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DEVELOPMENT OF RECTAL SUSPENSION FOR USE IN BOWEL TREATMENT

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ABSTRACT

Rectal administration is an effective drug for the local and systemic administration of active substances. The rectal environment is relatively stable and its enzyme activity is low, it is favorable for drugs with plow oral absorption, extensive first metabolism, gastric irritation, gastric environment persistent problems, local activity, and drugs that cannot be administered in other ways. This invention relates to the use of xanthan gum and Carbomer, especially in the form of an enema for treating inflammatory bowel disease (IBD), and compositions for rectal administration. Contains Mesalazine as a therapeutically active ingredient.

KEYWORDS: Mesalazine, Rectal suspension, Inflammatory bowel disease (IBD), Xanthan Gum, Carbomer, Enema, Product Development, Turbiscan Tower.

1. INTRODUCTION

The rectum is a chamber at the end of the large intestine where drugs can be easily administered and well absorbed. Direct administration is a secondary alternative to oral and intravenous (IV) routes of drug administration and offers several advantages, such as high-volume retention, immediate absorption of small molecule drugs, bypassing first-pass metabolism, controlled drug delivery, and absorption in the lymphatic system. İmprovement of topical therapy, improved absorption, and administration of unstable gastric drugs. The direct route of administration becomes the first choice for certain conditions such as nausea, vomiting, unpleasant taste, unconsciousness during postoperative treatment, and difficulty swallowing in patients with gastric motility problems such as dysphagia or inflammation of the stomach. intramuscular injection site. Rectal drug delivery systems have been neglected due to some obstacles such as irregular absorption, dissolution problems due to low rectal fluid content, limited absorption surface, drug metabolism, privacy issues, and poor patient compliance.[1]

The rectum is located at the end of the large intestine and ends in the anus, which serves as a temporary storage area for the fecal process. In an adult, the rectum is approximately 15-20 cm long and 15-30 cm in diameter; the volume of the liquid is 1-3 ml and the pH is 7.2-7.4. The shape of the rectum can be pear-shaped, balloon-shaped, or tubular, and its

size is larger in men than in women. The rectum consists of columnar epithelial cells that contain many daisy cells responsible for mucus secretion. Compared to the small intestine, the area of the rectum is smaller, approximately 200 to 4000 cm2, because the luminal surface of the rectum lacks villi and microvilli. Rectal drainage is controlled by three veins namely the superior, middle, and inferior rectal veins. The superior rectal vein drains the upper part of the rectum (via the inferior mesenteric vein) into the portal vein system; the middle and inferior rectal veins drain the lower part of the rectum into the internal vena cava (via the internal pubic vein) for systemic circulation, as shown in Figure 1.[2,3]

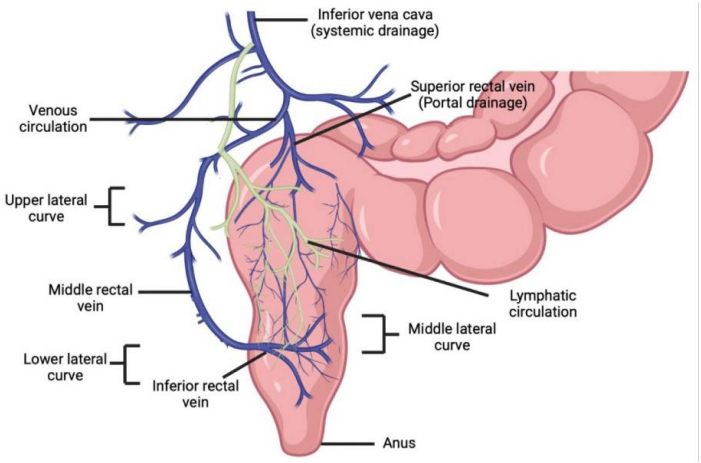


Figure 1: Diagram showing removal of venous and lymphatic tissue from the rectum and portosystemic bypass.

Factors Affecting Rectal Drug Delivery

Despite the most appropriate route of drug administration (oral), there are situations where oral administration is not possible. In such cases, the preferred route of administration is rectal, as it helps deliver drug doses for both systemic and local effects. Direct administration also bypasses hepatic metabolism, improves drug bioavailability, and ensures controlled and sustained drug release. Several factors can affect the rectal administration of drugs and these can be broadly divided into four categories as shown in Figure 2.

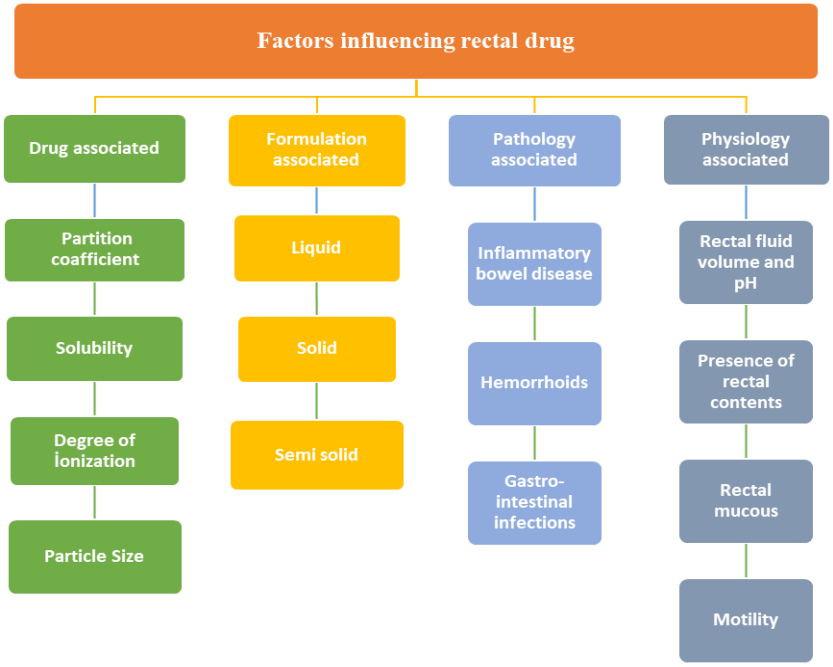


Figure 2: Factors Affecting Rectal Drug Delivery.

