

5

UNITARY PHARMACEUTICAL DOSAGE FORM

Background of the Invention

10 This application relates to products for the treatment of viral infections, in particular HIV infections, using the known antiviral compounds efavirenz (tradename Sustiva, also known as EFV), emtricitabine (tradename Emtriva, also known as FTC) and tenofovir DF (disoproxil fumarate, also known as TDF) (tradename Viread, sold in combination with emtricitabine under the
15 tradename Truvada).

 The Truvada product is produced by wet granulation of emtricitabine and tenofovir DF (WO 04/64845), which under the circumstances produces a chemically stable dosage form. This product does not contain efavirenz.

20

 HIV therapy using efavirenz as well as emtricitabine and tenofovir DF has been considered desirable (hereafter "triple combination"; see WO 04/64845). Manufacturing a commercially viable triple combination product, however, would require that the final product meet stringent FDA requirements
25 for bioequivalence to the commercial products, Viread (tenofovir disoproxil fumarate), Emtriva (emtricitabine), and Sustiva (efavirenz), and that the tablet be of suitable size for patients to easily swallow.

 Initial efforts to simply combine the three drugs (active pharmaceutical
30 intermediates, or APIs) into a unitary, essentially homogeneous composition manufactured by wet granulation failed to produce a chemically stable tablet. The tenofovir DF in this combination tablet was highly unstable and rapidly degraded in stability studies. The efavirenz formulation was unexpectedly

incompatible with tenofovir DF, a result now attributed to the surfactant (sodium lauryl sulfate) found in the efavirenz portion of the formulation.

Another attempt was made to produce the triple combination, this time
5 using a dry granulation of the three part combination and omitting the surfactant. This resulted in a tablet that failed to achieve bioequivalence with respect to efavirenz in human clinical trials. The peak efavirenz concentration in the blood stream and total drug exposure (Cmax and AUC) were both below the parameters determined for the commercial comparator, Sustiva (efavirenz)
10 tablets. The inventors concluded that at least the surfactant in the triple combination (efavirenz/emtricitabine/tenofovir disoproxil fumarate) tablets was necessary to achieve bioequivalence to Sustiva.

Next, combination tablets were manufactured by wet granulating the
15 efavirenz component with the surfactant and other excipients, separately manufacturing the Truvada component using dry granulation, mixing the granulates together, compressing the mixture into tablets, and then film-coating the tablets. Unexpectedly, this approach also failed to produce the desired bioequivalence in between the commercial product, Sustiva (efavirenz), and
20 clinical trial material (i.e., proposed commercial triple combination product). A novel and inventive step was needed to overcome the shortcomings of more straight-forward approaches to a triple combination dosage form.

Copending U.S.S.N. 60/771,353 (filed of even date and expressly
25 incorporated herein by reference) is directed to solving another obstacle encountered in the preparation of the triple combination dosage form, that of reducing the size of the combined product. While the prior art reports the successful manufacture of chemically stable Truvada preparations (WO04/64845), these preparations contain relatively low proportions of
30 excipient to API. Increasing the proportion of excipients and wet granulating the three API combination unexpectedly resulted in a preparation in which the

tenofovir DF was highly unstable. As reported in U.S.S.N. 60/771,353, it was believed that use of sufficient water to accomplish the wet granulation of efavirenz (which has relatively low solubility in comparison to emtricitabine and tenofovir DF) caused the latter two APIs to dissolve into a eutectic mixture.

5 The eutectic mixture dried during granulation to form a glassy or amorphous product in which the tenofovir DF is chemically unstable in comparison to the crystalline API. Supplying enough excipient to ameliorate the effect of the excess water was not consistent with the objective of obtaining a triple combination oral dosage form of manageable proportions.

10

As described further in U.S.S.N. 60/771,353, this obstacle was overcome by dry granulating the emtricitabine and tenofovir DF composition, i.e., granulating the composition without contacting same with a destabilizing amount of liquid water. Omitting water (particularly, liquid water) or reducing
15 the presence of water to an insubstantial amount eliminates the disadvantageous formation of a eutectic mixture and enhances the stability of the resulting pharmaceutical product.

Despite the advantages conferred by dry granulation of the
20 emtricitabine/tenofovir DF component, it was still necessary to overcome the unexpected incompatibility of tenofovir DF and the surfactant used in the Sustiva formulation.

25

Summary of the Invention

In accordance with this invention, the stability and bioequivalence objectives for the triple combination product have been achieved by providing a multicomponent dosage form, one component comprising tenofovir DF and,
30 optionally, emtricitabine, and the other comprising at least efavirenz. Another

embodiment of the invention is a dosage form comprising a tenofovir DF component and a surfactant component not in destabilizing contact with the tenofovir DF component.

Detailed Description of the Invention

The dosage form of this invention comprises efavirenz, emtricitabine and
5 tenfovir DF. As noted, tenofovir DF and efavirenz are in separate components.
Emtricitabine generally is included in the tenofovir DF component, but in other
embodiments the emtricitabine is present in its own component, or is mixed
with the efavirenz component. Its disposition is not critical to the practice of
this invention. All that is necessary is that emtricitabine be present in the
10 dosage form and that the tenofovir DF component be substantially separated
from the surfactant in the efavirenz component. Any method, additive, process
feature or configuration that suitably minimizes the contact of surfactant with
tenofovir DF is suitable in the practice of this invention.

