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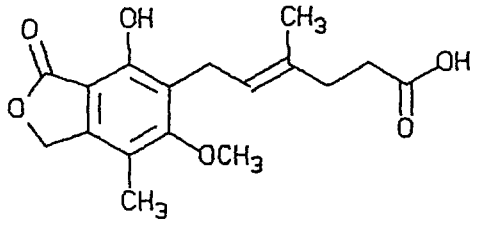
MYCOPHENOLATE MOFETIL HIGH DOSE ORAL SUSPENSIONS

Field of the Invention

The present invention relates to mycophenolate mofetil and mycophenolic acid, particularly to improved formulations thereof, and specifically to high dose oral suspension formulations. The invention is also directed to methods of manufacturing the formulations.

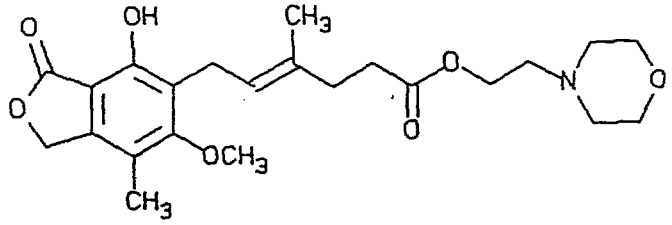
Background Information

Mycophenolic acid ("MPA") was initially described as a weakly-active antibiotic found in the fermentation broth of *Penicillium brevicompactum*, having the following structure:



Mycophenolic Acid

MPA and certain related compounds, such as mycophenolate mofetil (the morpholinoethyl ester of MPA), having the following structure:



Mycophenolate Mofetil

have more recently been described as having particularly advantageous therapeutic properties, e.g., as immunosuppressant drugs. See, for example, U.S. Patents Nos. 3,880,995; 4,727,069; 4,753,935; and 4,786,637, all incorporated herein by reference.

MPA and mycophenolate mofetil, notwithstanding the improved oral bioavailability characteristics of the latter, require daily doses on the order of 2.0 to as much as 3.5 or 4.0 grams per day (or even 5.0 grams per day in the case of MPA, for example as described in U.S. Patent No. 3,880,995) depending upon the patient and the disease state being treated. Using a conventional dosage formulation containing 250 mg in a standard size 1 (0.48 cc volume) capsule, a patient receiving a 3.0 gram daily dose is required to take twelve capsules each day, giving rise to patient convenience and compliance concerns.

Coarse dispersions, such as oral suspensions, contain a finely divided insoluble material suspended in a liquid medium. These are described, for example, in Remington's Pharmaceutical Sciences (Fifteenth

Ingredient	% wt/vol
mycophenolate mofetil	20
hydroxypropylmethylcellulose	0.25
microcrystalline cellulose	0.25
xanthan gum	0.1
sorbitol, 70% solution	30 - 50
Lycasin® (maltitol syrup)	10 - 30
sucrose	0 - 10
fructose	0 - 10
aspartame	0 - 0.5
lecithin	0 - 0.1
citric acid	0.02 - 0.25
sodium phosphate dibasic	0.19 - 0.67
methyl paraben	0 - 0.18
propyl paraben	0 - 0.02
flavor (selected from grape, (opt. w/anise), cherry, strawberry, or mint)	0.3 - 1.0
Magnasweet®	0 - 1
color(s) (selected from red 28, red 40, blue 1, blue 2, or green 3)	0.005
purified water	q.s. to 100

In another presently preferred aspect, the invention relates to a high dose oral suspension of mycophenolate mofetil having a composition as follows:

Ingredient	% wt/vol
mycophenolate mofetil	20
microcrystalline cellulose	0.25
xanthan gum	0.1
sorbitol, 70% solution	30 - 50
Lycasin® (maltitol syrup)	10 - 30
sucrose	0 - 10
fructose	0 - 10
aspartame	0 - 0.5
lecithin	0 - 0.5
citric acid	0.02 - 0.25
sodium phosphate dibasic	0.19 - 0.8
methyl paraben	0 - 0.18
propyl paraben	0 - 0.02
flavor (selected from grape (opt. w/anise), cherry, strawberry, mint, orange, berry, or mixed fruit)	0.1 - 3.0
Magnasweet®	0 - 1
color(s) (selected from red 28, red 40, red #3, yellow #6, blue 1, blue 2, or green 3)	0.005
purified water	q.s. to 100

In another aspect, the invention relates to a dry granulation formulation of mycophenolate mofetil for constitution with water to give a high dose oral suspension, having a composition as follows:

Ingredient	mg/mL*
mycophenolate mofetil or mycophenolic acid	75 - 300
suspending/viscosity agent	1 - 30
wetting agent	0 - 10
sweeteners	1 - 1200
flavor	0.1 - 100
flavor enhancer/bitter maskant	0 - 50
antimicrobial agent	0 - 10
color	0 - 2

(*concentration after constitution with water).

In a presently preferable aspect, the invention relates to a dry granulation formulation of mycophenolate mofetil for constitution with water to give a high dose oral suspension, having a composition as follows:

Ingredient	mg/mL*
mycophenolate mofetil	200
xanthan gum	1 - 1.5
collodial silicon dioxide	5 - 10
sorbitol	0 - 550
aspartame	0 - 3
soy lecithin	1 - 2
sodium methyl paraben	0 - 10
flavor ((selected from grape (opt. w/anise), cherry, strawberry, mint, orange, berry, or mixed fruit)	0.1 - 3.0
color (red, blue, and/or yellow to complement the flavor)	0.01 - 0.1

(*concentration after constitution with water).

DETAILED DESCRIPTION OF THE INVENTION

Definitions and General Parameters

The following definitions are set forth to illustrate and define the meaning and scope of the various terms used to describe the invention herein.

Reference to the active agent employed in the formulations of the present invention, "mycophenolate mofetil," is intended to include the pharmaceutically acceptable salts thereof.

The term "effective amount" means a dosage sufficient to provide treatment for the disease state being treated. This will vary depending on the patient, the disease and the treatment being effected.

The term "% wt/vol" or "percent weight/volume" refers to the amount of excipient and/or drug substance, measured by weight (grams), that is

contained in the final volume (milliliters) of a suspension. The amount of excipient and/or drug substance is expressed as a percent of the total, final volume of the liquid product.

Manufacturing Parameters

The term "q.s." means adding a quantity sufficient to achieve a stated function, e.g., to bring a solution to the desired volume (i.e., 100%).

Unless specified to the contrary, the procedures described herein take place at atmospheric pressure within a temperature range from 5°C to 100°C (preferably from 10°C to 50°C; most preferably at "room" or "ambient" temperature, e.g., 20°C).

Unless otherwise specified, the composition percentages, times and conditions are intended to be approximate, e.g., add about 10% wt/vol at about atmospheric pressure within a temperature range of about 5°C to about 100°C (preferably from about 10°C to about 50°C; most preferably about 20°C) over a period of about 1 to about 10 hours (preferably about 5 hours). Parameters given in the Examples are intended to be specific, not approximate.

