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(54) Title: ST-246 (TECOVIRIMAT MONOHYDRATE) SUSPENSION FORMULATIONS

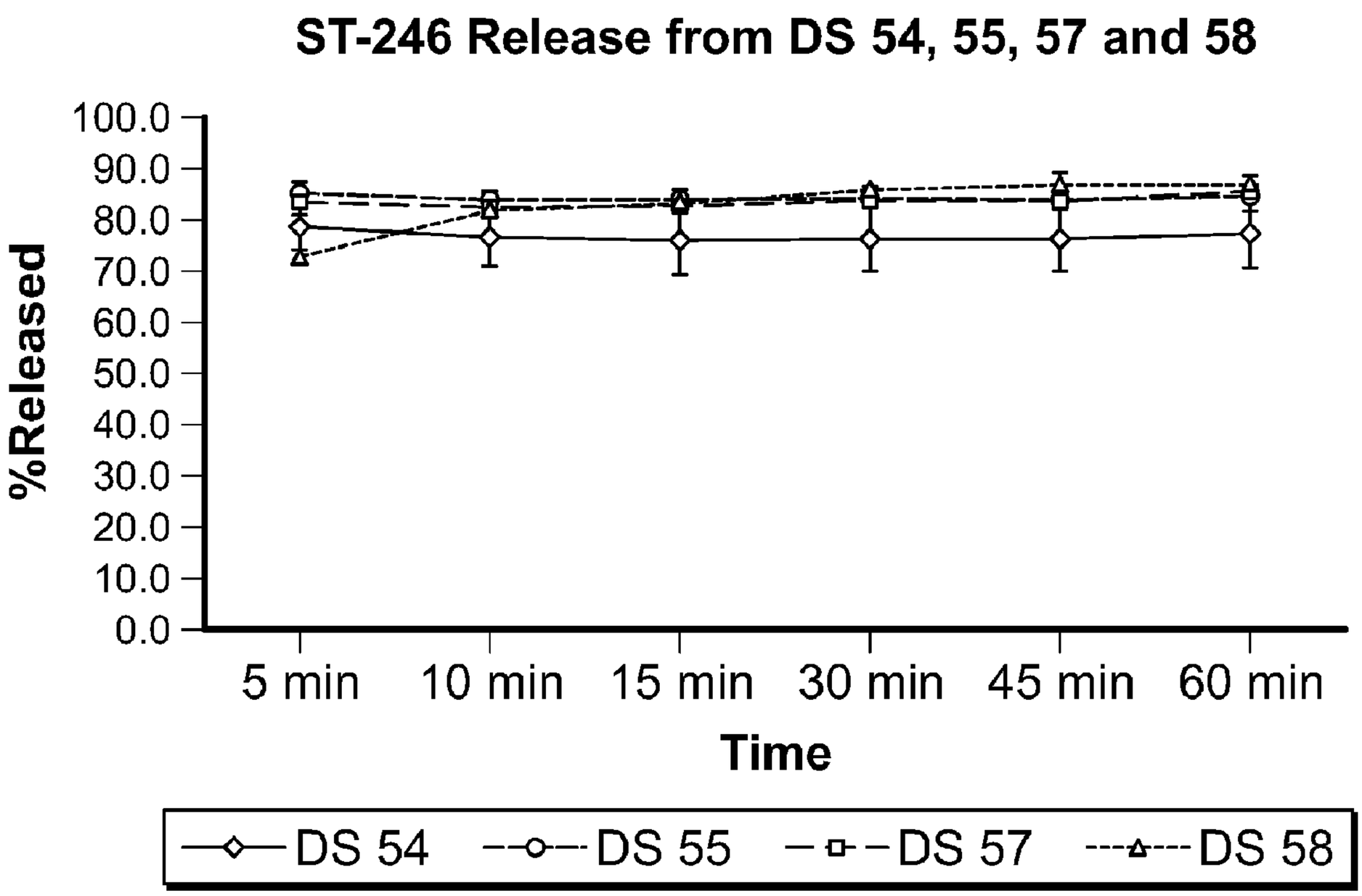

FIG. 1

(57) Abrégé/Abstract:
The present invention is directed to a dry suspension for reconstitution containing Tecovirimat (ST-246) powder and simethicone. The dry suspension is dispersed in water to provide an aqueous pharmaceutical suspension formulation for oral administration for

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(57) Abrégé(suite)/Abstract(continued):
treating orthopoxvirus infections and/or eczema vaccinatum. The suspension formulation exhibits excellent stability and good dissolution and has an improved taste and texture.

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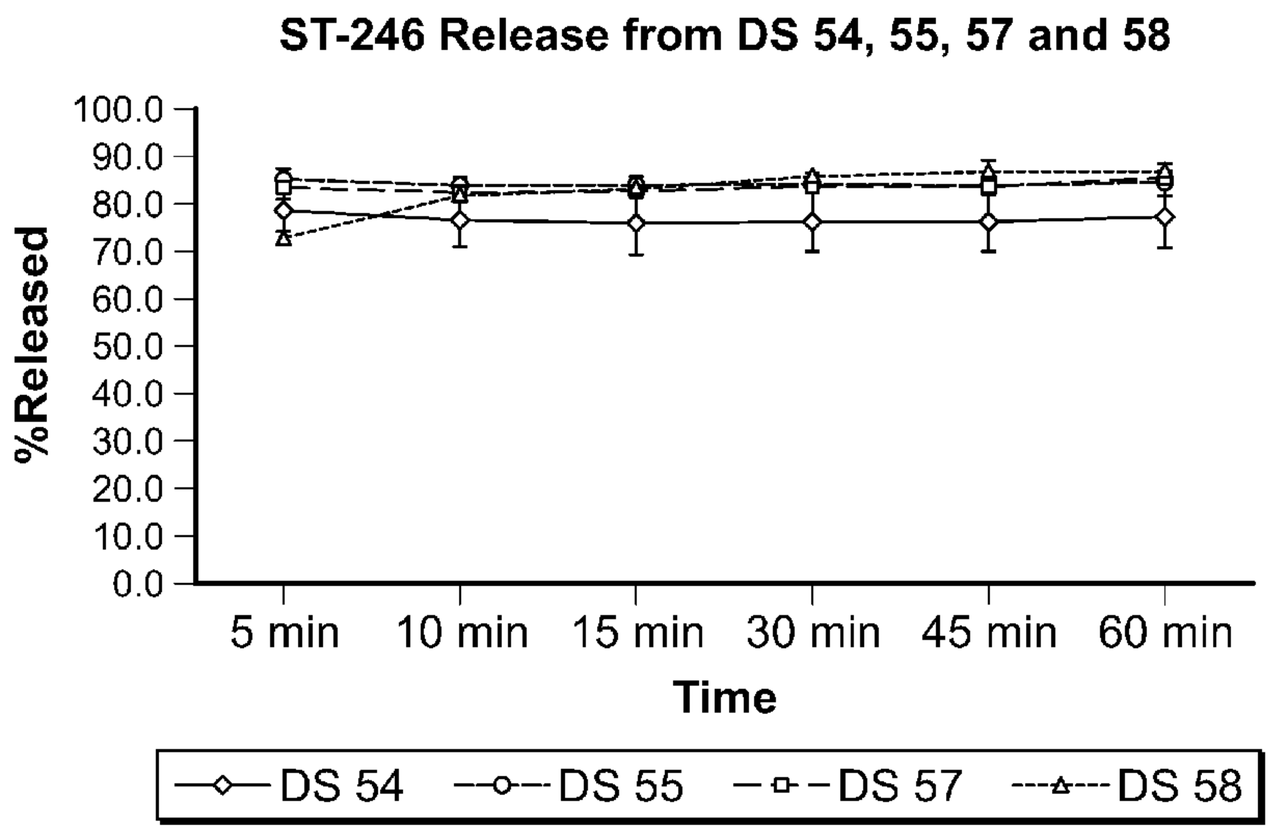

FIG. 1

(57) Abstract: The present invention is directed to a dry suspension for reconstitution containing Tecovirimat (ST-246) powder and simethicone. The dry suspension is dispersed in water to provide an aqueous pharmaceutical suspension formulation for oral administration for treating orthopoxvirus infections and/or eczema vaccinatum. The suspension formulation exhibits excellent stability and good dissolution and has an improved taste and texture.

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ST-246 (tecovirimat monohydrate) SUSPENSION FORMULATIONS

CROSS REFERENCE TO RELATED APPLICATIONS

[00001] This application claims priority to U.S. Provisional Application No. 62/295,710, filed February 16, 2016, which is hereby incorporated herein in its entirety.

FIELD OF THE INVENTION

[00002] The present invention relates to a novel oral powder for suspension (dry suspension) containing Tecovirimat (ST-246) powder for reconstitution and a process for making the dry suspension. The dry suspensions are dispersed in water to provide aqueous pharmaceutical suspension formulations for oral administration.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

[00003] This invention was made with U.S. government support under Contract No.: HHSO100201100001C awarded by the Biomedical Advanced Research and Development Authority (BARDA). The U.S. government has certain rights in this invention.

BACKGROUND OF THE INVENTION

[00004] Throughout this application, various publications are referenced within the text. The disclosure of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art as known to those skilled in therein as of the date of the invention described and claimed herein.

[00005] Historically, variola virus, the etiologic agent of smallpox, has been estimated to have killed, crippled, or disfigured nearly 10% of the human population prior to eradication (1). Smallpox is highly communicable and carries exceptionally high morbidity. Secondary attack rates among unvaccinated members of households in which someone had smallpox have been reported to range from r30% to 80%. Mortality rates range from 1% for variola minor to 30% for variola major. With the advent of biowarfare as an instrument of terrorism, smallpox can no longer be thought of as a disease of historic impact only.

[00006] There are currently no therapies other than early vaccination that can alter the outcome of disease or potentially prevent disease in a population that has been exposed to smallpox. Vaccination carries an inherent risk of adverse events for certain immunosuppressed recipients and even some healthy recipients (2). Moreover, vaccination is effective only if administered within 4 days post-exposure. Thus, antiviral drugs used alone or potentially in combination with vaccination can be used to treat individuals during the window of vulnerability which occurs prior to development of protective immunity. Additionally, antiviral drugs could also be used in the treatment of zoonotic poxvirus disease in humans, such as monkeypox.

[00007] ST-246 (4-trifluoromethyl-*N*-(3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-ethenocycloprop[f]isoindol-2(1H)-yl)-benzamide)(Tecrovirmat), has recently emerged as a potent candidate against orthopoxvirus. Several studies evaluating ST-246 for activity against orthopoxviruses have demonstrated excellent in vitro and in vivo efficacy (3, 4). When evaluated in vitro against vaccinia virus (VV), cowpox virus (CV), ectromelia virus (ECTV), monkeypox, camelpox, and variola viruses, ST-246 inhibited virus replication by 50% (50% effective concentration [EC50]) at or below a concentration of 0.07 μM. With animal models using lethal infections with ECTV, VV, or CV, ST-246 was reported to be nontoxic and highly effective in preventing or reducing mortality even when treatments were delayed up to 72 h post-viral inoculation (3, 4). ST-246 was also evaluated with the nonlethal mouse tail lesion model using intravenous VV. When ST-246 was administered orally twice a day at 15 or 50 mg/kg of body weight for 5 days, the tail lesions were significantly reduced (4). Most recently, an infant was given ST-246 as an FDA-authorized emergency treatment for eczema vaccinatum which developed after exposure to the parent's predeployment military smallpox immunization (5).

[00008] Given the high efficacy of ST-246 antiviral therapy against smallpox and a lack of FDA-approved medications for the treatment of smallpox infection, there is clearly a need for developing safe and effective ST-246 formulations that can be administered by various routes of administration. However, the poor solubility of ST-246 in water and in pharmaceutically acceptable pH buffers and commonly used pharmaceutical vehicles such as co-solvents, surfactants, complexing agents, and lipids creates an impediment to making safe and effective ST-246 liquid formulations.

[00009] Thus, there is a critical need in the pharmaceutical and other biological based industries to formulate water insoluble ST-246 into liquid suspensions for oral, parenteral, or topical administration.

[000010] However, the preparation of an aqueous pharmaceutical suspension formulation from micronized ST-246 presents problems that are difficult to overcome, such as retaining the colloidal stability, preventing particle size growth and foaming.

[000011] Furthermore, once an aqueous suspension has been prepared, sedimentation of the suspension should be avoided. However, if sedimentation arises, the restoration of the suspension must be achieved as easily and as quickly as possible and advantageously this should be achieved by simply shaking the mixture by hand.

[000012] Failure to attain rapid reconstitution of the suspension results in an unacceptably high risk of a dosage error. Furthermore, rapid reconstitution is crucial given that the suspension is often dispensed using a dropper or a dispensing syringe, thereby requiring a stable liquid suspension which is able to flow freely from the dispensing devices and ensure that significantly less material sticks therein.

[000013] Additionally, foaming of the suspension formulation should be avoided, given that this also results in the dosage being imprecise and uncertain.

[000014] Finally, suspension formulations that are used for oral administration, particularly for pediatric use, must not have a bitter taste.

SUMMARY OF THE INVENTION

[000015] The present invention provides an oral powder for suspension (dry suspension) containing 4-trifluoromethyl-N-(3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-ethenocycloprop[f]isoindol-2-(1H)-yl)-benzamide, commonly known as Tecovirimat or ST-246, granulated powder and simethicone, which is suitable for reconstitution.

[000016] The present invention also provides a process for making the dry suspension comprising mixing ST-246 powder with simethicone.

[000017] The present invention further provides an aqueous pharmaceutical suspension formulation comprising ST-246, simethicone and a suspending agent for oral administration.

[000018] Additionally, the present invention provides a process for making the aqueous pharmaceutical suspension formulation comprising dispersing the dry suspension and a suspending agent in water.

[000019] The present invention also provides methods of treating orthopoxvirus infections and/or eczema vaccinatum comprising administering to a subject in need thereof an aqueous pharmaceutical suspension formulation according to the present invention.

[000020] These and other objects, advantages, and features of the invention will become apparent to those persons skilled in the art upon reading the details of the methods and formulations as more fully described below.

DESCRIPTION OF THE DRAWINGS

[000021] Figure 1 shows the % ST-246 release from formulations DS 54, 55, 57 and 58.

[000022] Figure 2 shows the % ST-246 release from formulations DS 75, 77, 83 and 84.

[000023] Figure 3 shows the dissolution of ST-246 from formulations DS 85, 86, and 87.

[000024] Figure 4 shows the % ST-246 release from formulation DS 88 at different blending times.

[000025] Figure 5 shows the % ST-246 release from DS 88 at different lubrication times.

[000026] Figure 6 shows the % ST-246 release from DS 89 and 90.

[000027] Figure 7 shows the % ST-246 release from DS 91 and 92.

[000028] Figure 8 shows an observation when passing simethicone or co-milled simethicone-Tecovirimat granules through #20 screen. A and B: no-dilution simethicone stuck on screen. C and D: pre-diluted and co-milled simethicone-Tecovirimat granules passed screen easily without sticking.

[000029] Figure 9 shows retained clumps on #20 screen after sieve shaking of 100 g DS-92.

[000030] Figure 10 shows % ST-246 release from DS 93 and 94.

[000031] Figure 11 shows flavor profile definitions, including amplitude, amplitude scale, character notes, intensity scale and aftertaste.

[000032] Figure 12 shows a time intensity profile of musty aromatic off-notes, bitterness and tannin mouthfeel of the Tecovirimat granules lingered at patient-perceptible levels ($\geq$ 1) for about 3 minutes in the aftertaste.

[000033] Figure 13 shows a time intensity profile of Tecovirimat formulation #4 (micronized API).

[000034] Figure 14 shows a time intensity profile of formulation #1 (strawberry)

[000035] Figure 15 shows a time intensity profile of formulation #2(cherry)

DETAILED DESCRIPTION OF THE INVENTION

[000036] Tecovirimat (ST-246) is an antiviral agent used for smallpox and related orthopoxviruses. A suitable oral formulation, according to the present invention, is particularly useful in pediatric and/or geriatric populations. The typical maximum dosage is 1200 mg/day.

The drug has very low water solubility over the physiologically relevant pH range, namely approximately 2 μg/mL over a pH range of 1.2 to 6.5. Its solubility increases slightly above pH 6.5, however the chemical stability declines. The solution stability is optimum in the pH 4 to 7 range, for example the pH 3 to 5 range.

[000037] Due to low solubility, preferably the ST-246 is micronized in order to improve dissolution rate. ST-246 has the potential to undergo supersaturation and crystallization with increased particle size in an aqueous based vehicle, and hence, providing an acceptable ready-to-use liquid/suspension dosage form with better stability and longer shelf-life represents a major challenge.

[000038] Additionally, when forming a suspension formulation containing ST-246, a wetting agent, such as a surfactant, is typically used to improve wetting of ST-246 particles, and also to improve dissolution and solubility. However, the presence of a surfactant usually leads to foaming and results in the formulation tasting bitter and having an unpleasant odor.

[000039] The present invention provides a powder for a reconstitution product (dry suspension) comprising ST-246 granulated powder and simethicone which when suspended in water exhibits acceptable stability and dissolution. Furthermore it has been found that the use of semithicone with ST-246 provides excellent foam control upon reconstitution.

[000040] The present invention provides a similar drug release profile, a critical product attribute for product performance in patients, as compared to capsule oral dosage form of ST-246.

[000041] Additionally, the incorporation of additional excipients, flavorings and/or sweeteners to the dry suspension and/or the aqueous pharmaceutical suspension formulation improves the taste and texture of the formulation.

[000042] The dry suspension and/or the suspension formulation may also include one or more pharmaceutically acceptable ingredients selected from the group consisting of disintegrants, carriers, diluents, additives, fillers, lubricants, and binders.

[000043] Disintegrants may include agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrilin potassium, sodium starch glycolate, potato or tapioca starch, pre-gelatinized starch, other starches, clays, other algins, other celluloses, gums, and mixtures thereof.

[000044] Preferably, the dry suspension further comprises at least one suspending agent.

[000045] The suspending agents may include sorbitol syrup; sugar syrup; synthetic polymers such as carbomer and poloxamer; natural gums such as agar, xanthan gum, and tragacanth; cellulose derivatives (e.g., carboxy methyl cellulose, hydroxyl propyl cellulose or methylcellulose); or hydrogenated edible fats; emulsifying agents (e.g., lecithin or acacia); non-aqueous vehicles (e.g., almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g., methyl or propyl-p-hydroxybenzoates or sorbic acid).

[000046] The dry suspensions can also contain buffer salts, flavoring, coloring and sweetening agents as appropriate.

[000047] Furthermore, the dry suspensions may also contain wetting agents and/or surface active agents as appropriate.

[000048] Preferably, the wetting agent or surface active agent is sodium dodecyl sulfate, sodium docusate, tweens, spans, brij, or cetrimide.

[000049] Preferably, the suspending agent is methylcellulose and/or hydroxypropyl cellulose, and, advantageously, the dry suspension contains both methylcellulose and hydroxypropyl cellulose.

[000050] Preferably, the dry suspension contains methylcellulose 400cps and/or methycellulose 15cps and, advantageously, the dry suspension contains both methylcellulose 400cps and methycellulose 15cps methylcellulose.

[000051] Typically, the dry suspension comprises a lubricant, such as calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (e.g., peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, ethyl oleate, ethyl laureate, agar, and mixtures thereof.

[000052] Advantageously, the lubricant is magnesium stearate.

[000053] Excipients include, but are not limited to, agents used to improve taste, suspendability, texture, and flavor. In one embodiment, when the dry suspension contains an excipient, the excipient is advantageously lactose monohydrate. When present, the total amount of excipients are typically present in an amount of about 10 wt% to about 20 wt%.

[000054] The dry suspension may also contain a further antifoaming agent.

[000055] Preferably, the dry suspension also contains a sweetener, such as sucralose.

[000056] Advantageously, the dry suspension contains a flavoring such as strawberry or black cherry.

[000057] The ST-246 may be selected from the group consisting of ST-246 polymorph Form I, ST-246 polymorph Form II, ST-246 polymorph Form III, ST-246 polymorph Form IV, ST-246 polymorph Form V and ST-246 polymorph Form VI.

[000058] The ST-246 may be micronized and/or granulated with excipients , but is advantageously micronized and granulated powder.

[000059] Furthermore the simethicone may be in granular form or may be in liquid form and adsorbed on lactose monohydrate. Advantageously, the simethicone is in granular form.

[000060] The dry suspension typically contains between 10 to 70 wt% of ST-246, and preferably between 15 to 40 wt% of ST-246.

[000061] The dry suspension usually contains between 0.2 to 6.0 wt% simethicone, and preferably between 0.4 to 5.0 wt % simethicone.

[000062] Preferably, the dry suspension contains between 1 to 5 wt % of methylcellulose, and advantageously, between 2 to 3 wt % of methylcellulose.

[000063] Preferably, the dry suspension contains between 1.0 to 30 wt% of hydroxypropylcellulose, and, advantageously, between 2 to 20 wt% of hydroxypropylcellulose.

[000064] When the dry suspension contains a lubricant, typically the lubricant is present in the amount 0.1 to 1.0 wt%.

[000065] Similarly, when the dry suspension contains a sweetener, typically the sweetener is present in the amount of between 1.0 to 3.0 wt%, and when the dry suspension contains a flavoring, typically the flavoring is also present in the amount of between 0.1 to 1.0 wt%.

[000066] The dry suspension preferably has an active pharmaceutical ingredient (API) particle size of ST-246 of between 0.5 to 20 μm, or between 0.5 to 10 μm, or between 1 μm and 5 μm, and, advantageously, between 1 to 10 μm.

[000067] It has been found that the higher the API particle size, the slower the dissolution rate.

[000068] The present invention also provides an aqueous pharmaceutical suspension formulation comprising the dry suspension dispersed in water.

[000069] Typically the suspension, either dry or liquid, contains a suspending agent which is preferably selected from the group consisting of hydromellose, hydroxyethylcellulose, carrageenans, methylcellulose, xanthan gum, povidone, hydroxypropyl cellulose, microcrystalline cellulose, carboxymethylcellulose and sodium alginate.

[000070] When the suspension contains water and a suspending agent this is typically referred to as a 'formulation vehicle'.

[000071] Typically, the formulation, upon reconstitution with water, has a pH between 3 and 8, preferably between 5 and 7.

[000072] The present invention also provides a method of treating orthopoxvirus infections and/or eczema vaccinatum comprising oral administration to a subject in need thereof the above mentioned formulation. Typically, the formulation of the present invention is administered in an amount such that the dose of ST-246 is 200 mg to 2000 mg per day, preferably 400 mg to 2000 mg per day, and most preferably 600 mg to 1200 mg daily. Dosage is typically adjusted according to body weight, particularly in pediatric populations.

[000073] Additionally, the present invention also provides a process of making the dry suspension which involves mixing ST-246 or ST-246 granulated powder with simethicone.

[000074] Optionally, at least one suspending agent, at least one lubricant, at least one excipient, at least one further anti-foaming agent, at least one sweetener and/or at least one flavoring may be mixed with the ST-246 and the simethicone.

[000075] Advantageously, mixing is carried out using geometric mixing.

[000076] Finally, the present invention provides a method of making the above mentioned formulation wherein the dry suspension is dispersed in water, and wherein the water advantageously contains a suspending agent as herein described above.

[000077] As used herein, "percent," "percentage" or the symbol "%" means the percent of the component indicated in the composition based on the amount of the carrier present in the composition, on a weight/weight (w/w), weight/volume (w/v) or volume/volume (v/v) concentration, as indicated with respect to any particular component, all based on the amount of the carrier present in the composition. Thus, different types of carriers can be present in an amount of up to 100% as indicated, which does not preclude the presence of the API, the amount of which can be indicated as a % or as a certain number of mg present in the composition or a certain number of mg/mL present, where the % or mg/mL is based on the amount of the total carrier present in the composition. Certain types of carriers can be present in combination to make up 100% of the carrier.

[000078] As used herein, the terms “Tecovirimat” and “ST-246” refer to the compound 4-trifluoromethyl-N-(3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-ethenocycloprop[f]isoindol-2-(1H)-yl)-benzamide.

[000079] The invention is further described by the examples given below.

EXAMPLES

Example 1. Production of a dry suspension containing tecrovirimat monohydrate (ST-246) for reconstitution, 200 mg.

[000080] A stable oral powder containing ST-246 was prepared, particularly for pediatric and/or geriatric application. The development of the powder involved the following stages;

1. Formulation and evaluation of various dry suspensions.
2. Optimization and evaluation of various levels of anti-foaming agents and lubricant and their effect on product properties.
3. Optimization and evaluation of blending time and lubrication time in the product manufacturing process and its effect on product properties.
4. Manufacture of batches for stability studies.

Materials: The following materials were used.

S. #	Material	Supplier / Lot#
1	Tecovirimat Monohydrate, micronized, for discriminatory dissolution method development	Siga Technologies Lot # SG-10C12-T1039 (Trial #2, d90 = 21.51 µm)
2	Tecovirimat Monohydrate, micronized, for discriminatory dissolution method development	Siga Technologies Lot # SG-10C12-T1039 (Trial #3, d90 = 38.74 µm)
3	Tecovirimat Monohydrate, micronized, for discriminatory dissolution method development	Siga Technologies Lot # SG-10C12-T1039 (Trial #4, d90 = 81.53 µm)
4	Tecovirimat Granulate	Siga Technologies Lot # 1302679
5	Tecovirimat Granulate	Siga Technologies Lot # 1401165
6	Colloidal silicon dioxide, NF *(Cabosil M5P)*	Cabot Lot #1222272
7	Croscarmellose sodium, NF *(AcDiSol)*	FMC Biopolymer Lot # TN12824921
8	Lactose monohydrate, NF *(SuperTab11SD)*	DFE Lot # 10705838
9	Lactose monohydrate, NF *(SuperTab11SD)*	DFE Lot # 10700181
10	Lactose monohydrate, NF *(SuperTab11SD)*	DFE Lot # 10737298
11	Microcrystalline cellulose, NF (*Avicel PH101*)	FMC Biopolymer Lot # P113825526
12	Hypromellose, USP *(Methocel E3 LV Premium)*	Dow Lot # 1B020124L1
13	Sodium lauryl sulfate, NF	Spectrum Lot # 1DB0596
14	Purified Water, USP	Ricca Chemicals Lot # 4409016
15	Sucralose, NF	Spectrum Lot # 1CF0697
16	Sucralose, NF	Spectrum Lot # 1DF0586
17	Strawberry flavor, #133.16296	Bell Flavors
18	Black cherry nat type flavor	Kerry Lot # 260314
19	Simethicone, USP *(MED-340, simethicone content 100%)*	Nusil Technologies Lot # 63865
20	Simethicone Granular Solid, USP *(MED-342, simethicone content 30%)*	Nusil Technologies Lot # 63775

S. #	Material	Supplier / Lot#
21	Simethicone Granular Solid, USP *(MED-342, simethicone content 30%)*	Nusil Technologies Lot # 66777
22	Simethicone Granular Solid, USP *(MED-342, simethicone content 30%)*	Nusil Technologies Lot # 67719
23	Magnesium stearate, NF (*HyQual*)	Mallinckrodt Lot # 1301000109
24	Crospovidone, USP/NF *(Kollidon CL-M)*	BASF Lot # 10204988Q0
25	Povidone, USP/NF *(Kollidon 12PF)*	BASF Lot # 12714424U0
26	Povidone, USP/NF *(Kollidon, 90F)*	BASF Lot # 45877768E0
27	Hypromellose *(Methocel F50)*	Dow Lot # 2L03012N21
28	Hypromellose *(Methocel E50)*	Dow Lot # 2C01012N23
29	Methylcellulose, USP *(Methocel A4M Premium)*	Dow Lot # 2E19012N11
30	Methylcellulose, 400 cps, USP	Spectrum Lot # 2CJ0081
31	Methylcellulose, 400 cps, USP	Spectrum Lot # 2DC0205
32	Methylcellulose, 15 cps, USP	Spectrum Lot # 2DE0263
33	Hydroxypropyl cellulose, NF *(Klucel JF Pharm)*	Ashland Lot # 38296
34	Hydroxypropyl cellulose, NF *(Klucel JXF Pharm)*	Ashland Lot # 40289
35	Hydroxypropyl cellulose, NF *(Klucel HF Pharm)*	Ashland Lot # 49264
36	Hydroxypropyl cellulose, NF *(Klucel MF Pharm)*	Ashland Lot # 38949
37	Hydroxylethyl cellulose, NF *(Natrosol 250L Pharm)*	Ashland Lot # J1967
38	Carrageenan, NF *(Gelcarin GP379)*	FMC Biopolymer Lot # 50218031
39	Carrageenan, NF *(SeaSpen PF)*	FMC Biopolymer Lot # 20226021
40	Microcrystalline Cellulose and Sodium Carboxymethylcellulose, NF *(Avicel RC-581)*	FMC Biopolymer Lot # B1204C
41	Microcrystalline Cellulose and Sodium Carboxymethylcellulose, NF *(Avicel CL-611)*	FMC Biopolymer Lot # EN13825521

S. #	Material	Supplier / Lot#
42	Microcrystalline Cellulose and Sodium Carboxymethylcellulose, NF *(Avicel RC-591)*	FMC Biopolymer Lot # DN13825459
43	Sodium Alginate, USP/NF *(Protanal LFR5/60)*	FMC Biopolymer Lot # H191208
44	Xanthan gum, USP/NF *(Xantural 75)*	CP Kelco Lot # 2B4685K
45	Simethicone 50% Powder	AIC Lot # 4060-50205

[000081] Two typical dry suspensions are shown in Table 1. The dry suspensions according to the present invention contain granules of ST-246 and additional excipients to improve taste, suspendability, texture and flavor.