15 The term "component" means a physically discrete unit or compartment
which is associated physically with and in contact with other components. This
does not mean that the units or compartments are physically not in contact. In
fact, it generally is preferred that they are in physical contact and form a unitary
device, article or composition. The degree of association is only that which is
20 needed to facilitate the oral consumption of the composition as a single dosage
form. This invention does not include, for example, patient packs with the
Sustiva and Truvada products in separate wells or containers, or other
associations which are essentially packaging solutions alone (although, of
course, the compositions of this invention optionally are packed or packaged in
25 any conventional fashion suitable under the circumstances).

Typically, the components of the dosage form of this invention
conveniently are organized in multiple layers, ordinarily a bilayer as shown in
the exemplified embodiment. However, if emtricitabine is present in its own
30 component then the dosage form will constitute at least a trilayer structure.

There need not be a single component for each drug (for example, the dosage forms optionally include 2 layers for each of the components, for a total of 6). Thus, the dosage unit includes laminates of many components. There do not need to be equal numbers of each component, e.g., layers, for each drug or drug
5 combination so long as the total dosage of all components in sum is the desired amount.

Other means for spatially organizing the components are suitable so long as the desired degree of separation of tenofovir DF and surfactant is
10 accomplished. For example, rather than forming planar layers along the axis of a tablet, the components optionally are organized in an annular fashion, with each ring or cylinder containing a separate component. Another alternative is to employ a press coating process to associate the components.

15 The components generally are in direct contact with one another, i.e., no barrier or protective layer is present between them. In other embodiments, a barrier is introduced between the incompatible components. A suitable example of this embodiment of the invention would be a multi-compartment capsule in which the incompatible components are distributed into separate
20 compartments. Alternatively, a tablet is optionally provided that contains one encapsulated component disbursed or distributed within the incompatible component. In general, intimate, direct admixture of the incompatible components is undesirable unless means are provided to protect the tenofovir DF component from surfactant.

25

In typical embodiments the components of the dosage form of this invention are spatially organized so as to not place the tenofovir DF component into destabilizing contact with the surfactant in the efavirenz component.

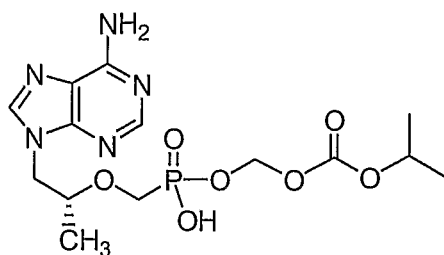
“Destabilizing” means any contact between tenofovir DF and the surfactant that
30 is capable causing pharmaceutically unacceptable degradation of tenofovir DF.

A stabilizing configuration is any spatial organization of the tenofovir DF and efavirenz components that does not result in the generation of a "pharmaceutically unacceptable amount" of any one of the following degradation products. A destabilizing contact is a spatial organization that results in the generation of any of the following degradation products in a "pharmaceutically unacceptable amount".

The spatial geometry and conditions of the permitted contact between tenofovir DF and surfactant-containing component are essentially unlimited. This spatial geometry is termed a "stabilizing configuration" or, stated differently, is a configuration that does not contain a "destabilizing contact" as defined below. There are many ways in which the central observation of this invention (that is, that sodium lauryl sulfate destabilizes tenofovir DF) can be harnessed to prevent the generation of pharmaceutically unacceptable levels of degradation of tenofovir DF.

In addition, when emtricitabine is present in the tenofovir DF component, the permitted contact also that which does not produce pharmaceutically unacceptable amounts of emtricitabine degradation product.

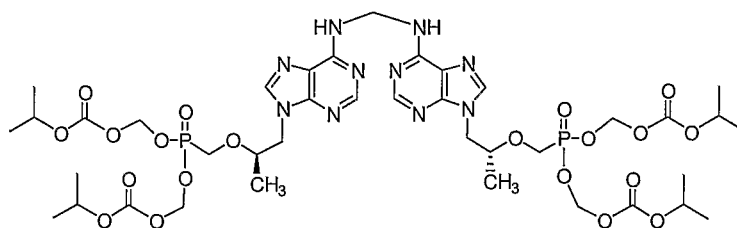
"Degradation" of tenofovir DF is the generation - in pharmaceutically unacceptable amounts - of at least one of the degradation products mono-POC PMPA, dimer or mixed dimer. "Degradation" of FTC is defined as the generation - in pharmaceutically unacceptable amounts, of FTU. These degradation products are shown below.

Mono-POC PMPA

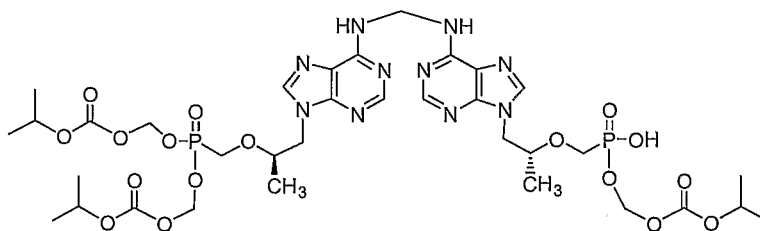
mono-POC PMPA

Dimeric Degradation Products

Dimer

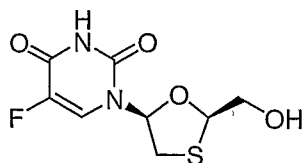


Mixed Dimer



5

FTU has the structure



10

A "pharmaceutically unacceptable amount" is defined as the following amounts of each degradation product. Degradation products optionally are

assayed in either an absolute or incremental amount. The absolute or total amount of degradation product is simply the amount found in the test article. The incremental amount is the additional amount of degradation product appearing in the product over that which was present (if any) in the API
5 starting material. Moreover, the amount of degradation product optionally is measured at two points in time. One is at the time of release into the marketplace. The other is after exposure to storage conditions under the conditions described below, i.e., the shelf life as set forth below.