This review discusses the physiological aspects of rectal drug administration in the treatment of various types of rectal disease. Traditional and new methods of direct drug administration are also systematically discussed. Later in the review, clinical trials, proprietary products, and various challenges associated with direct drug delivery systems are mentioned. Inflammatory bowel disease (IBD) is characterized by recurrent episodes of gastrointestinal inflammation caused by an abnormal immune response of the gut microflora. Inflammatory bowel disease includes two idiopathic bowel disorders that are distinguished by the location and depth of bowel wall involvement. Ulcerative colitis (UC) involves diffuse inflammation of the lining of the colon. UC most often affects the rectum (proctitis), but it can extend into the sigmoid (proctosigmoiditis), beyond the sigmoid (distal ulcerative colitis), or involve the entire colon to the appendix (pancolitis). Crohn's disease (CD) causes transmural ulceration of some parts of the gastrointestinal (GI) tract, most commonly affecting the terminal ileum and colon. Both diseases are classified according to extent (mild, moderate, or severe) and location. The CD is also classified according to phenotype - inflammatory, stenotic, or penetran.[4,5,6]

Inflammatory bowel disease (IBD) is a term that describes diseases that involve long-term (chronic) inflammation of the tissues of the digestive tract. Types of IBD include:

- **Ulcerative colitis:** This condition involves inflammation and sores (ulcers) in the lining of the large intestine (colon) and rectum.
- **Crohn's disease:** This type of IBD is characterized by inflammation of the lining of the digestive tract, which can often involve the deeper layers of the digestive tract. Crohn's disease most often affects the small intestine. However, it can also affect the colon and rarely the upper gastrointestinal tract.

Both ulcerative colitis and Crohn's disease are typically characterized by diarrhea, rectal bleeding, abdominal pain, fatigue, and weight loss.

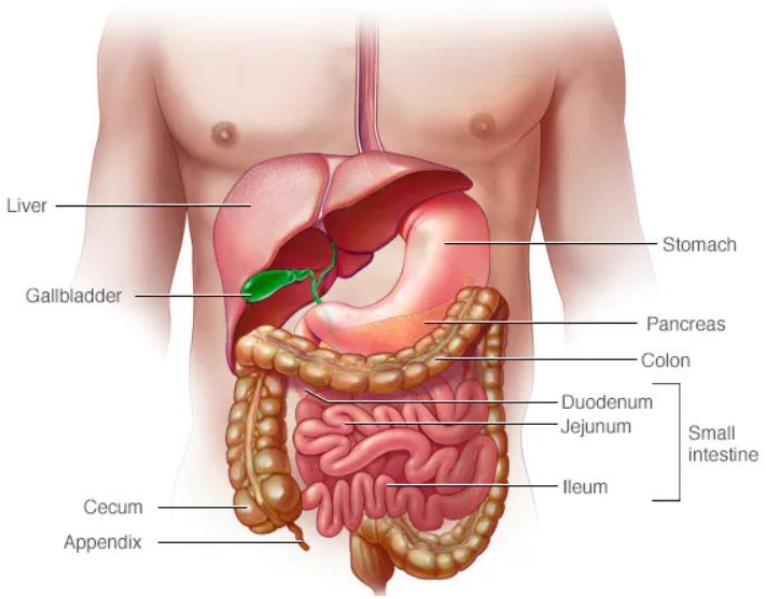
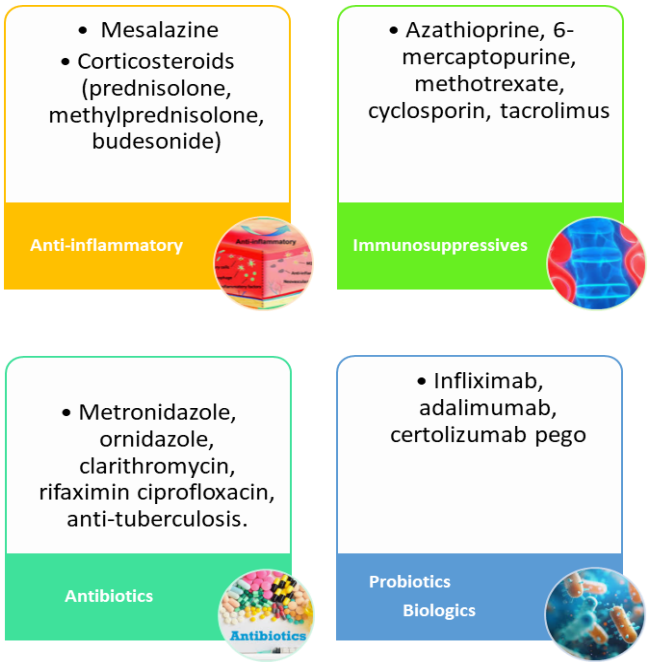


Figure 3: Digestive system.[4]

Established drug classes used to treat inflammatory bowel disease are presented in the table below.

Table 1: Established drug classes used to treat inflammatory bowel disease.

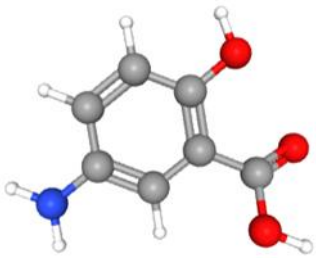


İnformation is given below about the main components used in rectal suspension.

Mesalazine

Mesalazine, also known as mesalamine or 5-aminosalicylic acid (5-ASA), is a medication used to treat inflammatory bowel disease, including ulcerative colitis and Crohn's disease.[7] It is usually used for mild to moderate disease.[7] It is taken orally or rectally.[7] Oral formulations appear to be equally effective.[8] Common side effects include headache, nausea, abdominal pain, and fever.[7] Serious side effects may include pericarditis, and liver and kidney problems.[7][8] Use during pregnancy and breastfeeding appears safe.[8] Some formulations may cause problems for people with sulfa allergies.[7] Mesalazine is an aminosalicylate and anti-inflammatory agent.[7][8] It works by direct contact with the intestines.[7]

Table 2: Physical, Chemical, and Characteristics of Mesalazine.