Table 1.

No.	Ingredient	Composition of Formulation DS83 (mg)	Composition of Formulation DS84 (mg)
1	Tecovirimat granulate	346.5	346.5
2	Lactose monohydrate (SuperTab 11SD, DMV Fonterra Excipients)	93.0	0.0
3	Klucel JF Pharm (Ashland)	125.0	118.0
4	Sucralose, USP	10.0	10.0
5	Flavor, black cherry (Virginia Dare, #23950)	3.0	3.0
6	Simethicone granular solid (NuSil MED-342)	20.0	20.0
7	Magnesium stearate	2.5	2.5
	Total	**600.0**	**500.0**

Example 2: Development of the dry suspensions for reconstitution, 200 mg:

[000082] The composition of the Tecovirimat granulate is shown in Table 2. An oral powder for suspension using a suspending agent containing microcrystalline cellulose and sodium carboxymethylcellulose (Avicel CL-611) was used as a Target formulation is shown in Table 3. The target formulation exhibits good physical properties. However, the xanthan gum which is co-processed along with microcrystalline cellulose results in coagulation behavior during the dissolution tests due to the interaction with the surfactant used in the dissolution medium and thus poor drug release.

Table 2. Composition of ST-246 commercial granules

S. No	Ingredients	Quantity per Unit (mg)
1	ST-246, Monohydrate, micronized	209.00
2	Microcrystalline Cellulose, NF (Avicel PH101)	49.628
3	Lactose Monohydrate, NF (Supertab 11SD)	33.15
4	Croscarmellose Sodium, NF (Ac-di-sol SD-711)	31.2
5	Colloidal Silicone Dioxide, NF (Cab-O-Sil® M5P)	1.95
6	Hypromellose, USP (Methocel E3)	13.65
7	Sodium Lauryl Sulfate, NF	7.80
8	Purified Water*, USP	q.s.
	Total	**346.4**

*water is removed during drying

Table 3: ST-246 oral powder for suspension (Target Formulation)

Ingredient	Prototype 1 (mg per dose)	Prototype 2 (mg per dose)
ST-246, granulate	346.5	346.5
Lactose monohydrate (SuperTab 11SD, DMV Fonterra Excipients)	503.3	505.1
Simethicone granular solid, (NuSil MED-342)	10.0	10.0
Avicel CL-611, NF (FMC BioPolymer)	125.0	125.0
Sucralose, USP	10.0	10.0
Flavor, strawberry (Kerry Item: U1-721636)	5.0	-
Flavor, black cherry (Kerry Item: U1-717664)	-	3.0
FD&C Red #3	0.10	-
FD&C red #40	-	0.3
Methylparaben, NF	0.08	0.08
Propylparaben, NF	0.02	0.02
Total	**1,000.0**	**1,000.0**

Example 3: Screening and Selection of Suspending Agent:

[000083] ST-246 granules prepared for capsule dosage form were used for the preparation of ST-246 oral powder for reconstitution, 200 mg. To evaluate the suspendability of the granules in various suspending agents, various suspending agents were dispersed in 50 mL purified water (Table 4). Concentrations of suspending agents in formulations DS-1 to DS-16 were produced according to the maximum potential from FDA Inactive Ingredient Guide (IIG). A placebo was

prepared and compared visually with the target formulation and the concentration of suspending agent was adjusted accordingly in formulation DS-17 to DS-38

Table 4. Composition and Observation of Suspending Agent Placebo Solutions/Suspensions.

Chemicals	Brand name	Formulation ID	Polymer quantity equilvalent to 10 doses (concentration)	Appearance	Disperse speed	Overnight sedimentation	Consistency (Visual observation in comparison with target formulation viscosity +++++)	Viscosity (cps, target formulation viscosity 50-100cps)
Crospovidone	Kollidon CL-M	**DS-1**	2.500 g (5%, w/v)	white suspension	fast	sedimentation, easy to redisperse by shaking	less viscous ++	not measured
Povidone (PVP)	Kollidon 90 F	**DS-2**	0.750 g (1.5%, w/v)	colorless solution	fast	none	less viscous +	not measured
		DS-17	1.500 g (3%, w/v)	colorless solution	fast	none	less viscous +	not measured
		DS-29	3.000 g (6%, w/v)	colorless solution	fast	none	comparable ++++	55.8
	Kollidon 12 PF	**DS-3**	0.750 g (1.5%, w/v)	colorless solution	fast	none	less viscous +	not measured
		DS-18	1.500 g (3%, w/v)	colorless solution	fast	none	less viscous +	not measured
		DS-30	3.000 g (6%, w/v)	colorless solution	fast	none	less viscous ++	not measured
Hypromellose (HPMC)	Methocel F50	**DS-4**	1.500 g (3%, w/v)	colorless solution	slow	none	comparable +++++	43.1
	Methocel E50	**DS-5**	1.500 g (3%, w/v)	colorless solution	slow	none	comparable +++++	85.6

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Chemicals	Brand name	Formulation ID	Polymer quantity equilvalent to 10 doses (concentration)	Appearance	Disperse speed	Overnight sedimentation	Consistency (Visual observation in comparison with target formulation viscosity +++++)	Viscosity (cps, target formulation viscosity 50-100cps)
		DS-19	0.750 g (1.5%, w/v)	colorless solution	slow	none	less viscous ++	not measured
Methylcellulose (MC)	Methocel A4MP	**DS-6**	0.595 g (1.19%, w/v)	colorless solution	slow	none	more viscous ++++++	not measured
		DS-26	0.250 g (0.5%, w/v)	colorless solution	slow	none	comparable ++++	24.9
	Methyl cellulose, 400cps	**DS-7**	0.595 g (1.19%, w/v)	colorless solution	slow	none	comparable +++++	not measured
		DS-27	0.250 g (0.5%, w/v)	colorless solution	slow	none	comparable ++++	17.1
Hydroxypropyl cellulose (HPC)	Klucel JF Pharm	**DS-8**	3.350 g (6.7%, w/v)	colorless solution	slow	none	more viscous +++++++	not measured
		DS-20	0.750 g (1.5%, w/v)	colorless solution	slow	none	less viscous ++	not measured
		DS-31	1.500 g (3%, w/v)	colorless solution	slow	none	comparable ++++	20.4
	Klucel HF Pharm	**DS-9**	3.350 g (6.7%, w/v)	colorless gel	slow	none	more viscous, gel, high viscosity	not measured
		DS-21	0.500 g (1.0%, w/v)	colorless solution	slow	none	more viscous	not measured

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Chemicals	Brand name	Formulation ID	Polymer quantity equilvalent to 10 doses (concentration)	Appearance	Disperse speed	Overnight sedimentation	Consistency (Visual observation in comparison with target formulation viscosity +++++)	Viscosity (cps, target formulation viscosity 50-100cps)
							+++++++	
		DS-33	0.375 g (0.75%, w/v)	colorless solution	slow	none	comparable ++++++	123.9
	Klucel MF Pharm	**DS-10**	3.350 g (6.7%, w/v)	colorless gel	slow	none	more viscous, gel, high viscosity	not measured
		DS-22	0.500 g (1.0%, w/v)	colorless solution	slow	none	more viscous +++++++	not measured
		DS-34	0.375 g (0.75%, w/v)	colorless solution	slow	none	comparable +++++	71.0
Hydroxyethyl cellulose (HEC)	Natrosol 250L Pharm	**DS-11**	1.500 g (3%, w/v)	yellowish solution	fast	none	comparable ++++	14.9
		DS-28	2.000 g (4%, w/v)	yellowish solution	fast	none	comparable ++++	not measured
Carrageenan	Gelcarin GP379	**DS-12**	0.750 g (1.5%, w/v)	yellowish gel	slow	none	more viscous, gel, high viscosity	not measured
		DS-23	0.200 g (0.4%, w/v)	yellowish solution	slow	none	comparable +++++	65.5

Chemicals	Brand name	Formulation ID	Polymer quantity equilvalent to 10 doses (concentration)	Appearance	Disperse speed	Overnight sedimentation	Consistency (Visual observation in comparison with target formulation viscosity +++++)	Viscosity (cps, target formulation viscosity 50-100cps)
	SeaSpen PF	**DS-13**	0.750 g (1.5%, w/v)	milky gel	slow	none	more viscous, gel, high viscosity	not measured
		DS-24	0.200 g (0.4%, w/v)	milky solution	slow	none	comparable ++++++	20.1
Microcrystalline cellulose/sodium carboxymethyl cellulose (MCC/CMCNa)	Avicel RC-581	**DS-14**	1.500 g (3%, w/v)	white suspension	fast	none	more viscous +++++++	not measured
		DS-35	1.250 g (2.5%, w/v)	white suspension	fast	none	comparable ++++++	84.3
	Avicel CL-611	**DS-15**	1.500 g (3%, w/v)	white suspension	fast	none	more viscous +++++++	not measured
		DS-36	1.250 g (2.5%, w/v)	white suspension	fast	none	comparable +++++	35.4
	Avicel RC-591	**DS-37**	1.250 g (2.5%, w/v)	white suspension	fast	none	comparable ++++++	93.8
Sodium Alginate	Protanal LFR 5/60	**DS-16**	0.062 g (0.123%, w/v)	colorless solution	fast	none	less viscous +	not measured
		DS-25	0.800 g (1.6%, w/v)	yellowish solution	slow	none	less viscous ++	not measured
		DS-32	1.600 g (3.2%, w/v)	yellowish solution	slow	none	less viscous ++++	not measured

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Chemicals	Brand name	Formulation ID	Polymer quantity equilvalent to 10 doses (concentration)	Appearance	Disperse speed	Overnight sedimentation	Consistency (Visual observation in comparison with target formulation viscosity +++++)	Viscosity (cps, target formulation viscosity 50-100cps)
		DS-38	2.000 g (4%, w/v)	yellowish solution	slow	none	comparable +++++	32.4

[000084] Povidone (Kollidon 90 F) 6 % , Hypromellose (Methocel F 50 and E50) 3%, Methylcellulose (Methocel A4MP), Methyl Cellulose 400 cps 0.5%, Hydroxypropyl cellulose (Klucel HF and MF) 0.75 %, Hydroxy Ethyl Cellulose (Natrosol 250L Pharm) 3%, Avicel RC-581- 2.5 %, Avicel RC-591- 2.5 % and Sodium alginate 4% show comparable viscosity to the Target formulation containing Avicel CL-611.

[000085] The suspending agent concentrations with comparable consistency to that of the Target formulation (containing Avicel CL-611 as suspending agent) were selected as the formulation viscosity modifier.

Example 4: Formulation of suspensions by mixing ST-246 granules with formulation vehicles:

[000086] To evaluate the suspendability of ST-246, ingredients such as sucralose, simethicone (adsorbed on lactose monohydrate) and suspension polymers were added. Lactose monohydrate was added to make up the weight of the composition. These ingredients were mixed with the selected suspending agent vehicle concentration from Example 3. The resultant compositions are given in Table 5.

[000087] The formulation procedure included:

1. Adsorbing 1 g of simethicone (MED-340, liquid) on 19 g lactose monohydrate (SuperTab 11SD).
2. Geometric mixing of the ST-246 granules, sucralose, simethicone adsorbed on lactose, and lactose monohydrate to make 5 g (5 doses) blends considering the quantity of polymer quantity sufficient (Q.S.) to 25 mL of vehicle.
3. Dispersing the blend in Q.S. to 25 mL of formulation vehicle prepared in Example 3.
4. Evaluation of the sedimentation, redispersibility, and pH of the suspensions.
5. Transfer of each of about 5 mL of suspension in screw cap glass vials, to store the samples at room temperature, at 2 to 8 °C and at 40°C /75%RH for 14 Days and recording the observations. Table 6 shows the results of physical properties of suspensions.

Table 5. Composition of suspensions - Suspending Agent Selection

S.#	Ingredients	Quantity (g) Equivalent to 5 doses														
		DS-39	DS-40	DS-41	DS-42	DS-43	DS-44	DS-45	DS-46	DS-47	DS-48	DS-49	DS-50	DS-51	DS-52	DS-53
1	ST-246 Granules	1.733	1.733	1.733	1.733	1.733	1.733	1.733	1.733	1.733	1.733	1.733	1.733	1.733	1.733	1.733
2	Sucralose, NF	0.050	0.050	0.050	0.050	0.050	0.050	0.050	0.050	0.050	0.050	0.050	0.050	0.050	0.050	0.050
3	Simethicone, USP (MED-340)	0.025	0.025	0.025	0.025	0.025	0.025	0.025	0.025	0.025	0.025	0.025	0.025	0.025	0.025	0.025
4	Lactose Monohydrate, NF (SuperTab 11SD)	0.475	0.475	0.475	0.475	0.475	0.475	0.475	0.475	0.475	0.475	0.475	0.475	0.475	0.475	0.475
5	Lactose Monohydrate, NF (SuperTab 11SD)	1.967	1.967	1.967	2.617	2.617	2.592	2.592	1.217	1.967	2.530	2.530	2.092	2.092	2.092	1.717
6	Hypromellose (Methocel F 50), 3% Dispersion	25.750	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Hypromellose (Methocel E 50), 3% Dispersion	-	25.750	-	-	-	-	-	-	-	-	-	-	-	-	-
	Hydroxyethyl cellulose (Natrosol 250L), 3% Dispersion	-	-	25.750	-	-	-	-	-	-	-	-	-	-	-	-
	Carrageenan (Iota) (Gelcarin GP379), 0.4% Dispersion	-	-	-	25.100	-	-	-	-	-	-	-	-	-	-	-
	Carrageenan (Iota) (SeaSpen PF), 0.4% Dispersion	-	-	-	-	25.100	-	-	-	-	-	-	-	-	-	-

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S.#	Ingredients	Quantity (g) Equivalent to 5 doses														
		DS-39	DS-40	DS-41	DS-42	DS-43	DS-44	DS-45	DS-46	DS-47	DS-48	DS-49	DS-50	DS-51	DS-52	DS-53
	Methyl Cellulose (Methocel A4MP), 0.5% Dispersion	-	-	-	-	-	25.125	-	-	-	-	-	-	-	-	-
	Methyl Cellulose, 400 cps, 0.5% Dispersion	-	-	-	-	-	-	25.125	-	-	-	-	-	-	-	-
	Povidone (Kollidon 90F), 6% Dispersion	-	-	-	-	-	-	-	26.500	-	-	-	-	-	-	-
	Hydroxypropyl cellulose (Klucel JF Pharm), 3% Dispersion	-	-	-	-	-	-	-	-	25.750	-	-	-	-	-	-
	Hydroxypropyl cellulose (Klucel HF Pharm), 0.75% Dispersion	-	-	-	-	-	-	-	-	-	25.187	-	-	-	-	-
	Hydroxypropyl cellulose (Klucel MF Pharm), 0.75% Dispersion	-	-	-	-	-	-	-	-	-	-	25.187	-	-	-	-
	Microcrystalline cellulose and carboxymethyl cellulose (Avicel RC-581), 2.5% Dispersion	-	-	-	-	-	-	-	-	-	-	-	25.625	-	-	-
	Microcrystalline cellulose and carboxymethyl cellulose (Avicel CL-611), 2.5% Dispersion	-	-	-	-	-	-	-	-	-	-	-	-	25.625	-	-
	Microcrystalline cellulose and carboxymethyl cellulose (Avicel RC-591), 2.5% Dispersion	-	-	-	-	-	-	-	-	-	-	-	-	-	25.625	-
	Sodium Alginate (Protanal LFR 5/60), 4% Dispersion	-	-	-	-	-	-	-	-	-	-	-	-	-	-	26.000

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[000088] The sedimentation coefficients were determined by measuring the height of the suspension in a 40 cc vial divided by the height of the sediment in a vial. Sedimentation coefficient versus time is used as an indicator as to the stability of suspension over the time.

[000089] The redispersibility was evaluated by centrifuging the suspension in Eppendorf tube at 5000 rpm for 10 minutes followed by shaking manually or with wrist action shaker, if the sediment in centrifuge suspended again, it was recorded as " redispersible."

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Table 6. Characterization of Physical Stability of Selected Formulations

Formulation ID		DS-39	DS-40	DS-41	DS-42	DS-43	DS-44	DS-45	DS-46	DS-47	DS-48	DS-49	DS-50	DS-51	DS-52	DS-53
Polymer		Methocel F50 3% w/v	Methocel E50 3% w/v	Natrosol 250L 3% w/v	Gelcarin GP379 0.4% w/v	SeaSpen PF 0.4% w/v	Methocel A4MP 0.5% w/v	MC, 400cps 0.5% w/v	Kollidon 90F 6% w/v	Klucel JF 3% w/v	Klucel HF 0.75% w/v	Klucel MF 0.75% w/v	Avicel RC-581 2.5% w/v	Avicel CL-611 2.5% w/v	Avicel RC-591 2.5% w/v	Protanal LFR5/60 4% w/v
Observations																
1	Appearance	White dispersion	White dispersion	White dispersion	White dispersion	White dispersion	White dispersion	White dispersion	White dispersion	White dispersion	White dispersion	White dispersion	White dispersion	White dispersion	White dispersion	White dispersion
2	Sedimentation Coeff (10 min)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
3	Sedimentation Coeff (30 min)	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
4	Sedimentation Coeff (12 h)	1.00	1.00	0.72	0.46	1.00	1.00	1.00	0.51	1.00	1.00	1.00	1.00	1.00	1.00	0.27
5	Sedimentation Coeff (24 h)	1.00	1.00	0.58	0.38	1.00	1.00	0.92	0.41	1.00	1.00	1.00	1.00	1.00	1.00	0.23
6	Observation at the time of mixing the solids with the formulation vehicle	None	None	None	None	None	None	None	None	Thickening of formulation	Thickening of formulation, gel	Thickening of formulation, gel	None	None	None	Thinning of formulation after overnight standing
7	Redispersibility after 24 hours (gentle shaking)	No sedimentation	No sedimentation	Redispersible	Redispersible	No sedimentation	No sedimentation	Redispersible	Redispersible	No sedimentation	No sedimentation	No sedimentation	No sedimentation	No sedimentation	No sedimentation	Redispersible, but agglomerates were found
8	pH	5.62	5.81	5.57	5.30	6.67	5.71	5.78	5.67	5.76	Not checked	Not checked	5.58	5.56	5.57	5.16

Formulation ID		DS-39	DS-40	DS-41	DS-42	DS-43	DS-44	DS-45	DS-46	DS-47	DS-48	DS-49	DS-50	DS-51	DS-52	DS-53
Polymer		Methocel F50 3% w/v	Methocel E50 3% w/v	Natrosol 250L 3% w/v	Gelcarin GP379 0.4% w/v	SeaSpen PF 0.4% w/v	Methocel A4MP 0.5% w/v	MC, 400cps 0.5% w/v	Kollidon 90F 6% w/v	Klucel JF 3% w/v	Klucel HF 0.75% w/v	Klucel MF 0.75% w/v	Avicel RC-581 2.5% w/v	Avicel CL-611 2.5% w/v	Avicel RC-591 2.5% w/v	Protanal LFR5/60 4% w/v
Observations																
Stability: 2-8 °C for 14 days																
1	Appearance (Color)	white	white	white	white	white	white	white	white	white	Not checked	Not checked	white	white	white	white
2	Signs of Creaming, flocculation	two layers	two layers	almost clear supernatant	clear supernatant	uniform	two layers	two layers	clear supernatant	two layers			creamy, phase separation	uniform	creamy	clear supernatant
3	Sedimentation Coeff	0.98	0.99	0.34	0.34	0.97	0.97	0.95	0.31	0.98			0.83	1.00	1.00	0.21
4	Redispersibility	redispersible	redispersible	redispersible	redispersible	redispersible	redispersible	redispersible	redispersible	redispersible			redispersible	redispersible	redispersible	redispersible
Stability: 40 °C/75% RH for 14 days																
1	Appearance (Color)	white	white	white	white	white	white	white	white	white	Not checked	Not checked	white	white	white	white
2	Signs of Creaming, floculation	two layers	two layers	clear supernatant	clear supernatant	clear supernatant	clear supernatant, sedimentation two layers	clear supernatant, sedimentation two layers	clear supernatant	a thin clear supernatant, a thick flocculation layer			creamy, phase separation	uniform	creamy	clear supernatant
3	Sedimentation Coeff	0.97	0.98	0.34	0.37	0.34	0.52	0.56	0.34	0.59			0.78	1.00	1.00	0.34
4	Redispersibility	redispersible	redispersible	redispersible	redispersible	redispersible	redispersible	redispersible	redispersible	redispersible			redispersible	redispersible	redispersible	redispersible
Stability: Room temperature for 14 days																
1	Appearance (Color)	white	white	white	white	white	white	white	white	white	white	white	white	white	white	white

Formulation ID		DS-39	DS-40	DS-41	DS-42	DS-43	DS-44	DS-45	DS-46	DS-47	DS-48	DS-49	DS-50	DS-51	DS-52	DS-53
Polymer		Methocel F50 3% w/v	Methocel E50 3% w/v	Natrosol 250L 3% w/v	Gelcarin GP379 0.4% w/v	SeaSpen PF 0.4% w/v	Methocel A4MP 0.5% w/v	MC, 400cps 0.5% w/v	Kollidon 90F 6% w/v	Klucel JF 3% w/v	Klucel HF 0.75% w/v	Klucel MF 0.75% w/v	Avicel RC-581 2.5% w/v	Avicel CL-611 2.5% w/v	Avicel RC-591 2.5% w/v	Protanal LFR5/60 4% w/v
Observations																
2	Signs of Creaming, flocculation	two layers	two layers	clear supernatant	clear supernatant	clear supernatant	two layers	two layers	opaque supernatant	opaque supernatant	very viscous gel	very viscous gel	creamy, phase separation	uniform	uniform	clear supernatant
3	Sedimentation Coeff	0.98	0.97	0.30	0.32	0.76	0.65	0.94	0.30	0.42	1.00	1.00	0.84	1.00	1.00	0.33
4	Redispersibility	redispersible	redispersible	redispersible	redispersible	redispersible	redispersible	redispersible	redispersible	redispersible	too viscous	too viscous	redispersible	redispersible	redispersible	redispersible
5	pH	5.62	5.58	5.49	5.25	6.77	5.65	5.66	5.44	5.49	4.74	5.65	5.53	5.49	5.50	5.14

[000090] Suspensions were prepared using 3% Methocel F50, 3% Methocel E50, 0.5% Methocel A4MP, 0.5% Methylcellulose 400 cps, or 3% Klucel JF as suspending agents and showed comparable physical properties as the Target formulation using 2.5% Avicel CL-611 as a vehicle, and also showed comparable results of physical stability when stored at 2 to 8°C, room temperature and at 40°C/75% RH for the reconstitution study.

Example 5: Formulation and Evaluation of Powders for Reconstitution using Selected Polymers:

[000091] Solid blends (including suspending agents selected in Example 4) were formulated, and the rates of reconstitution (hydration time) in water were evaluated. Compositions are given in Table 7.

Table 7. Composition of solid blends (including suspending agents) for reconstitution (40mg/ml).

S.#	Ingredients	Quantity per unit (mg)				
		DS-54	DS-55	DS-56	DS-57	DS-58
1	ST-246 Granules*	346.50	346.50	346.50	346.50	346.50
2	Sucralose, NF	10.00	10.00	10.00	10.00	10.00
3	Simethicone, USP (MED-340)	5.00	5.00	5.00	5.00	5.00
4	Lactose Monohydrate, NF (SuperTab 11SD)	95.00	95.00	95.00	95.00	95.00
5	Lactose Monohydrate, NF (SuperTab 11SD)	393.50	393.50	518.50	518.50	393.50
6	Hypromellose (Methocel F 50)	150.00	-	-	-	-
	Hypromellose (Methocel E 50)	-	150.00	-	-	-
	Methyl Cellulose (Methocel A4MP), USP	-	-	25.00	-	-
	Methyl Cellulose, 400 cps, USP	-	-	-	25.00	-
	Hydroxypropyl cellulose (Klucel JF Pharm), NF	-	-	-	-	150.00
7	Purified water, USP, Q.S. to 5 mL	-	-	-	-	-
Total		**1000.00**	**1000.00**	**1000.00**	**1000.00**	**1000.00**

* granules equivalent to 200 mg Tecovirimat

[000092] The formulation procedure was as follows;

1. Adsorbing of 1 g of simethicone (MED-340, liquid) on 19 g lactose monohydrate (SuperTab 11SD)
2. Geometric mixing of Tecovirimat granules, sucralose, and simethicone adsorbed lactose, then weighing of quantity equivalent to 10 units of blend and then geometric mixing with other components for each formulation;
3. Dispersing of the blend in purified water to make Q.S. to 50 mL;
4. Observing the rate of reconstitution, sedimentation, redispersibility, and pH of the suspensions (see Table 8);
5. Storing the samples at room temperature, at 2 to 8°C and at 40°C /75%RH for 14 Days and recording the observations (see Table 9);
6. Conducting a freeze-thawing cycle of 3-day -10 °C and 3-day room temperature and repeating 5 times and recording the observations (see Table 10 and 11).