Materials

Mycophenolate mofetil can be made as described in U.S. Patent No. 4,753,935, previously incorporated by reference. It is presently preferred to make mycophenolate mofetil as described in U.S. Patent No. 5,247,083, incorporated herein by reference. Mycophenolic acid is commercially available, e.g., from Sigma Chemical Company, St. Louis, MO. The sources of various excipients are disclosed below, e.g., where the material is not commonly available or when the product of a particular source is preferred.

Suspending and/or viscosity increasing agents useful in the formulations of the invention include, for example: hydroxypropyl methylcellulose (preferably USP: hydroxypropyl methylcellulose 2910); xanthan gum (preferably NF: xanthan gum, and most preferably Keltrol® CR, available from Kelco, San Diego, CA); microcrystalline cellulose (which is a colloidal suspending agent, preferably NF: microcrystalline cellulose, and most preferably Avicel® RC-591, available from FMC Corporation, Philadelphia, PA); sodium carboxymethylcellulose (preferably USP: carboxymethylcellulose sodium, or BP: carmellose sodium or sodium carboxymethylcellulose); and colloidal silicon dioxide (preferable NF: colloidal silicon dioxide, and more preferably Cab-o-sil® M-5, available from Cabot Corporation, Tuscola, IL).

Wetting agents useful in the formulations of the invention include, for example: lecithin (compendial or non-compendial soy lecithin) and poloxamer (available as pluronic F68 from BASF Wyandotte Corporation, Parsippany, NJ).

Sweeteners useful in the formulations of the invention include, for example: sorbitol, 70% solution (preferably USP: sorbitol solution); maltitol syrup (preferably USP or NF, most preferably Lycasin®, available

from Roquette Corporation, Gurnee, IL); sucrose (preferably NF or BP/EP); fructose (preferably USP); aspartame (preferably NF); xylitol (preferably compendial grade); mannitol (preferably USP or BP); sorbitol, powder (preferably NF or BP); maltitol, crystalline (non-compendial, or preferably Maltisorb® SF, available from Roquette Corporation, Gurnee, IL). In cases where there is a choice of physical form, the liquid sweeteners are preferably used for the suspension formulations, and the dry sweeteners are preferably used for the dry granulation. The sweeteners (except aspartame) can also function as viscosity-increasing agents and/or as antimicrobial preservatives).

Flavors useful in the formulations of the invention include, for example: mint, strawberry, cherry, orange, berry, mixed fruit, and grape (optionally mixed with anise). They are available from Tastemaker, Cincinnatti, OH; Crompton & Knowles Corporation, Mahwah, NJ; and International Flavors & Fragrances Inc., Camden, NJ.

Flavor enhancers (or bitter maskants) useful in the formulation of the invention include, for example Magnasweet® (available from MacAndrews & Forbes Company, Camden, N.J.).

Buffers useful in the formulations of the invention include as components, for example, citric acid (preferably USP) and sodium phosphate dibasic (preferably USP).

Antimicrobial agents useful in the formulations of the invention include, for example: sodium benzoate; sodium methyl paraben (preferably NF: sodium methyl paraben); methyl paraben (preferably NF: methyl paraben, or BP: methyl hydroxybenzoate, or EP: methylis parahydroxybenzoas); propylparaben (preferably NF: propylparaben, or BP/EP: propyl hydroxybenzoate); and potassium sorbate (preferably NF or BP).

Dyes (or colors) useful in the formulations of the invention include, for example: FD&C red 28, FD&C red 40, FD&C red 3, FD&C blue 1, FD&C blue 2, FD&C yellow 6, and FD&C green 3.

HIGH DOSE ORAL SUSPENSION

Composition

The high dose oral suspensions of the present invention have the following general composition:

Ingredient	% wt/vol
mycophenolate mofetil or mycophenolic acid	7.5 - 30.0
suspending/viscosity agent	0.1 - 3.0
wetting agent	0 - 0.5
sweeteners	30.0 - 70.0
flavor	0.1 - 2.0
flavor enhancer/bitter maskant	0 - 1.0
buffer	0.5 - 1.5
antimicrobial agent	0 - 10.0

color	0 - 0.01
purified water	q.s. to 100

Particularly when the active agent is MPA, pH must be kept below 7.0 to avoid dissolution.

Presently preferred oral suspensions of the invention have the following composition:

Ingredient	% wt/vol
mycophenolate mofetil	20
hydroxypropylmethylcellulose	0.25
microcrystalline cellulose	0.25
xanthan gum	0.1
sorbitol, 70% solution	30 - 50
Lycasin® (maltitol syrup)	10 - 30
sucrose	0 - 10
fructose	0 - 10
aspartame	0 - 0.5
lecithin	0 - 0.1
citric acid	0.02 - 0.25
sodium phosphate dibasic	0.19 - 0.67
methyl paraben	0 - 0.18
propyl paraben	0 - 0.02
flavor	0.3 - 1.0
Magnasweet®	0 - 1
color	0.005
purified water	q.s. to 100

Presently more preferred oral suspension of the invention have the following composition:

Ingredient	% wt/vol
mycophenolate mofetil	20
microcrystalline cellulose	0.2
xanthan gum	0.1
sorbitol, 70% solution	30 - 50
Lycasin® (maltitol syrup)	10 - 30
sucrose	0 - 10
fructose	0 - 10
aspartame	0 - 0.5
lecithin	0 - 0.5
citric acid	0.02 - 0.25
sodium phosphate dibasic	0.19 - 0.8
methyl paraben	0 - 0.18
propyl paraben	0 - 0.02
flavor	0.1 - 1.0
Magnasweet®	0 - 1
color	0.005

purified water	q.s. to 100

Manufacturing Method

1. To heated water (about 70°C), the antimicrobial agent was added and dispersed, followed by the suspending and/or viscosity agents (preferably microcrystalline cellulose, followed by xanthan gum).
2. With mixing, the buffer(s) (preferably citric acid, followed by sodium phosphate dibasic) were dissolved, followed by sweetener(s), wetting agent(s), dye(s), flavor enhancer(s), and flavor(s).
3. The active compound (mycophenolate mofetil or mycophenolic acid) was added to the mixture from step 2; the liquid was mixed well to form a suspension.

DRY GRANLUATION FORMULATION

Composition

The dry granulation formulations of the present invention have the following general composition:

Ingredient	mg/mL*
mycophenolate mofetil or mycophenolic acid	75 - 300
suspending/viscosity agent	10 - 30
wetting agent	3 - 10
sweeteners	200 - 1200
flavor	3 - 100
flavor enhancer/bitter maskant	0 - 50
antimicrobial agent	0 - 10
color	0 - 2

(*concentration after constitution with water)

A presently preferred dry granulation formulation has the following composition:

Ingredient	mg/mL*
mycophenolate mofetil	200
sodium carboxymethylcellulose	20
sucrose	0 - 700
fructose	0 - 700
xylitol	0 - 700
mannitol	0 - 1200
sorbitol	0 - 1080
maltitol	0 - 740
pluronic F68	4 - 8
flavor	10
potassium sorbate	0 - 1
color	0 - 1

(*concentration after constitution with water)

A presently more preferred dry granulation formulation has the following composition:

Ingredient	mg/mL*
mycophenolate mofetil	200
xanthan gum	1 - 1.5
colloidal silicon dioxide	5 - 10
sucrose	0 - 700
fructose	0 - 700
xylitol	0 - 700
mannitol	0 - 1200
sorbitol	0 - 1080
maltitol	0 - 740
soy lecithin	1 - 2
flavor	1 - 10
sodium methyl paraben	0 - 10
color	0 - 1

(*concentration after constitution with water)

Manufacturing Method

1. Mycophenolate mofetil, sweetener(s), wetting agent(s), and suspending and/or viscosity increasing agent(s) were weighed and combined in a mixer.
2. The dye(s) and buffer(s) were dissolved in water.
3. The solution of step (2) was added to the mixer bowl of step (1), until a desired granulation size was obtained.
4. The granulation was dried then milled to reduce particle size.
5. Using a blender, the suspending and/or viscosity increasing agent(s), flavor(s) and antimicrobial agent(s) were added.