Physical, Chemical, and Characteristics of Meclizine	
Appearance	Almost white or light grey or light pink powder or crystals.
Solubility	Very slightly soluble in water, practically insoluble in alcohol. It dissolves in a dilute solution of alkali hydroxides and dilute Hydrochloric acid.
Structural Formula	
BCS Class	It is in the Class IV Drugs Category. (Low Solubility, Low Permeability)
Molecular Weight	153.14
Chemical Formula	$C_7H_7NO_3$

Melting Point	Decomposes at about 280°C.
Storage Conditions	Store in an air-tight container, protected from light
CAS Number	89-57-6
Pharmacological Group	Digestive System and Metabolism
ATC Number	A07 ⟶ Diarrhea Drugs, Intestinal Anti-Inflammatories And Anti-Infectives A07E ⟶ Intestinal Antienflammatories A07EC ⟶ Aminosalicylic acid and its analogues A07EC02 ⟶ Mesalazine
Indication Information	For the treatment of active ulcerative proctitis. It should be used only in patients with diabetes who are not insulin-dependent, where hyperglycemia cannot be controlled by diet and exercise.

Xanthan Gum

Xanthan gum (CAS Registry Number 11138-66-2) is described in USP32–NF27 as a high molecular weight polysaccharide gum produced by the fermentation of a pure culture of carbohydrates with Xanthomonas campestris.[9] It contains D-glucose D-mannose and D-glucuronic acid as the dominant hexose units and is prepared as the sodium, potassium, or calcium salt. It is widely used as an emulsifier, stabilizer, and/or thickener in pharmaceutical compositions.[10] Xanthan gum is widely used as a suspending and stabilizing agent in oral and topical drugs, cosmetics, and foods.[10]

Carbomer

Carbomers with (9003-01-49) Cas number are synthetic high molecular weight acrylic acid polymers cross-linked with allyl ethers of allyl sucrose or pentaerythritol. Carbomers are used as rheology modifiers in liquid or semi-solid dosage forms. Formulations include ointments, gels, emulsions, and creams for ophthalmic,[11,12] rectal,[13-14] topical[15-16] and vaginal[17, 18] formulations. Carbomers are used in liquid or semi-solid medicinal preparations as rheology modifiers.

To prepare Mesalazin Rectal Suspension, pre-development devices such as Turbiscan Tower and Zeta Potential were used during the preliminary development studies of our product. To obtain a homogeneous mixture during manufacturing and pilot study using 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.

Turbiscan Tower Infromation

The TURBISCAN TOWER is a 6-sample macroscopic and colloid stability analyzer and the flagship of the TURBISCAN series. Based on efficient SMLS technology, it offers fast, accurate, and quantitative stability measurement of formulations (emulsions, suspensions, foams). The TURBISCAN TOWER offers 6 independent measurement points that allow simultaneous compositional comparisons or offer flexibility when working with different projects. It allows a quick and precise evaluation of the stability and aging of any formulation (from highly concentrated and opaque to water-like systems). Any changes in the dispersion such as settling, flocculation, scaling, and coalescence are detected and quantified immediately. It not only saves time thanks to the extreme sensitivity of SMLS technology, but it also enables accelerated stability tests by varying the temperature (a wider temperature range of 4-80 °C) and following ISO recommendations (ISO/TR 13097:2013, ISO).). (TR 18811:2018). Stability measurement is performed using a non-invasive and non-destructive technique that preserves the integrity and originality of the samples. The results are stored in the software but are also displayed on the front screen with a simple

stable reading thanks to simple color coding. TURBISCAN TOWER helps cost-effectively and reliably plan, improve, and control formulation and dispersion quality. It helps to quickly make fact-based decisions.[19]

Figure 4: Turbiscan Tower[21]

Static multiple distribution of a light-scattering concentrated liquid in its natural state is the most common optical method for direct characterization. It works on the principle that photons are sent to the sample through 800 nm light sources. These photons are removed from the samples after repeated scattering as dispersions of particles (or droplets) and using two simultaneous detectors.[19]

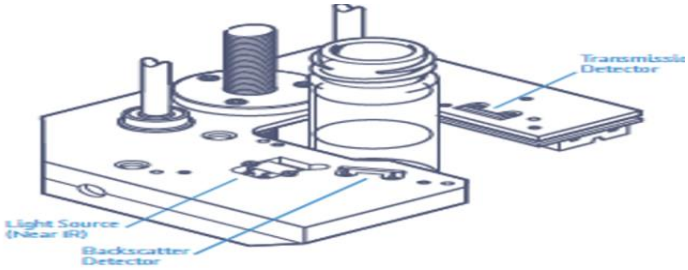


Figure 5: Turbiscan Tower Studying Principle.[19]

Evaluation of Turbiscan Analysis Results

The visual response TSI analysis measurements of the TSI values corresponding to a given instability state are evaluated using the TSI scale associated with the states. The results obtained are evaluated against the results given in the table below to give an idea about the behavior of the product in stable conditions.[19]

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.*

Figure 6: Turbiscan Stability Index Value.[19]

Our sample Turbiscan Turbine analysis results (TSI Global, Bottom, Middle, and Top) below 3.0 are stable under the set stability conditions, indicating that it remains in the structure.[19]

TSI (Top)

This is the estimation part where the creaming tendency of the sample is interpreted. Migration speed and particle size (mm) in products tend to a creamy form, the particle sizes of the raw materials used in the composition must be investigated by observing the change in the particle sizes of the product over time by performing a test.[19]

TSI (Middle)

This is an estimate of particle density. Particle granularity, surface disorder, and emulsified state. The composition provides information on whether the shrinkage of the surfactant is sufficient.[19]

TSI (Bottom)

Values that control the tendency of the sample to collapse (set out) under stability conditions.[19]

TSI (Global)

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

Law of Oswalt Ripeng

A non-homogeneous structure changes over time, that is, small particles describe its subsidence by dissolving over time and merging with large particles law.[19]

MATERIAL AND METHOD

Material

Mesalazine active substance was procured by (BEC Chemical, India). The excipients are used as respectively; Xanthan Gum (Jungbunzlauer, Switzerland), Carbopol (Lubrizol, Belgium), Disodium Edetat (Merck, Germany), Sodium Benzoat (Eastman, Netherlands), Potassium Metabisülfite (Anmol, India) and Potassium Acetate (Anmol, India) supplied. All raw materials used are suitable for European Pharmacopoeia.

Method

pH Trial Studies

Trial Studies have been conducted to develop a rectal suspension formulation with Mesalazine. The first trial studies are related to product pH. The formulation table of the trial studies is given in detail below.