Table 8. Observation of reconstitution and 1-day sedimentation of DS-54 to DS-58

Formulation ID		DS-54	DS-55	DS-56	DS-57	DS-58
Polymer		Methocel F50 3% w/v	Methocel E50 3% w/v	Methocel A4MP 0.5% w/v	MC, 400 cps 0.5% w/v	Klucel JF 3% w/v
Observations T=0, room temperature						
1	Time for reconstitution (min)	7	7	1	1	2
2	Observation for reconstitution	Still chunks remaining at bottom after shaking	Still chunks remaining at bottom after shaking	No chunks remaining, easy to disperse	No chunks remaining, easy to disperse	Small chunks remaining at bottom after shaking
3	Appearance (visual)	white, uniform	white, uniform	white, uniform	white, uniform	white, uniform
4	pH	5.76	5.81	5.86	5.89	5.78
5	Particle size (μm)	3.20 ± 2.56	3.03 ± 1.91	3.85 ± 3.11	3.31 ± 2.43	3.86 ± 3.31
6	Forced settling and Redispersibility	redispersible	redispersible	redispersible	redispersible	redispersible
Observations T=30 min, room temperature						
1	Sedimentation Coefficient	1.00	1.00	1.00	1.00	1.00
2	Appearance (visual)	white, uniform	white, uniform	white, uniform	white, uniform	white, uniform
3	Redispersibility	redispersible	redispersible	redispersible	redispersible	redispersible
Observations T=1 hr, room temperature						
1	Sedimentation Coefficient	1.00	1.00	1.00	1.00	1.00
2	Appearance (visual)	white, uniform	white, uniform	white, uniform	white, uniform	white, uniform
3	Redispersibility	redispersible	redispersible	redispersible	redispersible	redispersible
Observations T=24 hr, room temperature						
1	Sedimentation Coefficient	1.00	1.00	1.00	0.98	0.95
2	Appearance (visual)	white, uniform	white, uniform	two layers	two layers	opaque supernatant with floccules
3	Redispersibility	redispersible	redispersible	redispersible	redispersible	redispersible

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Table 9. 14-Days stability of DS-54 to DS-58

Formulation ID		DS-54	DS-55	DS-56	DS-57	DS-58
Polymer		Methocel F50 3% w/v	Methocel E50 3% w/v	Methocel A4MP 0.5% w/v	MC, 400 cps 0.5% w/v	Klucel JF 3% w/v
Observations T=7 days, room temperature						
1	Sedimentation Coefficient	0.95	0.97	0.95	0.96	0.65
2	Appearance (visual)	two layers	two layers	two layers	two layers	opaque supernatant with floccules
3	Redispersibility	redispersible	redispersible	redispersible	redispersible	redispersible
4	pH	5.72	5.79	5.77	5.78	5.70
5	Particle size (μm)	3.33 ± 2.67	3.37 ± 2.29	3.11 ± 1.88	3.37 ± 1.96	3.20 ± 2.13
Observations T=7 days, 2-8 °C						
1	Sedimentation Coefficient	0.97	0.97	0.98	0.99	0.87
2	Appearance (visual)	two layers	two layers	two layers	two layers	opaque supernatant with floccules
3	Redispersibility	redispersible	redispersible	redispersible	redispersible	redispersible
4	pH	5.75	5.82	5.81	5.79	5.75
5	Particle size (μm)	3.13 ± 2.18	3.20 ± 2.30	3.51 ± 2.37	3.37 ± 2.08	3.57 ± 2.52
Observations T=7 days, 40 °C/75% RH						
1	Sedimentation Coefficient	0.35	0.43	0.44	0.41	0.81
2	Appearance (visual)	milky supernatant	opaque supernatant	clear supernatant with floccules	opaque supernatant	opaque supernatant with floccules
3	Redispersibility	redispersible	redispersible	redispersible	redispersible	redispersible
4	pH	5.48	5.55	5.53	5.57	5.44
5	Particle size (μm)	3.51 ± 2.49	3.45 ± 2.54	3.86 ± 2.55	3.96 ± 3.00	3.81 ± 2.37
Observations T=14 days, room temperature						
1	Sedimentation Coefficient	0.96	0.96	0.49	0.96	0.69

Formulation ID		DS-54	DS-55	DS-56	DS-57	DS-58
Polymer		Methocel F50 3% w/v	Methocel E50 3% w/v	Methocel A4MP 0.5% w/v	MC, 400 cps 0.5% w/v	Klucel JF 3% w/v
2	Appearance (visual)	two layers	two layers	two layers, clear supernatant with floccules	two layers	opaque supernatant with floccules
3	Redispersibility	redispersible	redispersible	redispersible; sedimentation occurs at 30min after shaking	redispersible	redispersible
4	pH	5.68	5.69	5.72	5.71	5.64
5	Particle size (μm)	3.69 ± 2.45	3.54 ± 2.68	3.51 ± 2.78	3.68 ± 2.95	3.48 ± 2.66
Observations T=14 days, 2-8 °C						
1	Sedimentation Coefficient	0.96	0.96	0.96	0.95	0.90
2	Appearance (visual)	two layers	two layers	two layers	two layers	opaque supernatant with floccules
3	Redispersibility	redispersible	redispersible	redispersible	redispersible	redispersible
4	pH	5.74	5.75	5.75	5.78	5.76
5	Particle size (μm)	3.86 ± 2.86	3.57 ± 2.44	3.46 ± 2.58	3.76 ± 2.74	3.78 ± 2.68
Observations T=14 days, 40 °C/75% RH						
1	Sedimentation Coefficient	0.74	0.78	0.39	0.33	0.60
2	Appearance (visual)	clear supernatant with floccules	clear supernatant with floccules	clear supernatant with floccules, an opaque flocculation layer between clear supernatant and sedimentation	clear supernatant with floccules, an opaque flocculation layer between clear supernatant and sedimentation	clear supernatant with floccules, an opaque flocculation layer between clear supernatant and sedimentation
3	Redispersibility	redispersible	redispersible	redispersible; curdy, loose sedimentation right away after shaking	redispersible; curdy, loose sedimentation right away after shaking	redispersible
4	pH	5.32	5.32	5.40	5.40	5.32

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Formulation ID		DS-54	DS-55	DS-56	DS-57	DS-58
Polymer		Methocel F50 3% w/v	Methocel E50 3% w/v	Methocel A4MP 0.5% w/v	MC, 400 cps 0.5% w/v	Klucel JF 3% w/v
5	Particle size (μm)	3.93 ± 3.00	3.86 ± 3.08	3.94 ± 3.03	3.96 ± 3.10	3.83 ± 2.72

Table 10. Observations for freeze-thawing cycles of -10 °C (3-day) and RT (3-day)

Formulation ID		DS-54	DS-55	DS-56	DS-57	DS-58
Polymer		Methocel F50 3% w/v	Methocel E50 3% w/v	Methocel A4MP 0.5% w/v	MC, 400 cps 0.5% w/v	Klucel JF 3% w/v
Observations after Freeze-Thawing Cycle: storage at -10 °C for 3 days followed by at RT for 3 days						
Sedimentation Coefficient	1 Cycle	0.96	0.96	0.48	0.34	0.66
	2 Cycle	0.96	0.96	0.50	0.34	0.67
	3 Cycle	0.96	0.96	0.50	0.34	0.54
	4 Cycle	0.96	0.96	0.49	0.30	0.70
	5 Cycle	0.96	0.96	0.49	0.38	0.79
Appearance (visual)	1 Cycle	uniform	uniform	clear supernatant with floccules, a thin opaque flocculation layer between clear supernatant and sedimentation	sedimentation two layers, opaque supernatant with floccules	opaque supernatant with floccules
	2 Cycle	sedimentation two layers	uniform	clear supernatant	sedimentation two layers, opaque supernatant with floccules	opaque supernatant with floccules

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Formulation ID		DS-54	DS-55	DS-56	DS-57	DS-58
Polymer		Methocel F50 3% w/v	Methocel E50 3% w/v	Methocel A4MP 0.5% w/v	MC, 400 cps 0.5% w/v	Klucel JF 3% w/v
	3 Cycle	sedimentation two layers	uniform	clear supernatant, sedimentation two layers	opaque to clear supernatant, sedimentation two layers	A thin clear supernatant on top, a thick opaque flocculation layer between clear supernatant and sedimentation
	4 Cycle	uniform	uniform	clear supernatant	clear supernatant, a milky flocculation layer between clear supernatant and sedimentation	opaque supernatant with floccules
	5 Cycle	uniform	uniform	clear supernatant	clear supernatant, a milky flocculation layer between clear supernatant and sedimentation, sedimentation two layers	opaque supernatant with floccules
Redispersibility	1 Cycle	redispersible	redispersible	redispersible; sedimentation occurs at 10min after shaking	redispersible	redispersible
	2 Cycle	redispersible	redispersible	redispersible; sedimentation occurs at 10min after shaking	redispersible	redispersible

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Formulation ID		DS-54	DS-55	DS-56	DS-57	DS-58
Polymer		Methocel F50 3% w/v	Methocel E50 3% w/v	Methocel A4MP 0.5% w/v	MC, 400 cps 0.5% w/v	Klucel JF 3% w/v
	3 Cycle	redispersible	redispersible	redispersible; sedimentation occurs at 10min after shaking, sedimentation appears loose and curdy	redispersible; sedimentation occurs at 10min after shaking	redispersible
	4 Cycle	redispersible	redispersible	redispersible; sedimentation occurs at 10min after shaking, sedimentation appears loose and curdy	redispersible; sedimentation occurs at 10min after shaking	redispersible
	5 Cycle	redispersible	redispersible	redispersible; sedimentation occurs at 10min after shaking, sedimentation appears loose and curdy	redispersible; sedimentation occurs at 10min after shaking	redispersible
pH	1 Cycle	5.66	5.66	5.69	5.70	5.64
	2 Cycle	5.62	5.63	5.66	5.69	5.57
	3 Cycle	5.60	5.58	5.62	5.66	5.52
	4 Cycle	5.61	5.56	5.60	5.61	5.54
	5 Cycle	5.65	5.67	5.62	5.59	5.50
Particle size (μm)	1 Cycle	3.89 ± 3.33	3.88 ± 3.21	3.86 ± 2.81	3.92 ± 3.20	3.82 ± 2.46
	2 Cycle	3.94 ± 2.87	3.98 ± 2.97	3.97 ± 3.09	4.05 ± 3.25	3.99 ± 2.87
	3 Cycle	4.02 ± 3.25	4.08 ± 3.83	4.12 ± 3.15	4.06 ± 3.09	4.07 ± 3.69
	4 Cycle	4.21 ± 3.07	4.27 ± 3.01	4.26 ± 3.29	4.25 ± 2.78	4.26 ± 2.86
	5 Cycle	4.31 ± 3.04	4.29 ± 2.85	4.28 ± 2.99	4.32 ± 3.32	4.30 ± 3.30

Table 11. Observations for Freeze-Thaw cycles of RT (3-day) and 2-8 °C (3-day)

Formulation ID		DS-54	DS-55	DS-56	DS-57	DS-58
Polymer		Methocel F50 3% w/v	Methocel E50 3% w/v	Methocel A4MP 0.5% w/v	MC, 400 cps 0.5% w/v	Klucel JF 3% w/v
Observations after Thawing-freeze Cycle: storage at RT for 3 days followed by at 2-8 °C for 3 days						
Sedimentation Coefficient	1 Cycle	0.97	0.97	0.53	0.96	0.62
	2 Cycle	0.96	0.96	0.55	0.24	0.77
	3 Cycle	0.96	0.96	0.53	0.23	0.70
	4 Cycle	0.96	0.96	0.54	0.53	0.78
	5 Cycle	0.94	0.90	0.52	0.51	0.56
Appearance (visual)	1 Cycle	sedimentation two layers	sedimentation two layers	clear supernatant, a thin opaque flocculation layer between clear supernatant and sedimentation, sedimentation two layers	sedimentation two layers	opaque supernatant with floccules
	2 Cycle	sedimentation two layers	sedimentation two layers	clear supernatant	sedimentation two layers, milky supernatant with floccules	opaque supernatant with floccules

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Formulation ID		DS-54	DS-55	DS-56	DS-57	DS-58
Polymer		Methocel F50 3% w/v	Methocel E50 3% w/v	Methocel A4MP 0.5% w/v	MC, 400 cps 0.5% w/v	Klucel JF 3% w/v
	3 Cycle	sedimentation two layers	sedimentation two layers	clear supernatant	An opaque supernatant on top, a thick milky flocculation layer between opaque supernatant and sedimentation, sedimentation two layers	opaque supernatant with floccules
	4 Cycle	sedimentation two layers	sedimentation two layers	clear supernatant	clear supernatant, sedimentation two layers	opaque supernatant with floccules
	5 Cycle	sedimentation two layers	clear to opaque supernatant, sedimentation two layers	clear supernatant	clear supernatant, sedimentation two layers	A thin clear supernatant on top, a thick opaque flocculation layer between clear supernatant and sedimentation
Redispersibility	1 Cycle	redispersible	redispersible	redispersible; sedimentation occurs at 10min after shaking	redispersible	redispersible
	2 Cycle	redispersible	redispersible	redispersible; sedimentation occurs at 10min after shaking	redispersible	redispersible
	3 Cycle	redispersible	redispersible	redispersible; sedimentation occurs at 10min after shaking	redispersible	redispersible

Formulation ID		DS-54	DS-55	DS-56	DS-57	DS-58
Polymer		Methocel F50 3% w/v	Methocel E50 3% w/v	Methocel A4MP 0.5% w/v	MC, 400 cps 0.5% w/v	Klucel JF 3% w/v
	4 Cycle	redispersible	redispersible	redispersible; sedimentation occurs at 10min after shaking, sedimentation appears loose and curdy	redispersible; sedimentation occurs at 30min after shaking	redispersible
	5 Cycle	redispersible	redispersible	redispersible; sedimentation occurs at 10min after shaking, sedimentation appears loose and curdy	redispersible; sedimentation occurs at 10min after shaking	redispersible
pH	1 Cycle	5.70	5.72	5.71	5.70	5.63
	2 Cycle	5.67	5.68	5.67	5.73	5.61
	3 Cycle	5.61	5.58	5.70	5.65	5.53
	4 Cycle	5.57	5.58	5.62	5.64	5.55
	5 Cycle	5.62	5.58	5.57	5.62	5.47
Particle size (μm)	1 Cycle	4.10 ± 2.63	4.09 ± 3.04	3.96 ± 2.41	4.09 ± 3.14	4.08 ± 2.76
	2 Cycle	4.31 ± 3.66	4.37 ± 3.29	4.13 ± 2.77	4.22 ± 2.45	4.16 ± 2.58
	3 Cycle	4.36 ± 3.43	4.37 ± 3.01	4.36 ± 3.20	4.41 ± 3.42	4.41 ± 3.11
	4 Cycle	4.44 ± 3.31	4.38 ± 3.19	4.47 ± 3.05	4.48 ± 3.23	4.46 ± 3.00
	5 Cycle	4.47 ± 2.87	4.49 ± 2.98	4.47 ± 3.28	4.50 ± 3.06	4.48 ± 2.92

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[000093] It was observed that suspensions with 3% Methocel F50 or 3% Methocel E50 as suspending agents showed good stability for 14 days and after 5 freeze-thawing cycles, but slow reconstitution rates were observed when dispersing blends in purified water.

[000094] Suspensions using 0.5% Methocel A4MP as suspending agent showed loose and curdy sedimentation during stability study, indicating incompatibility.

[000095] However, 0.5% Methylcellulose (400 cps) or 3% Klucel JF Pharm as suspending agents showed good reconstitution rate and acceptable stability and therefore could be used as alternative suspending agents for the target formulation.

Example 6: Optimization of Suspending Agent Concentration for Dispersibility Study (Using Simethicone Granular MED-342):

[000096] According to the observations of DS-54 to DS-58, concentrations of Methocel F50, Methocel E50, and Klucel JF Pharm were decreased for better dispersibility, while concentration of Methylcellulose 400 cps was increased for a balance between dispersibility and viscosity. Simethicone in the formulations was changed to the granular solid form (MED-342), which simplifies the process by avoiding adsorbing liquid simethicone on lactose. The compositions are shown in Table 12.

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Table 12. Composition of blends using Simethicone granular solid

S.#	Ingredients	Quantity per unit (mg)											
		DS-54	**DS-55**	**DS-57**	**DS-58**	**DS-63**	**DS-64**	**DS-65**	**DS-66**	**DS-67**	**DS-68**	**DS-69**	**DS-70**
1	Tecovirimat Granules	346.50	346.50	346.50	346.50	346.50	346.50	346.50	346.50	346.50	346.50	346.50	346.50
2	Sucralose, NF	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00
3	Simethicone granular solid, USP (MED-342)	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00
4	Lactose Monohydrate, NF (SuperTab 11SD)	483.50	483.50	608.50	483.50	508.50	508.50	583.50	508.50	533.50	533.50	558.50	533.50
5	Hypromellose (Methocel F 50)	150.00	-	-	-	125.00	-	-	-	100.00	-	-	-
	Hypromellose (Methocel E 50)		150.00	-	-	-	125.00	-	-	-	100.00	-	-
	Methyl Cellulose, 400 cps, USP	-	-	25.00	-	-	-	50.00	-	-	-	75.00	-
	Hydroxypropyl cellulose (Klucel JF Pharm), NF	-	-	-	150.00	-	-	-	125.00	-	-	-	100.00
6	Purified water, USP, Q.S. to 5 mL	-	-	-	-	-	-	-	-	-	-	-	-
	Total	**1000.00**	**1000.00**	**1000.00**	**1000.00**	**1000.00**	**1000.00**	**1000.00**	**1000.00**	**1000.00**	**1000.00**	**1000.00**	**1000.00**

[000097] In general, the formulation procedures include:

1. blending of Tecovirimat granules and simethicone granular solid (MED-342), then passing through Quadro Comil equipped with 2B039R03125173*(991) screen;
2. weighing of quantity equivalent to 40 g of Simethicone-Tecovirimat granules blend and mixing geometrically with other components;
3. passing again of the blend through Quadro Comil using 2B039R03125173*(991) screen and
4. dispersing of 1 dose in purified water to make Q.S. to 5 mL, followed by evaluation of dispersibility and dissolution (Table 13).

Table 13. Observation of reconstitution and dissolution

S.#	Properties		Formulation ID							
			DS-54		DS-55		DS-57		DS-58	
1	Chunks remaining at bottom after shaking		Big chunks		Big chunks		None		Very small chunks	
2	Dissolution (n=3)	Time (mins)	% Released	SD	% Released	SD	% Released	SD	% Released	SD
		5	78.5	4.5	85.3	2.3	83.6	2.6	72.7	1.5
		10	76.6	5.7	83.7	1.9	82.4	1.9	81.8	1.5
		15	76.0	6.7	84.2	1.6	82.5	1.1	83.2	1.6
		30	76.1	6.3	84.2	2.0	84.0	0.2	85.8	0.8
		45	76.1	6.2	84.0	2.0	83.7	1.1	86.7	2.3

S.#	Properties	Formulation ID							
		DS-63	DS-64	DS-65	DS-66	DS-67	DS-68	DS-69	DS-70
1	Chunks remaining at bottom after shaking	Medium chunks	Medium chunks	Small chunks	None	Small chunks	Small chunks	Small chunks	None

[000098] The % ST-246 is shown in Figure 1.

[000099] It was observed that when concentrations of Methocel F50 and Methocel E50 decreased to 2.0% w/v (DS-67 and DS-68), there were still chunks remaining after shaking manually. Hydration rates of these two polymers are fast such that the gel layers developed

inhibit the wetting of inside materials, leading to fish eyes and bad dispersibility. Concentration of 0.5-1.0% w/v Methylcellulose 400 cps and 2.0-2.5% w/v Klucel JF Pharm can reach a balance between good dispersibility and viscosity.

Example 7: Evaluation of a Combination of Suspending Agents:

[0000100] Combinations of suspending agents were used for dissolution study. Compositions are given in Table 14. The Target formulation using Avicel CL-611 as a suspending agent exhibits floating in the form of lumps in dissolution test.

Table 14. Composition of solid blends using combination of suspending agents

S.#	Ingredients	Quantity per unit (mg)			
		Prototype 1 (DS-59)	**Prototype 2 (DS-60)**	**Prototype 3 (DS-61)**	**Prototype 4 (DS-62)**
1	Tecovirimat Granules	346.50	346.50	346.50	346.50
2	Simethicone granular solid, USP (MED-342)	10.00	10.00	10.00	10.00
3	Lactose Monohydrate, NF (SuperTab 11SD)	328.50	348.50	373.50	370.50
4	Avicel CL-611, NF	50.00	25.00		
5	Methyl Cellulose, 400 cps, USP	15.00	20.00	15.00	20.00
6	Xantural 75	-	-	5.00	3.00
7	Purified water, USP, Q.S. to 5 mL	-	-	-	-
Total		**750.00**	**750.00**	**750.00**	**750.00**

[0000101] The formulation procedures was as follows;

1. blending of Tecovirimat granules and Simethicone granular solid (MED-342), then passing through Quadro Comil equipped with 2B039R03125173*(991) screen;
2. weighing of the quantity equivalent to 30 units of Simethicone-Tecovirimat blend and then geometric mixing with other components; shaking and mixing of blend in a zip-lock bag;
3. dispersing of 1 dose in purified water to make Q.S. to 5 mL for dissolution test (Table 15).

Table 15. Dissolution of suspensions using combination of suspending agents

S.#	Properties	Formulation ID			
		Prototype 1 (DS-59)	**Prototype 2 (DS-60)**	**Prototype 3 (DS-61)**	**Prototype 4 (DS-62)**
1	Dispersibility	Small chunks remaining after shaking	Small chunks remaining after shaking	Small chunks remaining after shaking	Small chunks remaining after shaking
2	Viscosity	Good viscosity	Watery	Watery	Watery
3	Dissolution	Instant dispersion with formation of coarse particulates	Instant dispersion with formation of fine particulates	Gel clumps	Gel clumps

Example 8: Optimizing Anti-foaming Agent and Viscosity:

[0000102] The suspensions were optimized for defoaming and viscosity of suspension by changing the level of simethicone solid granular and methylcellulose 400 cps in reference formulation DS-60. The methylcellulose 400 cps was replaced with Klucel JF Pharm and formulated to test the effect on foaminess. The compositions are given in Table 16.

Table 16. Composition of DS-60A to DS-60E and DS-71

S.#	Ingredients	Quantity per unit (mg)					
		DS-60A	**DS-60B**	**DS-60C**	**DS-60D**	**DS-60E**	**DS-71**
1	Tecovirimat Granules	346.50	346.50	346.50	346.50	346.50	346.50
2	Simethicone granular solid, USP (MED-342)	16.67	25.00	16.67	16.67	16.67	16.67
3	Lactose Monohydrate, NF (SuperTab 11SD)	341.83	333.50	336.83	331.83	331.83	341.83
	Avicel CL-611, NF	25.00	25.00	25.00	25.00	25.00	25.00
4	Methyl Cellulose, 400 cps, USP	20.00	20.00	25.00	30.00	37.50	-
	Hydroxypropyl cellulose (Klucel JF Pharm), NF	-	-	-	-	-	20.00
5	Purified water, USP, Q.S. to 5 mL	-	-	-	-	-	-
Total		**750.00**	**750.00**	**750.00**	**750.00**	**757.50**	**750.00**

[0000103] The formulation procedures included

1. geometric mixing of quantity equivalent to 30 units of lactose monohydrate and simethicone (MED-342), then geometric mixing with other components;
2. passing of the blend through Quadro Comil equipped with 2B039R03125173*(991) screen and
3. dispersing of 1 dose in purified water to make Q.S. to 5 mL to test foaminess and viscosity (Table 17).

Table 17. Observation of foaminess and viscosity of DS-60A to DS-60E and DS-71

S.#	Properties	Formulation ID					
		DS-60A	**DS-60B**	**DS-60C**	**DS-60D**	**DS-60E**	**DS-71**
1	Dispersibility	Easy to disperse, no chunks remaining	Easy to disperse, no chunks remaining	Easy to disperse, no chunks remaining	Easy to disperse, no chunks remaining	Small chunks remaining after shaking	Easy to disperse, no chunks remaining
2	Foaminess	Less foam than DS-60	Decreased foam	Decreased foam	Decreased foam	Decreased foam	Less foam than DS-60A
3	Viscosity	Watery	Watery	Watery	Watery	Good viscosity	Watery

[0000104] It was observed that the level of 16.67-25 mg per unit of Simethicone (MED-342) attains a good anti-foaming effect. The replacement of Klucel JF Pharm with Methylcellulose 400 cps also decreases foaminess. Good viscosity in suspension was observed when Methylcellulose 400 cps level reached 0.75% w/v.

Example 9: Methylcellulose (400 cps and 15 cps) Combination as Suspending Agents:

[0000105] The level of Methylcellulose 15 cps was adjusted for better dispersibility. Compositions are given in Table 18.

Table 18. Composition of DS-72 to DS-74

S.#	Ingredients	Quantity per unit (mg)		
		DS-72	**DS-73**	**DS-74**
1	Tecovirimat Granules	346.50	346.50	346.50

S.#	Ingredients	Quantity per unit (mg)		
		DS-72	DS-73	DS-74
2	Simethicone granular solid, USP (MED-342)	16.67	16.67	16.67
3	Lactose Monohydrate, NF (SuperTab 11SD)	349.33	349.33	349.33
4	Methyl Cellulose, 400 cps, USP	37.50	33.50	30.00
	Methyl Cellulose, 15 cps, USP	-	4.00	7.50
5	Purified water, USP, Q.S. to 5 mL	-	-	-
Total		**750.00**	**750.00**	**750.00**

[0000106] The formulation procedure included

1. geometric mixing of Tecovirimat granules, lactose monohydrate and Simethicone (MED-342) and passing of blend through Quadro Comil equipped with 2B039R03125173*(991) screen;
2. weighing of quantity equivalent to 10 units of blend and then geometric mixing with polymer(s) and
3. dispersing of 1 dose in purified water to make Q.S. to 5 mL to test dispersibility.

It was observed that all three formulations were easy to disperse with no chunks remaining after shaking. With decreased level of Methylcellulose 400 cps in formulation, suspension was more watery, suggesting it's better to keep Methylcellulose 400 cps more than 0.75% w/v.

Example 10: Optimizing levels of Methylcellulose 15 cps and Simethicone in Methylcellulose Combination for Rapid Hydration:

[0000107] Methylcellulose 400 cps concentration was kept as 1.0% w/v, and the amount of Methylcellulose 15 cps was adjusted for better dispersibility /hydration and the level of Simethicone (MED-342) adjusted to investigate the anti-foaming effect. Compositions are given in Table 19. Total blends were decreased to 500 mg per unit.