Total amounts at release (first commercial sale)

- No more than about 3 %, ordinarily about 1.5%, of mono-POC PMPA,
No more than about 1%, ordinarily about 0.5% of Dimer,
5 No more than about 0.5%, ordinarily about 0.25% of Mixed Dimer.
Less than about 0.5%, ordinarily about 0.2% of FTU

Total amounts at shelf life (storage at 25°C/60% RH for 24 mo.)

- No more than about 10%, ordinarily about 5% of mono-POC PMPA,
No more than about 2%, ordinarily about 1% of Dimer,
10 No more than about 2%, ordinarily about 1% of Mixed Dimer.
No more than about 4%, ordinarily about 2% of FTU

Incremental amounts at release (first commercial sale)

- No more than about 2 %, ordinarily about 0.5%, of mono-POC PMPA,
No more than about 0.6%, ordinarily about 0.1% of Dimer,
15 No more than about 0.3%, ordinarily about 0.05% of Mixed Dimer.
Less than about 0.4%, ordinarily about 0.1% of FTU

Incremental amounts at shelf life (storage at 25°C/60% RH for 24 mo.)

- No more than about 9%, ordinarily about 4% of mono-POC PMPA,
No more than about 1.6%, ordinarily about 0.6% of Dimer,
20 No more than about 1.8%, ordinarily about 0.8% of Mixed Dimer.
No more than about 3.9%, ordinarily about 1.9% of FTU.

- The percentage of degradation products is the amount of degradation product as measured by HPLC retention time comparison. In the HPLC
25 retention time comparison, the retention time of the main peaks observed in the tablets is required to be within 2% of the retention time of the main peaks in the a reference standard preparation containing efavirenz, emtricitabine, and tenofovir DF in an assay which has been shown to be specific for efavirenz, emtricitabine, and tenofovir DF. The percentage is determined by dividing the
30 total amount of tenofovir DF plus the three degradation products into the

amount of individual degradation product as determined by the HPLC assay.

These parameters are employed to evaluate whether a test composition has met the requirements of a stabilizing contact. For example, a triple
5 combination dosage form optionally is designed as a shaped article comprising slugs of compressed granules of the tenofovir DF component dispersed within a matrix of the efavirenz component. A variety of slug sizes might be used in making the composition. This constellation of potential products then would be tested, or stored under the conditions above and then tested, to assay the
10 generation of tenofovir DF and/or FTC degradation products. If the resulting product upon release did not contain more than the specified approximate limits of any one or more of the 4 contaminants listed under any of the 4 assay paradigms above, then the contact would be considered stabilizing. Of course, the artisan may adopt more stringent standards, but this will be a matter of
15 choice and shall not limit the scope of this invention.

In preferred embodiments the emtricitabine and tenofovir DF are combined and this component is prepared by dry granulation (U.S.S.N. 60/771,353). In preferred embodiments, a composition comprising dry
20 granulated tenofovir DF and emtricitabine is employed in one component of the dosage forms of this invention.

Dry granulation is a well-known pharmaceutical manufacturing process per se. In general, API is combined with excipients and lubricant excipient and
25 then compressed to form a mass. This mass typically is then comminuted or milled, then sieved to obtain the desired size of particle. The granular product is compressed into tablets, filled into capsules or otherwise formed into a unitary dosage form in conventional fashion.

30 Compression into a mass is accomplished by conventional equipment.

Typically, the API and excipients are passed through a roller apparatus for compaction. However, other means for compacting the API mixture, e.g., compaction into slugs (or "slugging"), optionally are used.

5 A dry granulation process is one in which a dry composition of the API and selected excipient(s) is compressed to form a mass, which is comminuted or milled if necessary, and then optionally sieved to produce the desired size granules. Compression into a mass is accomplished by conventional equipment. Typically, the API and excipients are passed through a roller
10 apparatus for compaction. However, other means for compacting the API mixture, e.g., compaction into slugs (or "slugging"), can be used.

 A composition comprising dry granulated emtricitabine and tenofovir DF is the product of a dry granulation process. This composition essentially
15 retains the crystalline APIs and is substantially free of dried eutectic emtricitabine/tenofovir DF. It typically will contain less than about 15% by weight dried eutectic mixture, ordinarily less than about 10% and generally less than about 5%.

20 The dry granulation process is conducted in the absence of a destabilizing amount of water, "destabilizing" being that amount of liquid water that is capable causing pharmaceutically unacceptable degradation of tenofovir DF and/or FTC as defined herein. If the dosage form of this invention includes a dry granulated emtricitabine/tenofovir DF component, then the
25 amount of permitted degradation product in the final dosage form is still the same as that which is set forth above, i.e., the amount of water exposure and contact, together or alone, are not to result in degradation products failing to meet the standards described above. It is an option, of course, to test the dry granulates for their level of degradation product first, and if they pass, then to
30 formulate them into the dosage form of this invention and then determine if the

contact results in any increase in degradation products that takes the resulting dosage form outside the parameters established.

Bound, entrained or absorbed water are commonly present in excipients.