Table 1: Trial 1, Trial 2 and Trial Formulations Table.

Raw Material	Trial 1 g/60 ml	Trial 2 g/60 ml	Trial 3 g/60 ml
Mesalazin	4.000	4.000	4.000
Xanthan Gum	0.126	0.126	0.126
Carbopol	0.032	0.032	0.032
Disodium Edetate	0.052	0.052	0.052
Sodium Benzoate	0.026	0.026	0.026
Potassium Metabisülfit	0.247	0.247	0.247
Potassium Acetate	**0.123**	**0.246**	**0.492**
Purified water	55.394	55.271	55.025

Manufacturing method

- Pure water is taken into the production tank and homogenized under nitrogen by adding Xanthan Gum.
- Carbopol is added to the mixture and homogenized
- Disodium edetate is added to the mixture and is homogenized.
- Sodium Benzoate is added to the mixture and homogenized.
- Potassium Metabisulfite is added to the mixture and homogenized.
- Potassium Acetate is added to the mixture and homogenized.
- The final suspension is filled into bottles of 60 ml.

Evaluation: Salofalk 4/60 ml rectal suspension (Dr. Falk Pharma, Germany) reference product was used for comparison to see if we could obtain a suitable product. The buffering agent used in the formulation is potassium acetate. In the trial studies carried out by changing the amount of Potassium Acetate, the most suitable amount was found in Trial 2. pH results of trial productions are given in the table below.

Table 2: Trial 1, Trial 2, and Trial 3 pH Result.

Trials	pH result
Trial 1	3.38
Trial 2	4.47
Trial 3	5.13
Salofalk 4g/60 ml Rectal Süspension (Reference product)	4.49

Viscosity Adjustment Trials

Table 3: Trial 4, Trial 5 and Trial 6 Formulations Table.

Raw Material	Trial 4 g/60 ml	Trial 5 g/60 ml	Trial 6 g/60 ml
Mesalazin	4.000	4.000	4.000
Xanthan Gum	**0.126**	**0.189**	**0.252**
Carbopol	**0.032**	**0.048**	**0.064**
Disodium Edetate	0.052	0.052	0.052
Sodium Benzoate	0.026	0.026	0.026
Potassium Metabisülfit	0.247	0.247	0.247
Potassium Acetate	0.246	0.246	0.246
Purified water	55.271	55.192	55.113
Total	**60.000 g**	**60.000 g**	**60.000 g**

Manufacturing Method

- Pure water is taken into the production tank and homogenized under nitrogen by adding Xanthan Gum.
- Carbopol is added to the mixture and homogenized
- Disodium edetate is added to the mixture and is homogenized.
- Sodium Benzoate is added to the mixture and homogenized.
- Potassium Metabisulfite is added to the mixture and homogenized.
- Potassium Acetate is added to the mixture and homogenized.
- The final suspension is filled into bottles of 60 ml.

Evaluation: The reference product Salofalk 4/60 ml rectal suspension (Dr. Falk Pharma, Germany) was used for comparison to see if we could obtain a suitable product. The viscosity agents used in the formulation are Carbopol and Xanthan Gum. Three different results were obtained with similar properties to the reference product. Since Trial 5 was

close to the reference product according to the viscosity value obtained in these formulations, it was decided to observe its behavior under stress conditions by subjecting it to turbiscan analyses. The results of viscosity trial productions are given in the table below.

Table 4: Trial 4, Trial 5, and Trial 6 Viscosity Result.

Trials	Viscosity Result
Trial 4	63.73 cP
Trial 5	110.89 cP
Trial 6	130.23 cP
Salofalk 4g/60 ml Rectal Süspension (Reference product)	117.19 cP

Comparative Turbiscan Analysis Results

Table 5: Turbiscan parameter.

Symbol	Measurements	Ref Scan.	Duration	No Scans	T (C°)	Bottom Of The Cell	Meniscus
	Original Product	0 s.	21 hours 59 min. 59 s	89	39.99	5.18	47.40
	Trial 5	0 s.	21 hours 59 min. 59 s	89	39.99	5.04	47.06

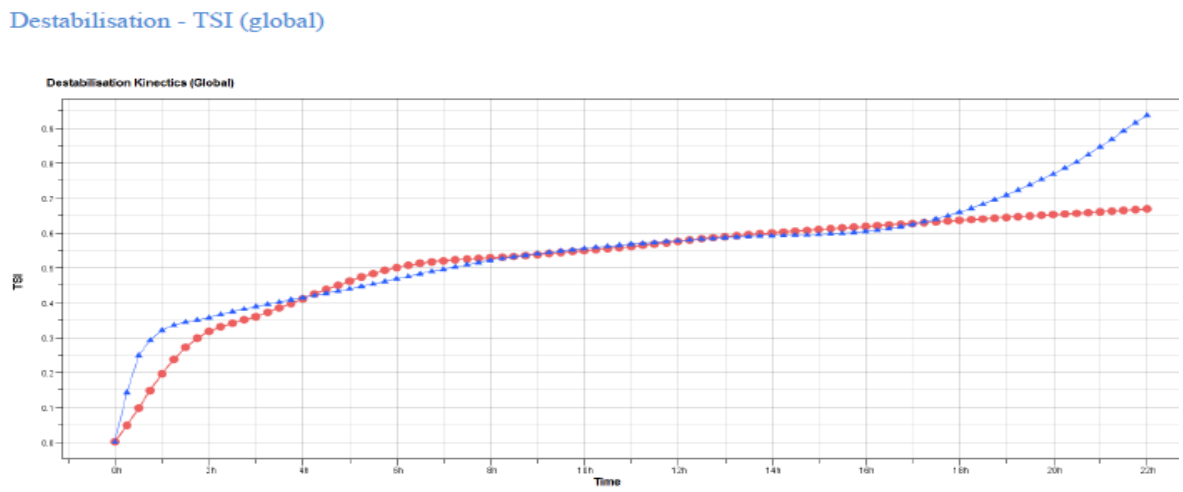


Figure 7: TSI (Global) Index Graph Against.