Table 19. Composition of DS-75 to DS-82

S.#	Ingredients	Quantity per unit (mg)							
		DS-75	DS-76	DS-77	DS-78	DS-79	DS-80	DS-81	DS-82
1	Tecovirimat Granules	346.50	346.50	346.50	346.50	346.50	346.50	346.50	346.50
2	Sucralose, NF	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00
3	Simethicone granular solid, USP (MED-342)	20.00	20.00	20.00	20.00	20.00	25.00	30.00	35.00
4	Lactose Monohydrate, NF (SuperTab 11SD)	43.50	63.50	53.50	43.50	58.50	53.50	53.50	53.50
5	Methyl Cellulose, 400 cps, USP	50.00	50.00	50.00	50.00	50.00	50.00	50.00	50.00
	Methyl Cellulose, 15 cps, USP	-	5.00	15.00	25.00	10.00	15.00	15.00	15.00
6	Strawberry flavor, #133.16296	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00
7	Purified water, USP, Q.S. to 5 mL	-	-	-	-	-	-	-	-
Total		**475.00**	**500.00**	**500.00**	**500.00**	**500.00**	**505.00**	**510.00**	**515.00**

[0000108] The formulation procedure was as follows;

1. geometric mixing of quantity equivalent to 100 units of Tecovirimat granules, sucralose, lactose monohydrate, Simethicone (MED-342) and Methylcellulose 400 cps in DS-75, then passing of blend through Quadro Comil equipped with 2B039R03125173*(991) screen;
2. for DS-75, weigh quantity equivalent to 50 units of blend and then geometric mixing with strawberry flavor;
3. for DS-77, weigh quantity equivalent to 30 units of blend and then geometric mixing with strawberry flavor, Methylcellulose 15 cps, and lactose monohydrate;
4. for DS-76 to DS-79, weigh quantity equivalent to 10 units of DS-75 and then geometric mixing with other components;
5. for DS-80 to DS-82, weigh quantity equivalent to 5 units of DS-77 and then geometric mixing with other components and
6. dispersing of 1 dose in purified water to make Q.S. to 5 mL to test dispersibility, foaminess and sedimentation (Table 20).

Table 20. Observation of suspensions of DS-75 to DS-82

S.#	Properties			Formulation ID							
				DS-75	DS-76	DS-77	DS-78	DS-79	DS-80	DS-81	DS-82
1	Dispersibility (chunks remaining at bottom after shaking)			small chunks	very tiny chunk	no chunks	no chunks	no chunks	big chunks	big chunks	big chunks
2	Settlement/foaminess	T=0		No sedimentation. Foam is similar in all formulations							
		T=30 min		No sedimentation. Individual bubbles are smaller in DS-80, DS-81, DS-82							
		T=1 hr		No sedimentation. Individual bubbles are smaller in DS-80, DS-81, DS-82. Quantity of foam is less in DS-80, DS-81, DS-82							
		T=2hr		No sedimentation. A very thin layer of foam in DS-80 and DS-81. No foam in DS-82.							
		T=17 hr	Foaminess	No foam in all formulations							
			Sedimentation coefficient	0.82	0.84	0.86	0.86	0.86	0.86	0.82	0.82
			Second layer (mm)	4	4	4	4	4	4	5	5

[0000109] It was observed that methylcellulose 15 cps level of 10-25 mg per Tecovirimat dosage unit can lead to good dispersibility/ hydration. There was no significant difference in foaminess of suspensions initially and after 17 hours of reconstitution in formations with Simethicone level of 20-35 mg per unit. The big chunks in formulation with 25-35 mg Simethicone per unit may be caused by Simethicone agglomeration, suggesting that it is advantageous to keep Simethicone as 20 mg per unit. All formulations showed good viscosity with 1% w/v Methylcellulose 400 cps.

Example 11: Scale- Up of the Optimized Compositions:

[0000110] Scale-up batches using methylcellulose (400 cps) and Klucel JXF Pharm as suspending agents were prepared and evaluated. Compositions are given in Table 21.

Table 21. Composition of Scale-Up batches

S. #	Ingredients	Quantity per unit (mg)			
		Goal: Using Methylcellulose (400 cps and 15 cps) as a suspending agent (500 g scale).		**Goal:** Using Hydroxypropyl Cellulose (Klucel JXF Pharm) as a suspending agent (500 g scale).	
		Batch: FSIG-20140826-1 (DS-75)	**Batch: FSIG-20140826-2 (DS-77)**	**Batch: FSIG-20141216-1 (DS-83)**	**Batch: FSIG-20141216-2 (DS-84)**
1	Tecovirimat Granulate	346.49	346.49	346.50	346.50
2	Lactose monohydrate, NF (SuperTab 11SD)	66.01	51.01	93.00	-
3	Methylcellulose, 400 cps, USP	50.00	50.00	-	-
4	Methylcellulose, 15 cps, USP	-	15.00	-	-
5	Hydroxylpropyl Cellulose (Klucel JXF Pham)	-	-	125.00	118.00
6	Sucralose, NF	10.00	10.00	10.00	10.00
7	Strawberry flavor, #133.16296	5.00	5.00	-	-
8	Black cherry Nat type flavor	-	-	3.00	3.00
9	Simethicone Granular Solid (MED-342), USP	20.00	20.00	20.00	20.00

S. #	Ingredients	Quantity per unit (mg)			
		Goal: Using Methylcellulose (400 cps and 15 cps) as a suspending agent (500 g scale).		**Goal:** Using Hydroxypropyl Cellulose (Klucel JXF Pharm) as a suspending agent (500 g scale).	
		Batch: FSIG-20140826-1 (DS-75)	**Batch: FSIG-20140826-2 (DS-77)**	**Batch: FSIG-20141216-1 (DS-83)**	**Batch: FSIG-20141216-2 (DS-84)**
10	Magnesium stearate, NF	2.50	2.50	2.50	2.50
Total weight (mg)		**500.00**	**500.00**	**600.00**	**500.00**

[0000111] The batch size of each composition was 0.500 kg. In general, the formulation procedure involved the following steps:

1. Sieving of the Tecovirimat granules and granular Simethicone through Quadro Comil equipped with 2B039R03125173*(991) screen.
2. Sieving of the Tecovirimat granulate and granular Simethicone through a #20 screen.
3. Sieving of lactose through a #20 screen, then addition of Flavor on lactose with geometric mixing using spatula.
4. Sieving of polymer and sucralose through a #40 screen.
5. Blending of the Tecovirimat-Simethicone blend and other extra-graular components in the V-blender for 15 minutes.
6. Passing of magnesium stearate through a #40 screen, then addition as a lubricant to above milled blend and lubricate for 5 minutes.
7. Evaluation of the physicochemical properties of blend (Table 22).
8. Transfer of 10 doses of blend to a 100 cc glass bottle. Add water Q. S. to 50 mL. Shake well to mix the content. Evaluate the physicochemical properties of suspension (Table 21).
9. Packing of 20 doses of blend in Stick pack PAKVF2.5M Fin seal pouches (part #25M0275FS06) Size 2.5 inch x 6 inch. Heat-seal properly. Prepare 15-20 pouches for stability/dissolution study (Table 24).

Table 22. Physicochemical properties of blends of scale-up batches

S#	Property	Batch: FSIG-20140826-1	Batch: FSIG-20140826-2	Batch: FSIG-20141216-1	Batch: FSIG-20141216-2
1	Appearance	White powder	White powder	White powder	White powder
2	Flow of Lubricated Blend (Flodex Orifice mm)	24	26	26	28
3	Bulk Density (g/cc)	0.541	0.520	0.505	0.468
	Tap Density (g/cc)	0.693	0.667	0.640	0.607
	Compressibility Index (%)	21.9	22.0	21.1	22.9
4	Granules Retained on Sieve # 20 (opening size 0.850 mm) (%)	0.01	0.01	0.02	0.02
	Granules Retained on Sieve # 30 (opening size 0.600 mm) (%)	1.85	2.22	3.29	3.52
	Granules Retained on Sieve # 40 (opening size 0.425 mm) (%)	9.37	10.46	8.60	10.61
	Granules Retained on Sieve # 50 (opening size 0.300 mm) (%)	8.64	9.72	10.72	12.48
	Granules Retained on Sieve # 60 (opening size 0.250 mm) (%)	4.12	4.36	4.06	5.24
	Granules Retained on Sieve # 80 (opening size 0.180 mm) (%)	10.53	11.84	12.33	12.29
	Retained on Pan (size < 0.180 mm) (%)	65.47	61.40	60.96	55.84
	Mean Size (mm)	0.106	0.119	0.121	0.139

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Table 23. Physicochemical properties of suspensions of scale-up batches

S#	Property	Batch: FSIG-20140826-1			Batch: FSIG-20140826-2			Batch: FSIG-20141216-1			Batch: FSIG-20141216-2		
1	Reconstitution	After manual shaking, fish eyes were observed at 4 positions at bottom of bottle.			After manual shaking, fish eye was observed at only one position at bottom of bottle.			After manual shaking, fish eyes were observed at 2 positions at bottom of bottle.			After manual shaking, no fish eye was observed, disperse very well.		
2	Appearance after reconstitution	White dispersion			White dispersion			White dispersion			White dispersion		
3	pH of suspension	5.98			6.00			5.99			6.15		
4	Microscopic observation	Particle size 3.16 ± 2.37 µm. No agglomeration observed.			Particle size 3.20 ± 2.63 µm. No agglomeration observed.			Particle size 3.04 ± 2.11 µm. No agglomeration observed.			Particle size 3.13 ± 2.53 µm. No agglomeration observed.		
5	Physical stability	No phase separation or agglomeration.			No phase separation or agglomeration.			No phase separation. Small agglomerations are observed when pouring out.			No phase separation. Small agglomerations are observed when pouring out.		
6	Forced settling and redispersibility	Redispersible			Redispersible			Redispersible			Redispersible		
7	Observation of sedimentation	10 min	30 min	24 hr	10 min	30 min	24 hr	10 min	30 min	24 hr	10 min	30 min	24 hr
	At 25 °C												
	Sedimentation coefficient	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	0.56	1.00	1.00	0.58
	Separation	None	None	Second layer (29% height)	None	None	Second layer (29% height)	None	None	None	None	None	None
	Redispersibility	Redispersible	Redispersible	Redispersible	Redispersible	Redispersible	Redispersible	Redispersible	Redispersible	Redispersible	Redispersible	Redispersible	Redispersible
	At 5 °C												
	Sedimentation coefficient	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	0.89	1.00	1.00	0.88
	Separation	None	None	Second layer (23% height)	None	None	Second layer (20% height)	None	None	None	None	None	None
	Redispersibility	Redispersible	Redispersible	Redispersible	Redispersible	Redispersible	Redispersible	Redispersible	Redispersible	Redispersible	Redispersible	Redispersible	Redispersible

Table 24. Stability and dissolution of scale-up batches

S#	Property		Batch: FSIG-20140826-1 (DS75)		Batch: FSIG-20140826-2 (DS77)		Batch: FSIG-20141216-1 (DS83)		Batch: FSIG-20141216-2 (DS84)	
		Time (mins)	% Released	SD	% Released	SD	% Released	SD	% Released	SD
1	Dissolution (n=6)	5	88.6	1.3	88.4	1.5	84.2	6.7	92.4	4.2
		10	90.2	1.7	92.3	1.5	93.9	4.4	97.6	1.7
		15	89.4	1.5	90.5	2.8	94.1	2.0	99.3	1.7
		30	90.4	1.3	90.2	1.4	96.9	0.9	101.4	2.2
		45	93.6	2.5	90.7	1.5	97.1	1.0	100.3	0.7

[0000112] The % ST-246 released is shown in Figure 2.

Example 12: Effect of Particle Sizes of API on Formulation Properties:

[0000113] To study the effect of particle sizes of API on formulation performance properties, such as dissolution, use API of different particle sizes for granulation process. Compositions are given in Table 25.

Table 25. Composition of DS-85 to DS-87 using API of different particle sizes

S. #	Ingredients	Quantity per unit (mg)		
		Goal: Using API of different particle sizes for granulation process (288.6 g scale). Ref. DS-77 (Batch # FSIG-20140826-2)		
		Batch: FSIG-20150120-1 (DS-85)	**Batch: FSIG-20150120-2 (DS-86)**	**Batch: FSIG-20150120-3 (DS-87)**
Intragranular Ingredients:				
1	Tecovirimat monohydrate, micronized	209.0 using API Lot# SG-10C12-T1039 (Trial #2, d90 = 21.51 µm)	209.0 using API Lot# SG-10C12-T1039 (Trial #3, d90 = 38.74 µm)	209.0 using API Lot# SG-10C12-T1039 (Trial #4, d90 = 81.53 µm)
2	Colloidal silicon dioxide, NF (Cabosil M5P)	1.95	1.95	1.95
3	Croscarmellose sodium, NF (AcDiSol)	31.32	31.32	31.32
4	Lactose monohydrate, NF (SuperTab 11SD)	33.15	33.15	33.15
5	Microcrystalline cellulose, NF (Avicel PH 101)	49.62	49.62	49.62
Intragranular Ingredients Total		**325.04**	**325.04**	**325.04**
Granulating Fluid:				
6	Hypromellose, USP (Methocel E3 LV Prem.)	13.65	13.65	13.65
7	Sodium lauryl sulfate, NF	7.80	7.80	7.80
8	Purified water, USP*	170.1	170.1	170.1
Granulating Fluid Solids Total		**21.45**	**21.45**	**21.45**

S. #	Ingredients	Quantity per unit (mg)		
		Goal: Using API of different particle sizes for granulation process (288.6 g scale). Ref. DS-77 (Batch # FSIG-20140826-2)		
		Batch: FSIG-20150120-1 (DS-85)	**Batch: FSIG-20150120-2 (DS-86)**	**Batch: FSIG-20150120-3 (DS-87)**
Granulate Solids		**346.49**	**346.49**	**346.49**
Extragranular Ingredients:				
9	Lactose monohydrate, NF (SuperTab 11SD)	51.01	51.01	51.01
10	Methylcellulose, 400 cps, USP	50.0	50.0	50.0
11	Methylcellulose, 15 cps, USP	15.0	15.0	15.0
12	Sucralose, NF	10.0	10.0	10.0
13	Strawberry flavor, #133.16296	5.0	5.0	5.0
14	Simethicone Granular Solid (MED-342), USP	20.0	20.0	20.0
15	Magnesium stearate, NF	2.5	2.5	2.5
Powder for Reconstitution Blend Total		**500.00**	**500.00**	**500.00**

* Removed during the drying process.

[0000114] The batch size of each composition was 0.2886 Kg. Detailed experimental procedures and results of each trial formulation were recorded in the executed batch records. In general, the formulation procedure involved the following steps:

1. Passing of intragranular components through a #20 screen.
2. Mixing of intragranular components containing diluents, disintegrant, in GMX- High Shear Granulator/ Mixer (1L bowl) at impeller blade speed 460 rpm and chopper speed of 2000 rpm for 2 minutes.
3. Addition of granulating solution containing surfactant, binder (7.1% w/w Hypromellose Methocel E3 solution) and mixing with the intragranular components in GMX- High Shear Granulator/ Mixer at impeller blade speed 460 rpm and chopper blade 2000 rpm for 8-10 minutes.
4. Addition of about 1.5 g water to rinse the container, granulation for additional 2 minutes, recording of the visual observation of the wet mixture.
5. Drying of wet granular mass using a Midi-Glatt fluid bed dryer/processor at inlet temperature 35-40 °C until the loss on drying (LOD) of the granules reached the range of 4.00-5.50 % w/w. following are the typical drying parameters.

Parameters	**Units**
Product Air Pressure (bar)	0.25- 0.30
Inlet Air Temperature (°C)	35
Filter Blowing Rate (Sec)	1
Product Temperature (°C)- at end	20-21

6. Passing of the dried granules through Quadro Comil equipped with 2B039R03125173*(991) screen.
7. Weighing of the granules, then recalculation and weighing of extragranular ingredients.
8. Passing of the Tecovirimat granules and granular Simethicone through Quadro Comil equipped with 2B039R03125173*(991) screen.
9. Passing of the Tecovirimat granulate and granular Simethicone through a #20 screen.

10. Passing of lactose through a #20 screen and addition of Flavor on lactose with geometric mixing using spatula.
11. Passing of polymer and sucralose through a #40 screen.
12. Blending of the Tecovirimat-Simethicone blend and other extragranular components in the V-blender for 15 minutes.
13. Passing of magnesium stearate through a #40 screen, then addition as a lubricant to above milled blend and lubricate for 5 minutes.
14. Evaluation of the physicochemical properties of blend (Table 26).
15. Transfer of 10 doses of blend to a 100 cc glass bottle. Add water Q. S. to 50 mL. Shake well to mix the content. Evaluate the physicochemical properties of suspension (Table 27).
16. Packing of 20 doses of blend in Stick pack PAKVF2.5M Fin seal pouches (part #25M0275FS06); size 2.5 inch x 6 inch. Heat-seal properly. Prepare 3 pouches for dissolution study (Table 28).

Table 26. Characterization of blends DS-85 to DS-87

S#	Property	Batch: FSIG-20150120-1 (DS-85)	Batch: FSIG-20150120-2 (DS-86)	Batch: FSIG-20150120-3 (DS-87)
1	Appearance	White powder	White powder	White powder
2	Flow of Lubricated Blend (Flodex Orifice mm)	24	24	24
3	Bulk Density (g/cc)	0.454	0.436	0.426
	Tap Density (g/cc)	0.605	0.590	0.568
	Compressibility Index (%)	25.0	26.1	25.0
4	Granules Retained on Sieve # 20 (opening size 0.850 mm) (%)	0.02	0.02	0.02
	Granules Retained on Sieve # 30 (opening size 0.600 mm) (%)	8.03	4.84	2.04
	Granules Retained on Sieve # 40 (opening size 0.425 mm) (%)	18.50	18.50	8.81
	Granules Retained on Sieve # 50 (opening size 0.300 mm) (%)	14.86	12.11	10.99
	Granules Retained on Sieve # 60 (opening size 0.250 mm) (%)	5.32	3.60	6.14
	Granules Retained on Sieve # 80 (opening size 0.180 mm) (%)	37.04	28.28	38.65
	Retained on Pan (size < 0.180 mm) (%)	16.24	32.65	33.35
	Mean Size (mm)	0.252	0.204	0.168

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Table 27. Characterization of suspensions of DS-85 to DS-87

S#	Property	Batch: FSIG-20150120-1 (DS-85)			Batch: FSIG-20150120-2 (DS-86)			Batch: FSIG-20150120-3 (DS-87)		
1	Reconstitution	After manual shaking, no fish eyes is observed, disperse very well.			After manual shaking, no fish eye is observed, disperse very well.			After manual shaking, no fish eye is observed, disperse very well.		
2	Appearance after reconstitution	White dispersion			White dispersion			White dispersion		
3	pH of suspension	6.11			6.10			6.12		
4	Microscopic observation	Particle size 4.10 ± 3.42 µm. No agglomeration observed.			Particle size 4.40 ± 3.52 µm. No agglomeration observed.			Particle size 4.84 ± 4.22 µm. No agglomeration observed.		
5	Physical stability	No phase separation or agglomeration.			No phase separation or agglomeration.			No phase separation or agglomeration.		
6	Forced settling and redispersibility	Redispersible			Redispersible			Redispersible		
7	Observation of sedimentation	10 min	30 min	24 hr	10 min	30 min	24 hr	10 min	30 min	24 hr
	At 25 °C									
	Sedimentation coefficient	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	Separation	None	None	Second layer (22% height)	None	None	Second layer (22% height)	None	None	Second layer (26% height)
	Redispersibility	Redispersible	Redispersible	Redispersible	Redispersible	Redispersible	Redispersible	Redispersible	Redispersible	Redispersible
	At 5 °C									
	Sedimentation coefficient	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	Separation	None	None	Second layer (22% height)	None	None	Second layer (25% height)	None	None	Second layer (25% height)
	Redispersibility	Redispersible	Redispersible	Redispersible	Redispersible	Redispersible	Redispersible	Redispersible	Redispersible	Redispersible

Table 28. Dissolution profile of DS-85 to DS-87

S#	Property		Batch: FSIG-20150120-1 (DS-85)		Batch: FSIG-20150120-2 (DS-86)		Batch: FSIG-20150120-3 (DS-87)	
1	Dissolution (n=6)	Time (mins)	% Released	SD	% Released	SD	% Released	SD
		5	72.5	1.6	58.8	1.5	36.0	1.2
		10	82.2	0.7	66.7	3.0	46.0	0.9
		15	85.5	1.1	71.8	2.3	51.7	0.8
		30	88.2	2.3	75.7	3.3	60.2	1.7
		45	90.3	2.0	80.4	3.0	64.7	1.0

[0000115] It was observed that DS-85 (API D90 = 21.51 µm) showed higher dissolution rate compared to DS-86 (API D90 = 38.74 µm) and DS-87 (API D90 = 81.53 µm). The particle size of the Tecovirimat monohydrate used for granulation is inversely proportional to the dissolution rate. Smaller particle API batches showed higher dissolution rate as; DS-85> DS-86 > DS-87 (see Figure 3).

Example 13: Optimization of Blending and Lubrication Time Tecovirimat monohydrate Powder for Reconstitution:

[0000116] To study the effect of blend/lubrication time on blend uniformity and dissolution, sample where taken at different time points during a blending range of 10-25 minutes and a lubrication of 3-10 minutes. Composition is given in Table 29.

Table 29. Composition of DS-88

S. #	Ingredients	Quantity per unit (mg)
		Goal: Blend or lube time DOE study (500 g scale). Ref. DS-75 (Batch # FSIG-20140826-1)
		Batch: FSIG-20150317-1 (DS-88)
1	Tecovirimat Granulate	346.49
2	Lactose monohydrate, NF (SuperTab 11SD)	66.01
3	Methylcellulose, 400 cps, USP	50.00
4	Sucralose, NF	10.00
5	Strawberry flavor, #133.16296	5.00

S. #	Ingredients	Quantity per unit (mg)
		Goal: Blend or lube time DOE study (500 g scale). Ref. DS-75 (Batch # FSIG-20140826-1)
		Batch: FSIG-20150317-1 (DS-88)
6	Simethicone Granular Solid (MED-342), USP	20.00
7	Magnesium stearate, NF	2.50
	Total weight (mg)	**500.00**

[0000117] The batch size was 0.500 Kg. In general, the formulation procedure involved the following steps:

1. Passing of the Tecovirimat granules and granular Simethicone through Quadro Comil equipped with 2B039R03125173*(991) screen;
2. Passing of the Tecovirimat granulate and granular Simethicone through a #20 screen;
3. Passing of lactose through a #20 screen, then addition of Flavor on lactose with geometric mixing using spatula;
4. Passing of polymer and sucralose through a #40 screen;
5. Blending of the Tecovirimat-Simethicone blend and other extragranular components in the V-blender, taking a 10 g sample at 10, 15, and 20 minutes. Halt the process at 25 minutes and repeat sampling;
6. Passing of magnesium stearate through a #40 screen, then addition of 2.3 g as a lubricant to the remaining blend for lubrication. Take a 10 g sample at 3, 5, and 7.5 minutes. Final lubrication time is 10 minutes and repeat sampling;
7. Evaluation of the physicochemical properties of blend (Table 30);
8. Transfer of 10 doses of blend to a 100 cc glass bottle. Add water Q. S. to 50 mL. Shake well to mix the content. Evaluate the physicochemical properties of suspension (Table 31);
9. Addition of Q.S. purified water to 10 g samples at different blending or lube time points to make 100 mL, then stirring well for tests of reconstitution and dissolution (Table 32A and 32 B).

Table 30. Characterization of Blend DS-88

S#	Property	Batch: FSIG-20150317-1 (DS-88)
1	Appearance	White powder
2	Flow of Lubricated Blend (Flodex Orifice mm)	24
3	Bulk Density (g/cc)	0.518
	Tap Density (g/cc)	0.700
	Compressibility Index (%)	26.0
4	Granules Retained on Sieve # 20 (opening size 0.850 mm) (%)	0.01
	Granules Retained on Sieve # 30 (opening size 0.600 mm) (%)	4.09
	Granules Retained on Sieve # 40 (opening size 0.425 mm) (%)	10.36
	Granules Retained on Sieve # 50 (opening size 0.300 mm) (%)	9.20
	Granules Retained on Sieve # 60 (opening size 0.250 mm) (%)	4.03
	Granules Retained on Sieve # 80 (opening size 0.180 mm) (%)	14.76
	Retained on Pan (size < 0.180 mm) (%)	57.55
	Mean Size (mm)	0.133

Table 31. Characterization of suspension of DS-88

S#	Property	Batch: FSIG-20150317-1 (DS-88)		
1	Reconstitution	After manual shaking, 1 fish eye is observed at bottom of bottle.		
2	Appearance after reconstitution	White dispersion		
3	pH of suspension	6.13		
4	Microscopic observation	Particle size 3.28 ± 2.72 μm. No agglomeration observed.		
5	Physical stability	No phase separation or agglomeration.		
6	Forced settling and redispersibility	Redispersible		
7	Observation of sedimentation	10 min	30 min	24 hr
	At 25 °C			
	Sedimentation coefficient	1.00	1.00	1.00
	Separation	None	None	Second layer (22% height)
	Redispersibility	Redispersible	Redispersible	Redispersible
	At 5 °C			
	Sedimentation coefficient	1.00	1.00	1.00
	Separation	None	None	Second layer (20% height)
	Redispersibility	Redispersible	Redispersible	Redispersible

Table 32A. Reconstitution and Dissolution of Samples at Different Blending Times (see Figure 4)

S#	Property		Batch: FSIG-20150317-1 (DS-88)							
			Blending 10 minutes (no lubricant)		Blending 15 minutes (no lubricant)		Blending 20 minutes (no lubricant)		Blending 25 minutes (no lubricant)	
1	Reconstitution		Tiny lumps, a little foam		Tiny lumps, a little foam		Tiny lumps, a little foam		Tiny lumps, a little foam	
2	Dissolution (n=6)	Time (mins)	% Released	SD	% Released	SD	% Released	SD	% Released	SD
		5	90.6	1.0	92.5	2.4	90.2	1.1	92.3	1.2
		10	92.8	1.7	93.6	0.5	91.8	1.7	93.3	1.4
		15	94.7	0.7	93.7	1.4	91.8	1.0	94.0	1.0
		30	94.2	0.9	92.6	1.9	91.5	1.8	93.2	1.0
		45	94.8	0.7	93.6	1.9	91.9	1.1	93.2	0.8

Table 32B. Reconstitution and Dissolution of Samples at Different Lubrication Time (see Figure 5)

S#	Property	Batch: FSIG-20150317-1 (DS-88)							
		Lubrication 3 minutes (with lubricant)		Lubrication 5 minutes (with lubricant)		Lubrication 7.5 minutes (with lubricant)		Lubrication 10 minutes (with lubricant)	
1	Reconstitution	Tiny lumps, a little foam		Tiny lumps, a little foam		Tiny lumps, a little foam		Tiny lumps, a little foam	
2	Dissolution (n=6)	% Released	SD	% Released	SD	% Released	SD	% Released	SD
		93.6	1.6	92.9	1.1	90.0	1.1	95.5	1.3
		94.8	1.7	93.3	0.8	90.6	1.6	94.9	1.2
		94.6	2.3	93.4	0.7	90.1	1.5	96.4	1.5
		96.2	2.6	93.3	1.1	90.5	1.9	94.4	1.1
		97.7	2.3	92.9	1.1	90.0	1.5	96.1	1.4

[0000118] It was observed that all samples showed above 90% dissolution in 5 minutes, indicating that a blending range of 10-25 minutes and a lubrication range of 3-10 minutes have no significant effect on sample dissolution. Blending time and lubrication time is now fixed as 15 minutes and 5 minutes respectively as previous trials.

Example 31: Evaluation of Effect of High/Low Lubrication:

[0000119] To evaluate the effect of lubrication on +/- 50% deviation of magnesium stearate level was used to test the effect of lubricant level on formulation physicochemical properties and dissolution. Compositions are given in Table 33.