When used as a pharmaceutical formulation to administer mycophenolate mofetil or mycophenolic acid, for example, the dry granulation formulation is added to water in an appropriate container. The container is then sealed, shaken to give a suspension, and administered orally.

Alternatively, the granulation is provided in a container, such that when constituted with an appropriate volume of water a supply of drug in suspension is provided for an extended period of time (e.g., 90 grams of mycophenolate mofetil provided in a bottle marked to be filled with purified water to a final volume of 450 mL, provides a 30 day supply).

Preferred Formulations

Presently preferred are the following formulations.

Ingredient	% wt/vol
mycophenolate mofetil	20
hydroxypropyl methylcellulose	0.25
microcrystalline cellulose	0.25

xanthan gum	0.1
sorbitol solution	50
sucrose	10
Lycasin®	10
lecithin	0.1
methyl paraben	0.036
propylparaben	0.004
grape	1.0
anise	0.01
color (red 28: blue 1, 90:10)	0.005
citric acid	0.0542
sodium phosphate dibasic	0.673
purified water	q.s. to 100

adjusted to a pH of 7, as a liquid suspension suitable for oral administration.

Ingredient	% wt/vol
mycophenolate mofetil	20
microcrystalline cellulose	0.2
xanthan gum	0.1
sorbitol solution	50
sucrose	10
Lycasin® (maltitol syrup)	10
soy lecithin	0.1
methyl paraben	0.04 - .1
mixed fruit	<0.3
color (to complement the flavor)	0.005
citric acid	0.06
sodium phosphate dibasic	0.7
purified water	q.s. to 100

adjusted to a pH of 7, as a liquid suspension suitable for oral administration.

Ingredient	mg
mycophenolate mofetil	90,000
sodium carboxymethylcellulose	9,000
mannitol	180,000
aspartame	1,575
pluronic F68	1,800
potassium sorbate	225
cherry	4,500
color (red 40:blue 1, 90:10)	4.5

in a container marked to be filled with purified water to a final predetermined volume of 450 mL.

Ingredient	mg
mycophenolate mofetil	90,000
xanthan gum	450

colloidal silicon dioxide	2,250
soy lecithin	450
sorbitol	247,500
aspartame	225
sodium methyl paraben	900
berry flavor	1,350
color (FD&C red #3	13.5
FD&C blue #1	2.7

in a container marked to be filled with purified water to a final predetermined volume of 450 mL.

Ingredient	mg
mycophenolate mofetil	90,000
xanthan gum	450
colloidal silicon dioxide	2,250
soy lecithin	450
sorbitol	135,000
aspartame	450
citric acid	225
sodium citrate	4,500
sodium methyl paraben	900
berry flavor	1,350
color (FD&C red #3	13.5
FD&C blue #1	2.7

in a container marked to be filled with purified water to a final predetermined volume of 450 mL.

Ingredient	mg
mycophenolate mofetil	90,000
xanthan gum	675
colloidal silicon dioxide	4,500
soy lecithin	900
aspartame	900
sodium methyl paraben	1,035
mixed fruit flavor	900
color (FD&C red #3	3.6
FD&C yellow #6)	0.9

in a container marked to be filled with purified water to a final predetermined volume of 450 mL.

Ingredient	mg
mycophenolate mofetil	90,000
xanthan gum	450
colloidal silicon dioxide	2,250
soy lecithin	450
sorbitol	247,500
aspartame	225
citric acid	225

sodium citrate	4,500
sodium methyl paraben	1,035
mixed fruit flavor	900
color (FD&C red #3	2.79
FD&C yellow #6)	0.675

in a container marked to be filled with purified water to a final predetermined volume of 450 mL.

Ingredient	mg
mycophenolate mofetil	90,000
xanthan gum	675
colloidal silicon dioxide	4,500
soy lecithin	900
aspartame	900
citric acid	225
sodium citrate	4,500
sodium methyl paraben	450
orange flavor	450
color (FD&C yellow #6)	45

in a container marked to be filled with purified water to a final predetermined volume of 450 mL.

Testing, Administration and Utility

Testing

The following tests are performed to evaluate the suitability of formulation combinations made in accordance with the present invention. The testing procedures are known by those skilled in the art.

1. Time to constitute (for a dry granulation).
2. Ease of resuspendability of solid(s).
3. Appearance.
4. Amount of drug dissolved in continuous aqueous phase.
5. Chemical stability (percent label strength of drug substance).
6. % Degradant(s) formed (e.g. mycophenolic acid from a suspension of mycophenolate mofetil).
7. Viscosity.
8. Density.
9. Freeze/thaw (aggregate formation).
10. Sedimentation rate.
11. Sedimentation volume.
12. Homogeneity of drug substance.
13. Particle size.
14. Antimicrobial efficacy (USP/BP test).
15. Gravitational and vibrational stresses (simulated shipping).

The following tests are performed to evaluate the acceptability of formulations made in accordance with the present invention. The testing

procedures are known by those skilled in the art.

1. Ease of resuspendability of solid(s).
2. Appearance.
3. Chemical stability (percent label strength of drug substance).
4. % Degradant(s) formed over time.
5. Viscosity.
6. Density.
7. Homogeneity of drug substance.
8. Particle size.
9. Antimicrobial efficacy (USP/BP test).

Criteria for acceptability include those set forth below.

Ease of resuspendability -- The suspension sediment should be loosely packed such that after minimal shaking the sediment redisperses and reforms the original suspension. From a practical standpoint, any sediment should redisperse within 10 seconds of minimal hand shaking.

Appearance -- In a freshly prepared suspension, all solids should be evenly and homogeneously dispersed in the liquid phase. Over time, sedimentation will occur; and ideally, the volume of sediment should encompass the volume of suspension. If the sediment volume is less than the volume of suspension, the supernatant which forms should be clear (indicating a flocculated system).

Chemical Stability -- The amount of drug substance must remain within 90 - 110% of the intended labelled concentration.

% Degradant(s) formed over time -- The formation of no more than 5% degradant(s) over a period of 2 years is considered acceptable.

