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Original Article

Exploring an Industrial Manufacturing Process of a Drug Containing Tenofovir

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ABSTRACT

Background: Tenofovir is an antiretroviral drug, a reverse transcriptase inhibitor formulated as tenofovir disoproxil in its saline form, which acts as a prodrug of tenofovir. Its clinical use is indicated in the treatment of Human Immunodeficiency Virus (HIV) and Hepatitis B Virus (HBV). In this work, a solid oral formulation in coated tablets of tenofovir disoproxil has been designed, using an appropriate manufacturing process to overcome any possible problems of stability, compressibility and bioavailability. **Materials and Methods:** Compatibility studies have been carried out through thermal analysis (Differential Scanning Calorimetry, DSC) and infrared spectroscopy (FT-IR), pharmacotechnical characterization through analysis of flow time, angle of repose, Hausner Ratio and Carr Index, and Pharmacochemical characteristics (weight, hardness, disintegration, thickness and friability). **Results:** In the pharmaceutical industry, the selection of the most correct tablet production method depends on the individual characteristics of the components and their ability to flow, compress and disintegrate. In this work, a wet granulation process was selected, key to achieving specific granulation, followed by compression and film coating. DSC and FT-IR spectral studies demonstrated that there is no interaction between the active pharmaceutical ingredient and the excipients. Excellent results were found in the pharmacotechnical and physicochemical characterization to obtain the tablets, demonstrating the adequate production process. **Conclusion:** Tenofovir film coated tablets were successfully formulated using the wet granulation compression method and film coating. The methodologies used demonstrated the appropriate selection of the excipients in terms of physical and chemical compatibility and the suitability of the mixture for use in the process of obtaining the tablet.

Keywords: Tenofovir disoproxil oxalate, Tablet, Film coating, Physicochemical characterization, Compatibility.

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INTRODUCTION

Viruses are biological entities that can only replicate within the cells of other organisms, as they lack their own cellular machinery. Although they are not considered cells, they have genetic material and a protein envelope that protects them.[1] Viruses infect their hosts by inserting their genetic material into the cells of the host organism. Then, they use the host's cellular machinery to replicate and produce new viral particles. This process can damage or destroy the infected cells, leading to symptoms of the disease. It is important to note that not all viruses cause diseases, some of them can have symbiotic or mutualistic relationships with their hosts, and however, there are many considered pathogens since they cause diseases in animals, plants, and bacteria.

A healthy immune system allows the billions of viral particles that enter the body to do so without posing a health risk, but this is not always the case.[2] The consequences of viral infection vary widely. Infections can cause acute illness with a short incubation period which may be asymptomatic, or progress with almost no symptoms, but some lead to chronic diseases. During the latency period, the DNA or RNA of the virus is present without replicating or generating any symptoms, but they can be transmitted, as is the case with the herpes virus, the Human Immunodeficiency Virus (HIV), the papovavirus, or Ebola.[3-5]

On the other hand, hepatitis is an inflammatory disease caused by hepatotropic viruses, which are those that have a particular affinity for liver tissue. This viral infection of the liver can lead to both an acute condition and a potentially life-threatening chronic inflammatory disease. The causative agent of hepatitis in humans

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is the hepatotropic virus type B, the Hepatitis B Virus (HBV), which is one of the five existing hepatotropic viruses (A, B, C, D, E).[6,7] The infection, characterized by liver inflammation, can progress to variable fibrosis and necrosis of the tissue. HBV is a public health issue that affects the general population, although it is more common in young people, adults, and groups with risk factors. [8] HBV has infected more than two billion people worldwide, and around 257 million of these people are chronically infected, meaning they are not able to effectively eliminate the virus. Approximately 700,000 people die each year from hepatitis B and its complications, mainly from cirrhosis or hepatocellular carcinoma (primary liver cancer). As of February 2023, hepatitis B is the most common liver infection worldwide.

An innovative industrial manufacturing proposal of coated tablets of Tenofovir Disoproxil Oxalate (TDO) is presented in this paper, which is a recognized antiretroviral drug, an adenosine-5-monophosphate analogue and reverse transcriptase inhibitor, with pharmacological activity not only against the Human Immunodeficiency Virus (HIV) but also against Hepatitis B Virus (HBV).[6,8] In order to prepare a pharmaceutical form for oral administration, the prodrug TDO was developed, which in turn is available in various salts, such as fumarate and oxalate, to improve its bioavailability through this route of administration. The reference medication is Viread™, which is marketed by Gilead Sciences International Limited.

The main objective of this article is to show the process of development of TDO-coated tablets as a strategy to offer a locally developed treatment that responds to the growth in the number of patients infected with HIV and HBV.[9,10] Tablets are among the most chosen oral dosage forms due to their numerous advantages, such as ease of administration, high patient compliance, and cost-effectiveness. In this way, the administration of a single dose of an antiviral encompasses the treatment of the two most prevalent viral pathologies in developing countries. The technology, manufacturing processes and ingredients used are designed to obtain an economical and high-quality product for the control of said pandemics, through the use of affordable technology for the production of oral medications. A pandemic is the worst situation in the field of infectious diseases. Innovative technologies have the potential to address the challenges associated with making drugs that can play an important role, being economical and easy to produce and administer.

Granulation is a well-known technology utilized to prepare granules of certain shapes and sizes, which improve fluidity, reduce segregation, and raise the dissolution rate and mechanical strength of solid particles. The properties of the granules not only define the processes and large-scale production but also contribute to achieving the therapeutic effect. In recent years, with the application of Quality by Design (QbD), a comprehensive and deep understanding of the relationships between the physical-chemical properties of materials, the production process and the final quality and safety of the product has been emphasized. In this paper wet granulation[11-16] followed by drying, final mixing, compression and film coating were selected.[17-19] Coating is a critical process commonly employed for functional and aesthetic reasons. The film coating chosen in this work was intended to significantly enhance patient compliance.