Table 33. Composition of DS-89 and 90

S. #	Ingredients	Quantity per unit (mg)	
		Goal: High/low lubricant DOE study (500 g scale). Ref. DS-75 (Batch # FSIG-20140826-1)	
		Batch: FSIG-20150325-1 (DS-89) 0.25% magnesium stearate	**Batch: FSIG-20150325-2 (DS-90) 0.75% magnesium stearate**
1	Tecovirimat Granulate	346.49	346.49
2	Lactose monohydrate, NF (SuperTab 11SD)	67.26	64.76
3	Methylcellulose, 400 cps, USP	50.00	50.00
4	Sucralose, NF	10.00	10.00
5	Strawberry flavor, #133.16296	5.00	5.00
6	Simethicone Granular Solid (MED-342), USP	20.00	20.00
7	Magnesium stearate, NF	1.25	3.75
Total weight (mg)		**500.00**	**500.00**

[0000120] The batch size of each composition was 0.500 kg. In general, the formulation procedure involved the following steps:

1. Passing of the Tecovirimat granules and granular Simethicone through Quadro Comil equipped with 2B039R03125173*(991) screen.
2. Passing of the Tecovirimat granulate and granular Simethicone through a #20 screen.

3. Passing of lactose through a #20 screen, then addition of Flavor on lactose with geometric mixing using spatula.
4. Passing of polymer and sucralose through a #40 screen.
5. Blending of the Tecovirimat-Simethicone blend and other extragranular components in the V-blender for 15 minutes.
6. Passing of magnesium stearate through a #40 screen, then addition as a lubricant to above milled blend and lubricate for 5 minutes.
7. Evaluation of the physicochemical properties of blend (Table 34).
8. Transfer of 10 doses of blend to a 100 cc glass bottle. Add water Q. S. to 50 mL. Shake well to mix the content. Evaluate the physicochemical properties of suspension (Table 35).
9. Packing of 20 doses of blend in Stick pack PAKVF2.5M Fin seal pouches (part #25M0275FS06); size 2.5 inch x 6 inch. Heat-seal properly. Prepare 3 pouches for dissolution study (Table 36).

Table 34. Characterization of blend DS-89 and DS-90

S#	Property	Batch: FSIG-20150325-1 (DS-89)	Batch: FSIG-20150325-2 (DS-90)
1	Appearance	White powder	White powder
2	Flow of Lubricated Blend (Flodex Orifice mm)	24	24
3	Bulk Density (g/cc)	0.544	0.531
	Tap Density (g/cc)	0.706	0.698
	Compressibility Index (%)	22.9	23.9
4	Granules Retained on Sieve # 20 (opening size 0.850 mm) (%)	0.01	0.06
	Granules Retained on Sieve # 30 (opening size 0.600 mm) (%)	4.32	4.30
	Granules Retained on Sieve # 40 (opening size 0.425 mm) (%)	10.01	9.89
	Granules Retained on Sieve # 50 (opening size 0.300 mm) (%)	10.89	13.49
	Granules Retained on Sieve # 60 (opening size 0.250 mm) (%)	6.16	5.92

S#	Property	Batch: FSIG-20150325-1 (DS-89)	Batch: FSIG-20150325-2 (DS-90)
	Granules Retained on Sieve # 80 (opening size 0.180 mm) (%)	15.86	16.26
	Retained on Pan (size < 0.180 mm) (%)	52.74	50.08
	Mean Size (mm)	0.145	0.153

Table 35. Characterization of suspension of DS-89 and DS-90

S#	Property	Batch: FSIG-20150325-1 (DS-89)			Batch: FSIG-20150325-2 (DS-90)		
1	Reconstitution	After manual shaking, no fish eye is observed, disperse very well.			After manual shaking, 2 fish eyes are observed at bottom of bottle.		
2	Appearance after reconstitution	White dispersion			White dispersion		
3	pH of suspension	6.07			6.12		
4	Microscopic observation	Particle size 3.22 ± 2.91 μm. No agglomeration observed.			Particle size 3.26 ± 3.00 μm. No agglomeration observed.		
5	Physical stability	No phase separation or agglomeration.			No phase separation or agglomeration.		
6	Forced settling and redispersibility	Redispersible			Redispersible		
7	Observation of sedimentation	10 min	30 min	24 hr	10 min	30 min	24 hr
	At 25 °C						
	Sedimentation coefficient	1.00	1.00	1.00	1.00	1.00	1.00
	Separation	None	None	Second layer (22% height)	None	None	Second layer (23% height)
	Redispersibility	Redispersible	Redispersible	Redispersible	Redispersible	Redispersible	Redispersible
	At 5 °C						
	Sedimentation coefficient	1.00	1.00	1.00	1.00	1.00	1.00
	Separation	None	None	Second layer (20% height)	None	None	Second layer (36% height)
	Redispersibility	Redispersible	Redispersible	Redispersible	Redispersible	Redispersible	Redispersible

Table 36. Dissolution of DS-89 and DS-90 (see Figure 6)

S#	Property		Batch: FSIG-20150325-1 (DS-89)		Batch: FSIG-20150325-2 (DS-90)	
		Time (min)	% Released	SD	% Released	SD
1	Dissolution (n=6)	5	91.2	0.7	94.8	2.2
		10	92.6	0.5	95.5	1.8
		15	92.9	1.1	95.1	1.5
		30	92.8	1.1	95.6	2.3
		45	93.8	1.8	95.8	2.0

[0000121] The quantity of magnesium stearate at 0.25 % and 0.75 % level of the formulation did not show any difference in physicochemical properties as well as dissolution of the product.

Example 15: Effect of Milling on Particle Size and Size Distribution of Tecovirimat Granules:

[0000122] The purpose is to study the effect of milling on particle size and size distribution of Tecovirimat granules. 100 g of Tecovirimat granules from Siga were used to test the size distribution. 110 g of Tecovirimat granules from the same Siga Lot# were passed through Quadra Comil equipped with 2B039R03125173*(991) screen, from which 100 g were weighed for size distribution test. The results are shown in Table 37.

Table 37. Particle size and size distribution of Tecovirimat Granules before/after milling

S#	Property	Lot # 1401165 (before milling)	Lot # 1401165 (after milling)
1	Granules Retained on Sieve # 20 (opening size 0.850 mm) (%)	0.05	0.04
	Granules Retained on Sieve # 30 (opening size 0.600 mm) (%)	6.38	4.47
	Granules Retained on Sieve # 40 (opening size 0.425 mm) (%)	10.34	12.31
	Granules Retained on Sieve # 50 (opening size 0.300 mm) (%)	10.80	11.64
	Granules Retained on Sieve # 60 (opening size 0.250 mm) (%)	5.05	5.36
	Granules Retained on Sieve # 80 (opening size 0.180 mm) (%)	8.48	8.55
	Granules Retained on Sieve # 100 (opening size 0.150 mm) (%)	4.74	4.70
	Retained on Pan (size < 0.150 mm) (%)	54.17	52.93
	Mean Size (mm)	0.150	0.150

[0000123] It was observed that no significant different between the size distribution of Tecovirimat granules before or after milling.

Example 16: Evaluation of Pre-dilution and as is Simethicone Before Mixing/ Blending:

[0000124] Simethicone granular grade is currently prediluted/ milled with Tecovirimat granules. The pre-dilution and no-dilution / as is Simethicone before mixing were compared, to establish the method of dilution that can be commercially reproduced at large scale. Compositions are given in Table 38.

Table 38. Composition of DS-91 and DS-92

S. #	Ingredients	Quantity per unit (mg)	
		Goal: Simethicone pre-dilution or no-dilution (500 g scale). Ref. DS-75 (Batch # FSIG-20140826-1)	
		Batch: FSIG-20150407-1 (DS-91) pre-diluted Simethicone	**Batch: FSIG-20150407-2 (DS-92) undiluted Simethicone**
1	Tecovirimat Granulate	346.49	346.49
2	Lactose monohydrate, NF (SuperTab 11SD)	66.01	66.01
3	Methylcellulose, 400 cps, USP	50.00	50.00
4	Sucralose, NF	10.00	10.00
5	Strawberry flavor, #133.16296	5.00	5.00
6	Simethicone Granular Solid (MED-342), USP	20.00	20.00
7	Magnesium stearate, NF	2.50	2.50
Total weight (mg)		**500.00**	**500.00**

[0000125] The batch size of each composition was 0.500 kg. In general, the formulation procedure involved the following steps:

1. For DS-91, passing of the Tecovirimat granules and granular Simethicone through Quadro Comil equipped with 2B039R03125173*(991) screen, then passing of the Tecovirimat granulate and granular Simethicone through a #20 screen;

2. For DS-92, passing of the Tecovirimat granulate through Quadro Comil equipped with 2B039R03125173*(991) screen; then passing of granular Simethicone through a #20 screen;
3. Passing of lactose through a #20 screen, then addition of Flavor on lactose with geometric mixing using spatula;
4. Passing of polymer and sucralose through a #40 screen;
5. Blending of Tecovirimat granulate and all the extragranular components in the V-blender for 15 minutes;
6. Passing of magnesium stearate through a #40 screen, then addition as a lubricant to above milled blend and lubricate for 5 minutes;
7. Evaluation of the physicochemical properties of blend (Table 39);
8. Transfer of 10 doses of blend to a 100 cc glass bottle. Add water Q. S. to 50 mL. Shake well to mix the content. Evaluate the physicochemical properties of suspension (Table 40);
9. Packing of 20 doses of blend in Stick pack PAKVF2.5M Fin seal pouches (part #25M0275FS06); size 2.5 inch x 6 inch. Heat-seal properly. Prepare 3 pouches for dissolution study (Table 41).

Table 39. Characterization of blend DS-91 and DS-92

S#	Property	Batch: FSIG-20150407-1 (DS-91)	Batch: FSIG-20150407-2 (DS-92)
1	Appearance	White powder	White powder
2	Flow of Lubricated Blend (Flodex Orifice mm)	24	26
3	Bulk Density (g/cc)	0.533	0.525
	Tap Density (g/cc)	0.701	0.700
	Compressibility Index (%)	24.0	25.0
4	Granules Retained on Sieve # 20 (opening size 0.850 mm) (%)	0.03	0.06
	Granules Retained on Sieve # 30 (opening size 0.600 mm) (%)	4.26	4.06
	Granules Retained on Sieve # 40 (opening size 0.425 mm) (%)	10.10	10.49
	Granules Retained on Sieve # 50 (opening size 0.300 mm) (%)	10.87	10.11

S#	Property	Batch: FSIG-20150407-1 (DS-91)	Batch: FSIG-20150407-2 (DS-92)
	Granules Retained on Sieve # 60 (opening size 0.250 mm) (%)	3.50	4.18
	Granules Retained on Sieve # 80 (opening size 0.180 mm) (%)	12.92	13.80
	Retained on Pan (size < 0.180 mm) (%)	58.32	57.30
	Mean Size (mm)	0.133	0.135

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Table 40. Physicochemical Properties of Suspension of DS-91 and DS-92

S#	Property	Batch: FSIG-20150407-1 (DS-91)			Batch: FSIG-20150407-2 (DS-92)		
1	Reconstitution	After manual shaking, no fish eye is observed, disperse very well.			After manual shaking, no fish eye is observed, disperse very well.		
2	Appearance after reconstitution	White dispersion. Foaminess similar to DS-92			White dispersion. Foaminess similar to DS-91.		
3	pH of suspension	6.11			6.05		
4	Microscopic observation	Particle size 3.02 ± 2.03 µm. No agglomeration observed.			Particle size 3.14 ± 2.47 µm. No agglomeration observed.		
5	Physical stability	No phase separation or agglomeration.			No phase separation or agglomeration.		
6	Forced settling and redispersibility	Redispersible			Redispersible		
7	Observation of sedimentation	10 min	30 min	24 hr	10 min	30 min	24 hr
	At 25 °C						
	Sedimentation coefficient	1.00	1.00	1.00	1.00	1.00	1.00
	Separation	None	None	Second layer (28% height)	None	None	Second layer (33% height)
	Redispersibility	Redispersible	Redispersible	Redispersible	Redispersible	Redispersible	Redispersible
	At 5 °C						
	Sedimentation coefficient	1.00	1.00	1.00	1.00	1.00	1.00
	Separation	None	None	Second layer (28% height)	None	None	Second layer (33% height)
	Redispersibility	Redispersible	Redispersible	Redispersible	Redispersible	Redispersible	Redispersible

Table 41. Dissolution of DS-91 and DS-92

S#	Property		Batch: FSIG-20150407-1 (DS-91)		Batch: FSIG-20150407-2 (DS-92)	
1	Dissolution (n=6)	Time (min)	% Released	SD	% Released	SD
		5	94.7	2.3	92.2	1.2
		10	94.6	1.9	91.3	1.2
		15	94.2	1.2	91.6	1.3
		30	93.8	1.1	90.6	1.2
		45	94.9	2.4	91.0	4.0

[0000126] It was observed that before blending when passing through the #20 screen, Simethicone with no-dilution partly stuck on sieve (Figure 8 A and B), while the pre-diluted and co-milled Simethicone and Tecovirimat granules passed through #20 screen easily (Figure 8 C and D). After sieve shaking for size distribution analysis, big clumps from DS-92 remained on #20 screen (Figure 9), indicating the formation of big Simethicone lumps when no-dilution before mixing.

[0000127] Figure 8 shows an observation when passing simethicone or co-milled simethicone-Tecovirimat granules through #20 screen. A and B: no-dilution simethicone stuck on screen. C and D: pre-diluted and co-milled simethicone-Tecovirimat granules passed screen easily without sticking.

[0000128] Figure 9 shows retained clumps on #20 screen after sieve shaking of 100 g DS-92.

Example 17: Evaluation of Simethicone from Alternate Source:

[0000129] Currently Simethicone Granular Solid (MED-342) from Nusil Technologies was used. An alternate source of Simethicone - Simethicone 50% Powder from AIC was used to test the effect on formulation. The pre-dilution and no-dilution of simethicone before mixing were compared. Compositions are given in Table 41.

Table 41. Composition of DS-93 and DS-94

S. #	Ingredients	Quantity per unit (mg)	
		Goal: Simethicone alternate source (500 g scale). Ref. DS-75 (Batch # FSIG-20140826-1)	
		Batch: FSIG-20150421-1 (DS-93) pre-diluted simethicone	**Batch: FSIG-20150421-2 (DS-94) Undiluted simethicone**
1	Tecovirimat Granulate	346.49	346.49
2	Lactose monohydrate, NF (SuperTab 11SD)	74.01	74.01
3	Methylcellulose, 400 cps, USP	50.00	50.00
4	Sucralose, NF	10.00	10.00
5	Strawberry flavor, #133.16296	5.00	5.00
6	Simethicone 50% Powder	12.00	12.00
7	Magnesium stearate, NF	2.50	2.50
Total weight (mg)		**500.00**	**500.00**

[0000130] The batch size of each composition was 0.500 Kg. Detailed experimental procedures and results of each trial formulation were recorded in the executed batch records. In general, the formulation procedure involved the following steps:

1. For DS-93, passing of the Tecovirimat granules and Simethicone powder through Quadro Comil equipped with 2B039R03125173*(991) screen, then passing of the Tecovirimat granulate and Simethicone powder through a #20 screen;
2. For DS-94, passing of the Tecovirimat granulate through Quadro Comil equipped with 2B039R03125173*(991) screen; then passing of Simethicone powder through a #20 screen;
3. Passing of lactose through a #20 screen, then addition of Flavor on lactose with geometric mixing using spatula;
4. Passing of polymer and sucralose through a #40 screen;
5. Blending of Tecovirimat granulate and all the extragranular components in the V-blender for 15 minutes;
6. Passing of magnesium stearate through a #40 screen, then addition as a lubricant to above milled blend and lubricate for 5 minutes;
7. Evaluation of the physicochemical properties of blend (Table 43);

8. Transfer of 10 doses of blend to a 100 cc glass bottle. Add water Q. S. to 50 mL. Shake well to mix the content. Evaluate the physicochemical properties of suspension (Table 44);
9. Packing of 20 doses of blend in Stick pack PAKVF2.5M Finseal pouches (part #25M0275FS06); size 2.5 inch x 6 inch. Heat-seal properly. Prepare 3 pouches for dissolution study (Table 45).

Table 43. Characterization of blend DS-93 and DS-94

S#	Property	Batch: FSIG-20150421-1 (DS-93)	Batch: FSIG-20150421-2 (DS-94)
1	Appearance	White powder	White powder
2	Flow of Lubricated Blend (Flodex Orifice mm)	20	20
3	Bulk Density (g/cc)	0.547	0.540
	Tap Density (g/cc)	0.720	0.720
	Compressibility Index (%)	24.0	25.0
4	Granules Retained on Sieve # 20 (opening size 0.850 mm) (%)	0.02	0.02
	Granules Retained on Sieve # 30 (opening size 0.600 mm) (%)	3.23	2.81
	Granules Retained on Sieve # 40 (opening size 0.425 mm) (%)	8.73	8.52
	Granules Retained on Sieve # 50 (opening size 0.300 mm) (%)	9.28	8.48
	Granules Retained on Sieve # 60 (opening size 0.250 mm) (%)	3.56	3.75
	Granules Retained on Sieve # 80 (opening size 0.180 mm) (%)	13.96	11.28
	Retained on Pan (size < 0.180 mm) (%)	61.23	65.15
	Mean Size (mm)	0.118	0.108

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Table 44. Physicochemical properties of suspension of DS-93 and DS-94

S#	Property	Batch: FSIG-20150421-1 (DS-93)			Batch: FSIG-20150421-2 (DS-94)		
1	Reconstitution	After manual shaking, no fish eye is observed, disperse very well.			After manual shaking, no fish eye is observed, disperse very well.		
2	Appearance after reconstitution	White dispersion, foaminess similar to DS-94, more foam than DS-91 and DS-92.			White dispersion, foaminess similar to DS-93, more foam than DS-91 and DS-92.		
3	pH of suspension	6.11			6.07		
4	Microscopic observation	Particle size 3.40 ± 3.04 µm. No agglomeration observed.			Particle size 3.46 ± 2.96 µm. No agglomeration observed.		
5	Physical stability	No phase separation or agglomeration.			No phase separation or agglomeration.		
6	Forced settling and redispersibility	Redispersible			Redispersible		
7	Observation of sedimentation	10 min	30 min	24 hr	10 min	30 min	24 hr
	At 25 °C						
	Sedimentation coefficient	1.00	1.00	1.00	1.00	1.00	1.00
	Separation	None	None	Second layer (26% height)	None	None	Second layer (29% height)
	Redispersibility	Redispersible	Redispersible	Redispersible	Redispersible	Redispersible	Redispersible
	At 5 °C						
	Sedimentation coefficient	1.00	1.00	1.00	1.00	1.00	1.00
	Separation	None	None	Second layer (25% height)	None	None	Second layer (25% height)
	Redispersibility	Redispersible	Redispersible	Redispersible	Redispersible	Redispersible	Redispersible

Table 45. Dissolution of DS-93 and DS-94

S#	Property		Batch: FSIG-20150421-1 (DS-93)		Batch: FSIG-20150421-2 (DS-94)	
1	Dissolution (n=6)	Time (min)	% Released	SD	% Released	% Released
		5	82.5	1.7	89.3	89.3
		10	84.7	1.4	86.8	86.8
		15	85.4	0.7	86.9	86.9
		30	86.5	1.1	88.2	88.2
		45	86.2	1.9	88.4	88.4

[0000131] It was observed that the undiluted simethicone 50% powder passed #20 screen easily without any sticking. The flowability of DS-93 and DS-94 using simethicone powder was better than that of previous batches using granular simethicone. The suspensions of DS-93 and DS-94 after reconstitution were similarly foamy, both containing much more foam than DS-91 and DS-92. Therefore the antifoaming effect of simethicone powder is not as efficient as that of granular simethicone.

Example 18: Taste assessment of the aqueous pharmaceutical suspension formulations

[0000132] The taste of the aqueous pharmaceutical suspension formulations according to the present invention is critically important to the successful oral administration.

[0000133] Consequently the present invention provides a palatable powder for suspension dosage form of Tecovirimat which is suitable for pediatric and geriatric dosing

[0000134] The following examples identify and quantify the sensory attributes (basic tastes, e.g., bitterness; aromatics and trigeminal effects) of a series of Tecovirimat aqueous suspensions.

[0000135] Six experienced pharmaceutical sensory panelists were used to evaluate the above mentioned sensory attributes.

[0000136] Samples were evaluated using the Flavor Profile method 1 of descriptive sensory analysis to identify, characterize and quantify the sensory attributes of the study samples. The Flavor Profile method was originally developed to assist The Upjohn Company in identifying off tastes in their gelatin capsules and provides a complete description of the sensory attributes of products, e.g., texture, aroma, taste, mouthfeel.

[0000137] The method consists of formal procedures for describing and assessing the aroma (if appropriate) and flavor of a product in a reproducible manner. The Flavor Profile terms are shown in Fig 11.

[0000138] Flavor Profile is used to identify the individual attributes of product flavor, including:

1. Basic tastes**:** sweet, sour, salty, and bitter;
2. Aromatics**:** volatile components perceived by the olfactory system via the nasopharyngeal passage (retronasal) and
3. Feeling factors: numbing, cooling, warming, burning, drying, oily, astringent, etc.

[0000139] Flavor Profile also includes measures of the strength, or intensity, at which these character notes appear; the order in which the character notes appear; and a description of all sensations i.e. basic tastes, feeling factors, and aromatics remaining at specified time intervals after swallowing.

[0000140] For some oral pharmaceuticals texture attributes such as hardness (chewable tablets) or particulates /grittiness (chewable tablets, sachets, suspensions) are also noted and assessed.

[0000141] For oral pharmaceuticals, both the initial flavor quality and the aftertaste flavor quality are important to patient acceptability, and therefore it is important that each be evaluated. The initial flavor characteristics of the study products were evaluated during the first 10-20 seconds, and the aftertaste attributes were evaluated at multiple time intervals to 30 minutes as described below.

Sample Constitution and Taste Evaluation Protocols

[0000142] The compounded Tecovirimat powder for suspension, micronized tecovirimat API as well as tecovirimat granules taste assessment samples were constituted immediately prior to evaluations as follows:

1. The API-containing powder in an amber bottle was agitated to ensure the powder moves around freely.
2. The purified (reverse osmosis) water premeasured was added to each bottle containing the powder.
3. The bottles were mixed by hand for a few minutes. The unflavored bottles were mixed vigorously and the flavored bottles were mixed gently.
4. 5mL samples were taken from each test formulation and dispensed to each panelist for evaluation.

[0000143] The panelists evaluated the constituted samples as follows:

1. The panelists cleansed their palates with spring water and unsalted crackers.
2. 5mL of sample was dispensed into individual 1-ounce plastic cups using a graduated oral syringe and distributed to each panelist.
3. Starting at the same time, the panelists poured the sample directly in to their mouths, swished the contents around the oral cavity for 10 seconds and expectorated. During this time the panelists independently evaluated and recorded the initial flavor characteristics.
4. The panelists then independently evaluated and recorded the aftertaste characteristics at periodic intervals out to 30 minutes as flavor persisted.
5. The panelists recited their individual results and a preliminary Flavor Profile was generated for the sample.
6. Steps 1 through 4 were repeated for a second evaluation of the sample using the preliminary Flavor Profile from Step 5 as a guide, with the panelists noting any necessary modifications.
7. The panelists recited their individual results and a final Flavor Profile was developed for the sample.

Flavor Leadership Criteria

[0000144] The flavor quality of the flavored drug product prototypes was interpreted using the relevant Flavor Leadership Criteria. Research reveals that the perennial sales leaders in many categories, including pharmaceuticals, have a set of sensory characteristics in common, which are known as the Flavor Leadership Criteria. The flavor profiles associated with products typically having the highest sales within a product category possess the following characteristics:

1. Have a quickly recognizable identifying flavor;
2. Develop full flavor that rapidly blends with and covers the active and base characteristics;
3. Have no unpleasant mouth sensations (e.g., tongue sting);
4. Have no off-notes in the early impression or in the aftertaste;
5. Have a short (or appropriate) aftertaste.

[0000145] The concepts of Flavor Leadership were used to interpret the sensory analysis results and are described more fully below.

Immediate Impact of the Identifying Flavor.

[0000146] Flavor Leaders exhibit an immediate impact of the identifying flavor. When a consumer tastes a product, the first character notes provide for product identification and set expectations for the remainder of the flavor experience. For example, many inexpensive chocolates have an initial waxy impression whereas high-quality chocolates are identified by an initial chocolate flavor and cocoa butter mouthfeel. Unfortunately for many oral pharmaceuticals, the first impression is bitterness or an aromatic off-note (e.g., green stemmy, musty, chalky) that many patients find unacceptable.

Rapid Development of Balanced, Full Flavor.

[0000147] A well-blended flavor is key to product success. Flavor Leaders have a flavor that develops rapidly and is full bodied and well balanced. Blended flavor means that a complex body of underlying sensory impressions that are not separately identified support the expected character notes. For example, Coca-Cola® comprises hundreds of individual flavoring

components that are hard to single out individually, the components are very well blended. Unlike most foods and beverages, the challenge for pharmaceuticals is to "blend away" the negative sensory attributes of the drug substance, while simultaneously minimizing the number of excipients in the formulation. Amplitude is an integrative measure of balance and fullness (see Figure 11). It is an overall measure of the quality of the initial flavor and has been shown to correlate with palatability and patient acceptance. Amplitude of 1 is appropriate for most oral pharmaceuticals.

Compatible Mouthfeel Factors.

[0000148] Flavor leaders have a mouthfeel that is compatible with consumers' expectations. Many drug actives and excipients can cause trigeminal effects such as tongue sting or throat burn that may be unacceptable to patients and consumers. For example, a slight amount of mouth irritation would be acceptable in a citrus flavored formulation ("citrus rind mouth irritation") but would be totally out-of-context in a bubblegum flavored formulation. Unexpected or stronger than expected mouthfeel factors can have an adverse effect on patient acceptability.

[0000149] Examples of excipients that produce trigeminal effects include:

1. Methyl and propyl paraben (common preservatives in many oral pharmaceuticals) produce a tongue sting and numbing that can be unacceptable above a certain level.
2. Benzyl alcohol (solvent/preservative) produces both tongue sting and burn.

No "Off-Flavors."

[0000150] Flavor leaders are notable for their consistent lack of off-flavors. An off-flavor is the appearance of an unexpected or unacceptable character note (off-note). For most oral pharmaceuticals the API is the principal source of off-notes, which can include basic tastes (e.g., bitter) and/or aromatics (e.g., sulfurous). Other sources of off-notes include excipients, e.g., paraben aromatics poor flavor systems that result in terpy, solventy, or perfumy off-notes, packaging interactions that "taint" or transfer of off-notes from the package to the product and "flavor scalping" or transfer (loss) of flavor aromatics from the product to the package.

Short (or Appropriate) Aftertaste.

[0000151] The last impression i.e. the aftertaste is especially important to flavor quality. Aftertaste is caused by the persistence of one or a few character notes well after swallowing. For most products, a short, clean aftertaste is important. Products with a short, clean aftertaste encourage the consumer to take another bite or sip, and thereby to consume more of the product. For example, one of the major complaints about saccharin is its particularly long, bitter aftertaste and throat catch.

[0000152] However, the goal for pharmaceuticals is patient compliance, not consumption. For many APIs, the aftertaste is most critical as many flavor systems provide adequate coverage in the early aftertaste but the beneficial effects quickly decrease, exposing the API.

[0000153] As a general rule it is easier to mask a strongly bitter (or other) tasting API that "fades" quickly (steep decay curve) versus a moderately bitter API initially that lingers well into the aftertaste (flat decay curve). In any event, the challenge for the formulator is to mask the taste of the active throughout the duration of the aftertaste – be it 30 seconds or 30 minutes.