Viscosity -- The viscosity should be sufficiently high to hinder rapid sedimentation. However, too high a viscosity is not acceptable from a user's standpoint. An acceptable range is about 200 - 1000 centipoise, with a preferred range of 250 - 500 centipoise.

Density -- Ideally, the density of the vehicle will equal the density of the dispersed solids (drug substance); matching vehicle and drug densities will hinder sedimentation. An acceptable range for the formulations of the present invention is 1.10 - 1.25 g/mL.

Homogeneity -- After minimal hand shaking of the package containing suspension, the amount of drug substance present at the top, middle, and bottom of the packaged suspension, will be equivalent within 10%.

Particle Size -- Over time the mean particle size of the suspension will remain within 20% of the mean particle size of freshly prepared suspension.

Antimicrobial Efficacy -- The suspension will be tested for antimicrobial efficacy via the methods provided in the USP and BP. To be acceptable, the suspension must pass these tests according to the respective specifications.

The formulations of the invention are satisfactory when subjected to the foregoing tests. As will be apparent from the present specification to those skilled in the art, the selection of particular ingredients and their relative concentrations will modify the characteristics balances of the resulting formulations. For example, a 200 mg/mL of mycophenolate mofetil can be suspended in Ora-Plus™ combined with Ora-Sweet™, but, the characteristics balance of the resulting formulation is unacceptably viscous and expected to have too much drug dissolved in the continuous aqueous phase giving rise to increased degradant formation and loss of chemical stability (given the pH of the vehicles, i.e., below 5.0, the lowest acceptable pH for mycophenolate mofetil in the present formulations).

Administration

The formulations of the present invention are useful for oral administration in any oral treatment regimen for mycophenolate mofetil or mycophenolic acid. While human dosage levels have yet to be finalized, generally, a daily dose of mycophenolate mofetil or mycophenolic acid is from about 2.0 to 5.0 grams, preferably about 2.0 to 3.5 grams. The amount of active compound administered will, of course, be dependent on the subject and disease state being treated, the severity of the affliction, the manner and schedule of administration and the judgment of the prescribing physician. For example, a treatment regimen for administering 3.0 grams of mycophenolate mofetil per day, which previously entailed taking 12 capsules (250 mg) (e.g., six, twice daily), when administered with a formulation of the present invention entails taking one 7.5 mL dose (e.g., a spoonfull) twice daily. The formulations of the present invention are also particularly well suited to administration via gastric lavage.

Utility

The formulations of the present invention are useful for the administration of mycophenolate mofetil or mycophenolic acid (the "compounds") as immunosuppressive agents, anti-inflammatory agents, anti-tumor agents, anti-proliferative agents, anti-viral agents and anti-psoriatic agents (as discussed in greater detail below) in mammals, whether domestic (cattle, pigs, sheep, goats, horses), pets (cats, dogs), or preferably humans. The compounds are inhibitors of inosine monophosphate dehydrogenase (IMPDH) and thus inhibit *de novo* purine synthesis; they have anti-proliferative effects (e.g., against smooth muscle cells and both B and T lymphocytes) and inhibit antibody formation and the glycosylation of cell adhesion molecules in lymphocytes and endothelial cells.

As immunosuppressive agents, the compounds are useful in treating auto-immune related disorders, for example: Type I Diabetes Mellitus; Inflammatory Bowel Disease (e.g., Crohn's Disease and Ulcerative Colitis); Systemic Lupus Erythematosus; Chronic Active Hepatitis; Multiple Sclerosis; Grave's Disease; Hashimoto's Thyroiditis; Behcet's Syndrome; Myasthenia Gravis; Sjogren's Syndrome; Pernicious Anemia; Idiopathic Adrenal

Insufficiency; and Polyglandular Autoimmune Syndromes Type I and II.

The compounds are also useful as therapeutic immunosuppressive agents in the treatment of Asthma, Immunohemolytic Anemia, Glomerulonephritis, and Hepatitis. Preventative uses of the compounds as immunosuppressive agents include the treatment of allograft rejection, for example, in cardiac, lung, pancreatic, renal, liver, skin and corneal allografts, and prevention of Graft vs. Host Disease.

The compounds are useful for inhibiting proliferative responses to vascular injury, for example, stenosis following an insult to a blood vessel wall in post-angioplasty restenosis, and post-cardiac by-pass surgery restenosis.

The compounds are useful as anti-inflammatory agents, for example, in treating Rheumatoid Arthritis, Juvenile Rheumatoid Arthritis and Uveitis.

As anti-tumor agents, the compounds are useful in treating solid tumors and malignancies of lymphoreticular origin. For example, the compounds' utility for treatment of solid tumors includes: cancers of the head and neck, including squamous cell carcinoma; lung cancer, including small cell and non-small cell lung carcinoma; mediastinal tumors; esophageal cancer, including squamous cell carcinoma and adenocarcinoma; pancreatic cancer; cancer of the hepatobiliary system, including hepatocellular carcinoma, cholangiocarcinoma, gall bladder carcinoma and biliary tract carcinoma; small intestinal carcinoma, including adenocarcinoma, sarcoma, lymphoma and carcinoids; colorectal cancer, including colon carcinoma and rectal carcinoma; metastatic carcinoma; cancers of the genitourinary system, including ovarian cancer, uterine sarcoma, and renal cell, ureteral, bladder, prostate, urethral, penile, testicular, vulvar, vaginal, cervical, endometrial, and fallopian tube carcinoma; breast cancer; endocrine system cancer; soft tissue sarcomas; malignant mesotheliomas; skin cancer, including squamous cell carcinoma, basal cell carcinoma and melanoma; cancer of the central nervous system; malignant bone tumors; and plasma cell neoplasms.

As anti-tumor agents for the treatment of malignancies of lymphoreticular origin, the compounds are useful in treating, for example: Lymphomas and Leukemias, including B, T and promonocyte cell line malignancies, Mycoses Fungoides, Non-Hodgkins Lymphoma, Malignancies of Burkitt Lymphoma Cells and other EBV-transformed B-lymphocytes, Lymphomas resulting from Epstein-Barr viral infections in allograft recipients, Chronic Lymphocytic Leukemia, Acute Lymphocytic Leukemia and Hairy Cell Leukemia.

As anti-viral agents, the compounds are useful in treating, for example: retroviruses, including Human T-leukemia Viruses, Types I and II (HTLV-1 and HTLV-2), Human Immuno Deficiency Viruses, Types I and II (HIV-1, HIV-2) and, Human Nasopharyngeal Carcinoma Virus (NPCV) and in treating Herpes Viruses, including EBV infected B-lymphocytes, CMV infection, Herpes Virus Type 6, Herpes Simplex, Types 1 and 2, (HSV-1,

HSV-2) and Herpes Zoster.

As anti-psoriatic agents, the compounds are useful in treating, for example, psoriasis and psoriatic arthritis.

EXAMPLES

The following preparations and examples are given to enable those skilled in the art to more clearly understand and to practice the present invention. They should not be considered as limiting the scope of the invention, but merely as being illustrative and representative thereof.