Conducting a study on the industrial manufacturing process of a pharmaceutical dosage form of oral administration containing TDO involves comprehensive examination. The development of coated tablets of TDO, an antiretroviral medication utilized in the treatment of HIV/AIDS and chronic hepatitis B, necessitates an in-depth analysis of each stage of the process, encompassing raw material sourcing, Active Pharmaceutical Ingredient (API) synthesis, formulation development, that includes diverse unitary operations such as granulation, compression, coating, packaging and the establishment of appropriate quality control tests according to environmental considerations, regulatory compliance, and post-marketing surveillance.

MATERIALS AND METHODS

Materials

Tenofovir Disoproxil Oxalate (TDO) (molar mass: 608.97 g/mol, IUPAC name: [(2R)-1-(6-aminopurin-9-il) propan-2-yl] oxymethyl- (propan-2-yloxycarbonyloxymethosi) phosphoryl] oxymethylpropan-2-yl (E)-ethandioic acid).[20] CAS Nº 147127-20-6. Molecular structure is shown in Figure 1. Tenofovir batch TDO/1508005 was acquired from Tyche Industries Limited (India), while lactose monohydrate, microcrystalline cellulose, crospovidone, pregelatinized corn starch, talcum powder and magnesium stearate were purchased from Guinama (Spain), local dealer in Spain for pharmaceutical excipients all of them with certified quality. Opadry II® for film coating was provided by Colorcon (Spain).

Methods

Preformulation studies

The initial stage in the rational development of pharmaceutical forms is the study prior to formulation of the physicochemical and pharmacotechnical characteristics of the API individually and in combination with possible excipients. The evaluation carried out in preformulation aims to generate enough data for the formulator to construct safe, bioavailable dosage forms that are feasible to produce at an industrial level.

Excipient-Drug Compatibility Research

Mixtures of TDO and each one of the excipients under evaluation, in a weight ratio of 1:1, were prepared by homogenizing thoroughly the constituents for 10 minutes in a mortar until a physically homogeneous binary mixture was obtained.

Differential Scanning Calorimetry (DSC) analysis

Differential Scanning Calorimetry (DSC) measurements were performed with a Mettler TA 4000 DSC Star System instrument (Switzerland), the key details used are described in Table 1. The choice of parameters, such as the heating rate, temperature range, gas atmosphere, and sample weight, was carefully considered to ensure the accuracy and repeatability of the measurements.

Fourier transform-infrared spectroscopy (FT-IR) analysis

Infrared spectra (FT-IR) were examined over the scanning range of 4000-500 cm^{-1} using a Fourier Spectrum 2000 spectrometer Perkin Elmer® System 20000FT-IR (United States). In Table 2 appears a breakdown and explanation of the key details. The recorded spectra are presented in terms of % transmittance, providing information about the absorption characteristics of the analysed samples over the specified wavenumber range.

Formulation studies

For the development of the TDO film tablet formulation, it was decided to carry out compression by wet granulation.[17-19] As a final stage, the cores were covered with a film coating whose purpose is aesthetic and not functional. The flow chart of the proposed process is shown in Figure 2. The powders were mixed by geometrical dilution method in a mortar and mixed thoroughly for 15 min. Tablets were manufactured with different doses: 123 mg, 163 mg, 204 mg, and 245 mg.

Pharmacochemical characteristics

The tablets characterization was determined by the methods of the Pharmacopoeia.[21]

Weight

In pharmaceutical quality control, ensuring the weight uniformity of tablets is crucial to maintain the consistency and efficacy of the medication. The use of an electronic balance and the selection of a representative sample of tablets from each batch contribute to the accuracy and representativeness of the weight assessment. The percentage deviation values provide insights into the variability of individual tablet weights within a batch. The goal is to ensure that each tablet in a batch has a weight close to the average, indicating uniform manufacturing processes. Twenty tablets were representative and randomly selected from each batch. The weighing was performed using an electronic balance, specifically a Mettler Toledo AG 245 (Switzerland). Electronic balances are commonly used in pharmaceutical and laboratory settings for their precision. The average weight of all the tablets in each batch was calculated. This provides a measure of the central tendency of the tablet weights in a given batch. The percentage deviation from the mean value was determined for each tablet. This is likely calculated as the percentage difference between the individual tablet's weight and the average weight of the batch.

Diameter

Diameter testing is a crucial aspect of quality control in tablet manufacturing. The diameter of final product was evaluated by means of a tablet testing instrument Pharmatest PTB 311 (Germany).

Hardness

In the preformulation step, the hardness expressed as the force in Newton required to crush the tablets, was evaluated using a manual tablet hardness testing instrument (Bonals nº 337, Spain). The evaluation of tablet hardness using the Pharmatest PTB 311 (Germany) tablet testing instrument is part of the quality

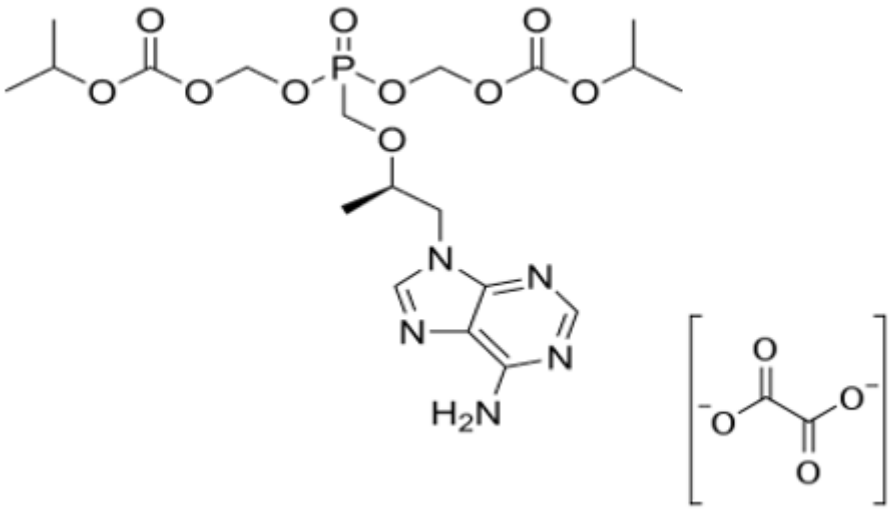

Figure 1: Tenofovir Disoproxil Oxalate (TDO) (Tyche Industries Limited, India).

control measures applied to the final product. Hardness testing is a crucial aspect of quality control in tablet manufacturing. It ensures that the tablets have the appropriate mechanical strength, which is important for factors such as stability, packaging, and patient compliance.