5 This water will not significantly adversely affect the stability of tenofovir DF and thus is not excluded from the dry granulates optionally used in the dosage form of this invention. In general, liquid water (added or generated in situ) from any source, e.g., chemical reactions, condensation, entrained ice, or the like is to be excluded from the granulation. However, minor amounts of liquid
10 water optionally are added during granulation. These amounts typically would be less than about 5% by weight, ordinarily less than about 1% by weight, however the water is generated or supplied. Water is present in the final granulation product up to about 10% by weight (Karl Fischer), but preferably is less, as low as 0.1% by weight. However, permitted quantities of water may
15 vary depending upon other factors in the granulation, e.g., excipient type, temperature and so forth. For example, if a hygroscopic excipient is included this will convert added water into a bound form. All that is necessary is that the water not result in degradation of tenofovir DF and/or emtricitabine in the final product. In general, water is excluded both from the pregranulation stage
20 (preparation of the composition to be used directly in the granulation) as well as during the granulation process itself.

Absence of water or "dry" does not mean the absence of liquid.

Granulations with organic solvents are also feasible provided that destabilizing
25 amounts of water are excluded.

Dry granulation results in a product that contains minimal amounts of water. The amount of water in the product granulate or dosage forms made therefrom are measured by loss on drying (LOD) or by the Karl Fischer method.

30 The LOD of compositions of this invention are about 15%, about 10%, about 5%

or typically less than about 3% by weight. The Karl Fischer water is about from 0.1 to 10% by weight, usually less than about 5% by weight, or less than about 2%. The amount of water in the final preparations, as opposed to the granulates, is a function of granulate water as well as minor amounts of water used during subsequent process steps such as coating. These amounts of water added in later steps than granulation generally will not affect the stability of the emtricitabine/tenofovir DF APIs, and therefore are subject to considerable permitted variation.

The manufacturing process described below is directed to the preparation of a triple combination tablet containing efavirenz, emtricitabine and tenofovir DF. In this particular embodiment the last two drugs are emplaced in a portion of the tablet which is separate from, but in contact with, the portion of the tablet containing efavirenz. It will be understood, however, that the emtricitabine and tenofovir DF component of the tablet, which is an embodiment of this invention, optionally is manufactured as a stand-alone product and not necessarily in assembly with an efavirenz component. In this option, the emtricitabine/tenofovir DF dry granulation intermediate described below is simply compressed into tablets or conventionally processed into other conventional unitary dosage forms such as capsules, cachets, suppositories, or the like.

The dosage forms of this invention are stored in containers, preferably under desiccant such as silica gel in amounts generally sufficient to maintain the RH over the dosage forms at under about 10%, preferably under about 5%.

Materials

The quantitative compositions of the efavirenz powder blend, FTC/TDF powder blend, and film-coated bi-layer EFV/FTC/TDF tablets are listed in Table 1, Table 2, and Table 3, respectively. The quantities of efavirenz, emtricitabine,

and tenofovir DF were adjusted for drug content factors (DCF) if the value was less than 0.99 with a concomitant reduction to the quantity of microcrystalline cellulose in each granulation.

5 Table 1. Quantitative composition of efavirenz powder blend

Ingredient	% w/w of Total	Unit Formula (mg/tablet)
Efavirenz	38.71	600.0
Microcrystalline Cellulose, NF/EP	11.52	178.6
Hydroxypropyl cellulose, NF/EP	2.48	38.4
Sodium Lauryl Sulfate, USP/EP	0.77	12.0
Croscarmellose Sodium, NF/EP	3.87	48.0
Magnesium Stearate, NF/EP	0.58	9.6
Total for Tablet Core	57.94	898.0

Table 2. Quantitative composition of FTC/TDF powder blend

Ingredient	% w/w of Total	Unit Formula (mg/tablet)
Emtricitabine	12.90	200.0
Tenofovir Disoproxil Fumarate	19.35	300.0
Microcrystalline Cellulose, NF/EP	5.77	89.5
Croscarmellose Sodium, NF/EP ^a	3.10	48.0
Magnesium Stearate, NF/EP ^a	0.94	14.5
Total for Tablet Core	42.06	652.0

^a To be incorporated into both the intragranular and extragranular portions of the formulation during the manufacturing process.

Table 3. Quantitative composition of film-coated bi-layer EFV/FTC/TDF Tablets

Ingredient	% w/w of Total	Unit Formula (mg/tablet)
Efavirenz Powder Blend	57.94	898.0
FTC/TDF Powder Blend	42.06	652.0
Total for Tablet Cores	100.00	1550.0
Opadry II Pink	3.00	46.5
Purified Water, USP/EP ^a		
Total for Film-Coated Tablets		1596.5

^a Water removed during film-coating process.

- 5 The excipients were all compendial grade materials:

Efavirenz Wet Granulation

Efavirenz was wet granulated using a Niro-Fielder PMA-400 equipment train. Efavirenz, microcrystalline cellulose and sodium lauryl sulfate (Table 1) were added to the PMA-400 and blended for 3 minutes. Croscarmellose sodium and hydroxyl propyl cellulose (Table 1) were added to the pre-mix and blended for an additional 2 minutes. Purified water was added to form a suitable granulation followed by additional wet massing after water addition. Table 4 lists the summary of granulation parameters used for two representative lots and sub parts. All sub parts used a water to efavirenz ratio of 1.30 except for AB509 Mix C which used a 1.25 ratio of water to efavirenz.

Table 4. Efavirenz wet granulation process parameter summary

Process	Parameter	AB507			AB509		
		Mix A	Mix B	Mix C	Mix A	Mix B	Mix C
Granulation	Total Water Added (kg)	33.57	33.56	33.56	33.56	33.56	32.18
	Ratio of Water:EFV	1.30	1.30	1.30	1.30	1.30	1.25
	Total Addition Time (Min:Sec)	9:36	9:29	9:24	9:17	9:32	9:02
	Final Impeller Power (% Load)	10.4	9.8	8.5	11.3	11.3	9.9
Wet Massing	Total Time (Min:Sec)	4:00	3:00	3:00	2:00	1:15	2:00
	Final Impeller Power (% Load)	11.6	12.0	11.7	18.0	17.7	10.5
Drying ^a	Inlet Temperature (°C)	70			70		
	Time (Hr:Min)	1:45			1:51		
	Final Outlet Temp. (°C)	50			50		
	Final LOD (%)	0.3			0.8		

^a Mixes A, B, and C for each lot were combined before drying.

