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. [15]



Picture 1: Malvern Zetasizer Device [16]

In order 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. [17]

Stabilty Characteristics Of Zeta Potential	Avg. Zeta Potantial 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 Stabilty	-31 to -40
Fairly Good Stability	-41 to -60
Verry Good Stability	-61 to -80
Extremely Good Stabilty	-81 to -100

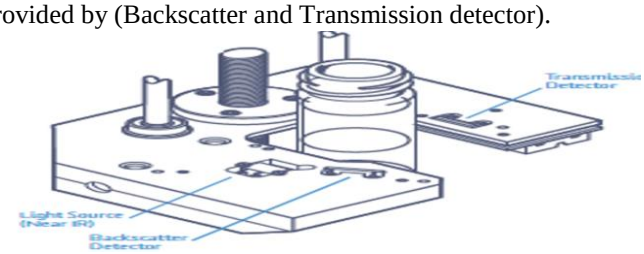
Table 2: Zeta Potantial Stabilty Characterstics İndex [18]

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. There are 6 stability cabinets that can be used at the same or different times, but a single temperature can be set for all cabinets. [19]

Picture 2: Formulaction Turbiscan Tower [20]

Static multiple light scattering concentrated liquid distributions in their natural state it 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 3: Turbiscan Tower Studiying Principle [21]

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 it shows that it remains 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. Granularity of particles, surface interference and emulsified state.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 particlesdescribing 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 by means of 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 in stability conditions.

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, large changes in particle size or color.

Table 3 : Turbiscan Stabilty Index Value [22]

Lab-Scale Studies

5-Trial study conducted with a double container system, the carbomer gel was opened in the part, while the active substance and preservatives were suspended in a container, and the joining process was applied. Each trial production was made of 1 liter.

Trial 1: Carbomer is discarded in pure state and carbomer is added under high mixture water. By by adding Sodium

Hydroxide to the mixture, Carbomer gel is formed.Add Sodium Bicarbonate, Calcium Carbonate and Sodium Alginate respectively to the mixture until the mixture is suspended..Finally, Xanthan Gum, Methyl Paraben, Propyl Paraben, Sodium Saccharin and Peppermint Oil are added to the mixture and the suspension is completed to the volume.

Trial 2: Carbomer is added under high mixture by throwing carbomer in pure water.By adding sodium hydroxide to the mixture, Carbomer gel is formed.By adding, Sodium Bicarbonate, Calcium Carbonate and Sodium Alginate respectively to the pure water taken into a different container, the mixture is provided until the mixture becomes süspande.The mixture is provided for 30 minutes by adding the carbomer gel to the part under the mixture container containing the active substances.Finally, Xanthan Gum, Methyl Paraben, Propyl Paraben Sodium Saccharin and Peppermint Oil are added to the mixture and the suspension is completed to the volume.

Trial 3: Carbomer is added under high mixture by throwing carbomer in pure water.By adding Sodium Hydroxide to the mixture, Carbomer gel is formed.By adding Xanthan Gum, Sodium Bicarbonate, Calcium Carbonate and Sodium Alginate respectively to the pure water taken into a different container, the mixture is provided until the mixture becomes süspande.The mixture is provided for 30 minutes by adding the carbomer gel to the part under the mixture container containing the active substances.Finally, Methyl Paraben, Propyl Paraben Sodium Saccharin and Peppermint Oil are added to the mixture and the suspension is completed to the volume.

Trial 4: Carbomer is added under high mixture by throwing carbomer in pure water. By adding sodium hydroxide to the mixture, Carbomer gel is formed. By adding Xanthan Gum, Methyl Paraben, Propyl Paraben, Sodium Bicarbonate, Calcium Carbonate and Sodium Alginate respectively to the pure water taken into a different container, the mixture is provided until the mixture becomes süspande.The mixture is provided for 1 hour by adding the carbomer gel to the part under the mixture container containing the active substances.Finally, sodium saccharin and peppermint oil are added to the mixture and the suspension is completed to the volume.

Trial 5: Carbomer is added under high mixture by throwing carbomer in pure water.By adding sodium hydroxide to the mixture, Carbomer gel is formed.By adding Xanthan Gum, Methyl Paraben, Propyl Paraben, Sodium Bicarbonate, Calcium Carbonate and Sodium Alginate respectively to the pure water taken into a different container, the mixture is provided until the mixture becomes süspande.The mixture is provided for 1 hour by adding the carbomer gel to the part under the mixture container containing the active substances.Finally, Sodium Saccharin and Peppermint Oil are added to the mixture and the suspension is completed to the volüme.

(In this study, unlike Trial-4, it was expected to be opened by mixing slowly without the use of a sodium alginate shredder mixer head.)

The potential results of all trial studies of Turbiscan and Zeta are as follows.