EXAMPLES 1-24

These examples illustrate the preparation of high dose oral suspension formulations. In each Example, the formulation was manufactured by one of the following alternative methods:

A. 1. To heated water, hydroxypropylmethylcellulose was added and dispersed.

2. Microcrystalline cellulose was added to the dispersion of #1 and dispersed.

3. Xanthan gum was added to the mixture of #2 and dispersed.

4. The sweeteners, flavors, color dyes and lecithin were added individually to the mixture of #3 with mixing.

5. In a small separate aliquot of water, citric acid and sodium phosphate dibasic were dissolved, then added to the mixture of step 4, adjusting pH as indicated.

6. In a small separate aliquot of water (heated to 80°C), methyl paraben and propylparaben were dissolved, then added to the mixture of step 5.

7. Mycophenolate mofetil was added to the mixture of step 6 and mixed well to form a suspension suitable for oral administration.

B. 1. To heated water (70 - 75°C), sodium methyl paraben was dissolved with mixing.

2. Microcrystalline cellulose was added to the dispersion of #1 and dispersed.

3. The sorbitol solution was added and mixed to the dispersion of #2. Xanthan gum was added to the mixture and dispersed. This was followed by addition of the maltitol solution with mixing.

4. In a separate vessel containing purified water, citric acid was added and dissolved, followed by the addition and dissolution of sodium phosphate dibasic, anhydrous. This was followed by the dissolution of sucrose and the addition and dispersion of soy lecithin. Mycophenolate mofetil was added and dispersed.

5. The dispersions of steps 3 and 4 were combined and mixed.

6. A stock solution of the dye was prepared. The dye and flavor were added to the dispersion of step 5, with mixing.

7. The dispersion of step 6 was brought to volume with purified water,

as necessary.

EXAMPLE 1

Ingredient	wt/vol %
Mycophenolate mofetil	20
Hydroxypropylmethylcellulose	0.25
Microcrystalline cellulose	0.25
Xanthan gum	0.1
Sorbitol, 70% solution	50
Sucrose	10
Lycasin® (maltitol syrup)	10
Lecithin	0.1
Methyl paraben	0.036
Propyl paraben	0.004
Grape flavor	1.0
Anise flavor	0.01
Color (red 28:blue 1, 90:10)	0.005
Buffer	
Citric acid	0.241
Sodium phosphate dibasic	0.547
Purified water	pH 6 q.s. to 100

EXAMPLE 2

Ingredient	wt/vol %
Mycophenolate mofetil	20
Hydroxypropylmethylcellulose	0.25
Microcrystalline cellulose	0.25
Xanthan gum	0.1
Sorbitol, 70% solution	50
Sucrose	10
Lycasin® (maltitol syrup)	10
Lecithin	0.1
Methyl paraben	0.036
Propyl paraben	0.004
Grape flavor	1.0
Anise flavor	0.01
Color (red 28:blue 1, 90:10)	0.005
Buffer	
Citric acid	0.0542
Sodium phosphate dibasic	0.673
Purified water	pH 7 q.s. to 100

EXAMPLE 3

Ingredient	wt/vol %
Mycophenolate mofetil	20
Hydroxypropylmethylcellulose	0.25
Microcrystalline cellulose	0.25
Xanthan gum	0.1
Sorbitol, 70% solution	50
Sucrose	10
Lycasin® (maltitol syrup)	10
Grape flavor	1.0
Anise flavor	0.01
Color (red 28:blue 1, 90:10)	0.005
Buffer	
Citric acid	0.0542
Sodium phosphate dibasic	0.673
	pH 7
Purified water	q.s. to 100

EXAMPLE 4

Ingredient	wt/vol %
Mycophenolate mofetil	20
Hydroxypropylmethylcellulose	0.2
Microcrystalline cellulose	0.2
Xanthan gum	0.075
Sorbitol, 70% solution	50
Sucrose	10
Lycasin® (maltitol syrup)	10
Lecithin	0.1
Grape flavor	1.0
Anise flavor	0.01
Color (red 28:blue 1, 90:10)	0.005
Buffer	
Citric acid	0.0962
Sodium phosphate dibasic	0.219
	pH 6
Purified water	q.s. to 100

EXAMPLE 5

Ingredient	wt/vol %
Mycophenolate mofetil	20
Hydroxypropylmethylcellulose	0.25
Microcrystalline cellulose	0.25
Xanthan gum	0.1
Sorbitol, 70% solution	50
Sucrose	10
Lycasin® (maltitol syrup)	10

Lecithin	0.1
Grape flavor	1.0
Anise flavor	0.01
Color (red 28:blue 1, 90:10)	0.005
Buffer	
Citric acid	0.0217
Sodium phosphate dibasic	0.269
	pH 7
Purified water	q.s. to 100

EXAMPLE 6

Ingredient	wt/vol %
Mycophenolate mofetil	20
Hydroxypropylmethylcellulose	0.35
Microcrystalline cellulose	0.3
Xanthan gum	0.125
Sorbitol, 70% solution	30
Sucrose	10
Lycasin® (maltitol syrup)	30
Grape flavor	0.75
Anise flavor	0.01
Color (red 28:blue 1, 90:10)	0.005
Buffer	
Citric acid	0.0217
Sodium phosphate dibasic	0.269
	pH 7
Purified water	q.s. to 100

EXAMPLE 7

Ingredient	wt/vol %
Mycophenolate mofetil	20
Hydroxypropylmethylcellulose	0.25
Microcrystalline cellulose	0.25
Xanthan gum	0.1
Sorbitol, 70% solution	30
Sucrose	10
Lycasin® (maltitol syrup)	30
Lecithin	0.1
Grape flavor	1.0
Anise flavor	0.01
Magnasweet®	0.2
Color (red 28:blue 1, 90:10)	0.005
Buffer	
Citric acid	0.142
Sodium phosphate dibasic	0.438

	pH 6
Purified water	q.s. to 100

EXAMPLE 8

Ingredient	wt/vol %
Mycophenolate mofetil	20
Hydroxypropylmethylcellulose	0.25
Microcrystalline cellulose	0.25
Xanthan gum	0.1
Sorbitol, 70% solution	30
Lycasin® (maltitol syrup)	10
Aspartame	0.5
Lecithin	0.1
Grape flavor	1.0
Anise flavor	0.01
Color (red 28:blue 1, 90:10)	0.005
Buffer	
Citric acid	0.0217
Sodium phosphate dibasic	0.269
	pH 7
Purified water	q.s. to 100

EXAMPLE 9

Ingredient	wt/vol %
Mycophenolate mofetil	20
Hydroxypropylmethylcellulose	0.25
Microcrystalline cellulose	0.25
Xanthan gum	0.1
Sorbitol, 70% solution	30
Sucrose	10
Lycasin® (maltitol syrup)	30
Lecithin	0.1
Grape flavor	1.0
Anise flavor	0.01
Color (red 28:blue 1, 90:10)	0.005
Buffer	
Citric acid	0.136
Sodium phosphate dibasic	0.192
	pH 5
Purified water	q.s. to 100

EXAMPLE 10

Ingredient	wt/vol %
Mycophenolate mofetil	20
Hydroxypropylmethylcellulose	1

Microcrystalline cellulose	0.25
Sorbitol, 70% solution	50
Sucrose	10
Lycasin® (maltitol syrup)	10
Lecithin	0.1
Grape flavor	1.0
Anise flavor	0.01
Magnasweet®	1
Color (red 28:blue 1, 90:10)	0.005
Buffer	
Citric acid	0.0217
Sodium phosphate dibasic	0.192
	pH 7
Purified water	q.s. to 100

EXAMPLE 11

Ingredient	wt/vol %
Mycophenolate mofetil	20
microcrystalline cellulose	0.2
xanthan gum	0.1
Sorbitol, 70% solution	50
Sucrose	10
Lycasin® (maltitol syrup)	10
soy Lecithin	0.1
citric acid	0.06
sodium phosphate dibasic (pH 7)	0.7
methyl paraben	0.04 - 0.1
flavor	<0.3
Color (to complement the flavor)	0.005
Purified water	q.s. to 100

EXAMPLE 12

This example illustrates the preparation of a dry granulation of the invention.