In general, the wet granules were milled, then dried to an LOD less than or equal to 1.5%. The dried granules were milled and blended with magnesium stearate (Table 1).

5

The bulk density, particle size, and moisture content by LOD of the efavirenz granulations are listed in the first three lines of Table 5 (the B lot numbers are efavirenz products, the C lot numbers are emtricitabine/tenofovir DF). Particle size was determined by sifting 10-gram samples through 3-inch diameter screens using a sonic sifter (Model L3P, ATM Corporation, Milwaukee, WI, USA). The following US Standard Mesh sizes (openings) were used: #20 (850 μm), #30 (600 μm), #40 (425 μm), #60 (250 μm), #80 (180 μm), and #250 (63 μm). The agitation and pulse were set at 7 and the sifting time was 5 minutes. The amount of powder retained on the sieves and the fines collector was determined by calculating the difference in weight before and after sifting. The geometric mean particle size was calculated by logarithmic weighting of the sieved distribution.

Bulk density was determined by filling a 100-mL graduated cylinder with sample and calculating the difference in weight between the empty and full graduated cylinder per unit volume.

Moisture content measurements by loss on drying (LOD) were performed by heating a 2.5 g sample at 85 degrees C for 15 minutes using a heat lamp/balance system (Model LP16/PM400, Mettler-Toledo, Columbus, OH, USA).

The granulations had similar bulk densities (0.54 to 0.56 g/mL) and similar geometric mean particle size distributions (215 to 268 μm). The LOD

values of the final blend were consistent from 0.98 to 1.80%. The individual sieve distributions for the efavirenz granulations are listed in Table 6.

Table 5. Summary of efavirenz powder blend and emtricitabine/tenofovir DF powder blend physical properties

Gilead Lot Number	Geometric Mean Diameter Particle Size (μm)	Bulk Density (g/mL)	LOD (%)
AB507	247	0.56	1.80
AB508	215	0.55	1.08
AB509	268	0.54	0.98
AC507	330	0.60	0.91
AC508	344	0.60	1.02
AC509	343	0.59	0.99

Table 6. Particle size distribution for efavirenz and FTC/TDF powder blends

Gilead Lot Number	% Weight Retained on Screen^a						
	US Standard Screen Size (mesh opening)						
	20 (>850 μm)	30 (600 μm)	40 (425 μm)	60 (250 μm)	80 (180 μm)	230 (63 μm)	pan (< 63 μm)
AB507	5.9	10.9	16.2	22.2	11.4	22.6	10.9
AB508	6.1	10.4	15.8	20.0	9.0	20.8	17.9
AB509	9.6	13.3	17.4	20.1	8.9	17.2	13.3
AC507	22.0	19.8	15.2	11.2	4.6	10.5	16.6
AC508	22.1	20.1	15.4	11.6	5.1	10.6	14.9
AC509	22.4	19.7	15.3	11.7	4.8	11.1	14.8

Emtricitabine/Tenofovir DF Dry Granulation

Emtricitabine, microcrystalline cellulose, tenofovir DF, and
5 croscarmellose (Table 2) were blended in a 650 L tote bin using a Gallay blender
for 10 minutes. Magnesium stearate (Table 2) was added and blended for an
additional 5 minutes. This pre-blend was then transferred to a 320-L Matcon bin
fitted with a cone valve discharging station to assist with material transfer into
the roller compactor hopper.

10

The pre-blend was roller compacted using a Gerteis Macro-Pactor model
250/25/3 with 250 mm diameter by 50 mm wide smooth rolls. The roll gap
thickness (2 mm), roll speed (10 rpm), compaction force (4 kN/cm), oscillating
mill speed (75 rpm clockwise and counterclockwise), and oscillating mill screen
15 opening (1.25 mm) were kept constant for all batches. The oscillating mill angle
of rotation was also the same for all lots at 150° clockwise and 140°
counterclockwise.

There was no material handling issues among all three batches while
20 feeding into the roller compactor. The entire roller compaction process
proceeded without any apparent sign of heat accumulation on the equipment,
product build-up, or melting. The granulations then were blended with
extragranular croscarmellose sodium (34% of total amount) and magnesium
stearate (47% of total amount).

25

The particle size, bulk density, and LOD of the emtricitabine/tenofovir
DF dry granulations were all similar for the three batches and are listed in Table
5 (bottom 3 compartments). The geometric particle sizes were very similar at
from 330 to 344 μm . Bulk densities ranged from 0.59 to 0.60 g/mL. The final

blend LOD values were consistent from 0.91 to 1.02%. The final powder blends have remarkably consistent physical properties.

The efavirenz and tenofovir DF granulations each have geometric mean
5 particle sizes that optionally range about from 100 to 600 μm , bulk densities optionally ranging about from 0.1 to 1 g/mL and LOD values optionally ranging about from 0.1 to 10% by weight.