Disintegration time

The disintegration test of tablets used a disintegration apparatus (Disaggregation machine Turu-Grau, Spain) in distilled water at 37.0±0.5ºC, for six tablets. The disintegration time was calculated. Conducting tests provides information on how the tablets act for oral drug delivery. The use of a standardized disintegration test apparatus ensures consistency and reliability in the testing process.

Thickness

The use of a calibrated instrument like a Vernier calibrator (Japan) during the preformulation stage and a specialized tablet testing instrument for the final product allows for accurate and standardized measurements. Monitoring and controlling tablet thickness are critical aspects of ensuring uniformity and performance of the final pharmaceutical product. Six tablets were used for measurement. A tablet testing instrument, Pharmatest PTB 311 from Germany was used.

Friability test

Friability analysis of tablets measured by a tablet friability instrument, exactly with the Pharmatest PTF E® (Germany). A sample of tablets representing 6.5 g was taken for the friability test. The tablets were carefully dedusted before testing. Dedusting is a process to remove excess dust or loose particles from the tablet surface, ensuring accurate weight measurements. The tablets were accurately weighed before the friability test. This initial weight is used as a reference for calculating the percentage of friability. The drum containing the tablets was rotated 100 times at a speed of 25 rpm. This rotation simulates mechanical stress that tablets may experience during handling, transportation, or packaging. The tablets were removed and then accurately re-weighed to determine any weight loss due to friability.

The percentages of friability were calculated using the formula:

$$\% \text{ Friability} = \frac{(\text{initial weight} - \text{final weight})}{\text{initial weight}} \text{x } 100$$

This calculation provides the percentage of weight loss or friability experienced by the tablets during the testing process. A maximum loss of mass not greater than 1.0 % is considered acceptable.[21]

Pharmacotechnical characterization

The physical properties were determined by the methods of the Pharmacopoeia.[21] Different parameters to determine flow property, such as, Carr index, Hausner ratio and flowability (angle of repose and fluidity), were proposed.

Carr's index

The instrument used was the powder density tester, PT-TD200 (Germany), Carr's index is used to calculate the compression capacity of the powder mixture in percent:

$$\text{Carr's Index (IC)} = \frac{(Dc - Da)}{Dc} \text{x } 100$$

Dc (Density compressibility) is de the volume occupied by the same amount of powder after 2500 hits on the sample. It represents the compressed state of the powder. Dc gives insights into the behaviour of the powder under compression, simulating the effects of compaction or compression during processes like tablet manufacturing. Da (Density apparent) is the occupied volume of 10 g of the powder mixture was determined, and its density in g/mL was calculated. It represents the volume occupied by a specified mass of the powder without compaction. Da offers information about the volume occupied by a specified mass of the powder without compaction, reflecting the powder's loose state. The units of g/mL for both Dc and Da indicate the mass per unit volume, facilitating consistent comparisons and analysis.

Hausner's ratio

The flow and slip capacity of the powder is calculated by:

$$\text{Hausner's Index (IH)} = \frac{Dc}{Da}$$

Flowability

The angle of repose is a parameter commonly used for the evaluation of interparticle force. A funnel with a wide outlet is affixed at a distance of 10 cm above the bench, where a piece of paper is placed directly beneath the funnel. Powder is added while the funnel is closed. The contents flow through and collect on the paper. The average radius (Martin's radius, denoted as "r") of the circular cross-section of the cone is measured along 5 directions. The height of the cone (denoted as "h") is measured. The angle of repose (α) is calculated using the following formula:

$$\text{tg } (\alpha) = \frac{h}{r}$$

The calculated angle of repose provides information about the flowability and cohesion of the powder. A lower angle generally indicates better flowability.

RESULTS

Drug-excipient compatibility studies by DSC

Differential Scanning Calorimetry (DSC) can easily determine the amount of heat absorbed or released by a chemical at a constant temperature, in which time of exposure to endothermic or exothermic processes can be selected. Figure 3 shows the behaviour of the drug and each different excipient individually.

Two endothermic peaks were uncovered in the DSC-thermogram of TDO, which would represent the melting of two polymorphic forms of the API analysed, followed by its decomposition. Thus, the first endothermic peak displayed in the DSC curve ($T_{onset=}$120.80 °C; ΔH_{fus}=13.62 J g^{-1}) would indicate the melting point of the polymorphic form 1. This first endothermic peak is then followed by a small exothermic event, which could be attributed to the recrystallization of the melted API into form 1, which has a melting peak at 144.93 °C (ΔH_{fus}=62.82 J g^{-1}).[22,23]

In the DSC of lactose monohydrate, several endothermic peaks were observed, the first two undifferentiated, around 143°C, are a consequence of water loss. The third peak at 156.76 °C could be the anomerization of -lactose to -lactose, due to the presence of residual water. The last peak above 230°C is the result of the fusion of the lactose crystal and its subsequent decomposition. The microcrystalline cellulose shows an endothermic peak (T_{onset}=175.36°C) that is attributed to the acid hydrolysis of crystalline cellulose. Crospovidone presents a single endothermic peak (T_{onset}=178.91°C) corresponding to its melting point, as described in the literature, and in that of crospovidone a peak corresponding to a glass Transition phase (T_g) is observed close to 200°C. In the case of starch, you can see in Figure 3-d the gelatinization temperature below 90°C; this result depends on the factors of the production process. Gelatinization is a process in which bonds are broken. intra and intermolecular within starch granules. Therefore, any change in the number of hydrogen bonds will cause a change in the heat required to gelatinize the starch. In addition, a third endothermic peak appears related to a glass

Table 1: Experimental conditions for DSC analysis.