Drug Product

[0000154] The study samples in Table 46 were compounded by Custom Medicine Pharmacenter, a compounding-only pharmacy in Beverly, Massachusetts following SIGA-approved batch records (logged formula worksheets). The Tecovirimat drug active was supplied by SIGA as bulk powder (granulated and micronized), and the excipients provided by SIGA approved suppliers.

Table 46: Study Formulations at 40mg/mL Tecovirimat Concentration

Ingredient	Manufacturer	Lot Number	Expiry	Form # 1 (Strawberry mg/ml)	Form #2 (Cherry mg/ml)	Form #3 (API Granulated 200 mg/ml)	Form #4 (API Micronized 200 mg/ml)
				Batch Weight (g)	Batch Weight (g)	Batch Weight (g)	Batch Weight (g)
Tecovirimat, Granulate	SIGA	1401165	9/14/2015	3.465	3.465	3.465	-
Tracovirimat Monohydrate, Micronized	SIGA	9199001	8/25/2016	-	-	-	2.090
Sucralose	EMD	K93441194	3/8/2016	0.100	0.100	-	-
Simethicone Granular Solid	NUSIL	66777	5/12/2015	0.200	0.200	-	-
Methocel, A4C	DOW	2H22012N11	8/22/2015	0.500	0.500		-
Strawberry Flavor, 133.1529	Bell Flavors	521145	6/23/2016	0.500	-	-	-
Cherry Flavor, 23950	Virginia Dare	T02198	8/23/2016	-	0.030	-	-
Lactose Monohyrdrate	DFE Pharma	10700181	2/28/2015	0.685	0.705	-	-
Purified Water	CMP	--	12/31/2015	47mL	47mL	47mL	50mL
			Volume Tasted	50mL	50mL	50mL	50mL

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Taste Assessment Days

[0000155] The four formulations shown in Table 46 were evaluated over a three-day period as necessary to ensure that the maximum daily exposure of 600mg per day was not exceeded. The schedule was as follows:

Day 1:

Tecovirimat Formulation 3 (200mg/5mL) – Tasted twice

Tecovirimat Formulation 4 (200mg/5mL) – Tasted once

Day 2:

Tecovirimat Formulation 4 (200mg/5mL) – Tasted once

Tecovirimat Formulation 1 (200mg/5mL) – Tasted twice

Day 3:

Tecovirimat Formulation 1 (200mg/5mL) – Tasted once

Tecovirimat Formulation 2 (200mg/5mL) – Tasted twice

Flavor Profile Results

[0000156] The panelists evaluated the samples by the procedure outlined above. The results are summarized by formulation in tabular and graphical formats below. The tabular format contains the final Flavor Profile for the sample along with interpretation of the results using the Flavor Leadership Criteria.

[0000157] The challenge for many oral pharmaceuticals is to mask the critical ("undesirable") sensory characteristics of the active in the initial flavor and throughout the aftertaste.

[0000158] To visualize the temporal sensory effects (aftertaste) it is useful to plot selected attribute intensities as a function of time. Thus, following each tabular summary is a graph. In each graph, the area above a slight intensity (>1) has been shaded. Negative sensory characteristics above this intensity are clearly perceptible to patients and are often found to be unacceptable.

[0000159] To increase the likelihood of product acceptability the intensity of negative sensory characteristics should remain below this critical intensity throughout a product's flavor profile.

Tecovirimat – Formulation 3 (Granules)

[0000160] Tecovirimat (200mg/mL) Formulation #3 (Granule) is characterized by musty aromatic off notes, bitter basic taste and tannin/chalky mouth feels as shown in Table 47.

Table 47: Flavor Profile for Tecovirimat – Formulation 3 (Granules)

Flavor Profile SIGA Tecovirimat Formulation #3 200mg/mL (Granule)									
	Initial	1 Min	3 Min	5 Min	10 Min	15 Min	20 Min	25Min	30 Min
Musty Aromatic	2	1 ½	1	½	-	-	-	-	-
Sour	½	-	-	-	-	-	-	-	-
Bitter	1	1-1½	1	½	½	½	0 -		-
Chalky Mouthfeel	1	1	½ - 1	½	-	-	-	-	-
Tannin Mouthfeel	1½	1-1½	1	1	-	-	-	-	-
Drying Mouthfeel	½	1	1½	1½	1-1½	1-1½	1	½	-

Flavor Leadership Interpretation				
1 – Aromatic Identity	*2- Amplitude*	*3- Mouthfeel*	*4- Off-Notes*	*5-Aftertaste*
Not applicable for unflavored products	Not applicable for unflavored products	Chalky, tannin and drying mouthfeels	Slight-to-moderate intensity bitterness and moderate intensity musty aromatic off-notes	Lingering bitterness, mouthfeels and aromatic off-notes

[0000161] The musty aromatic off-notes, bitterness and tannin mouthfeel of the Tecovirimat granules (Formulation #3) lingered at patient-perceptible levels ($\geq$ 1) for about 3 minutes in the Aftertaste, see Fig.12.

Tecovirimat – Formulation 4 (Micronized)

[0000162] Tecovirimat (200mg/mL) Formulation #4 (micronized API) is characterized by aromatic offnotes (chalky, soapy/waxy), bitter basic taste and tannin/chalky mouthfeels, though generally lower in intensity than the API granules as shown in Table 48.

Table 48: Flavor Profile for Tecovirimat – Formulation 4 (Micronized)

Flavor Profile SIGA Tecovirimat Formulation #4 200mg/mL (Micronized API)									
	Initial	1 Min	3 Min	5 Min	10 Min	15 Min	20 Min	25Min	30 Min
Chalky Aromatic	1-1½	1	½	-	-	-	-	-	-
Soapy/Waxy Aromatic	1-1½	1	½	-	-	-	-	-	-
Bitter	1	1-1½	½-1	½	½	0-½	-		-
Chalky Mouthfeel	½-1	1	1-1½	-	-	-	-	-	-
Tannin Mouthfeel	1	1	1	½-1	½	-	-	-	-
Drying Mouthfeel	½	1	1	1	1	1	½	0-½	-

Flavor Leadership Interpretation				
1 – Aromatic Identity	*2- Amplitude*	*3- Mouthfeel*	*4- Off-Notes*	*5-Aftertaste*
Not applicable for unflavored products	Not applicable for unflavored products	Chalky, tannin and drying mouthfeels	Slight-to-moderate intensity bitterness and moderate intensity musty aromatic off-notes	Lingering bitterness, mouthfeels and aromatic off-notes

[0000163] The negative (aversive) sensory attributes of the micronized API (Formulation #4) are marginally above a slight (1) intensity, which is the perception threshold for most patients as shown in Fig. 13.

Tecovirimat – Formulation 1 (Strawberry)

[0000164] Tecovirimat Formulation #1 (Strawberry) is somewhat low in initial flavor quality as measured by Amplitude (balance and fullness) as shown in Table 49.

Table 49: Flavor Profile for Tecovirimat – Formulation 1 (Strawberry)

Flavor Profile SIGA Tecovirimat Formulation #1 200mg/mL (Strawberry)									
	Initial	1 Min	3 Min	5 Min	10 Min	15 Min	20 Min	25Min	30 Min
Amplitude	1								
Sweet	1½	1-1½	½-1	½	0-½	-	-	-	-
Sour	½	-	-	-	-	-	-	-	-
Strawberry Aromatics(Fresh and Cream)	1½	1	½	-	-	-	-	-	-
Chalky/Musty Aromatic	1½	1	½	0-½	-	-	-	-	-
Bitter	1	½-1	½	½	0-½	-	-	-	-
Chalky Mouthfeel	1	1	1	½	-	-	-	-	-
Tannin Mouthfeel	½-1	1	½-1	½	½	0-½	-	-	-
Drying Mouthfeel	-	1	1½	1	1	1	1	½	-
Synthetic Sweetener Sensation (SSS)	-	½-1	½	0-½	-	-	1	-	-

Flavor Leadership Interpretation				
1 – Aromatic Identity	***2- Amplitude***	***3- Mouthfeel***	***4- Off-Notes***	***5-Aftertaste***
Slight-to-moderate intensity strawberry flavoring aromatics	A low level of balance and fullness	Chalky, tannin, drying and SSS mouthfeels	Slight intensity bitterness and slight-to-moderate intensity chalky/musty aromatic off-notes	Lingering basic tastes, aromatic off-notes and mouthfeels

[0000165] The flavor system (flavoring aromatics and sweet basic taste) of Formulation #1 (Strawberry) provides reasonable coverage of the bitter basic taste and chalky/musty aromatics as shown in Fig.14.

Tecovirimat – Formulation 2 (Cherry)

[0000166] As shown in Table 50, Tecovirimat Formulation #2 (Cherry) is slightly lower in initial flavor quality than the Formulation #1 (Strawberry) as measured by Amplitude.

Table 50: Tecovirimat – Formulation 2 (Cherry)

Flavor Profile SIGA Tecovirimat Formulation #2 200mg/mL (Cherry)									
	Initial	1 Min	3 Min	5 Min	10 Min	15 Min	20 Min	25Min	30 Min
Amplitude	½-1								
Sweet	1½	1-1½	½-1	½	0-½	0-½			
Sour	½	0-½	-	-	-	-	-	-	-
Strawberry Aromatics(Fresh and Cream)	1½	1	½	-	-	-	-	-	-
Chalky/Musty Aromatic	1½	1	½	-	-	-	-	-	-
Bitter	1	1	½-1	½	½	-	-	-	-
Chalky Mouthfeel	1	1-½	1	½	-	-	-	-	-
Tannin Mouthfeel	1	1-½	1	½	½	0-½	-	-	-
Drying Mouthfeel	-	1	1-1½	1-1½	1	1	1	½	-
Synthetic Sweetener Sensation (SSS)	-	1	½-1	½	½	-	-	-	-

Flavor Leadership Interpretation				
1 – Aromatic Identity	***2- Amplitude***	***3- Mouthfeel***	***4- Off-Notes***	***5-Aftertaste***
Slight-to-moderate intensity strawberry flavoring aromatics	A low level of balance and fullness	Chalky, tannin, drying and SSS mouthfeels	Slight intensity bitterness and slight-to-moderate intensity chalky/musty aromatic off-notes	Lingering basic tastes, aromatic off-notes and mouthfeels

[0000167] The flavor system (flavoring aromatics and sweet basic taste) of Formulation #2 (Cherry) provides reasonable coverage of the bitter basic taste and chalky/musty aromatics as shown in Fig.14.

[0000168] The results show that he unsweetened/unflavored Tecovirimat formulations are characterized by aromatic offnotes, (musty, chalky, soapy/waxy), bitter basic taste and tannin/chalky mouthfeels. However, overall, these attributes are lower in intensity in the micronized API compared to the granules.

[0000169] The negative attributes of the micronized API are near the perception threshold for most patients (i.e., may not be patient-perceptible).

[0000170] The two sweetened/flavored Tecovirimat suspensions are somewhat low in overall flavor quality and both flavored suspensions are somewhat low in initial flavor quality as measured by Amplitude (Target = 1.) due to their aromatic off-notes (chalky/musty), bitter basic taste and mouthfeels (tannin/chalky).

[0000171] Both flavored suspensions are somewhat low in flavor and sweetness impact (intensity). However the strawberry-flavored suspension is slightly more blended and full (i.e., higher in Amplitude) than cherry-flavored suspension, which was somewhat "solventy" (benzaldehyde-like) in character and both flavored suspensions provide a reasonable coverage of the bitter basic taste and chalky/musty aromatics, though the flavoring aromatics fade quickly.

[0000172] Thus it can be seen that Tecovirimat is relatively "bland" in flavor (basic tastes, aromatics, mouthfeel and texture), with the micronized API having a lower flavor than the API granules and the sweetened /flavored formulations are somewhat low in flavor quality (strawberry higher than cherry), primarily due to low impact (intensity) and duration of the flavoring aromatics and to a lesser extent the underlying sweet basic taste.

[0000173] While the present invention has been described with reference to the specific embodiments thereof, it should be understood by those skilled in the art that various changes

may be made, and equivalents may be substituted, without departing from the true spirit and scope of the invention. In addition, many modifications may be made to adapt a particular situation, material, composition of matter, process, process step or steps, to the objective, spirit and scope of the present invention. All such modifications are intended to be within the scope of the invention.

References

1. Fenner et al., The epidemiology of smallpox. In: Smallpox and its eradication. Switzerland: World Health Organization; 1988)

2. *Bray* et al., Antiviral Research 58: 101-114 (2003).

3. Quenelle et al. 2007. Efficacy of delayed treatment with ST-246 given orally against systemic orthopoxvirus infections in mice. Antimicrobial Agents and Chemotherapy Feb; 51(2):689-95

4. Smee et al. (2002) Antimicrob. Agents Chemother. 46:1329-1335)

5. Vora et al., 2008, Severe eczema vaccinatum in a household contact of a smallpox vaccine. Clinical Infectious Disease 15; 46(10):1555-61).

CLAIMS

1. A dry suspension comprising 4-trifluoromethyl-N-(3,3a,4,4a,5,5a,6,6a-octahydro-1,3-dioxo-4,6-ethenocycloprop[f]isoindol-2-(1H)-yl)-benzamide (Tecovirimat (ST-246)) and simethicone.

2. A dry suspension according to claim 1 further comprising at least one suspending agent.

3. A dry suspension according to claim 2 wherein the suspending agent is methylcellulose.

4. A dry suspension according to claim 3 wherein the methylcellulose is methylcellulose 400 Cps.

5. A dry suspension according to claim 3 wherein the methylcellulose is methylcellulose 15 Cps.

6. A dry suspension according to claim 2 wherein the suspending agent is hydroxypropyl cellulose.

7. A dry suspension according to any one claims 2 to 6 comprising methylcellulose and hydroxypropyl cellulose.

8. A dry suspension according to any one of the preceding claims further comprising a lubricant.

9. A dry suspension according to claim 8 wherein the lubricant is magnesium stearate.

10. A dry suspension according to any one of the preceding claims further comprising an excipient.

11. A dry suspension according to claim 10 wherein the excipient is lactose monohydrate.

12. A dry suspension according to any one of the preceding claims further comprising a further antifoaming agent.

13. A dry suspension according to any one of the preceding claims further comprising a sweetener.

14. A dry suspension according to any one of the preceding claims comprising a flavoring.

15. A dry suspension according to any one of the preceding claims wherein the ST-246 is selected from a group consisting of ST-246 polymorph Form I, ST-246 polymorph Form II, ST-246 polymorph Form III, ST-246 polymorph Form IV, ST-246 polymorph Form V and ST-246 polymorph Form VI.

16. A dry suspension according to any one of the preceding claims wherein the ST-246 is micronized.

17. A dry suspension according to any one of claim 1 to 15 wherein the ST-246 is granulated.

18. A dry suspension according to any one of the preceding claims wherein the simethicone is granular form.

19. A dry suspension according to any one of claim 1 to 17 wherein the simethicone is in liquid form and adsorbed on lactose monohydrate.

20. A dry suspension according to any one of the preceding claims comprising 10 to 70 wt% of ST-246.

21. A dry suspension according to any one of the preceding claims comprising 15 to 40 wt% of ST-246.

22. A dry suspension according to any one of the preceding claims comprising 0.2 to 6.0 wt% simethicone.

23. A dry suspension according to any one of the preceding claims comprising 0.4 to 5.0 wt % simethicone.

24. A dry suspension according to any one of claims 3 to 23 comprising 1 to 5 wt % methylcellulose.

25. A dry suspension according to any one of claims 3 to 24 comprising 2 to 3 wt % methylcellulose.

26. A dry suspension according to any one of claims 4 to 25 comprising 1.0 to 30 wt% hydroxypropylcellulose.

27. A dry suspension according to any one of claim 4 to 26 comprising 2 to 20 wt% of hydroxypropylcellulose.

28. A dry suspension according to any one of claims 8 to 27 comprising 0.1 to 1.0 wt% of lubricant.

29. A dry suspension according to any one of claims 10 to 28 comprising 10 to 20 wt% of excipient.

30. A dry suspension according to any one of claims 13 to 29 comprising 1.0 to 3.0 wt% of sweetener.

31. A dry suspension according to any one of claims 14 to 30 comprising 0.1 to 1.0 wt% of flavoring.

32. A dry suspension according to any one of the preceding claims wherein the particle size of ST-246 is 0.5 to 10μm.

33. A dry suspension according to any one of the preceding claims wherein the particle size of ST-246 is 1 to 5 μm.

34. An aqueous pharmaceutical suspension formulation comprising a dry suspension according to any one of the preceding claims and water.

35. A formulation according to claim 34 further comprising a pharmaceutically acceptable ingredient.

36. A formulation according to claim 35 wherein the pharmaceutically acceptable ingredient is selected from the group consisting of carrier, excipient, diluent, additive, filler, lubricant and binder.

37. A formulation according to any one of claims 34 to 36 having a pH between 4 and 7.

38. A method of treating orthopoxvirus infections and/or eczema vaccinatum comprising oral administration to a subject in need thereof a formulation according to any one of claims 34 to 37.

39. The method of claim 38, wherein the subject is administered 400 mg to 2000 mg daily of ST-246.

40. The method of claim 38, wherein the subject is administered 600 mg to 1200 mg daily of ST-246.

41. A process of making the dry suspension according to any one of claims 1 to 33 comprising mixing ST-246 with simethicone and optionally at least one suspending agent, at least one lubricant, at least one excipient, at least one further anti-foaming agent, at least one sweetener and/or at least one flavoring.

42. A process according to claim 41 wherein the mixing is carried out using geometric mixing.

43. A method of making the formulation according to any one of claims 34 to 37 comprising dispersing the dry suspension in water.

44. A method of making the formulation according to claim 43 wherein the water contains a suspending agent.

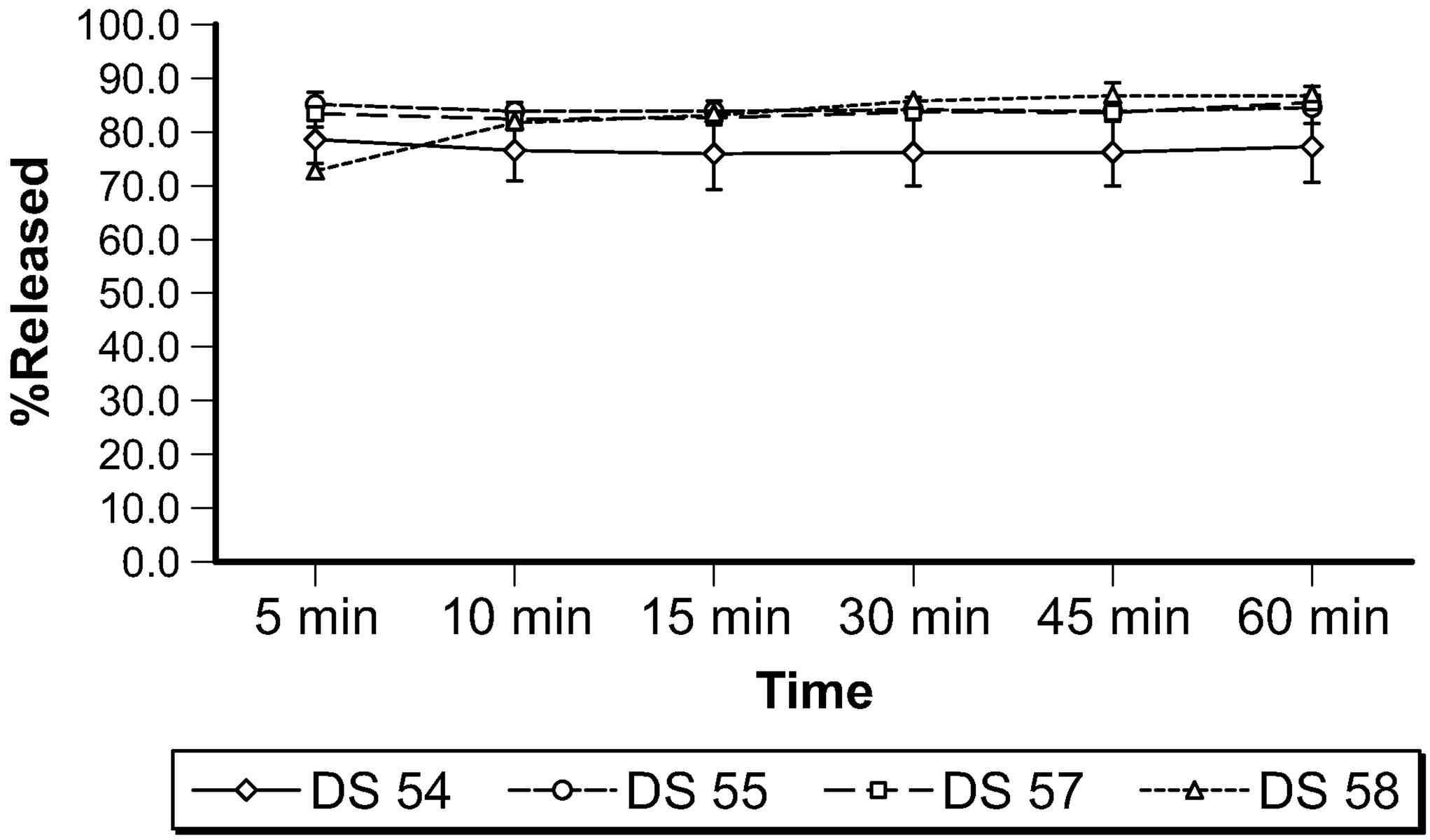

ST-246 Release from DS 54, 55, 57 and 58
%Released
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
5 min
10 min
15 min
30 min
45 min
60 min
Time
DS 54
DS 55
DS 57
DS 58

FIG. 1

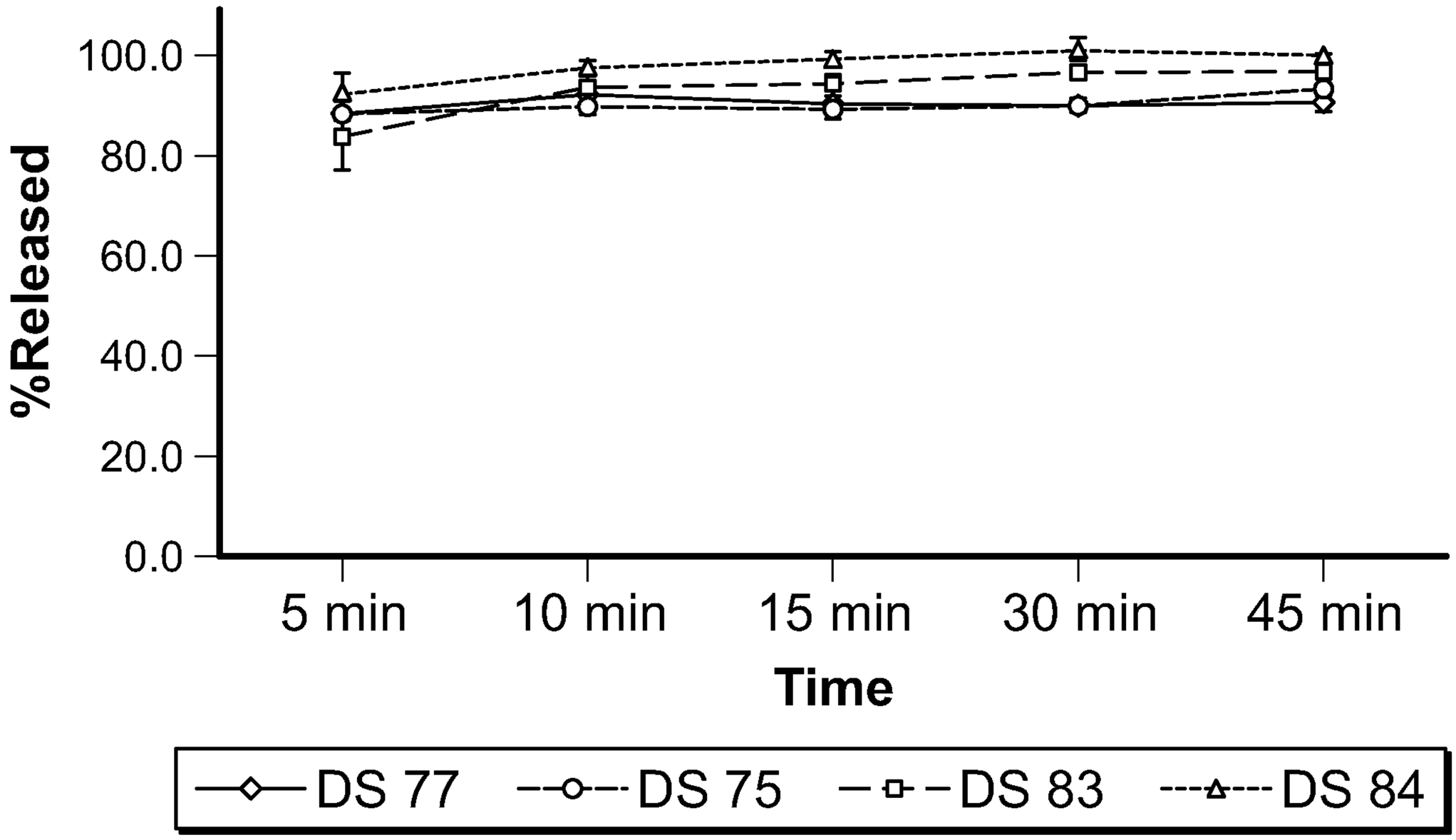

ST-246 Release from DS 75, 77, 83 and 84
%Released
100.0
80.0
60.0
40.0
20.0
0.0
5 min
10 min
15 min
30 min
45 min
Time
DS 77
DS 75
DS 83
DS 84