Final Blends

The mass of efavirenz granulation and extragranular magnesium stearate
10 were adjusted appropriately based on the yield of emtricitabine/tenofovir DF dry granulation. Efavirenz granulation and emtricitabine/tenofovir DF dry granulation were blended in a 3 cubic foot V-blender for 10 minutes. Magnesium stearate was added and blended an additional 5 minutes. Samples of the final powder blend were taken from 10 different locations after blending
15 and analyzed for blend uniformity. The efavirenz and emtricitabine/tenofovir DF final powder blends showed acceptable blend uniformity and homogeneity for all three active ingredients indicating the robustness of the formulation regardless of the particle size or bulk density of emtricitabine/tenofovir DF dry granulations and efavirenz granulations. The granulations and blending
20 procedure would be satisfactory for the formulation on a larger scale.

Tablet Core Compression

Efavirenz/emtricitabine/tenofovir DF final powder blend was compressed into tablet cores using a Stokes Genesis Model 757, 41 station bilayer tablet press equipped plain-faced upper/ embossed "123" lower,
25 capsule-shaped (20.0 mm $\times$ 10.4 mm) punches. The target mass of the tablet cores was 1550 mg. Samples of the core tablets were taken from a minimum of 20 equally spaced locations during the compression run and analyzed for content uniformity. In general, all powder blends compressed satisfactory on

the rotary tablet press with respect to tablet hardness, friability, tablet thickness, tablet appearance, and tablet weight variation. The compression operation was performed at a rate of approximately 500 tablets/minute (12 rpm press speed) or approximately 0.8 kg/minute to deliver satisfactory tablet weight uniformity.

5 Tablet Film-Coating

Suitable film coatings are selected by routine screening of commercially available preparations. This activity is well within the skill of the ordinary artisan. Each lot of tablet cores was divided into two coating sub-lots that were film coated in a 48-inch Thomas Engineering COMPU-LAB coating pan using a dual-nozzle spraying system. All the tablet cores were film-coated using a 15% w/w aqueous coating suspension Opadry II Pink, which was used within 24 hours of preparation. All tablet cores were coated to a target weight gain of 3.0% using a target spray rate of 180 g/min, which corresponds to a normalized spray rate of 1.5 to 2.3 g/min/kg tablets.

HPLC Assay for Degradation products

Efavirenz/emtricitabine/tenofovir DF tablets (EFV/FTC/TDF tablets) are assayed by HPLC for EFV, FTC, and TDF using external reference standards. The degradation products of EFV, FTC, and TDF are determined by area normalization with the application of relative response factors, as appropriate. The identity of EFV, FTC, and TDF are confirmed by comparison of their retention times with those of the reference standards.

STANDARD AND SAMPLE SOLUTION PREPARATION

Standard and Sample Solvent

25 mM Phosphate Buffer, pH 3

Weigh and transfer 3.4 g of potassium phosphate monobasic, anhydrous into a 1 L volumetric flask. Add about 800 mL of water and mix until dissolved.

Adjust the pH to 3.0 ± 0.1 with phosphoric acid, then dilute to volume with water.

Sample Solvent (40:30:30 25 mM Phosphate Buffer, pH 3:Acetonitrile:Methanol)

- 5 Combine 400 mL of 25 mM Phosphate Buffer, pH 3, 300 mL of acetonitrile, and 300 mL of methanol and mix. Allow to equilibrate to ambient temperature.

50:50 Acetonitrile:Methanol

Combine 500 mL of acetonitrile and 500 mL of methanol and mix. Allow to equilibrate to ambient temperature.

10

Standard Solution

Accurately weigh approximately 60 mg of EFV reference standard, 20 mg of FTC reference standard, and 30 mg of TDF reference standard and transfer into a 100 mL volumetric flask. Add approximately 80 mL of *sample solvent* (40:30:30) to the flask and mix or sonicate until dissolved. Dilute to volume with *sample solvent* (40:30:30) and mix well. The final concentration of each component is approximately 0.6 mg/mL of EFV, 0.2 mg/mL of FTC, and 0.3 mg/mL of TDF.

20 System Suitability Test Solutions

Sensitivity Check Standard

- Prepare a 10 µg/mL FTU stock solution by accurately weighing out approximately 10 mg of the FTU authentic substance into a 100 mL volumetric flask. Add *sample solvent* (40:30:30) to approximately 80% of volume and mix or sonicate until dissolved. Dilute to volume with *sample solvent* (40:30:30) and mix well. Pipet 10 mL of this solution into a 100 mL volumetric flask. Dilute to volume with *sample solvent* (40:30:30) and mix well.
- 25

- Prepare the *sensitivity check standard* containing 0.2 mg/mL of FTC and 0.2 µg/mL of FTU (0.10% relative to FTC). Accurately weigh out 20 mg FTC into a 100 mL volumetric flask. Using a Class A pipet, transfer 2.0 mL of the FTU stock solution into the same flask. Add additional *sample solvent* (40:30:30) to the flask and mix or sonicate until dissolved. Dilute to volume with *sample solvent* (40:30:30) and mix well. Alternately, 2.0 mL of the 10 µg/mL FTU stock solution may be added to the *standard solution* prior to diluting to volume.

10 Sample Preparation for EFV/FTC/TDF Tablets

The strength and degradation product content of EFV/FTC/TDF tablets is determined by the analysis of a composite solution prepared from ten tablets.

The final concentration of each component in the *sample solution* is approximately 0.6 mg/mL of EFV, 0.2 mg/mL of FTC, and 0.3 mg/mL of TDF.