Experimental procedure	Number of measurements	Triplicate measurements were performed, indicating that each experiment was repeated three times for reliability.
	Heating rate	A heating rate of 10°C/min was used, implying that the temperature increased at a rate of 10°C/min.
Operating conditions	Temperature range	The DSC measurements were conducted over a temperature range from 20°C to 280°C.
	Gas atmosphere	The experiments were conducted under a nitrogen flow (20 mL/min). This is done to prevent oxidation or combustion of the samples.
Sample preparation	Sample type	Both drugs and excipients were analysed.
	Sample weight	Samples weighing about 3-4 mg were accurately measured and placed into aluminium sealed pans. The sample weight is crucial for obtaining accurate calorimetric data.
Calibration	Baseline and temperature calibration	The equipment was calibrated for baseline and temperature using indium (156.6±0.3°C; 28.45±0.60 J/g) and zinc (419.6±0.7°C; 107.5±3.2 J/g) as standards.
Data analysis		The data of the onset temperature was used instead of the melting or decomposition temperature. This choice is made to avoid the influence of mass on the measurements.

Table 2: Experimental conditions for FT-IR analysis.

Resolution		The resolution was set to 1 cm^{-1}. This value indicates the smallest difference in wavenumber that can be distinguished by the instrument. Higher resolution provides more detailed spectra but may require longer scanning times.
Sample preparation	Sample type	Drugs and excipients were analysed.
	Sample amount	Samples of 2 mg were used for the analysis.
	KBr mixture	The samples were mixed with 100 mg of KBr (potassium bromide). KBr is commonly used as a diluent in FT-IR spectroscopy to form a pellet for analysis.
	Grinding procedure	The mixture of sample and KBr was gently ground in a mortar.
Disk preparation		Disks of about 13 mm in diameter were prepared with KBr. The disks were compressed in a hydrostatic press at a force of 5 T (tons) for 2 min. This step ensures the formation of a homogeneous and compact pellet for the FT-IR analysis.
Data collection	Transmittance	The spectra were recorded in terms of % transmittance. FT-IR spectra are often presented as the percentage of transmitted light, allowing for the analysis of the absorption characteristics of the sample.

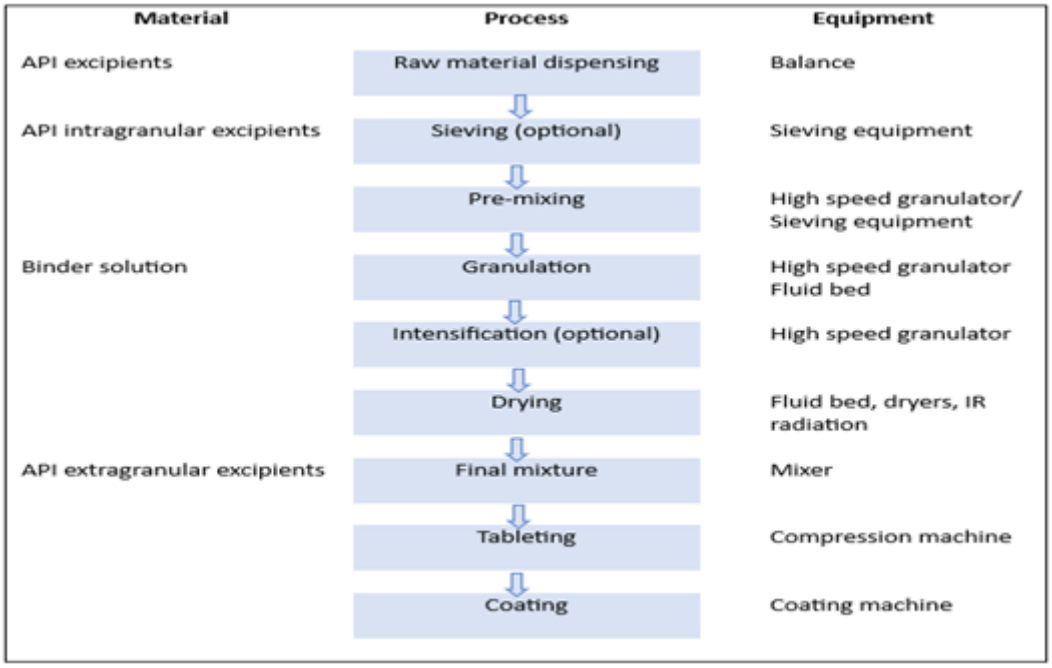

Figure 2: Flow chart for the development of TDO tablet formulation (Own elaboration).