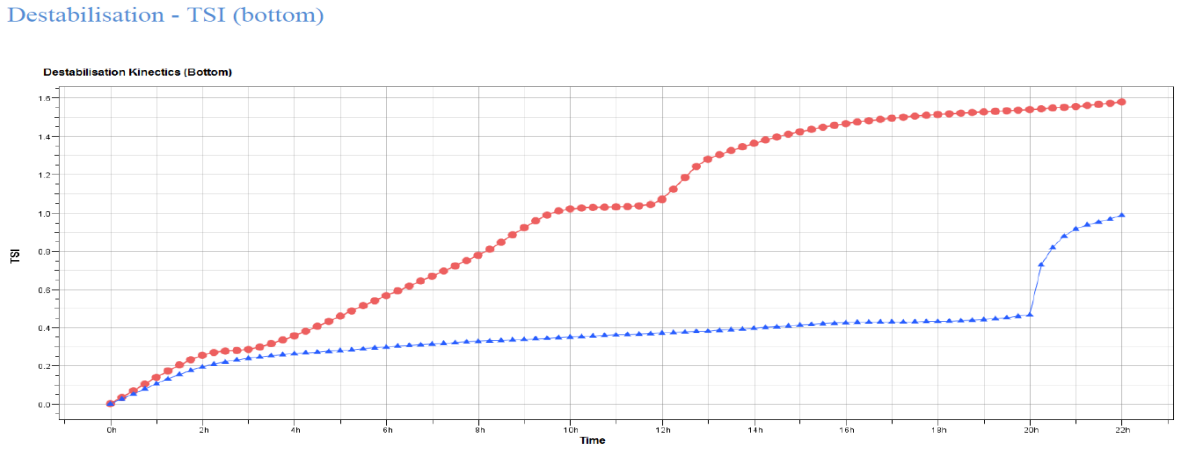


Figure 8: TSI (Bottom) Index Graph Against.

Destabilisation - TSI (middle)

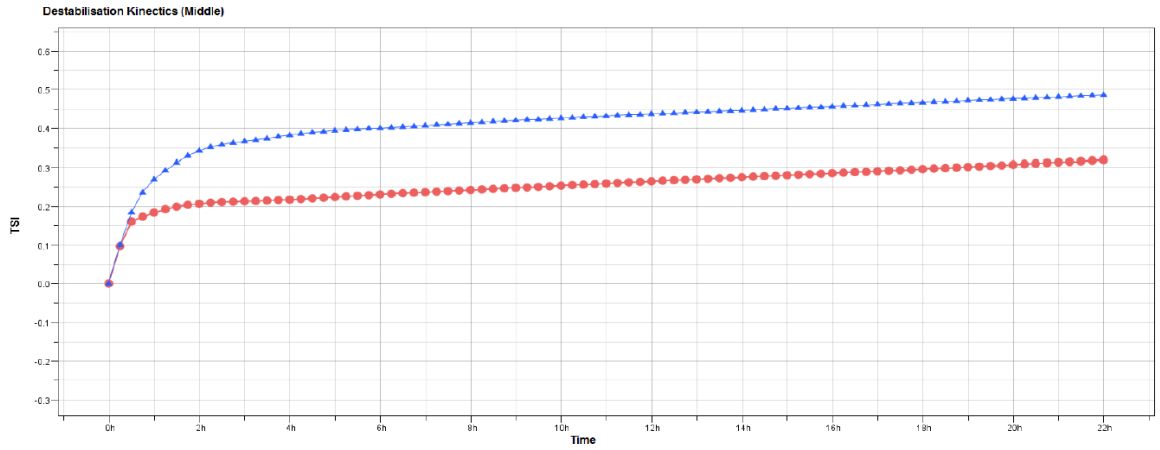


Figure 9: TSI (Middle) Index Graph Against.

Destabilisation - TSI (top)

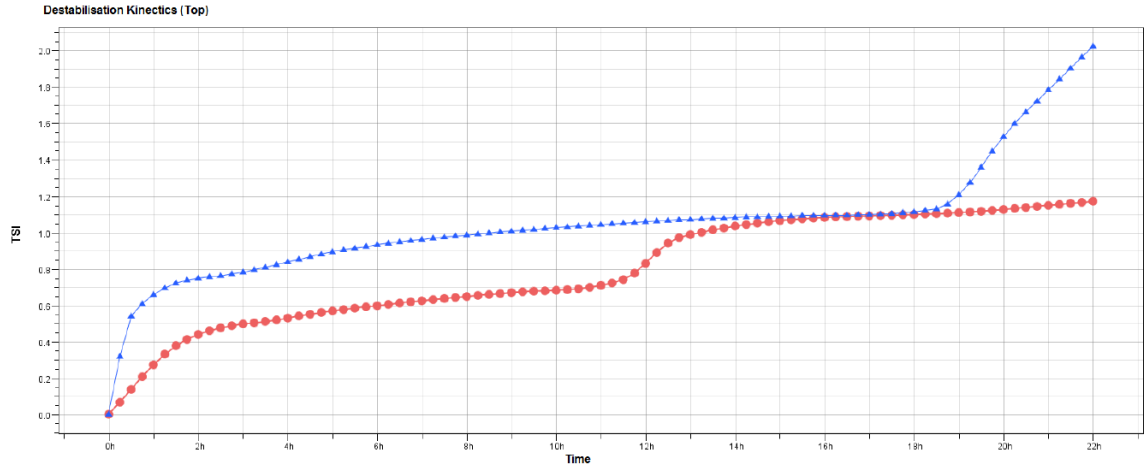


Figure 10: TSI (Global) Index Graph Against.

Table 6: Trials 5 and Original Product Turbiscan Analysis Results.

Turbiscan Tower Analysis Results						
Measurement	***TSI (Top)***	***TSI (Middle)***	***TSI (Bottom)***	***TSI (Global)***	***TSI Index Classification***	***General Assessment***
Trial -5	*1.2*	*0.3*	*1.6*	*0.7*	*A+*	*Visually Perfect*
Original Product	*2.0*	*0.5*	*1.0*	*0.9*	*A+*	*Visually Perfect*

It was decided to continue formulation studies with Trial 5, which exhibits similar stable behavior to the reference product under stress conditions.

Antimicrobial Preservative Trials

The raw materials used as antimicrobial preservatives in its formulation are Sodium Benzoate and Potassium Metabisulfite. The following trial studies were carried out to determine the most appropriate amount.

Table 3: Trial 7, Trial 8, Trial 9, and Trial 10 Formulation Table.