Ingredient	mg
mycophenolate mofetil	3,000
sodium carboxymethylcellulose	300
sorbitol, powder	3,000
xylitol	2,000
maltitol	2,000
pluronic F68	60
mint	150
FD&C green 3	0.1

The above ingredients are combined and blended to a homogeneous

Microcrystalline cellulose	0.25
Sorbitol, 70% solution	50
Sucrose	10
Lycasin® (maltitol syrup)	10
Lecithin	0.1
Grape flavor	1.0
Anise flavor	0.01
Magnasweet®	1
Color (red 28:blue 1, 90:10)	0.005
Buffer	
Citric acid	0.0217
Sodium phosphate dibasic	0.192
	pH 7
Purified water	q.s. to 100

EXAMPLE 11

Ingredient	wt/vol %
Mycophenolate mofetil	20
microcrystalline cellulose	0.2
xanthan gum	0.1
Sorbitol, 70% solution	50
Sucrose	10
Lycasin® (maltitol syrup)	10
soy Lecithin	0.1
citric acid	0.06
sodium phosphate dibasic (pH 7)	0.7
methyl paraben	0.04 - 0.1
flavor	<0.3
Color (to complement the flavor)	0.005
Purified water	q.s. to 100

EXAMPLE 12

This example illustrates the preparation of a dry granulation of the invention.

Ingredient	mg
mycophenolate mofetil	3,000
sodium carboxymethylcellulose	300
sorbitol, powder	3,000
xylitol	2,000
maltitol	2,000
pluronic F68	60
mint	150
FD&C green 3	0.1

The above ingredients are combined and blended to a homogeneous

mixture, with the addition of adequate purified water to give a desired granule size. The mixture is granulated and then dried to give a dry granulation suitable for use as a pharmaceutical formulation by the addition of 15mL purified water followed by shaking to form a suspension having 3.0 grams of mycophenolate mofetil in 15 mL.

EXAMPLE 13

This example illustrates a dry granulation of the invention.

Ingredient	mg
mycophenolate mofetil	2,000
sodium carboxymethylcellulose	200
mannitol	4,000
aspartame	35
pluronic F68	40
cherry	100
FD&C red 40	0.1
FD&C blue 1	0.01

EXAMPLE 14

This example illustrates a dry granulation of the invention.

Ingredient	mg
mycophenolate mofetil	2,000
sodium carboxymethylcellulose	200
sorbitol, powder	10,000
pluronic F68	40
cherry	100
FD&C red 40	0.1
FD&C blue 1	0.01

EXAMPLE 15

This example illustrates a dry granulation of the invention.

Ingredient	mg
mycophenolate mofetil	2,000
sodium carboxymethylcellulose	200
mannitol	4,000
aspartame	35
potassium sorbate	5
pluronic F68	40
cherry	100
FD&C red 40	0.1
FD&C blue 1	0.01

EXAMPLE 16

This example illustrates a dry granulation of the invention.

Ingredient	mg
mycophenolate mofetil	3,000
xanthan gum	15
colloidal silicon dioxide	75
soy lecithin	15
sorbitol	8,250
aspartame	7.5
sodium methyl paraben	30
berry flavor	45
color (FD&C red #3	0.45
FD&C blue #1	0.09

in a container marked to be filled with purified water to a final predetermined volume of 15 mL.

EXAMPLE 17

Ingredient	mg
mycophenolate mofetil	3,000
xanthan gum	15
colloidal silicon dioxide	75
soy lecithin	15
sorbitol	4,500
aspartame	15
citric acid	67.5
sodium citrate	150
sodium methyl paraben	30
berry flavor	45
color (FD&C red #3	0.45
FD&C blue #1	0.09

in a container marked to be filled with purified water to a final predetermined volume of 15 mL.

EXAMPLE 18

Ingredient	mg
mycophenolate mofetil	3,000
xanthan gum	15
colloidal silicon dioxide	75
soy lecithin	15
sorbitol	8,250
aspartame	7.5
citric acid	7.5
sodium citrate	150
sodium methyl paraben	34.5
mixed fruit flavor	30
color (FD&C red #3	0.093
FD&C yellow #6)	0.0225

in a container marked to be filled with purified water to a final predetermined volume of 15 mL.

EXAMPLE 19

Ingredient	mg
mycophenolate mofetil	2,000
sodium carboxymethylcellulose	200
mannitol	4,000
aspartame	35
potassium sorbate	5
pluronic F68	40
cherry	100
FD&C red 40	0.1
FD&C blue 1	0.01

EXAMPLE 20

This example illustrates a dry granulation of the invention, provided as in a container marked to be filled with purified water to a final predetermined volume of 450 mL.

Ingredient	mg
mycophenolate mofetil	90,000
sodium carboxymethylcellulose	9,000
mannitol	180,000
aspartame	1,575
pluronic F68	1,800
potassium sorbate	225
cherry	4,500
color (red 40:blue 1, 90:10)	4.5

EXAMPLE 21

This example illustrates the preparation of a dry granulation formulation of the invention.

Ingredient	mg/ml*
mycophenolate mofetil	200.0
xanthan gum	1.0
colloidal silicon dioxide	5.0
soy lecithin	1.0
sorbitol	300.0
aspartame	1.0
citric acid	0.5
sodium citrate	10.0
sodium methyl paraben	2.0
berry flavor	3.0
color (FD&C red #3	0.034
FD&C blue #1)	0.006

(*concentration after constitution with water)

To prepare the dry granulation mycophenolate mofetil, sorbitol, aspartame, soy lecithin, and xanthan gum were combined in a mixer for 5 minutes. The dye was dissolved with sodium citrate, and citric acid in purified water at approximately 45-55°C. The solution was then cooled to room temperature. This dye/buffer solution was added to the mycophenolate mofetil mixture in a cooled mixer bowl at a rate of approximately 60 ml/min with mixing. In the granulation temperature exceeds 30°C, mixing was stopped and the granulation allowed to cool to 20-24°C. Once the granulation temperature reached 20-24°C, it was mixed for an additional 2 to 8 minutes and then dried. If necessary the granulation was milled to reduce particle size. Colloidal silicon dioxide, flavor and sodium methyl paraben were then added using a blender.