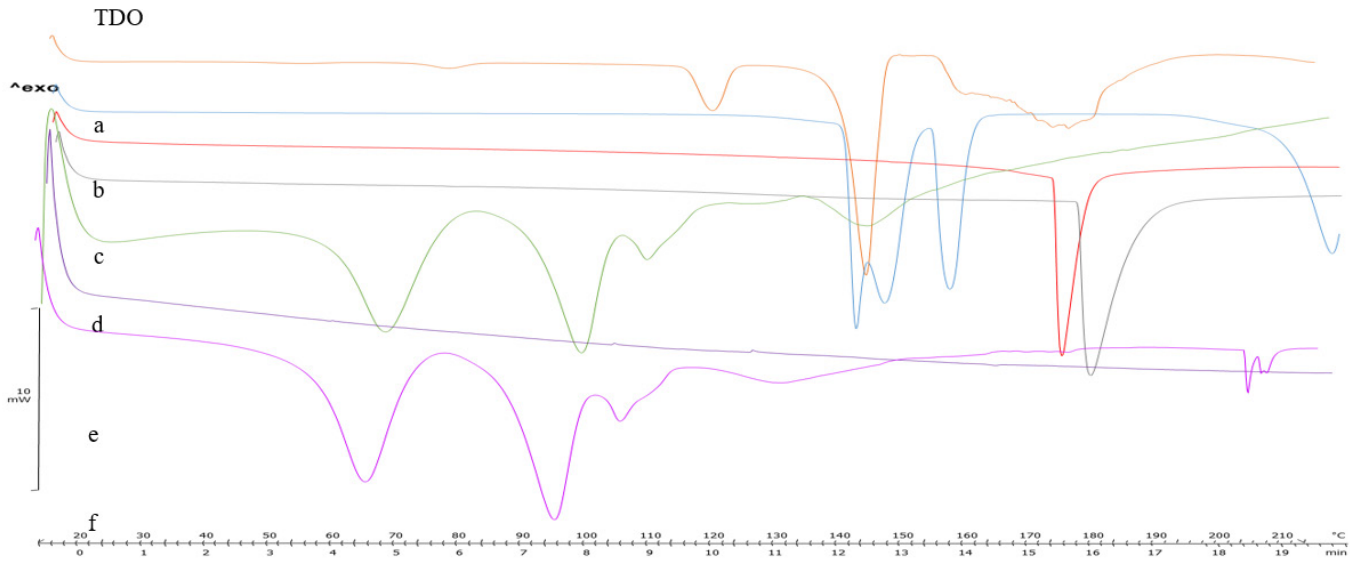

Figure 3: DSC-thermogram of pure TDO. DSC-thermogram of lactose monohydrate (a), microcrystalline cellulose (b), crospovidone (c), pregelatinized corn starch (d), talcum (e) and magnesium stearate (f) (Own elaboration Mettler TA 4000 DSC Star System).

Transition (T_g), at 158°C. In the case of talc, no peak was observed in the studied temperature range. Magnesium stearate shows two first peaks corresponding to the evaporation of water, at 61.72°C and 93.02°C, followed by a third peak at T_{onset}=107.97°C which is due to the fusion of magnesium palmitate, since that stearic acid and palmitic acid appear in its composition (this impurity is usually found in commercial batches).

DSC has proven to be an excellent tool for detecting drug-excipient interaction. According to the results of the physical mixtures with each of the excipients in a 1:1 proportion (Figure 4) it can be said that the small variations in relation to the melting temperature of the drug are due to the decrease in individual purity, without indicating an incompatibility. It can be stated therefore in view of the results found that the DSC facilitated compatibility studies between TDO and tablet excipients selected. The endothermic peaks of TDO were well retained in all individual samples of drug and excipients selected.

Drug-excipient compatibility studies by FT-IR

FT-IR spectroscopy was applied for complete the compatibility studies. The spectrum for the TDO in the Figure 5 reveals the characteristic peaks of this drug located at 3085, 1760, and 1270 cm^{-1}. Figure 6 shows the individual FT-IR spectra of each one of

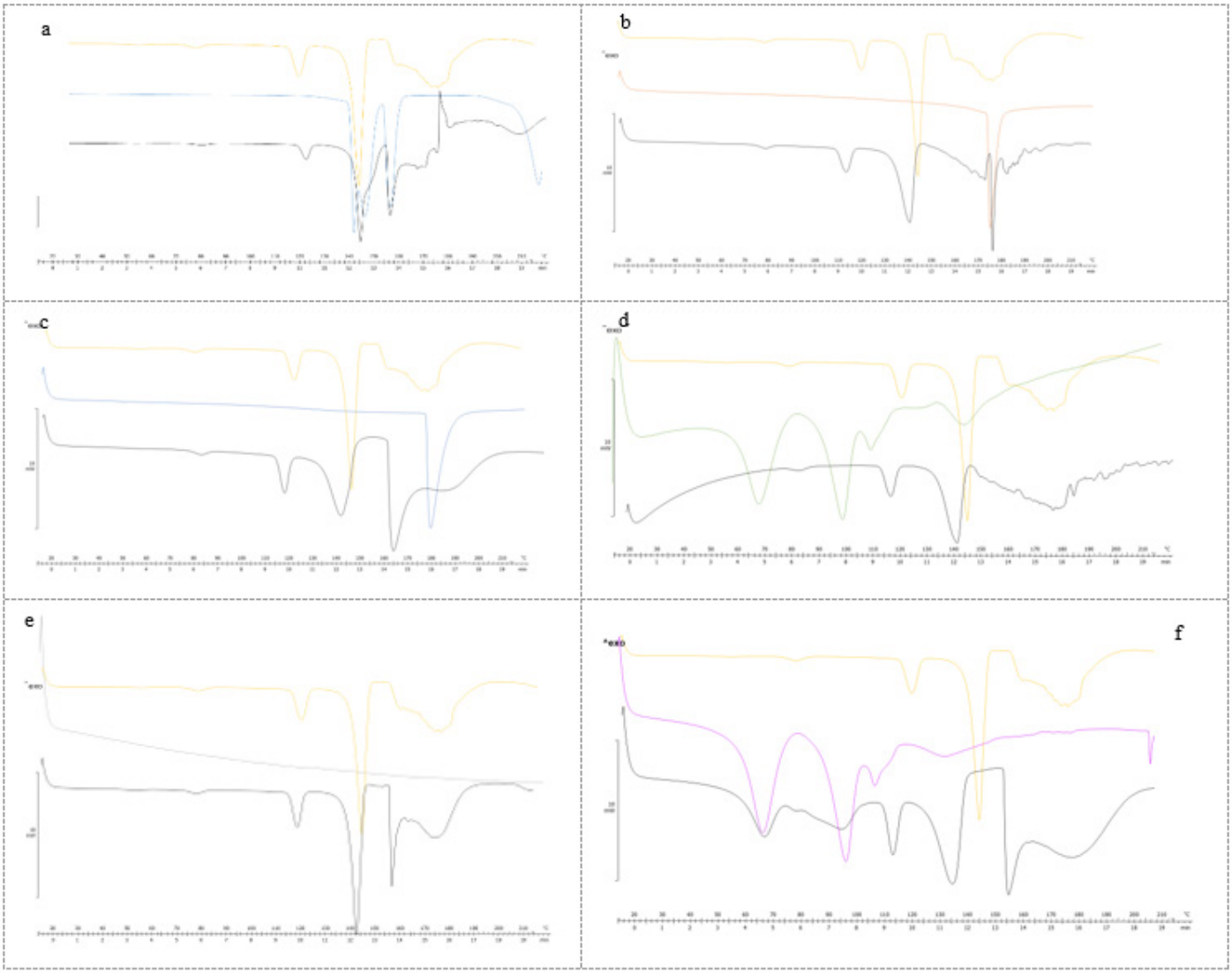

Figure 4: DSC-TDO-lactose monohydrate (a), TDO-microcrystalline cellulose (b), TDO-crospovidone (c), TDO-pregelatinized corn starch (d), TDO-talcum (e) and TDO-magnesium stearate (f) (Own elaboration Mettler TA 4000 DSC Star System).

the excipients used in the preparation of the core of the coated tablet.