FIG. 2

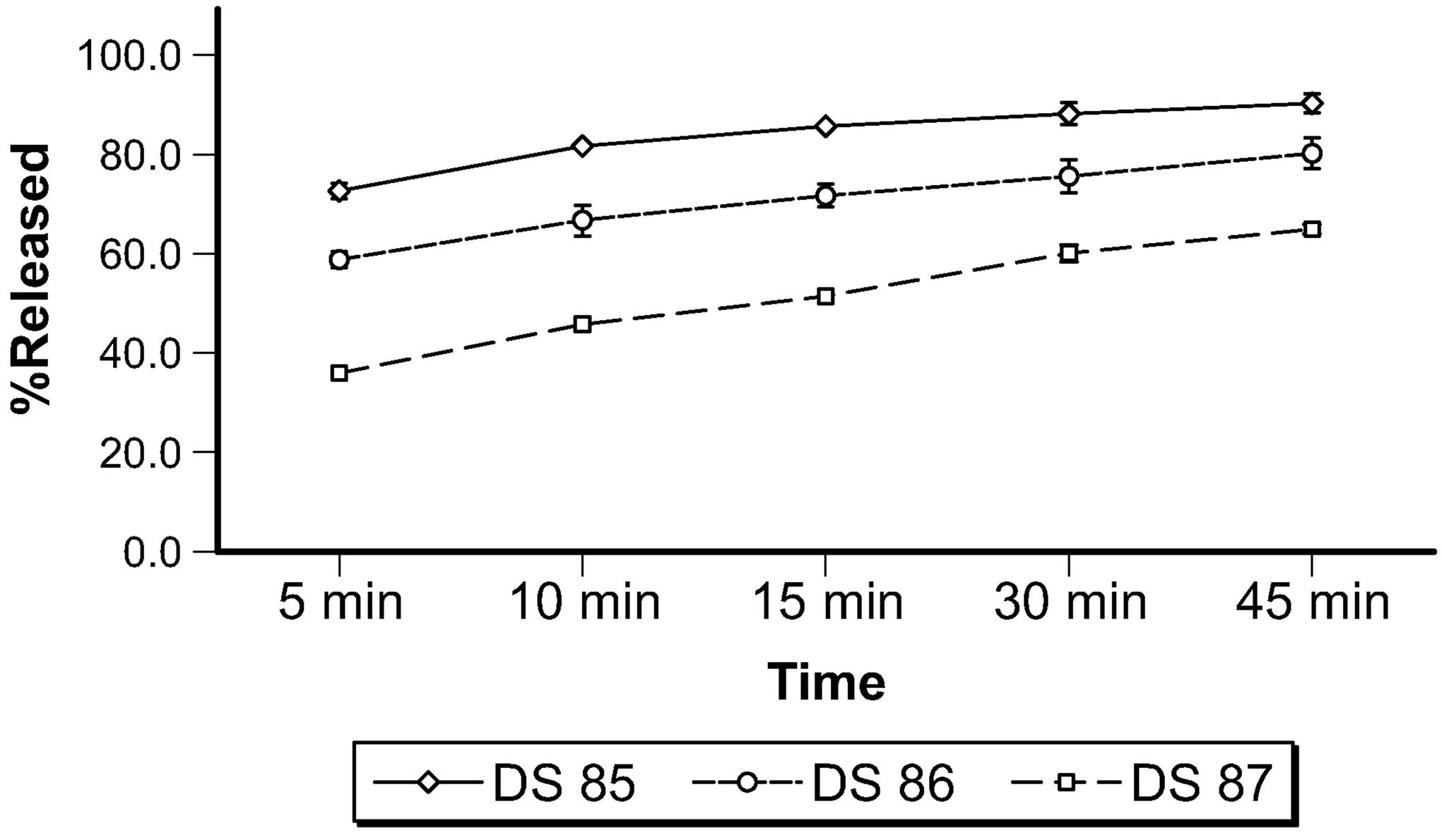

Dissolution of ST-246 from DS 85, 86, and 87
%Released
100.0
80.0
60.0
40.0
20.0
0.0
5 min
10 min
15 min
30 min
45 min
Time
DS 85
DS 86
DS 87

FIG. 3

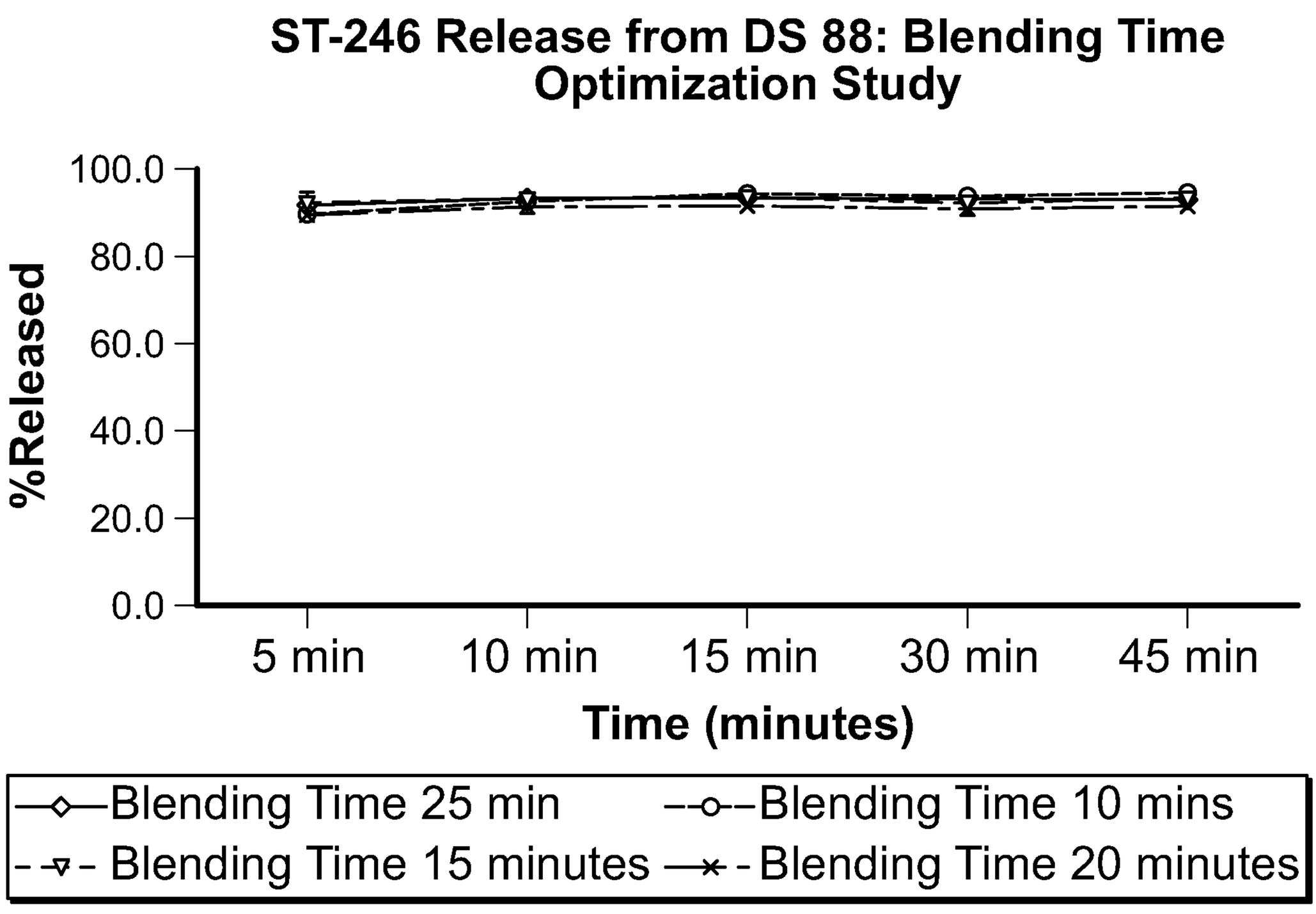

ST-246 Release from DS 88: Blending Time Optimization Study
%Released
100.0
80.0
60.0
40.0
20.0
0.0
5 min
10 min
15 min
30 min
45 min
Time (minutes)
Blending Time 25 min
Blending Time 10 mins
Blending Time 15 minutes
Blending Time 20 minutes

FIG. 4

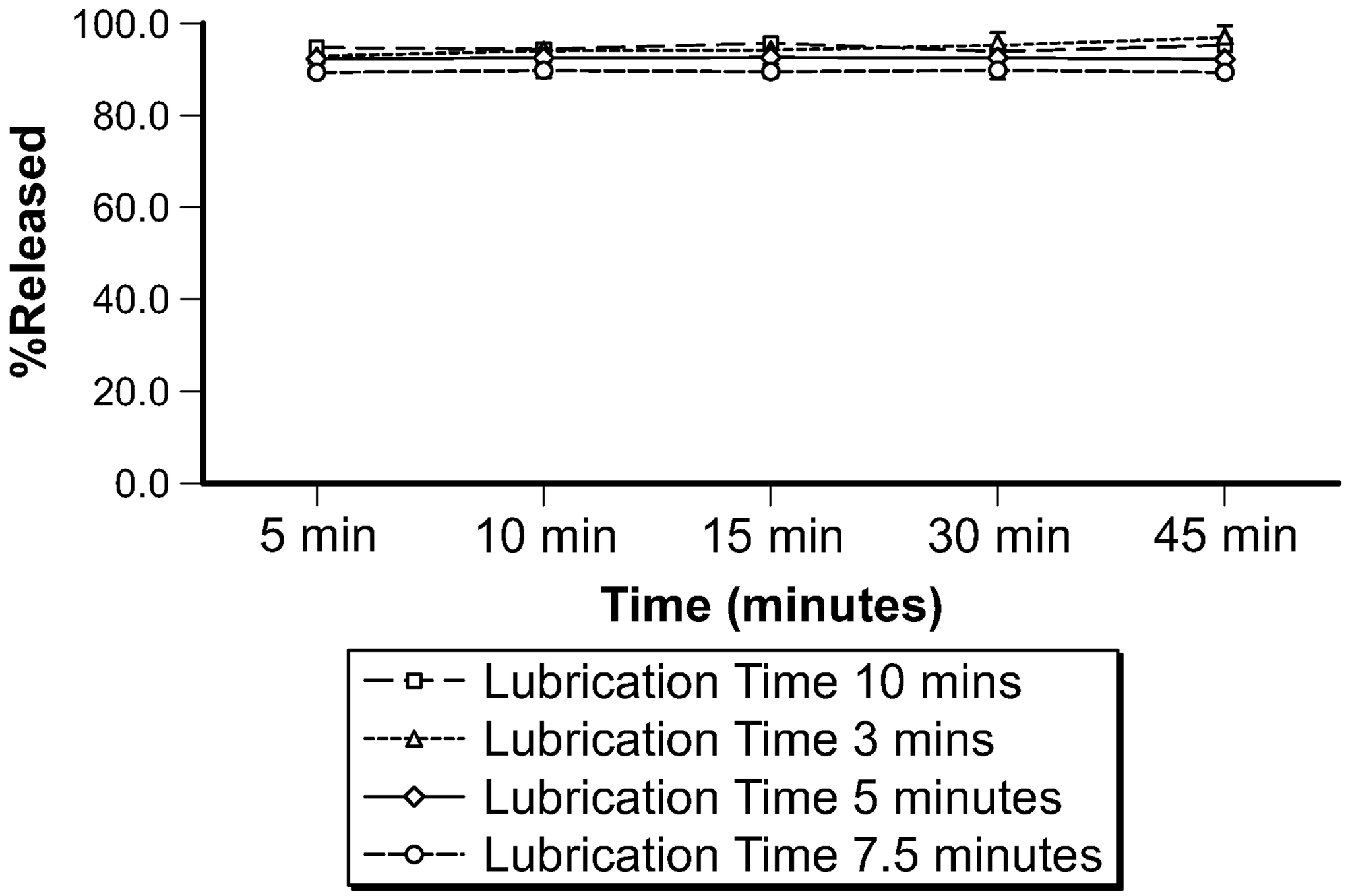

ST-246 Release from DS 88: Lubrication Time Optimization Study
%Released
100.0
80.0
60.0
40.0
20.0
0.0
5 min
10 min
15 min
30 min
45 min
Time (minutes)
Lubrication Time 10 mins
Lubrication Time 3 mins
Lubrication Time 5 minutes
Lubrication Time 7.5 minutes

FIG. 5

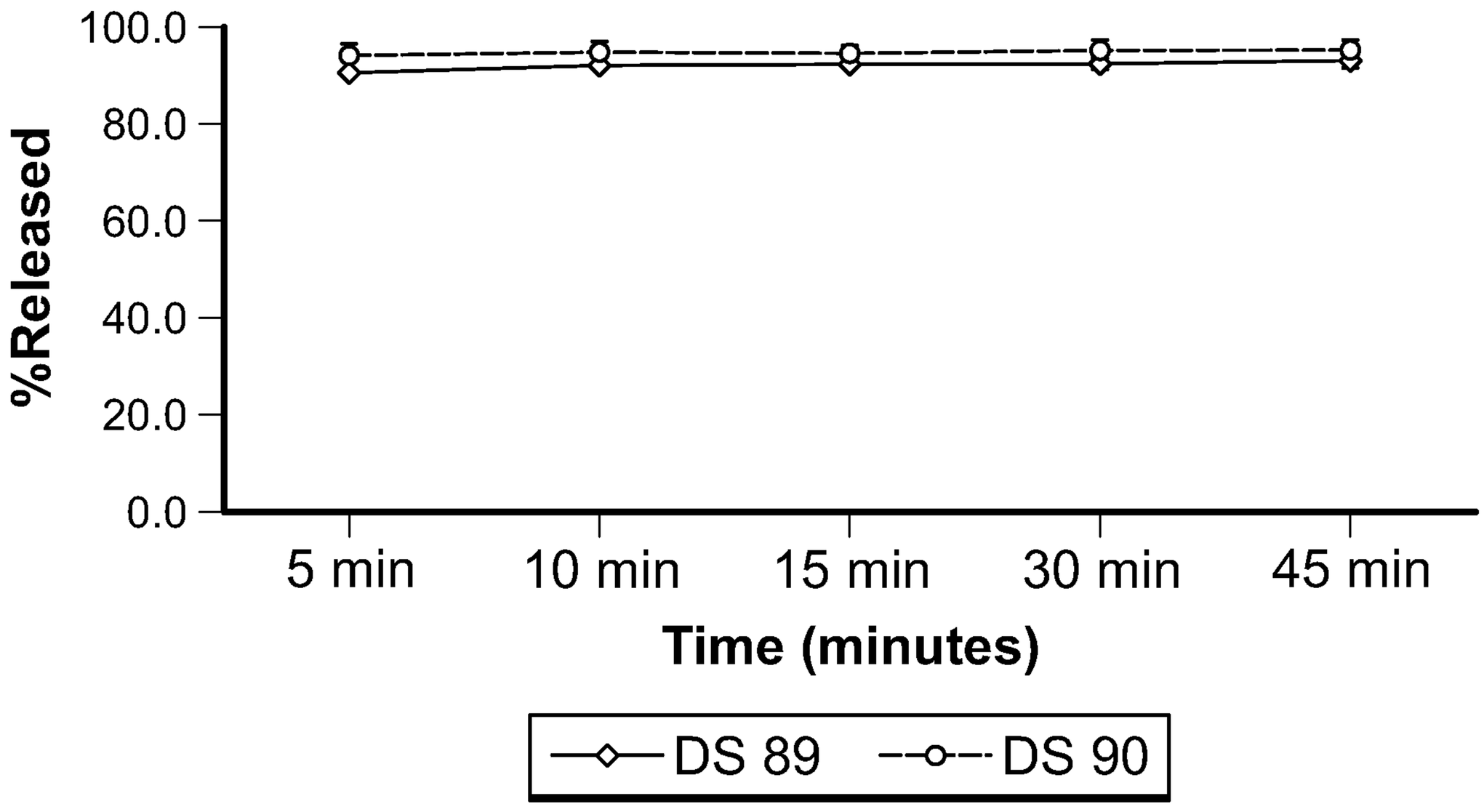

ST-246 Release from DS 89, and 90
%Released
100.0
80.0
60.0
40.0
20.0
0.0
5 min
10 min
15 min
30 min
45 min
Time (minutes)
DS 89
DS 90

FIG. 6

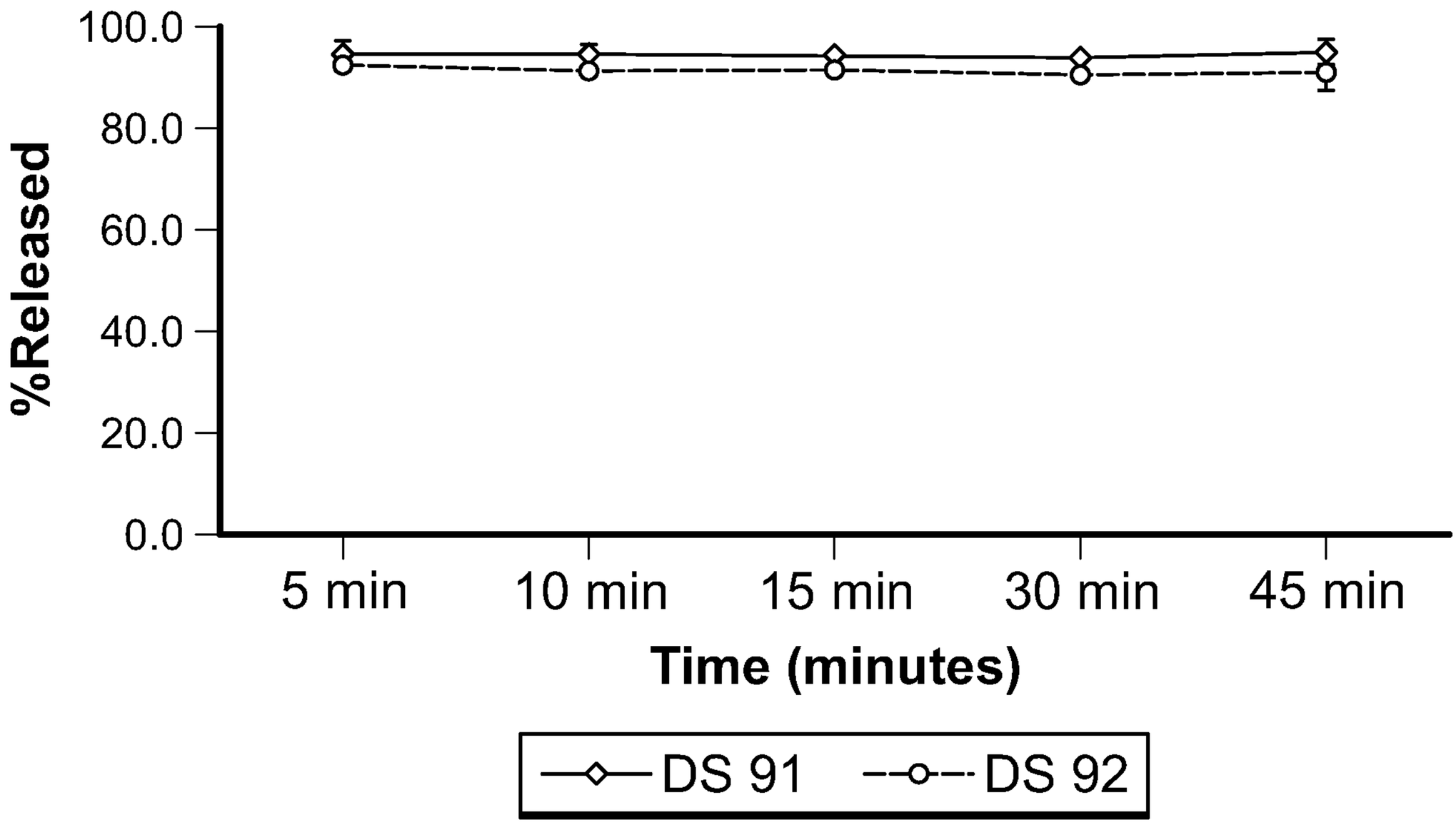

ST-246 Release from DS 91, and 92
%Released
100.0
80.0
60.0
40.0
20.0
0.0
5 min
10 min
15 min
30 min
45 min
Time (minutes)
DS 91
DS 92

FIG. 7

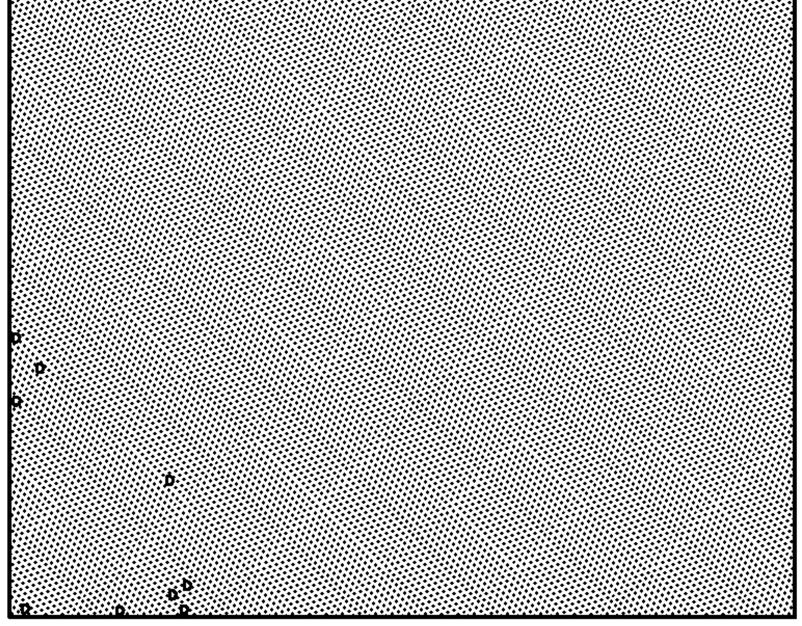


FIG. 8B

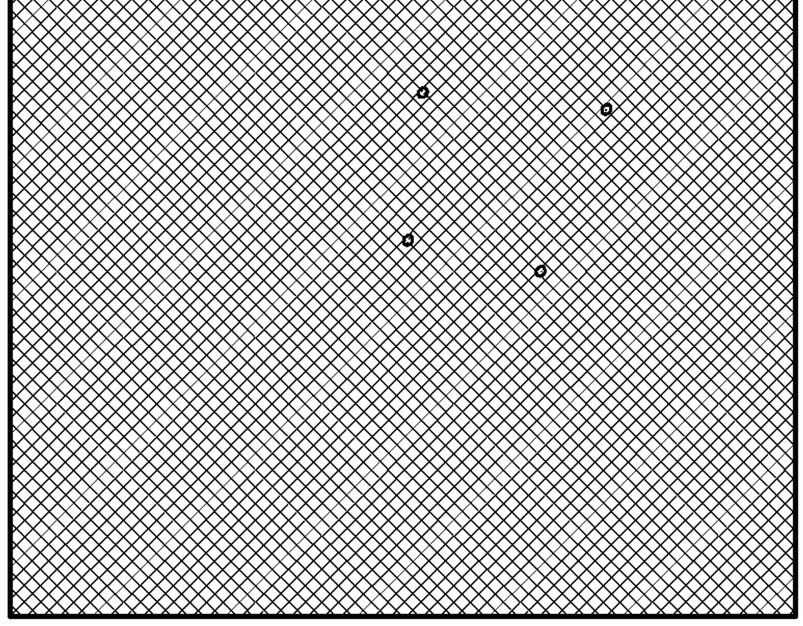


FIG. 8D

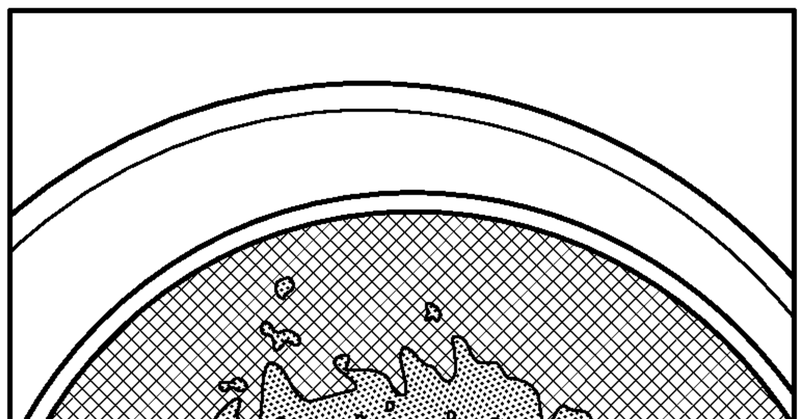


FIG. 8A

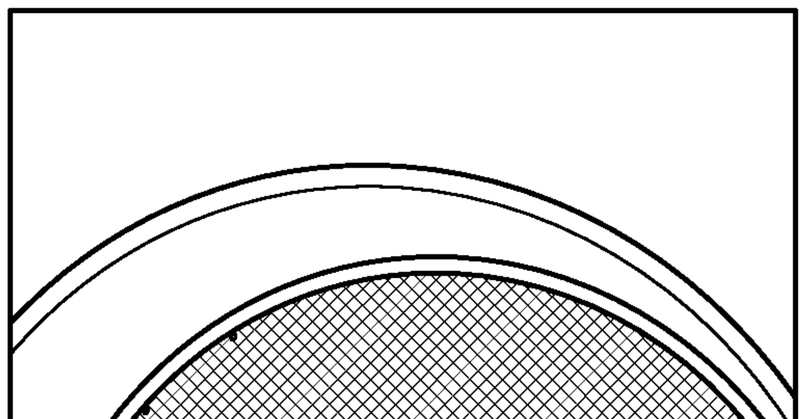
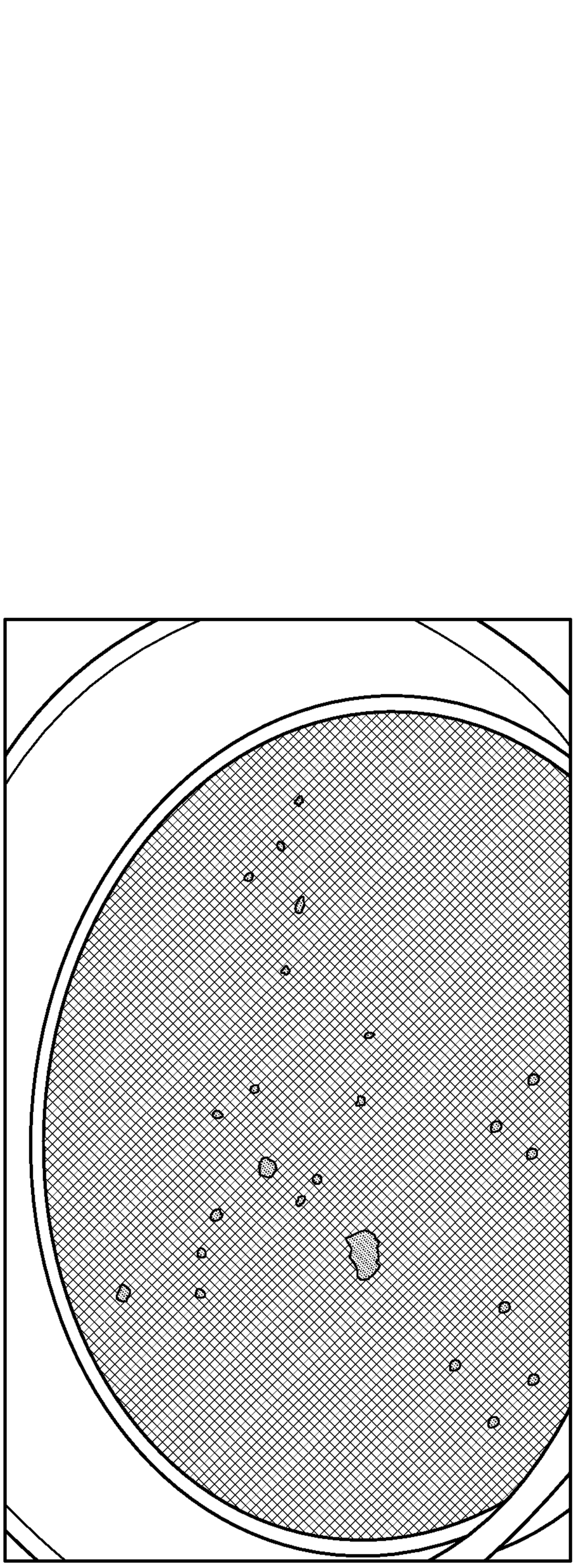