Zeta Potantial Analysis Results

Zeta Potantial Analysis Results		
Measurement	**Zeta Potantial**	**General Assessment**
Trial -1	-8 MV	Range of Strong Agglomeration and Precipitation
Trial -2	-15 MV	Threshold of Agglomeration
Trial -3	-35 MV	Moderate Stability
Trial -4	-28 MV	Threshold of Agglomeration
Trial -5	-46,9 MV	Fairly Good Stabilty

Table 4 : All Trials Zeta Potential Results

Turbiscan Tower Analysis Results						
Measurement	**TSI (Top)**	**TSI (Middle)**	**TSI (Bottom)**	**TSI (Global)**	**TSI Index Classification**	**General Assessment**
Trial -1	5,1	4,2	5,7	4,8	C	Visually At The Transition Stage
Trial -2	4,4	3,6	1,8	3,1	C	Visually At The Transition Stage
Trial -3	3,9	2,5	3,8	3,1	C	Visually At The Transition Stage
Trial -4	1,8	2,7	3,2	2,5	B	Visually At The Transition Stage
Trial -5	0,6	0,2	0,6	0,3	A+	Visually Perfect

Table 5 : All Trials Turbiscan Analysis Results

R&D Study	Turbiscan General Assessment	Zeta Potantial General Assessment
Trial -5	Visually Perfect (A+)	Fairly Good Stabilty

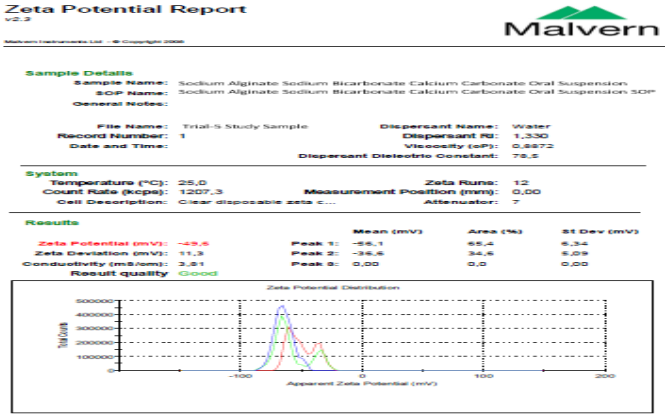
Table 6: Trial-5 Zeta Potential and Turbiscan Analysis

Result:

5 different batch sizes 1 liter made in the R & D study, and zeta potential of samples obtained during the turbiscan analysis results are evaluated when the trial-5 belongs to remain stable in the formulation of stability conditions, it was decided that this formulation could pilot study we decided to do a batch.

Trial-5 Zeta Potential Analysis Results

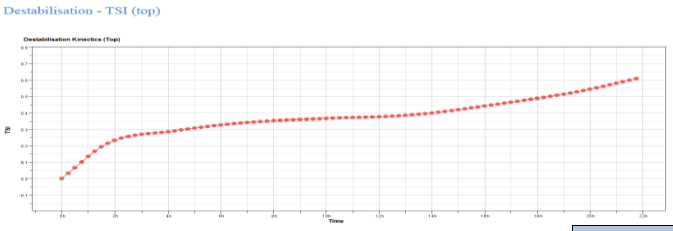
Detailed Zeta Potential results of Trial 5 diluted with saline solution in 1/10 , 1/20 and 1/30 are as follows.



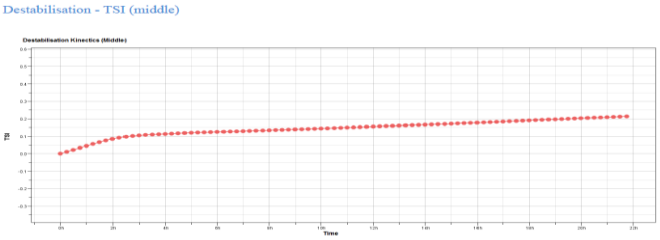
Picture 4 : Detailed Trial-5 Zeta Potential Result

Trial-5 Turbiscan Tower Analysis Results

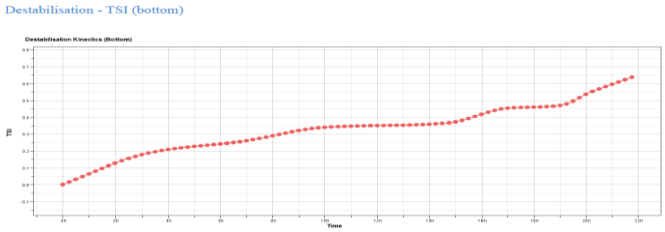
40 ° C – 21 hours Turbiscan analysis of 5 different R & D trials that can remain decidedly in stress conditions (A+ Visually Perfect) when the results are evaluated, the results of Turbiscan analysis in detail are as follows.