- 15 a) Place ten tablets into a 1 L volumetric flask and add 400 mL 25 mM phosphate buffer, pH 3 to the volumetric flask.
- b) Mix by stirring vigorously for about 75 minutes.
- c) Add 50:50 acetonitrile:methanol to the flask to approximately 2 cm below the volume mark.
- 20 d) Equilibrate the solution to ambient temperature by mixing for an hour. Dilute to volume with 50:50 acetonitrile:methanol. Mix well by inverting the flask or stirring with a magnetic stir bar.
- e) Using a 0.45 µm syringe filter with a syringe, filter approximately 10 mL of step (d) for the next dilution. Discard the first 2 mL of filtrate.
- 25 f) Using a Class A pipet, transfer 5.0 mL of the filtrate from step (e) into a 50 mL volumetric flask and dilute to volume with *sample solvent* (40:30:30). Mix well.

CHROMATOGRAPHY

1. An HPLC equipped with a UV detector and an electronic data acquisition system is used.
2. An HPLC column, 4.6 mm i.d. by 250 mm long, packed with C12 reversed phase, 4 μ m particle size, 80 Å pore size material is used.
3. Mobile phase buffer: Prepare a 20 mM ammonium acetate buffer, pH 4.6; adjust pH with acetic acid as needed.
4. Mobile phase gradient: Elute with Mobile Phase Buffer:acetonitrile from 99:1 to 1:99 over 67 minutes.
5. Peak detection: UV at 262 nm
6. Injection volume: 10 μ L.

Under the stated chromatographic conditions, the retention times of the FTC, TDF and EFV peaks are typically 11, 33, and 50 minutes, respectively.

INJECTION SEQUENCE

Inject the *sample solvent* at least twice as a blank to ensure that the column is equilibrated and to identify any potential artifact peaks.

Inject the *sensitivity check standard* or *standard solution* containing approximately 0.10% FTU to measure the sensitivity of detection.

- Inject five replicates of *standard solution 1* (R1), followed by a single injection of *standard solution 2* (R2). Calculate the theoretical plates and tailing factors from the *standard solution* injections.

For identity, strength, and degradation product determination, perform duplicate injections of the *sample solution*.

- All *sample solutions* must be bracketed by *standard solution* injections. Generally, not more than ten *sample solution* injections between bracketing standard injections is recommended.

SYSTEM SUITABILITY

Theoretical Plates and Tailing Factor

- Calculate the number of theoretical plates (N) and the tailing factors (T) for the EFV, FTC, and TDF peaks from the Standard Solution chromatogram. The
- 5 formulas for N and T determination are defined in the current United States Pharmacopeia. The values of these parameters must conform to the criteria :N ≤ 40,000 and $0.8 \leq T \leq 2.0$.

Sensitivity Check

- The sensitivity check will utilize the FTU peak in the *sensitivity check standard* present at approximately 0.10%. Calculate the area percent of the FTU peak
- 10 with the appropriate RRF (listed in Table 2) applied for the *sensitivity check standard* using the calculation for percent individual degradation product. Compare this result to the theoretical percent of FTU for the *sensitivity check standard* as follows:

$$15 \quad \text{Sensitivity} = \frac{\text{FTU}_{\text{Determined}}}{\text{FTU}_{\text{Theoretical}}}$$

Where: $\text{FTU}_{\text{Determined}}$ = area percent of FTU determined for the *sensitivity check standard* or *standard solution*

$\text{FTU}_{\text{Theoretical}}$ = theoretical area percent of FTU for the *sensitivity check standard* or *standard solution*

The sensitivity must be between 0.70-1.30.

EVALUATION AND CALCULATIONS

Identification of Degradation Products

- 20 Employ the appropriate detection parameters (such as peak threshold, minimum peak area, etc.) to allow detection of peaks present at 0.05% or less.

Identify the impurities and degradation products of EFV, FTC, and TDF present in the chromatograms of the *sample solution* injections by noting the relative retention times (RRT) of the observed secondary peaks, discounting any peaks not related to the sample. Only degradation products are quantified. Calculate the average of the results from all *sample solution* injections to the nearest 0.01%. In cases where the degradation product was not detected or was below the threshold of integration in one injection and/or sample, use only the quantified results in the calculation (i.e., do not treat as a zero value).

$$\text{RRT} = \frac{\text{retention time of the secondary peak}}{\text{retention time of the tenofovir disoproxil peak}}$$

The RRTs and the relative response factor (RRF) values of the potential impurities and degradation products for EFV are shown in Table 1, and the degradation products are shown in bold-face. The impurities and degradation products for FTC are shown in Table 2, and the degradation products are in bold-face. The impurities and degradation products for TDF are shown in Table 3, and the degradation products are in bold face.

As the RRT may vary, the identity of impurities and degradation products may be confirmed by comparison to authentic substances (or to impurity and degradation product peaks in the reference standard), if required.

Degradation Product Content Determination

Quantification of FTC Degradation Products

Determine the level of each degradation product of FTC observed in the chromatograms of the *sample solution* injections using the following formula:

$$\text{Degradation Product (\%)} = \frac{I}{\text{TPA}} \times \text{RRF} \times 100$$

Where: I = Area of the degradation product peak

TPA = Total peak area (area of FTC and all related degradation products, excluding impurities and artifacts), corrected by RRF

5 RRF = Relative response factor with respect to FTC

8.4.3 Quantification of TDF Degradation Products

Determine the level of each degradation product of TDF observed in the chromatograms of the *sample solution* injections using the following formula:

10
$$\text{Degradation Product (\%)} = \frac{I}{TPA} \times RRF \times 100$$

Where: I = Area of the degradation product peak or unassigned peak

TPA = Total peak area (area of the TDF main peak, all related degradation products, and all unassigned peaks, excluding impurities and artifacts), corrected by RRF

15 RRF = Relative response factor with respect to TDF

Results and reporting

Degradation Product Content

Report individually the average of the results for each degradation product observed to the nearest 0.01 %. Report the total degradation product content of EFV, FTC, and TDF respectively to the nearest 0.1%, as the sum of the average levels of all degradation product peaks observed. For degradation products found at levels less than 0.05%, report their levels as *trace* and do not include their levels in the calculation of total degradation product content.