EXAMPLE 22

This example illustrates the preparation of a dry granulation formulation of the invention.

Ingredient	mg/ml*
mycophenolate mofetil	200.0
xanthan gum	1.5
colloidal silicon dioxide	10.0
soy lecithin	2.0
aspartame	2.0
citric acid	0.5
sodium citrate	10.0
sodium methyl paraben	1.0
orange flavor	1.0
color (FD&C yellow #6)	0.1

(*concentration after constitution with water)

EXAMPLE 23

This example illustrates the preparation of a dry granulation formulation of the invention.

Ingredient	mg/ml*
mycophenolate mofetil	200.0
xanthan gum	1.0
colloidal silicon dioxide	5.0
soy lecithin	1.0
sorbitol	550.0
aspartame	0.5
sodium methyl paraben	2.0
berry flavor	3.0
color (FD&C red #3	0.034
FD&C blue #1)	0.006

(*concentration after constitution with water)

EXAMPLE 24

This example illustrates the preparation of a dry granulation formulation of the invention.

Ingredient	mg/ml*
mycophenolate mofetil	200.0
xanthan gum	1.5
colloidal silicon dioxide	10.0
soy lecithin	2.0
aspartame	2.0
sodium methyl paraben	2.3
mixed fruit flavor	2.0
color (FD&C red #3	0.008
FD&C yellow #6)	0.002

(*concentration after constitution with water)

EXAMPLE 25

This example illustrates the preparation of a dry granulation formulation of the invention.

Ingredient	mg/ml*
mycophenolate mofetil	200.0
xanthan gum	1.0
colloidal silicon dioxide	5.0
soy lecithin	1.0
sorbitol	550.0
aspartame	0.5
citric acid	0.5
sodium citrate	10.0
sodium methyl paraben	2.3
mixed fruit flavor	2.0
color (FD&C red #3	0.0062
FD&C yellow #6)	0.0015

(*concentration after constitution with water)

EXAMPLES 26-50

By following the procedures of Examples 1-25 and substituting mycophenolate mofetil with mycophenolic acid, there are obtained the corresponding respective suspensions and dry granulations.

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 claims appended hereto. All patents and publications cited above are hereby incorporated by reference.

* C L M S *

WHAT IS CLAIMED IS:

1. A pharmaceutical formulation comprising:

Ingredient	% wt/vol
mycophenolate mofetil or mycophenolic acid	7.5 - 30.0
suspending/viscosity agent	0.1 - 3.0
wetting agent	0 - 0.5
sweeteners	30.0 - 70.0
flavor	0.1 - 2.0
flavor enhancer/bitter maskant	0 - 1.0
buffer to pH 5.0 - 7.0	0.5 - 1.5
antimicrobial agent	0 - 1.0
color	0 - 0.01
purified water	q.s. to 100

as a liquid suspension suitable for oral administration.

2. The pharmaceutical formulation of Claim 1 having:

Ingredient	% wt/vol
mycophenolate mofetil	20
hydroxypropylmethylcellulose	0.25
microcrystalline cellulose	0.25
xanthan gum	0.1
sorbitol, 70% solution	30 - 50
Lycasin® (maltitol syrup)	10 - 30
sucrose	0 - 10
fructose	0 - 10
aspartame	0 - 0.5
lecithin	0 - 0.1
citric acid	0.02 - 0.25
sodium phosphate dibasic	0.19 - 0.67
methyl paraben	0 - 0.18
propyl paraben	0 - 0.02
flavor	0.3 - 1.0
Magnasweet®	0 - 1
color	0.005
purified water	q.s. to 100

as a liquid suspension suitable for oral administration.

3. A pharmaceutical formulation of Claim 1 having 20 % wt/vol mycophenolate mofetil.

4. The pharmaceutical formulation of Claim 1 having:

Ingredient	% wt/vol
mycophenolate mofetil	20
microcrystalline cellulose	0.2

xanthan gum	0.1
sorbitol, 70% solution	30 - 50
Lycasin® (maltitol syrup)	10 - 30
sucrose	0 - 10
fructose	0 - 10
aspartame	0 - 0.5
lecithin	0 - 0.5
citric acid	0.02 - 0.25
sodium phosphate dibasic	0.19 - 0.8
sodium methyl paraben	0 - 0.18
propyl paraben	0 - 0.02
flavor	0.1 - 1.0
Magnasweet®	0 - 1
color	0.005
purified water	q.s. to 100

as a liquid suspension suitable for oral administration.

5. The pharmaceutical formulation of Claim 4 having:

Ingredient	% wt/vol
mycophenolate mofetil	20
microcrystalline cellulose	0.2
xanthan gum	0.1
sorbitol, 70% solution	50
Lycasin® (maltitol syrup)	10
sucrose	10
soy lecithin	0.1
citric acid	0.06
sodium phosphate dibasic	0.7
sodium methyl paraben	0.04
flavor	<0.3
color	0.005
purified water	q.s. to 100

as a liquid suspension suitable for oral administration.

6. A pharmaceutical formulation comprising:

Ingredient	mg/mL
mycophenolate mofetil or mycophenolic acid	75 - 300
suspending/viscosity agent	1 - 30
wetting agent	0 - 10
sweeteners	1 - 1200
flavor	0.1 - 100
flavor enhancer/bitter maskant	0 - 50
antimicrobial agent	0 - 10
color	0 - 2

as a dry granulation suitable, when constituted with water, for forming a suspension for oral administration, where mg/mL represents concentration after constitution with water.

7. A pharmaceutical formulation of Claim 6 having 200 mg/mL mycophenolate mofetil.

8. A pharmaceutical formulation of Claim 6, having:

Ingredient	mg/mL
mycophenolate mofetil	200
sodium carboxymethylcellulose	20
mannitol	400
aspartame	3.5
pluronic F68	4
potassium sorbate	0.5
cherry	10
color (red 40:blue 1, 90:10)	0.01

as a dry granulation suitable, when constituted with water, for forming a suspension for oral administration, where mg/mL represents concentration after constitution with water.

9. A pharmaceutical formulation of Claim 6, having:

Ingredient	mg/mL
mycophenolate mofetil	200
xanthan gum	1 - 1.5
colloidal silicon dioxide	5 - 10
sorbitol	0 - 550
aspartame	0 - 3.0
soy lecithin	1 - 2
sodium methyl paraben	0.5 - 2.5
flavor	1 - 3
color (to complement the flavor)	1 - 3

as a dry granulation suitable, when constituted with water, for forming a suspension for oral administration, where mg/mL represents concentration after constitution with water.

10. A pharmaceutical formulation of Claim 6, comprising:

Ingredient	mg
mycophenolate mofetil	90,000
sodium carboxymethylcellulose	9,000
mannitol	180,000
aspartame	1,575
pluronic F68	1,800
potassium sorbate	225
cherry	4,500

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color (red 28:blue 1, 90:10)	4.5

in a container marked to be filled with purified water to a final predetermined volume of 450 mL.