Raw Material	Trial 7 g/60 ml	Trial 8 g/60 ml	Trial 9 g/60 ml	Trial 10 g/60 ml
Mesalazin	4.000	4.000	4.000	4.000
Xanthan Gum	0.189	0.189	0.189	0.189
Carbopol	0.048	0.048	0.048	0.048
Disodium Edetate	0.052	0.052	0.052	0.052
Sodium Benzoate	**0.026**	**0.039**	**0.052**	**0.065**
Potassium Metabisulfite	**0.124**	**0.185**	**0.247**	**0.309**
Potassium Acetate	0.246	0.246	0.246	0.246
Purified water	55.315	55.241	55.166	55.091
Total	**60.000 g**	**60.000 g**	**60.000 g**	**60.000 g**

Manufacturing method

- Pure water is taken into the production tank and homogenized under nitrogen by adding Xanthan Gum.
- Carbopol is added to the mixture and homogenized
- Disodium edetate is added to the mixture and is homogenized.
- Sodium Benzoate is added to the mixture and homogenized.
- Potassium Metabisulfite is added to the mixture and homogenized.
- Potassium Acetate is added to the mixture and homogenized.
- The final suspension is filled into bottles of 60 ml.

Evaluation: Trial studies were subjected to antimicrobial activity testing. As a result of the AET test, Trial 9 and Trial 10 had the same values, so Trial 9 was selected as the appropriate formulation. The results of the AET test are given below. Stability studies will be carried out with the appropriate formulation obtained.

Table 4: Trial 7 Antimicrobial Effectiveness Test Result.

TRİAL 7 ANTIMICROBIAL EFFECTIVENESS TEST REPORT FORM					
Test Microorganism	**Number of Inoculated Microorganisms cfu/ml (Positive Control)**	**14. days**	**Log_{10} reduction**	**28. days**	**Log_{10} reduction**
S.aureus (ATCC6538)	$6,7*10^6$	0	10,82	0	10,82
P.acruginosa (ATCC 9072)	$7,5*10^7$	0	9,87	0	9,87
C.albicans (ATCC 10231)	$7,8*10^5$	0	8,89	0	8,89
A.brasiliensis (ATCC 16404)	$3,3*10^5$	0	8,51	0	8,51

Table 5: Trial 8 Antimicrobial Effectiveness Test Result.

TRİAL 8 ANTIMICROBIAL EFFECTIVENESS TEST REPORT FORM					
Test Microorganism	**Number of Inoculated Microorganisms cfu/ml (Positive Control)**	**14. days**	**Log_{10} reduction**	**28. days**	**Log_{10} reduction**
S.aureus (ATCC6538)	$6,7*10^6$	0	8,91	0	8,91
P.acruginosa	$7,5*10^7$	0	7,69	0	7,69

(ATCC 9072)					
C.albicans (ATCC 10231)	$7,8*10^5$	0	6,71	0	6,71
A.brasiliensis (ATCC 16404)	$3,3*10^5$	0	6,34	0	6,34

Table 6: Trial 9 Antimicrobial Effectiveness Test Result.

TRİAL 9 ANTIMICROBIAL EFFECTIVENESS TEST REPORT FORM					
Test Microorganism	**Number of Inoculated Microorganisms cfu/ml (Positive Control)**	**14. days**	**Log_{10} reduction**	**28. days**	**Log_{10} reduction**
S.aureus (ATCC6538)	$6,7*10^6$	0	6,82	0	6,82
P.acruginosa (ATCC 9072)	$7,5*10^7$	0	7,87	0	7,87
C.albicans (ATCC 10231)	$7,8*10^5$	0	5,89	0	5,89
A.brasiliensis (ATCC 16404)	$3,3*10^5$	0	5,51	0	5,51

Table 7: Trial 10 Antimicrobial Effectiveness Test Result.

TRİAL 10 ANTIMICROBIAL EFFECTIVENESS TEST REPORT FORM					
Test Microorganism	**Number of Inoculated Microorganisms cfu/ml (Positive Control)**	**14. days**	**Log_{10} reduction**	**28. days**	**Log_{10} reduction**
S.aureus (ATCC6538)	$6,7*10^6$	0	6,82	0	6,82
P.acruginosa (ATCC 9072)	$7,5*10^7$	0	7,87	0	7,87
C.albicans (ATCC 10231)	$7,8*10^5$	0	5,89	0	5,89
A.brasiliensis (ATCC 16404)	$3,3*10^5$	0	5,51	0	5,51

Trial 11

Batch size: 4000 ml

Table 8: Trial 11 Formulation Table.

Raw Material	Function	Unit formula g/60 ml	Serial Formula Trial 11 g/4000 ml
Mesalazin	Active substance	4.000	266,667
Xanthan Gum	Viscosity agent	0.189	12,600
Carbopol	Viscosity agent	0.048	3,200
Disodium Edetate	Chelating agent.	0.052	3,467
Sodium Benzoate	Antimicrobial preservative	0.052	3,467
Potassium Metabisülfit	Antimicrobial preservative	0.247	16,467
Potassium Acetate	pH agent	0.246	16,400
Purified water	Solvent	55.166	3677,733
Total		**60.000 g**	**4000 g**

Manufacturing method

- Pure water is taken into the production tank and homogenized under nitrogen by adding Xanthan Gum.
- Carbopol is added to the mixture and homogenized
- Disodium edetate is added to the mixture and is homogenized.
- Sodium Benzoate is added to the mixture and homogenized.

- Potassium Metabisulfite is added to the mixture and homogenized.
- Potassium Acetate is added to the mixture and homogenized.
- The final suspension is filled into bottles of 60 ml.

Evaluation: The finished product analysis results of the samples obtained from the trial 11 studies were also found to be appropriate when compared with the reference product. Since the analysis results of the samples obtained from the Trial 11 study were appropriate, a stability study was carried out on the product. The samples that 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) were analyzed and observed. Impurity specifications for the series where stability was observed 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 9: Trial 11 and Original Product Analysıs Result Table.