Additionally, it can be seen in Figure 6-g the behaviour of the TDO in the physical mixture prepared with all ingredients of the formula. It was exhibited no change in the characteristic positions of the bands, with a similar intense peak at 1760 cm^{-1} due to the amide C=O group of the TDO molecule, that could indicate compatibility, this is how the same bands can be distinguished without considerable displacements. It is remarkable beside bands of the carbonyl group (1760 cm^{-1}) due to the C=O tension, the bands around 1270 cm^{-1} due to symmetric and asymmetric tension vibrations characteristic of P=O and the broadband in the region 3100-2900 cm^{-1} as an indication of the presence of the hydroxyl group. In summary, it was found that the spectrum with all excipients studied were very similar to the original powder. These results are in agreement with the results obtained by DSC.

Pharmacochemical characteristics

Table 3 shows the results of the controls carried out throughout the manufacturing process: weight, hardness, disintegration, thickness, friability. [21]

The unique mixture of ingredients to produce tablets of the four strengths is verified to meet the specifications, which is an advantage with a view to the industrial production of the product. None of the tablet batches tested completed the disintegration tests implemented successfully, independently of the localisation of the disintegration test. Thus, for each composition, an exponential relation was detected between compression pressure and disintegration time. However, the difference in disintegration time at the lowest and the highest compression pressure seemed to be reduced when increasing intragranular disintegrant concentration.[24-26]

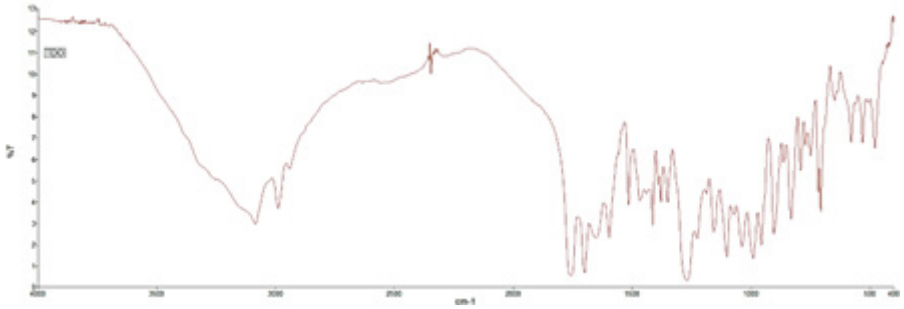

Figure 5: FT-IR Spectra of pure TDO in mid infrared region (4000-500 cm^{-1}) (Own elaboration Fourier Spectrum 2000 spectrometer Perkin Elmer® System 20000FT-IR).