11. A pharmaceutical formulation of Claim 6, comprising:

Ingredient	mg
mycophenolate mofetil	90,000
xanthan gum	450
colloidal silicon dioxide	2,250
soy lecithin	450
sorbitol	247,500
aspartame	225
sodium methyl paraben	900
berry flavor	1,350
color (FD&C red #3	13.5
FD&C blue #1	2.7

in a container marked to be filled with purified water to a final predetermined volume of 450 mL.

12. A pharmaceutical formulation of Claim 6, comprising:

Ingredient	mg
mycophenolate mofetil	90,000
xanthan gum	450
colloidal silicon dioxide	2,250
soy lecithin	450
sorbitol	135,000
aspartame	450
citric acid	225
sodium citrate	4,500
sodium methyl paraben	900
berry flavor	1,350
color (FD&C red #3	13.5
FD&C blue #1	2.7

in a container marked to be filled with purified water to a final predetermined volume of 450 mL.

13. A pharmaceutical formulation of Claim 6, comprising:

Ingredient	mg
mycophenolate mofetil	90,000
xanthan gum	675
colloidal silicon dioxide	4,500
soy lecithin	900
aspartame	900
sodium methyl paraben	1,035

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mixed fruit flavor	900
color (FD&C red #3	3.6
FD&C yellow #6)	0.9

in a container marked to be filled with purified water to a final predetermined volume of 450 mL.

14. A pharmaceutical formulation of Claim 6, comprising:

Ingredient	mg
mycophenolate mofetil	90,000
xanthan gum	450
colloidal silicon dioxide	2,250
soy lecithin	450
sorbitol	247,500
aspartame	225
citric acid	225
sodium citrate	4,500
sodium methyl paraben	1,035
mixed fruit flavor	900
color (FD&C red #3	2.79
FD&C yellow #6)	0.675

in a container marked to be filled with purified water to a final predetermined volume of 450 mL.

15. A pharmaceutical formulation of Claim 6, comprising:

Ingredient	mg
mycophenolate mofetil	90,000
xanthan gum	675
colloidal silicon dioxide	4,500
soy lecithin	900
aspartame	900
citric acid	225
sodium citrate	4,500
sodium methyl paraben	450
orange flavor	450
color (FD&C yellow #6)	45

in a container marked to be filled with purified water to a final predetermined volume of 450 mL.

16. The pharmaceutical formulation of Claim 6 provided in a container marked to be filled with purified water to a final predetermined volume.

17. A pharmaceutical formulation consisting essentially of:

Ingredient	% wt/vol
mycophenolate mofetil	20

hydroxypropyl methylcellulose	0.25
microcrystalline cellulose	0.25
xanthan gum	0.1
sorbitol solution	50
sucrose	10
Lycasin®	10
lecithin	0.1
methyl paraben	0.036
propylparaben	0.004
grape	1.0
anise	0.01
color (red 28: blue 1, 90:10)	0.005
citric acid	0.0542
sodium phosphate dibasic	0.673
purified water	q.s. to 100

adjusted to a pH of 7, as a liquid suspension suitable for oral administration.

18. A pharmaceutical formulation consisting essentially of:

Ingredient	% wt/vol
mycophenolate mofetil	20
microcrystalline cellulose	0.2
xanthan gum	0.1
sorbitol solution	50
Lycasin®	10
sucrose	10
lecithin	0.1
citric acid	0.06
sodium phosphate dibasic	0.7
sodium methyl paraben	0.04
flavor	<0.3
color (to complement the flavor)	0.005
purified water	q.s. to 100

adjusted to a pH of 7, as a liquid suspension suitable for oral administration.

19. A process for the preparation of a pharmaceutical formulation of Claim 1 comprising:

a. adding and dispersing the antimicrobial agent to heated water (about 70°C), followed by adding the suspending and/or viscosity agents (preferably microcrystalline cellulose, followed by xanthan gum);

b. dissolving, with mixing, the buffer(s) (preferably citric acid, followed by sodium phosphate dibasic), followed by adding the sweetener(s), wetting agent(s), dye(s), flavor enhancer(s), and flavor(s); and

c. adding the active compound (mycophenolate mofetil or mycophenolic

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acid) to the mixture from step b; followed by mixing the liquid well to form a suspension.

20. A process for the preparation of a dry granulation of Claim 6 comprising:

a. combining mycophenolate mofetil, sweetener(s), wetting agent(s), and suspending and/or viscosity increasing agent(s) in a mixer;

b. dissolving the dye(s) and buffer(s) in water;

c. combining the solution of step (b) to the mixer bowl of step (a) and mixing until a desired granulation size is obtained;

d. drying the granulation then milling to reduce particle size;

e. adding the suspending and/or viscosity increasing agent(s), flavor(s) and antimicrobial agent(s) to the granulation of step (d) using a blender.

21. Use of a formulation of Claim for the treatment of immunosuppressive diseases, inflammatory diseases, tumors, proliferative diseases, viral diseases and psoriatic diseases.

22. Use of a dry granulation of Claim 6 for the preparation of a pharmaceutical formulation for the treatment of immunosuppressive diseases, inflammatory diseases, tumors, proliferative diseases, viral diseases and psoriatic diseases.

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ABSTRACT

MYCOPHENOLATE MOFETIL HIGH DOSE ORAL SUSPENSIONS

High dose, dry granulations and aqueous oral suspensions of mycophenolate mofetil or mycophenolic acid, contain: active compound (7.5-30%), suspending/viscosity agent, sweetener, flavor, buffer (to a pH of 5-7), and optionally contain flavor enhancer, wetting agent, antimicrobial agent and color.

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acid) to the mixture from step b; followed by mixing the liquid well to form a suspension.

20. A process for the preparation of a dry granulation of Claim 6 comprising:

a. combining mycophenolate mofetil, sweetener(s), wetting agent(s), and suspending and/or viscosity increasing agent(s) in a mixer;

b. dissolving the dye(s) and buffer(s) in water;

c. combining the solution of step (b) to the mixer bowl of step (a) and mixing until a desired granulation size is obtained;

d. drying the granulation then milling to reduce particle size;

e. adding the suspending and/or viscosity increasing agent(s), flavor(s) and antimicrobial agent(s) to the granulation of step (d) using a blender.

21. Use of a compound as claimed in Claim 1 to 20 for the treatment of immunosuppressive diseases, inflammatory diseases, tumors, proliferative diseases, viral diseases and psoriatic diseases.

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acid) to the mixture from step b; followed by mixing the liquid well to form a suspension.

20. A process for the preparation of a dry granulation of Claim 6 comprising:

a. combining mycophenolate mofetil, sweetener(s), wetting agent(s), and suspending and/or viscosity increasing agent(s) in a mixer;

b. dissolving the dye(s) and buffer(s) in water;

c. combining the solution of step (b) to the mixer bowl of step (a) and mixing until a desired granulation size is obtained;

d. drying the granulation then milling to reduce particle size;

e. adding the suspending and/or viscosity increasing agent(s), flavor(s) and antimicrobial agent(s) to the granulation of step (d) using a blender.

21. Use of a formulation of Claim 1 for the preparation of a medicament for the treatment of immunosuppressive diseases, inflammatory diseases, tumors, proliferative diseases, viral diseases and psoriatic diseases.

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