ANALYSIS RESULTS			
Test	**Specification**	**Mesalazine 4g/60 ml Rectal Süspension**	**Salofalk 4g/60 ml Rectal Süspension**
Appearance	Whitish colored suspension	Complies	Complies
İdentification			
Mesalazine	The retention time of the main peak in the chromatogram of the sample solution should be the same as the retention time of the main peak in the chromatogram of the Standard solution.	Complies	Complies
Sodium benzoate	The retention time of the main peak in the chromatogram of the sample solution should be the same as the retention time of the main peak in the chromatogram of the Standard solution.	Complies	Complies
Potassium Metabisulfite	The retention time of the main peak in the chromatogram of the sample solution should be the same as the retention time of the main peak in the chromatogram of the Standard solution.	Complies	Complies
Assay			
Mesalazine	66.667 mg/g ±5% (63,333 mg/g - 70.0 mg/g)	65.67 mg/g	64.43 mg/g
Sodium benzoate	1.0mg/g ± 75.0%-%115 (0.75 mg/g – 1.15 mg/g)	0.99 mg/g	0.86 mg/g
Potassium Metabisulfite	4.68 mg/g ± 75.0%-%115 (3.51 mg/g – 5.38 mg/g)	4.63 mg/g	4.32 mg/g
pH	4.0-5.0	4.77	4.81
Related compounds			
Impurity C	Not more than 200 ppm	DL	DL
Impurity K	Not more than 10 ppm	DL	DL
Impurity H	Not more than 0.3%	DL	DL
Impurity E	Not more than 0.15%	DL	0.12%
Impurity F	Not more than 0.15%	DL	DL
Impurity G	Not more than 0.15%	DL	DL
Impurity J	Not more than 0.15%	DL	DL
Impurity L	Not more than 0.15%	DL	DL
Impurity M	Not more than 0.15%	DL	DL
Impurity P	Not more than 0.15%	DL	DL
Impurity R	Not more than 0.15%	DL	DL
Unknown impurity	Not more than 0.1%	DL	DL
Total impurity	Not more than 0.5%	0.04%	0.12%
Viscosity	Not more than 500 cP	110.53 cP	115.67 cP
Dissolution	At least 85% of the label value after 15 minutes Q = (% 80)	%98.46	%97.56
Density	0.95 g/ml-1.15 g/ml	1.025 g/ml	1.018 g/ml

Table 10: 25 ±2°C -60% RH ± 5 Stability Study of Mesalazine 4 g/60 ml Rectal Suspension, Trial 11.

25 ±2°C -60% RH ± 5 Stability Study of Mesalazine 4 g/60 ml Rectal Suspension, Trial 11						
Tests	**Specifications**	**Start**	**3. Months**	**6. Months**	**9. Months**	**12. Months**
Appearance	Whitish colored suspension	Complies	Complies	Complies	Complies	Complies
İdentification						
Mesalazine	The retention time of the main peak in the chromatogram of the sample solution should be the same as the retention time of the main peak in the chromatogram of the Standard solution.	Complies	Complies	Complies	Complies	Complies
Sodium benzoate	The retention time of the main peak in the chromatogram of the sample solution should be the same as the retention time of the main peak in the chromatogram of the Standard solution.	Complies	Complies	Complies	Complies	Complies
Potassium Metabisulfite	The retention time of the main peak in the chromatogram of the sample solution should be the same as the retention time of the main peak in the chromatogram of the Standard solution.	Complies	Complies	Complies	Complies	Complies
Assay						
Mesalazine	66.667 mg/g ±5% (63,333 mg/g - 70.0 mg/g)	65.67 mg/g	65.16 mg/g	63.42 mg/g	65.11 mg/g	63.21mg/g
Sodium benzoate	1.0mg/g ± 75.0%-%115 (0.75 mg/g – 1.15 mg/g)	0.99 mg/g	0.93 mg/g	0.91 mg/g	0.91 mg/g	0.88 mg/g
Potassium Metabisulfite	4.68 mg/g ± 75.0%-%115 (3.51 mg/g – 5.38 mg/g)	4.63 mg/g	4.58 mg/g	4.53 mg/g	4.50 mg/g	4.45 mg/g
pH	4.0-5.0	4.77	4.67	4.55	4.42	4.40
Related compounds						
Impurity C	Not more than 200 ppm	DL	DL	DL	DL	DL
Impurity K	Not more than 10 ppm	DL	DL	DL	DL	DL
Impurity H	Not more than 0.3%	DL	DL	DL	DL	DL
Impurity E	Not more than 0.15%	DL	DL	DL	DL	DL
Impurity F	Not more than 0.15%	DL	DL	DL	DL	DL
Impurity G	Not more than 0.15%	DL	DL	DL	DL	DL
Impurity J	Not more than 0.15%	DL	DL	DL	DL	DL
Impurity L	Not more than 0.15%	DL	DL	DL	DL	DL
Impurity M	Not more than 0.15%	DL	DL	DL	DL	DL
Impurity P	Not more than 0.15%	DL	DL	DL	DL	DL
Impurity R	Not more than 0.15%	DL	DL	DL	DL	DL
Unknown impurity	Not more than 0.1%	DL	DL	DL	DL	DL
Total impurity	Not more than 0.5%	0.04%	0.08%	0.06%	0.06%	0.08%
Viscosity	Not more than 500 cP	110.53 cP	121.34 cP	117.31 cP	110.11 cP	107.89 cP
Dissolution	At least 85% of the label value after 15 minutes Q = (% 80)	%98.46	%99.12	%96.45	%97.76	%96.89
Density	0.95 g/ml-1.15 g/ml	1.025 g/ml	1.024 g/ml	1.024 g/ml	1.027 g/ml	1.025 g/ml

Table 11: 30 ±2°C -65% RH ± 5 Stability Study of Mesalazine 4 g/60 ml Rectal Suspension, Trial 11.