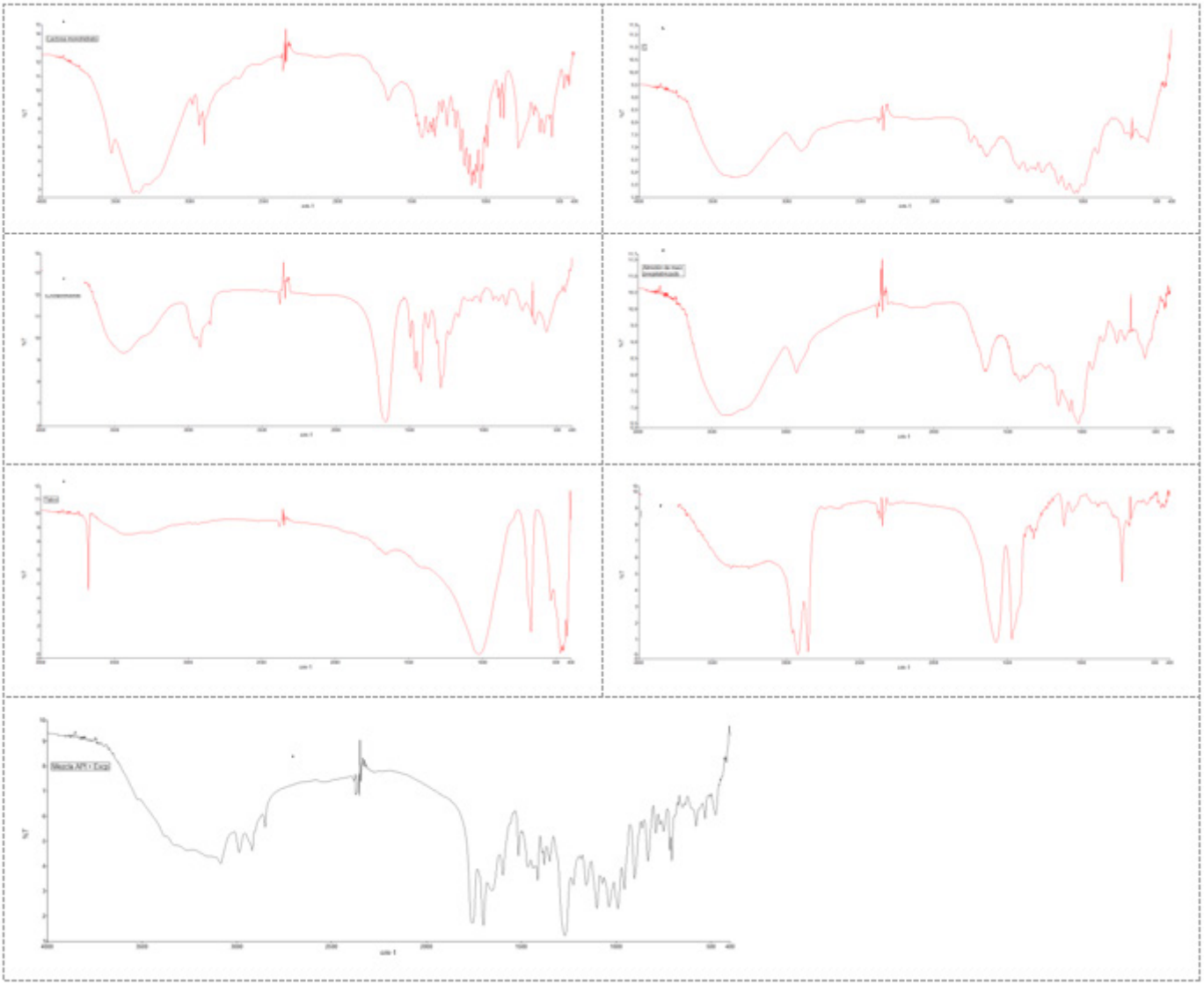

Figure 6: FT-IR Spectra of pure TDO-lactose monohydrate (a), TDO-microcrystalline cellulose (b), TDO-crospovidone (c), TDO-pregelatinized corn starch (d), TDO-talcum (e) and TDO-magnesium stearate (f). Spectra of pure TDO and all excipients (g) in mid infrared region (4000-500 cm^{-1}) (Own elaboration Fourier Spectrum 2000 spectrometer Perkin Elmer® System 20000 FT-IR).

Pharmacotechnical characterization

The pharmacotechnical parameters determined experimentally during the determination of flow and compressibility parameters are showed in Table 4. The suitability for the preparation of tablets with the formula developed was confirmed with the results of its pharmacotechnical parameters.

Hausner ratio and Carr index results obtained were appropriate, suggesting a good flow of all flow parameters, with positive effects

Table 3: Results of requirements of the process of compression.

Control in process	Tenofovir 123 mg	Tenofovir 163 mg	Tenofovir 204 mg	Tenofovir 245 mg
Individual weight	246.0 mg (227.6-264.5)	326.0 mg (301.6-350.5)	408.0 mg (377.4-438.6)	490.0 mg (453.3-526.8)
Mean weight	246.0 mg (233.7-258.3)	326.0 mg (309.7-342.3)	408.0 mg (387.6-428.4)	490.0 mg (465.5-514.5)
Mean hardness	>39.0 N	>49.0 N	>49.0 N	>49.0 N
Disintegration	≤15 min	≤15 min	≤15 min	≤15 min
Thickness	3.9 mm (3.6-4.2 mm)	4.8 mm (4.5-5.1 mm)	4.8 mm (4.5-5.1)	5.5 mm (5.2-5.8)
Friability	≤1.0 %	≤1.0 %	≤1.0 %	≤1.0 %
Aspect	Round cores, white or almost white, without engraving.			

Table 4: Pharmacotechnical parameters of the mixture powders.

Parameter	Results
Angle of repose	36.6 °±0.5 °
Fluidity	8.4 s±0.1 s
Carr index	12.5±0.9
Hausner index	1.14±0.01

Table 5: Applied material.

Excipient	Function
Intragranular	
Lactose monohydrate	Filler
Microcrystalline cellulose	Diluent and disintegrant
Crospovidone	Disintegrant
Pregelatinized corn starch	Binder
Extragranular	
Crospovidone	Disintegrant
Microcrystalline cellulose	Diluent and disintegrant
Talcum	Glidant and lubricant
Magnesium stearate	Glidant and lubricant

on the flowability and compressibility properties of the locally TDO coated tablet generated.

Experimental design

The granulator through a mill with a mesh size of 0.5 mm used lactose monohydrate, microcrystalline cellulose, crospovidone and pregelatinized corn starch (Table 5). Kneading or wetting: the binder (purified water in this case) is added to the premix in order to bind the particles. The binder liquid can be incorporated by jet or through an atomizer (spray), the latter being the most recommended. Kneading is carried out with the paddles and the chopper is responsible for breaking up agglomerates and giving the dough enough strength to form granules.

Sifting of the wet granules in order to homogenize the granules. This stage is carried out during the discharge of the high-speed granulator through an automatic sieve; the most used being the conical type and the oscillating ones. The wet granules can be discharged or, in the case of continuous lines, it is not necessary, since it is automatically transported to the next equipment. The wet solids are dried through a stream of air. As the granules dry, the product temperature increases. [27-29] The end point of this stage is determined by the process control of Loss on Drying (LOD) that determines the amount of water remaining in the granules. Addition of extragranular excipients through a mill with a mesh size of 0.5 mm, crospovidone, microcrystalline cellulose, magnesium stearate and talcum powder (Table 3).[30,31]

Table 4 displays the setting up of the compression machine, a Fette 102i rotary tablet press, to generate tablets with the appropriate weight and hardness requirements needed (Table 6). This machine was used as it can simulate the conditions of the manufacturing, as it is equipped with a three-chamber feed frame (Fill-O-Matic) to ensure an accurate powder flow from the hopper to the dies. Moreover, the presence of these three chambers allowed the processing of large volumes of the drugs, limiting the appearance of potential disturbances during the manufacturing process, such as a brief stop of the powder flow from the hopper to the feed frame.

Secondly, the coating suspension was prepared and gently stirred throughout the process. The coating solution was used within the first 24 hr after preparation:

- Opadry II® yellow (for tenofovir 123 mg).
- Opadry II® blue (for tenofovir 163 mg).
- Opadry II® orange (for tenofovir 204 mg).
- Opadry® clear (for tenofovir 245 mg).

Opadry II® is a complete film coating system, composed of polymer, plasticizer, pigment, and other additives (polyvinyl

Table 6: Requirements of process of compression.

Parameter	Set
Speed of compression (tablet/h)	100000 - 500000
Speed of F-O-M (rpm)[a]	30 - 90
Compression force (kN)	8.0 - 24.0

[a] Speed of Fill-O Matic.

Table 7: Requirements of process of spray.