FIG. 8C



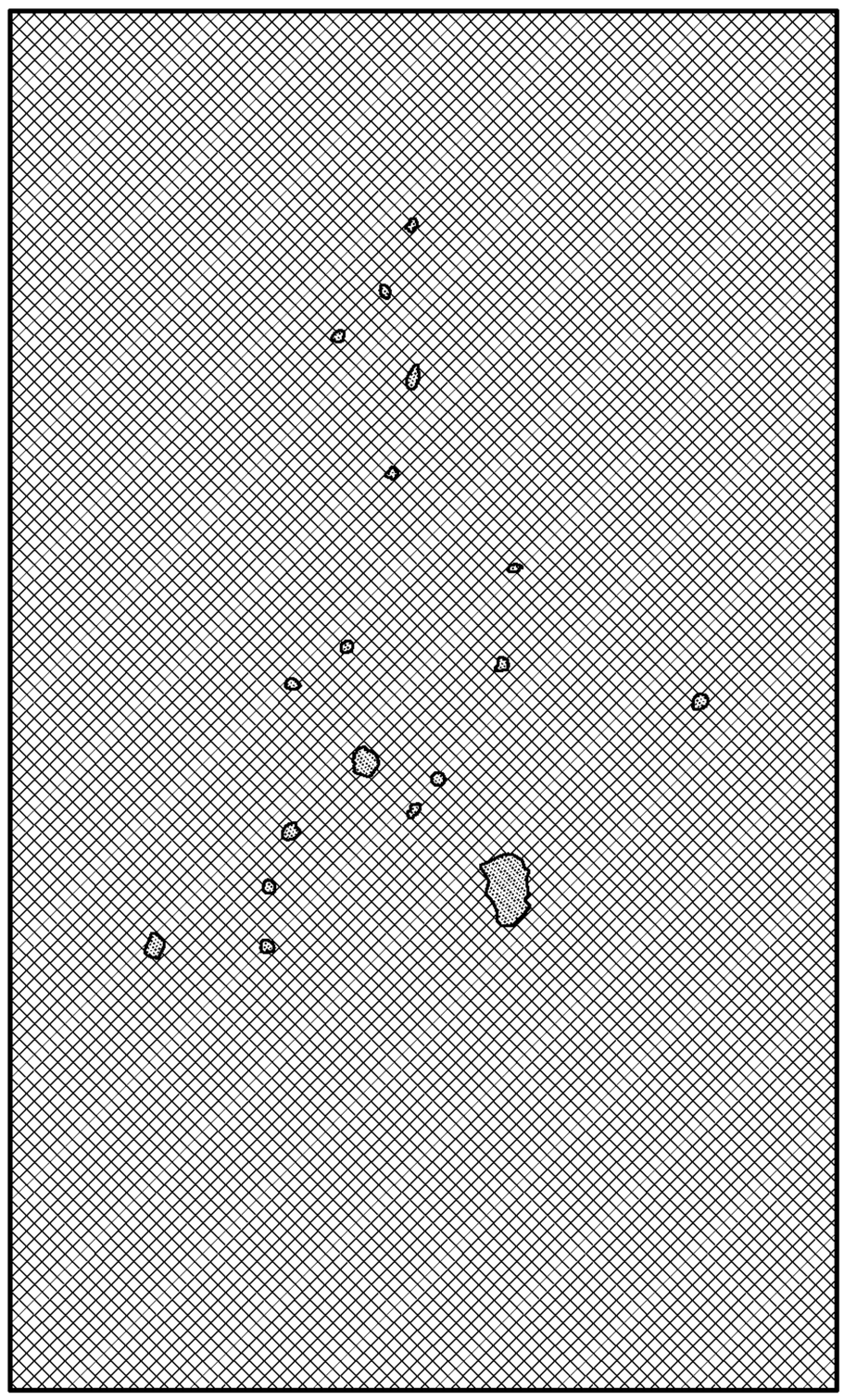


FIG. 9

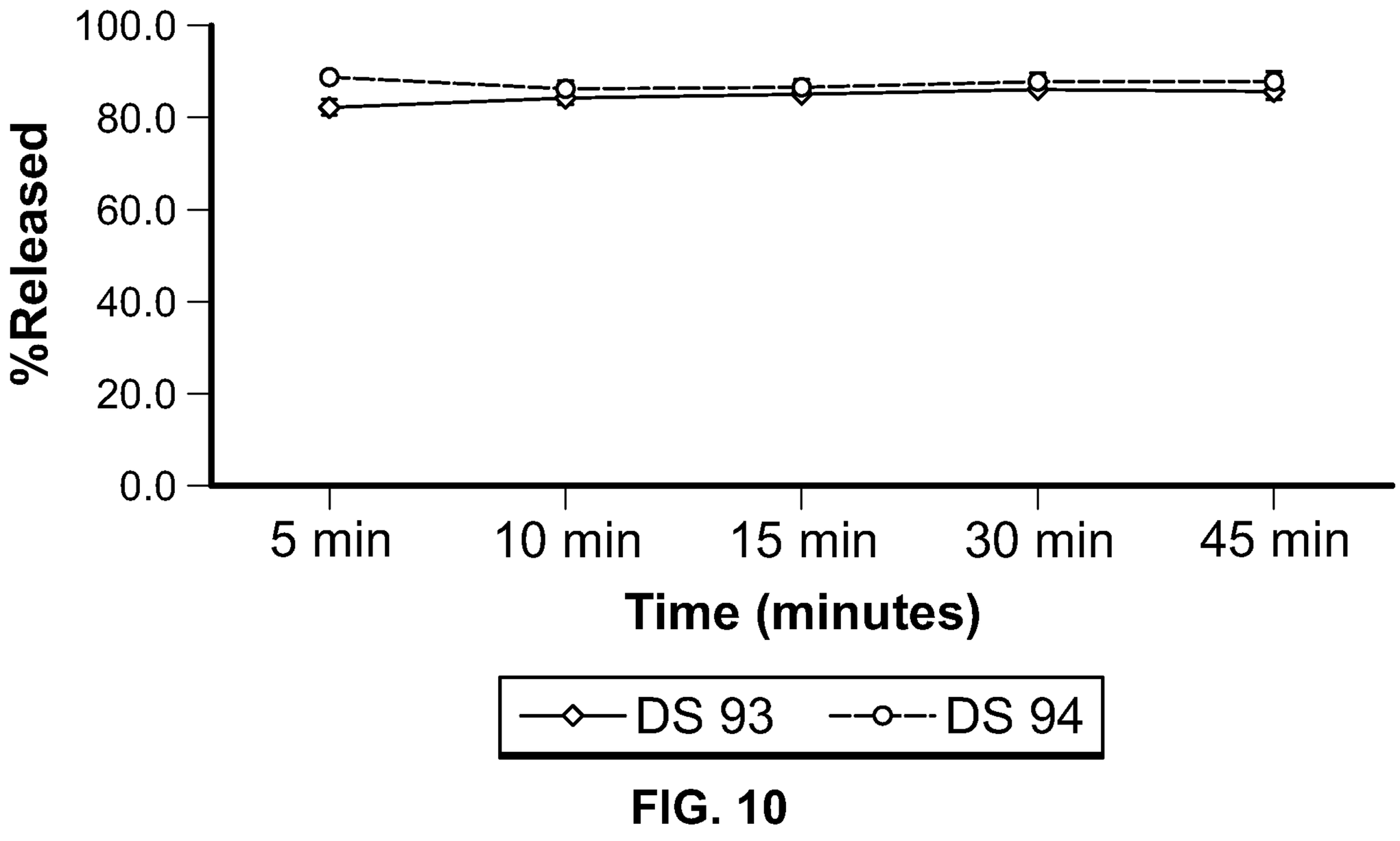


FIG. 10

Flavor Profile Definitions
Amplitude: Initial overall perception of the balance and fullness of a flavored product; considering the appropriateness of aromas and flavor notes present, their blend and intensity and existence of off-notes. **Amplitude Scale:** 0 ½ 1 1½ 2 2½ 3 — None Low Moderate High **Character Notes:** Aromatics, basic tastes, and feeling factors (listed in order of appearance along with a measurement of strength). **Intensity Scale:** 0 ½ 1 1½ 2 2½ 3 — None Slight Moderate Strong **Aftertaste:** Measurement of all sensation remaining at selected time intervals

FIG. 11

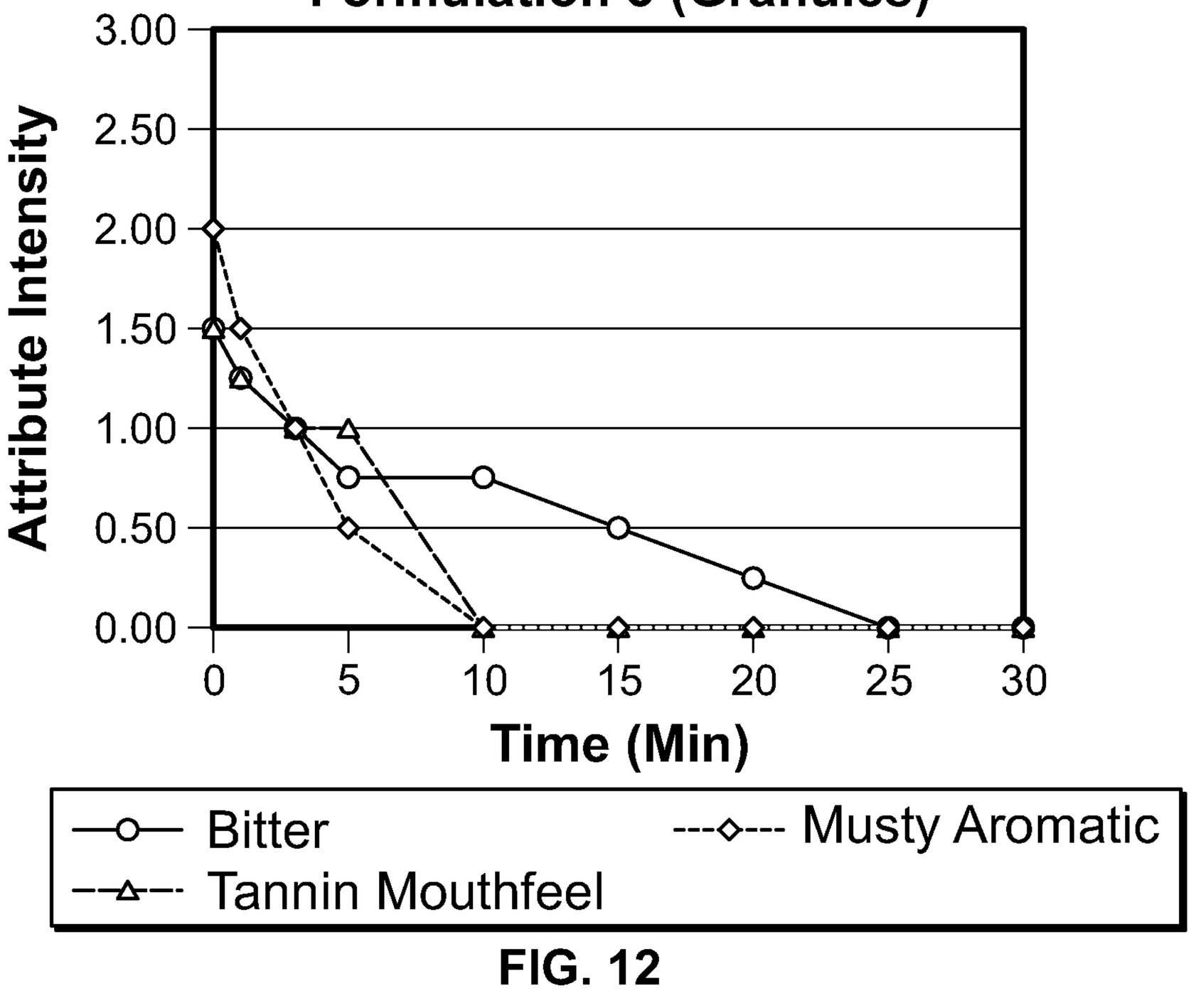

Time-Intensity Profile - Tecovirimat
Formulation 3 (Granules)
Attribute Intensity
3.00
2.50
2.00
1.50
1.00
0.50
0.00
0
5
10
15
20
25
30
Time (Min)
Bitter
Musty Aromatic
Tannin Mouthfeel

FIG. 12

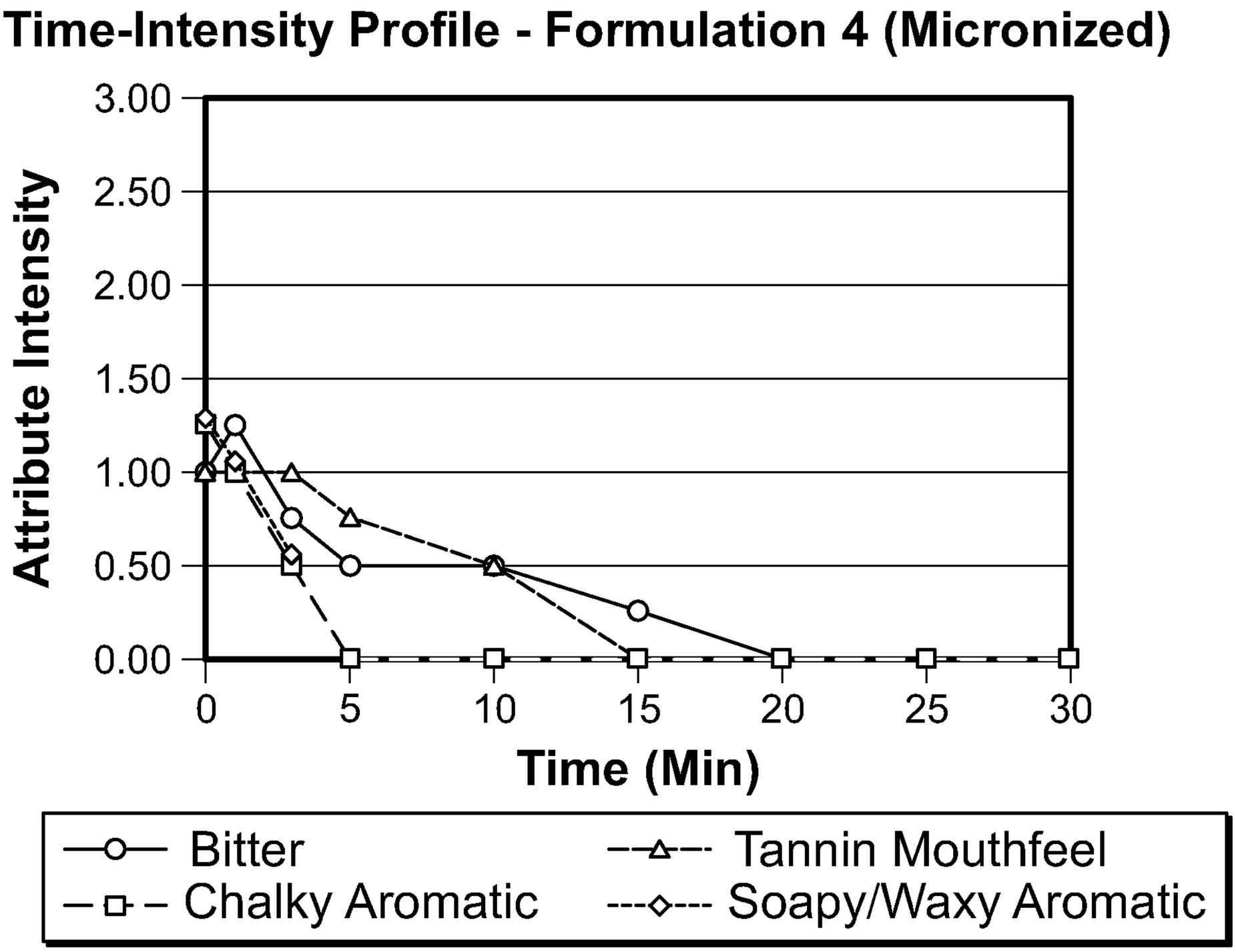

Time-Intensity Profile - Formulation 4 (Micronized)
Attribute Intensity
3.00
2.50
2.00
1.50
1.00
0.50
0.00
0
5
10
15
20
25
30
Time (Min)
Bitter
Tannin Mouthfeel
Chalky Aromatic
Soapy/Waxy Aromatic

FIG. 13

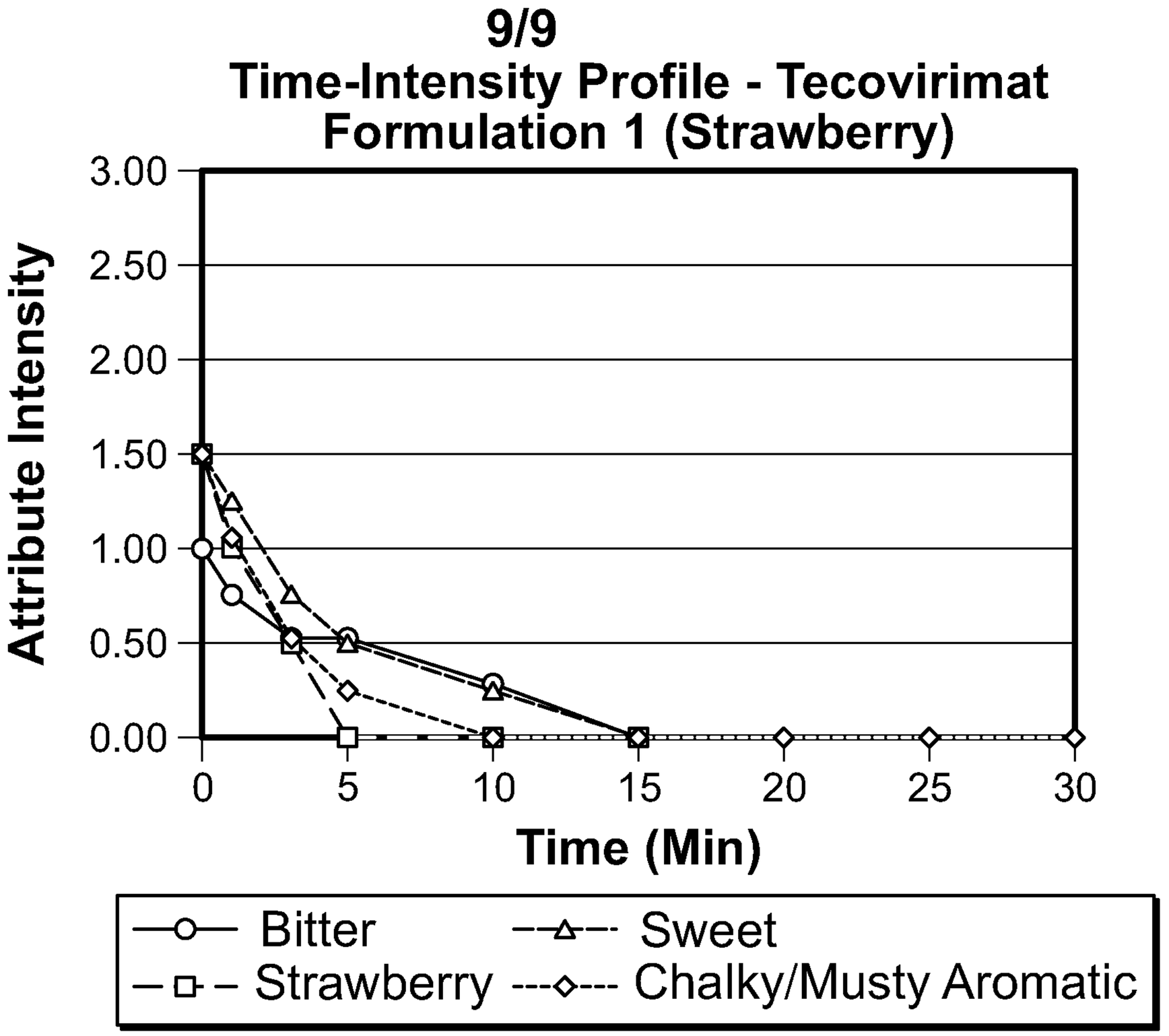

Time-Intensity Profile - Tecovirimat
Formulation 1 (Strawberry)
Attribute Intensity
3.00
2.50
2.00
1.50
1.00
0.50
0.00
0
5
10
15
20
25
30
Time (Min)
Bitter
Sweet
Strawberry
Chalky/Musty Aromatic

FIG. 14

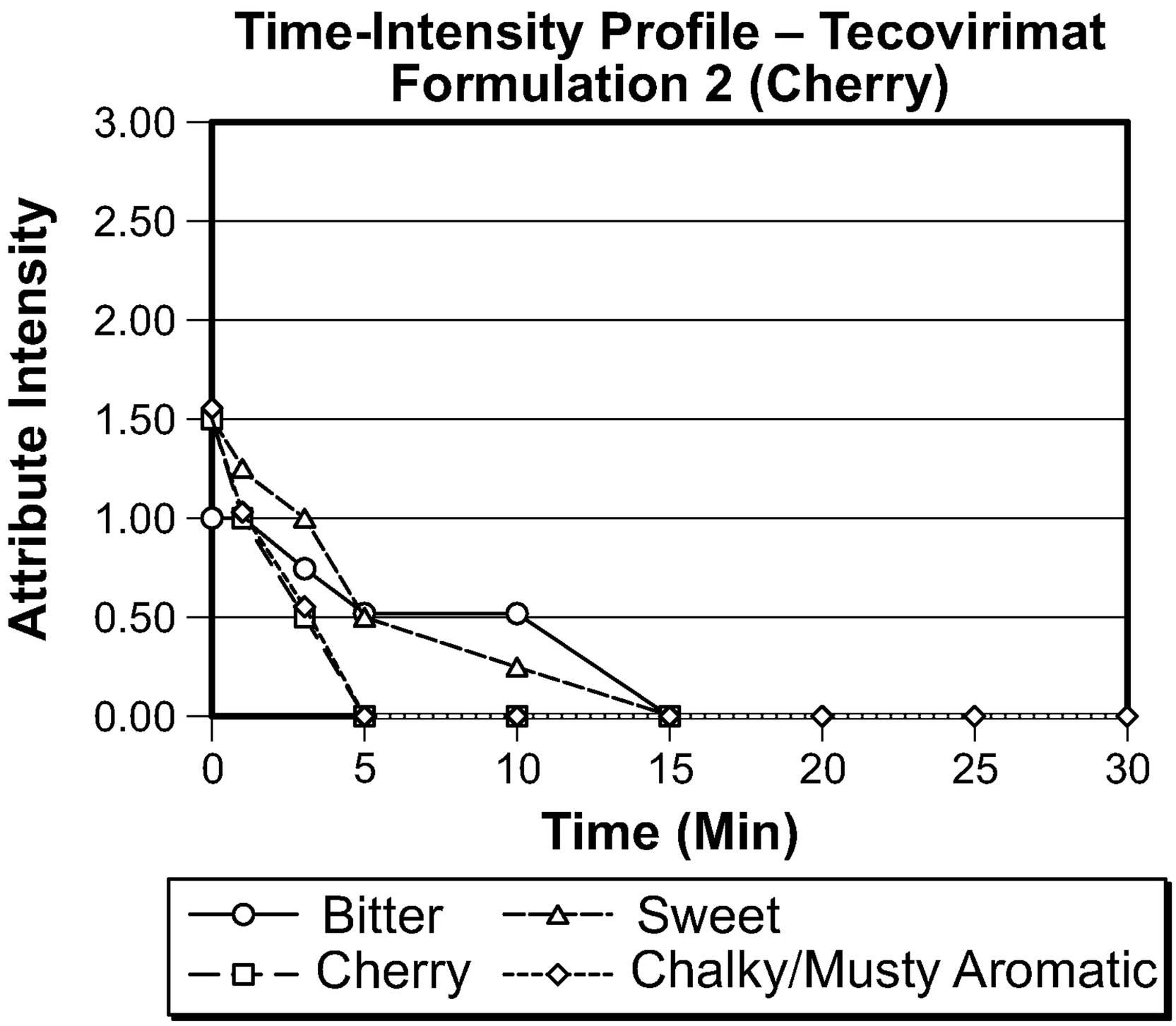

Time-Intensity Profile – Tecovirimat
Formulation 2 (Cherry)
Attribute Intensity
3.00
2.50
2.00
1.50
1.00
0.50
0.00
0
5
10
15
20
25
30
Time (Min)
Bitter
Sweet
Cherry
Chalky/Musty Aromatic

FIG. 15

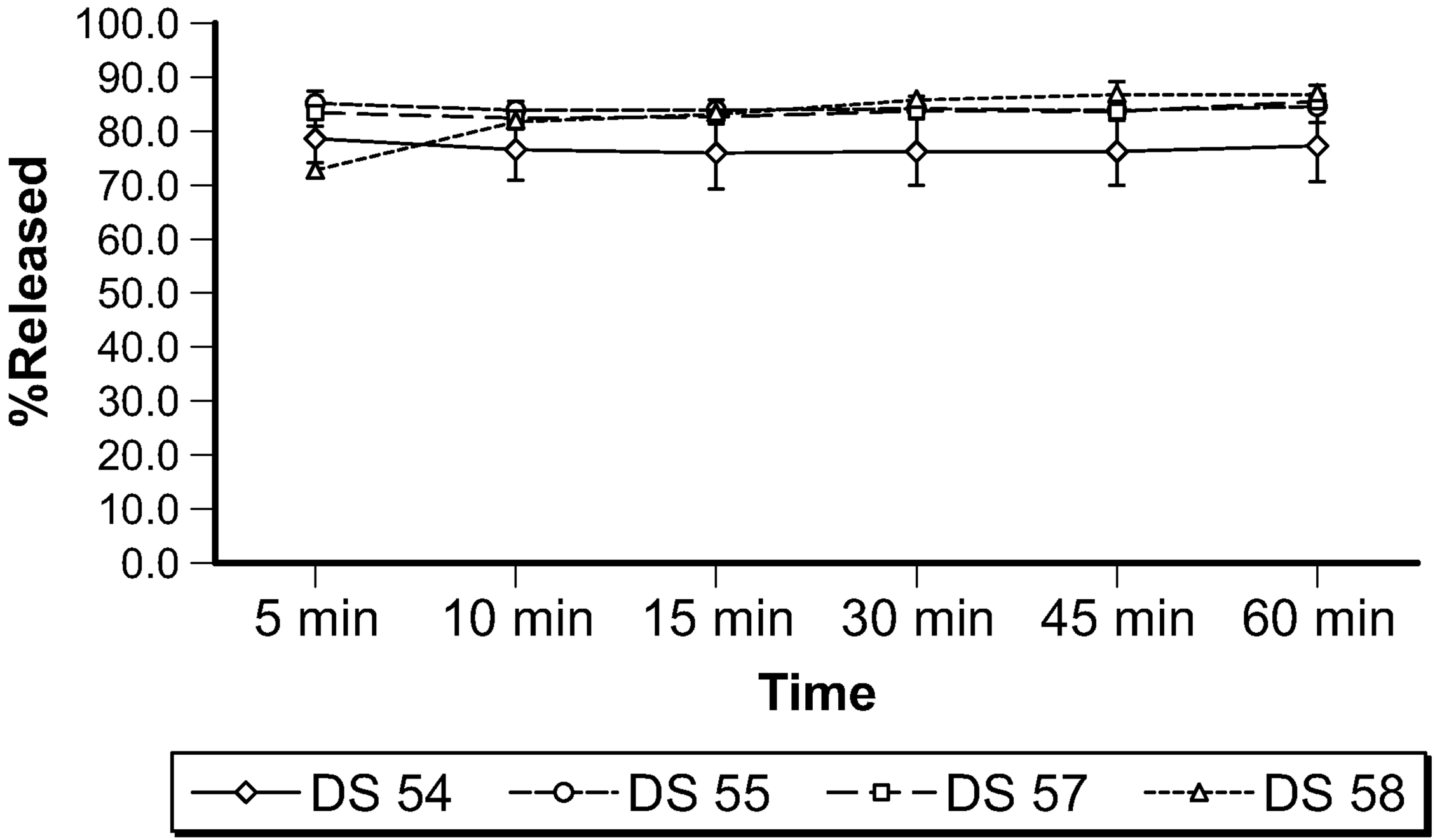

ST-246 Release from DS 54, 55, 57 and 58
%Released
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
5 min
10 min
15 min
30 min
45 min
60 min
Time
DS 54
DS 55
DS 57
DS 58

FIG. 1