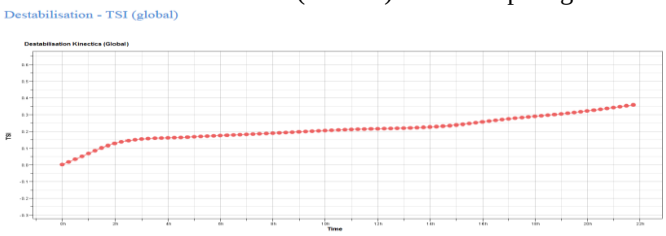
Picture 5 : Trial-5 TSI (Top) Index Graph Against



Picture 6: Trial-5 TSI (Middle) Index Graph Against



Picture 7 : Trial-5 TSI (Bottom) Index Graph Against



Picture 8: Trial-5 TSI (Global) Index Graph Against

Measurement	TSI (Global) 21h	TSI (bottom) 21h	TSI (middle) 21h	TSI (top) 21h
TRIAL-5 SAMPLE	0.3	0.6	0.2	0.6

Picture 9: Trial-5 Turbiscan Stabilty Index Results

RESULTS AND DISCUSSION

To prove the accuracy of all the work, according to the results of zeta potential analysis, and turbiscan stability, which is expected to exhibit unstable behavior in the conditions of the trial 1 and trial-3 trial, which is expected to exhibit stable behavior analysis with stability conditions sonuclaria-pilot study samples 5 and 25 ° C – 24 month stability to the cabin has been removed. The physical consequences are as follows.

Oral Süspansion Appearance Specification: Light Cream Colored, Opaque, Viscous Suspension

R&D Trials Physical Stability Data

R&D Trials Physical Stability Data								
	Spesifications	Start	3.Month	6. Month	9. Month	12. Month	18. Month	24. Month
F	Aggregation	Com	N.A	N.A	N.A	N.A	N.A	N.A

	plies						
occulation	Com plies	N.A	N.A	N.A	N.A	N.A	
oalescence	Com plies	N.A	N.A	N.A	N.A	N.A	
edimentatio	Com plies	N.A	N.A	N.A	N.A	N.A	
hase ecompositi n	Com plies	N.A	N.A	N.A	N.A	N.A	
e-spersibility	Com plies	N.A	N.A	N.A	N.A	N.A	
ggregation	Com plies	N.A	N.A	N.A	N.A	N.A	N.A
occulation	Com plies	N.A	N.A	N.A	N.A	N.A	N.A
oalescence	Com plies	N.A	N.A	N.A	N.A	N.A	N.A
edimentatio	Com plies	N.A	N.A	N.A	N.A	N.A	N.A
hase ecompositi n	Com plies	N.A	N.A	N.A	N.A	N.A	N.A
e-spersibility	Com plies	N.A	N.A	N.A	N.A	N.A	N.A
ggregation	Com plies	Com plies	Com plies	Com plies	Comp lies	Compl ies	Comp lies
occulation	Com plies	Com plies	Com plies	Com plies	Comp lies	Compl ies	Comp lies
oalescence	Com plies	Com plies	Com plies	Com plies	Comp lies	Compl ies	Comp lies
edimentatio	Com plies	Com plies	Com plies	Com plies	Comp lies	Compl ies	Comp lies
hase ecompositi n	Com plies	Com plies	Com plies	Com plies	Comp lies	Compl ies	Comp lies
e-spersibility	Com plies	Com plies	Com plies	Com plies	Comp lies	Compl ies	Comp lies
ggregation	Com	Com	Com	Com	Comp	Compl	Comp

	plies	plies	plies	plies	lies	ies	lies
Flocculation	Com plies	Com plies	Com plies	Com plies	Comp lies	Compl ies	Comp lies
Coalescence	Com plies	Com plies	Com plies	Com plies	Comp lies	Compl ies	Comp lies
Sedimentatio n	Com plies	Com plies	Com plies	Com plies	Comp lies	Compl ies	Comp lies
Phase Decompositi on	Com plies	Com plies	Com plies	Com plies	Comp lies	Compl ies	Comp lies
Re-dispersibility	Com plies	Com plies	Com plies	Com plies	Comp lies	Compl ies	Comp lies

Table 9 : R&D Trials Physical Stability Data

After the completed R & D studies, 5 different trial Productions and 1 pilot production were made Dec.According to the results of Turbiscan and Zeta potential analysis, Trial-1 and Trial-3, which showed more unstable behavior than other trials, as well as Trial-5 and Pilot production, which gave appropriate results in the analysis results, were removed to stability cabinets. 25 ° C – 24 months physical and chemical analysis of Zeta potential and Turbiscan in the analysis with reference to the European Pharmacopoeia, while our samples with appropriate results remained stable, the results of Trial-1 and Trial-3 analysis were not suitable.As a result of these results, it was understood that when developing sodium alginate sodium Decarbonate Calcium Carbonate combination suspension, it could be developed in accordance with the standards by referencing the results of zeta potential and Turbiscan analysis in R & D Product Development Studies.later in the progression. Adult subjects having COVID-19 cutaneous presentations may demonstrate a range of illness. These dermatological rashes should trigger consideration of COVID-19, and understanding these manifestations is important to help identify potential COVID-19 patients and properly treat complications. We believe modern handful research and updated reporting will more precisely determine the incidence, underlying pathophysiology, potential prognostication, and best treatment options of dermatological manifestations in COVID-19 disease.