Parameter	Value set
Gun-bed distance	20 cm±2 cm
Gun-gun distance	15 cm±1 cm
Solution flow rate	90 g/min±5 g/min
Atomization pressure	100 SLPM±10 SLPM[a]
Fan pressure	40 SLPM±10 SLPM[a]
Outlet temperature	41°C±3°C
Air flow	1000 m^3/h±200 m^3/h
Pan pressure	-20 mm WC±5 mm WC[b]
Pan speed	7 rpm±2 rpm

[a] Standard Liters Per Minute; [b] Water column.

alcohol, titanium dioxide, macrogol, talc, quinoline yellow and iron oxide yellow).[32] Opadry II® systems are water soluble, pH independent film coatings, which allow immediate disintegration for fast release of drug actives. Different colours have been chosen based on the different doses of each tablet, minimizing possible medication errors, and achieving a more attractive pharmaceutical form that improves therapeutic compliance. The spraying process and control weight gain throughout the entire process (Table 7), resulted in tablets with a homogeneous coating with a finish that clearly improved appearance.

DISCUSSION

The manufacturing of the antiviral drug TDO is a complex process involving a variety of critical aspects that affect its production, quality, and accessibility, especially in regions with limited resources. Therefore, it is vital to carefully select the manufacturing processes and technology used in production. The oral route is the chosen formulation route due to its high physical, chemical, and biological stability, accurate dosing, simple and practical application, good control over drug release, and low cost. The manufacturing of coated tablets involves a series of complex stages that require meticulous process optimization to reduce costs and ensure the quality and efficacy of the final product. Wet granulation is the technique that allows obtaining an intermediate granulation product which can be subjected to purity controls, thus ensuring homogeneity and avoiding deviations in the final tablet product. Furthermore, this technology is widely used in the pharmaceutical industry, and its scaling has demonstrated reliability, making it easy to transfer from one factory or country to another, especially in developing countries, and it is also easy to produce in campaigns. Therefore, the selected process is wet granulation, followed by drying, final mixing, compression, and film coating. Additionally, the manufacturing process must follow Good Manufacturing Practices (GMPs) and comply with regulations and quality standards established by regulatory authorities such as the Food and Drug Administration (FDA) in the United States and the European Medicines Agency (EMA) in Europe to ensure the safety and efficacy of the medication.

Before developing and optimizing each of the presentations, studies on the physical and chemical compatibility between the drug and the selected excipients to meet quality standards were carried out using Differential Scanning Calorimetry (DSC) and Fourier-Transform Infrared Spectroscopy (FT-IR). The use of spectroscopic and thermal methods in the preformulation stage is of vital importance for the detection of possible incompatibilities and physicochemical interactions between the active ingredient and the excipients, thus selecting the most suitable excipients for the formulation design.

Lactose monohydrate is selected because it is a widely used diluent in tablets. Its advantages include being easily soluble in water, having a pleasant taste, low moisture adsorption capacity, and good compression characteristics. Pre-gelatinized starch is elected for being one of the most commonly used excipients in solid oral dosage formulations due to its versatility as a binder, diluent, and disintegrant. It increases tablet fracture resistance and decreases friability. Crospovidone belongs to the category of superdisintegrants, which have aroused significant interest due to their ability to enhance the bioavailability of certain drugs, increase available surface area, and promote rapid release. Therefore, it is chosen for this formulation. Microcrystalline cellulose is a purified partially depolymerized cellulose with diluent, binding, and disintegrating properties. It is chosen because it acts as a cohesive agent in wet granulation and exhibits uniform and rapid drying, facilitating the quick evaporation of liquid in wet granulation.

Talc is a purified and hydrated magnesium silicate primarily used as a lubricant and anti-adherent in solid oral formulations. It is chosen for this reason. Magnesium stearate is a hydrophobic excipient that can negatively affect various parameters such as the flow of blends, drug dissolution, or the friability of solid dosage forms. To mitigate these undesirable effects, it is best to add it in the lowest possible proportion and control mixing times. It is widely used in tablet manufacturing due to its excellent lubricating properties.

To close, Opadry II® was chosen as the film coating material for its simple preparation, flexibility, and excellent appearance on coated tablets. It reduces preparation and coating times while providing a finish product of very high quality. The coating also facilitates easy identification of different doses through its

application of distinct colors. Opadry II® offers a range of benefits including product protection, visual enhancement, taste masking, ease of identification, swallowability improvement and stability enhancement, making it a widely used coating in pharmaceutical formulation.

CONCLUSION

The specific excipients used and their concentrations, in conjunction to the manufacturing process are applicable and cost-effective methods to develop this novel TDO film coated tablet. Selected excipients did not interact in the mixed sample and facilitated the production of the new coated tablets at short dissolution times following a wet granulation method. The API used shows a good solubility, which could be attributed to the introduction of crospovidone intra and extra granularly, possibly due to its good disintegrant properties. Thus, the granularity characteristics of crospovidone enhanced the water absorption and increased surface area of the mixing product, reducing its disintegration time and, therefore, its dissolution time. Hardness, disintegration, dissolution, and friability displayed by the new TDO tablet were shown to meet the pharmacopoeia requirements. It is important to note the significant reduction in process times, thanks to the choice of the selected coating system.

An appropriate characterisation and compatibility study of the API-excipients used have permitted the team to quickly identify and perform any necessary adaptation throughout the different technological stages, highlighting the value of the techniques (DSC and FT-IR) and methods followed to develop improved new tables of high quality.

Finally, the pharmacotechnical characteristics of the tablets showed excellent flowing and compressibility characteristics of the mixture of powders, conformed to the standards of the European Pharmacopoeia.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

AIDS: Acquired Immunodeficiency Virus; **API:** Active Pharmaceutical Ingredient; **DNA:** Deoxyribonucleic acid; **DSC:** Differential Scanning Calorimetry; **EMA:** European Medicines Agency; **FDA:** Food and Drug Administration; **FT-IR:** Fourier- Transform Infrared Spectroscopy; **GMPs:** Good Manufacturing Practices; **HBV:** Hepatitis B Virus; **HIV:** Human Immunodeficiency Virus; **LOD:** Loss on Drying; **IC:** Carr's Index; **IH:** Hausner's Index; **QbD:** Quality by design; **RNA:** Ribonucleic acid; **SLPM:** Standard liters per minute; **TDO:** Tenofovir Disoproxil Oxalate; **WC:** Water column.

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