30 ±2°C -65% RH ± 5 Stability Study of Mesalazine 4 g/60 ml Rectal Suspension, Trial 11						
Tests	**Specifications**	**Start**	**3. Months**	**6. Months**	**9. Months**	**12. Months**
Appearance	Whitish colored suspension	Complies	Complies	Complies	Complies	Complies
İdentification						
Mesalazine	The retention time of the main peak in the chromatogram of the sample solution should be the same as the retention time of the main peak in the chromatogram of the Standard solution.	Complies	Complies	Complies	Complies	Complies
Sodium benzoate	The retention time of the main peak in the chromatogram of the sample solution should be the same as the retention time of the main peak in the chromatogram of the Standard solution.	Complies	Complies	Complies	Complies	Complies
Potassium Metabisulfite	The retention time of the main peak in the chromatogram of the sample solution should be the same as the retention time of the main peak in the chromatogram of the Standard solution.	Complies	Complies	Complies	Complies	Complies
Assay						
Mesalazine	66.667 mg/g ±5% (63,333 mg/g - 70.0 mg/g)	65.67 mg/g	64.89 mg/g	65.14 mg/g	64.73 mg/g	65.04 mg/g
Sodium benzoate	1.0mg/g ± 75.0%-%115 (0.75 mg/g – 1.15 mg/g)	0.96 mg/g	0.92mg/g	0.90 mg/g	0.86 mg/g	0.82 mg/g
Potassium Metabisulfite	4.68 mg/g ± 75.0%-%115 (3.51 mg/g – 5.38 mg/g)	4.63 mg/g	4.59 mg/g	4.55 mg/g	4. 47mg/g	4.27 mg/g
pH	4.0-5.0	4.77	4.67	4.55	4.42	4.40
Related compounds						
Impurity C	Not more than 200 ppm	DL	DL	DL	DL	DL
Impurity K	Not more than 10 ppm	DL	DL	DL	DL	DL
Impurity H	Not more than 0.3%	DL	DL	DL	DL	DL
Impurity E	Not more than 0.15%	DL	DL	DL	DL	DL
Impurity F	Not more than 0.15%	DL	DL	DL	DL	DL
Impurity G	Not more than 0.15%	DL	DL	DL	DL	DL
Impurity J	Not more than 0.15%	DL	DL	DL	DL	DL
Impurity L	Not more than 0.15%	DL	DL	DL	DL	DL
Impurity M	Not more than 0.15%	DL	DL	DL	DL	DL
Impurity P	Not more than 0.15%	DL	DL	DL	DL	DL
Impurity R	Not more than 0.15%	DL	DL	DL	DL	DL
Unknown impurity	Not more than 0.1%	DL	0.09%	0.07%	0.06%	0.07%
Total impurity	Not more than 0.5%	0.04%	0.09%	0.06%	0.06%	0.07%
Viscosity	Not more than 500 cP	110.53 cP	116.98 cP	112.18 cP	108.11 cP	106.21 cP
Dissolution	At least 85% of the label value after 15 minutes Q = (% 80)	%98.46	%96.94	%97.13	%96.91	%97.55
Density	0.95 g/ml-1.15 g/ml	1.025 g/ml	1.026 g/ml	1.025 g/ml	1.025 g/ml	1.026 g/ml

Table 12: 40 ±2°C -75% RH ± 5 Stability Study of Mesalazine 4 g/60 ml Rectal Suspension, Trial 11.

40 ±2°C -75% RH ± 5 Stability Study of Mesalazine 4 g/60 ml Rectal Suspension, Trial 11				
Tests	**Specifications**	**Start**	**3. Months**	**6. Months**
Appearance	Whitish colored suspension	Complies	Complies	Complies
İdentification				
Mesalazine	The retention time of the main peak in the chromatogram of the sample solution should be the same as the retention time of the main peak in the chromatogram of the Standard solution.	Complies	Complies	Complies
Sodium benzoate	The retention time of the main peak in the chromatogram of the sample solution should be the same as the retention time of the main peak in the chromatogram of the Standard solution.	Complies	Complies	Complies
Potassium Metabisulfite	The retention time of the main peak in the chromatogram of the sample solution should be the same as the retention time of the main peak in the chromatogram of the Standard solution.	Complies	Complies	Complies
Assay				
Mesalazine	66.667 mg/g ±5% (63,333 mg/g - 70.0 mg/g)	65.67 mg/g	66.13mg/g	64.19 mg/g
Sodium benzoate	1.0mg/g ± 75.0%-%115 (0.75 mg/g – 1.15 mg/g)	0.96 mg/g	0.85 mg/g	0.80 mg/g
Potassium Metabisulfite	4.68 mg/g ± 75.0%-%115 (3.51 mg/g – 5.38 mg/g)	4.63 mg/g	4.35 mg/g	4.15 mg/g
pH	4.0-5.0	4.77	4.23	4.14
Related compounds				
Impurity C	Not more than 200 ppm	DL	DL	DL
Impurity K	Not more than 10 ppm	DL	DL	DL
Impurity H	Not more than 0.3%	DL	DL	DL
Impurity E	Not more than 0.15%	DL	DL	DL
Impurity F	Not more than 0.15%	DL	DL	DL
Impurity G	Not more than 0.15%	DL	DL	DL
Impurity J	Not more than 0.15%	DL	DL	DL
Impurity L	Not more than 0.15%	DL	DL	DL
Impurity M	Not more than 0.15%	DL	DL	DL
Impurity P	Not more than 0.15%	DL	DL	DL
Impurity R	Not more than 0.15%	DL	DL	DL
Unknown impurity	Not more than 0.1%	DL	0.08%	0.08%
Total impurity	Not more than 0.5%	0.04%	0.08%	0.08%
Viscosity	Not more than 500 cP	110.53 cP	110.18 cP	97.78 cP
Dissolution	At least 85% of the label value after 15 minutes Q = (% 80)	%98.46	%98.98	%97.67
Density	0.95 g/ml-1.15 g/ml	1.025 g/ml	1.023 g/ml	1.020 g/ml

RESULTS AND DISCUSSION

It has been tried to obtain a product similar to the reference product by using Mesalazine two different polymers, which is preferred in inflammatory bowel disease (IBD). In the formulation development studies, pH trials were performed first. At the end of the studies, the most suitable formula was found to be Trial 2, and viscosity studies were performed using Trial 2. As a result of the conducted trials, it was found that the formulation that is most similar to the reference product is trial 5. The Trial 5 formulation was placed in the turbiscan device in comparison with the reference product and observed for 22 hours. It has been seen that a product similar to the reference product has been developed based on the data obtained from the Turbiscan device. Based on the appropriate result, a study was conducted for the antimicrobial efficacy test and the most appropriate formulation, Trial 9, was found. As a result of the appropriate trials, Trial 11 was conducted and examined under stability conditions and the suitability of the found formulation was shown.

Within the scope of the completed R&D studies, a total of 11 trial productions were carried out for Mesalazine 4g/60 ml Rectal Suspension. 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 was clearly understood that our developed product was developed to be suitable for use in patient populations of inflammatory bowel disease (IBD) in the treatment and prevention.

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