25 References

United States Pharmacopeia <621>
Pharmacopeial Forum 26(4) 2000

Table 1. EFV related impurities and degradation products

EFV Related Compound	Approximate RRT ^a	RRF ^b
SD-573^c	1.46	0.5
SR-695 ^d	1.50	
EFV	1.50	
SP-234	1.57	
SW-965	1.60	
SE-563	1.73	0.5
SM-097^c	1.83	

^aApproximate RRTs, and the values are relative to the TDF peak

^bRRFs for EFV related degradation products are relative to EFV

^cEFV related degradation products

^dSR-695 elutes before EFV (approximately 0.1 min separation)

Degradation products are marked in bold face

Table 2. FTC related degradation product

FTC Related Compound	Approximate RRT ^a	RRF ^b
FTC	0.33	0.7
FTU^c	0.38	

^aApproximate RRTs, and the values are relative to the TDF peak

^bRRFs for FTC related degradation products are relative to FTC

^cFTC related degradation products

Table 3. Tenofovir DF related degradation products

TDF Related Compound	Approximate RRT ^a	RRF ^b
mono-POC PMPA^c	0.47	0.6
Mixed Dimer^c	0.98	1.0
TDF	1.00	
Dimer^c	1.34	0.9

^aApproximate RRTs, and the values are relative to the TDF peak

^bRRFs for TDF related degradation products are relative to TDF

^cTDF related degradation products

5

What is Claimed:

1. A composition comprising tenofovir DF and a surfactant whereby
5 the surfactant is in a stabilizing configuration with the tenofovir DF.
2. The composition of claim 1 additionally including efavirenz and
emtricitabine.
- 10 3. The composition of claim 2 wherein the tenofovir DF and
emtricitabine are in a first component and the efavirenz and the surfactant are
in a second component.
4. The composition of claim 3 wherein the first component and the
15 second component are physically discrete but are in contact with one another.
5. The composition of claim 4 wherein the components are layers.
6. The composition of claim 5 which is suitable for oral
20 administration.
7. The composition of claim 5 which is a bilayer tablet weighing less
than about 2.5 grams.
- 25 8. The composition of claim 3 wherein component 2 is produced by
high shear wet granulation.
9. The composition of claim 1 wherein the detergent is sodium lauryl
sulfate.
- 30 10. The composition of claim 3 wherein component 1 is produced by

dry granulation.

11. The composition of claim 2 wherein the total amount of efavirenz, emtricitabine and tenofovir DF is greater than about 60% by weight of the composition.

12. The composition of claim 2 which further comprises magnesium stearate, croscarmellose sodium, microcrystalline cellulose and hydroxypropyl cellulose.

10

13. The composition of claim 12 wherein the approximate percentages by weight of efavirenz, tenofovir DF, emtricitabine, magnesium stearate, croscarmellose sodium, microcrystalline cellulose, sodium lauryl sulfate, and hydroxypropyl cellulose are, respectively, about 39, about 19, about 13, about 2, about 7, about 17, about 1 and about 2.

15

14. The composition of claim 2 wherein efavirenz, emtricitabine and tenofovir DF are provided to a patient upon oral administration at substantially the same AUC and Cmax as the FDA approved products Truvada and Sustiva.

20

15. The composition of claim 7 which weighs about from 1200 mg to 2300 mg (including any film coating that is optionally present).

16. The composition of claim 7 wherein the layers are oriented horizontally along an axis of the tablet.

25

17. A container comprising the composition of claim 1 and a desiccant.

30

18. A method comprising preparing component 1 comprising tenofovir DF, preparing component 2 comprising efavirenz and a surfactant, and placing both components into stabilizing configuration with one another.

5 19. The method of claim 18 wherein component 1 also comprises emtricitabine.

20. The method of claim 19 wherein component 1 is made by dry granulation and component 2 is made by wet granulation.

10

21. The method of claim 20 wherein dry granulated tenofovir DF and emtricitabine are combined with magnesium stearate, wet granulated efavirenz is combined with magnesium stearate and the two magnesium stearate compositions compressed into a bilayer tablet.

15

22. A method comprising orally administering the dosage form of claim 1 to a patient in need of antiviral therapy.

20 23. The method of claim 22 wherein the dosage form is administered only once daily.

24. The method of claim 23 wherein the antiviral therapy is anti-HIV therapy.

25 25. A product comprising emtricitabine, tenofovir DF and efavirenz, a surfactant, and a means for preventing destabilizing contact between the surfactant and tenofovir DF.

30 26. A composition comprising emtricitabine, tenofovir DF and efavirenz which is free of pharmaceutically unacceptable concentrations of FTU,

mono-POC PMPA, dimer and mixed dimer.

27. The composition of claim 26 wherein the concentrations of FTU,
5 mono-POC PMPA, dimer and mixed dimer are, respectively by weight %, 3.9, 9,
1.6, and 1.8.

28. The composition of claim 27 wherein the concentrations are
determined after storage of the composition at 25°C/60% RH for 24 months.
10

29. A unitary dosage form comprising component 1 comprising
tenofovir DF, and emtricitabine and component 2 comprising efavirenz and a
surfactant, component 1 being spatially disposed in stabilizing configuration
with component 2.
15

30. The dosage form of claim 29 which is suitable for oral
administration.