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FORMULATION DEVELOPMENT AND EVALUATION OF FILM COATED TABLETS OF TENOFOVIR DISOPROXIL FUMARATE: RESEARCH ARTICLE

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ABSTRACT

The management of drug resistance has become part of the management of HIV disease in the treated individual. As two or more nucleoside reverse transcriptase inhibitors (NRTIs) are generally part of each antiretroviral regimen, there is a need to fully understand resistance and cross-resistance within this class of drugs. Broad cross-resistance to NRTIs caused by the group of HIV RT mutations associated with zidovudine and stavudine therapy (thymidine analogue mutations or TAMs) has been well established. The response to tenofovir disoproxil fumarate (TDF) therapy is also limited by certain patterns of TAMs (> or = 3 TAMs with M41L or L210W). The K65R mutation can result from tenofovir DF, abacavir, stavudine, zalcitabine or didanosine therapy. From in vitro phenotypic analysis, the K65R mutation shows no cross-resistance to zidovudine, but low-level resistance to tenofovir and the other NRTIs. Based on clinical cut-offs established for the individual NRTIs, the phenotypic results with K65R suggest full-to-partial drug activity for multiple NRTIs, including tenofovir, against the K65R mutant. Similar to the M184V mutation, the K65R mutation is also associated with reduced in vitro viral replication capacity, hallmarks of which can be demonstrated at the enzymatic level. From cross-sectional genotypic analyses, the K65R mutation and TAMs appear to represent separate patterns of NRTI resistance. Among treatment-naive patients who developed the K65R mutation in clinical trials, successful second line regimens were established. Thus, the K65R mutation appears manageable for the sequencing of treatment regimens in the case of its development.

INTRODUCTION

1.1 Definition: Tablet is a well known drug oral dose structure. The tablet comprise of the API along with different Excipients. Coating is a covering material cycle by which a layer of is applied to the outer layer. A measurement structure to get certain advantages that principally goes from. (Arora Rimjhim, 2019).

1.2 ADVANTAGES & DISADVANTAGES: (Balaji G, 2013)

1.2.1. Advantages

- Elevated patient compliance.
- Their cost is lowly of all dosage forms
- One of the major reward of tablet over capsules is that the tablet is basically "tamper proof dosage form".
- Easiest & cheapest to packaging & consignment
- They best all property of chemical, mechanical & microbiological properties
- Accuracy of dose is maintain.
- Least amount microbial spillage.
- Large scale manufacturing to dosage forms.
- Product recognition is easy & marketing done with the help of ribbed punches & printing with fit for human consumption ink.
- As a tablet is not a sterile dosage form, rigorous environmental conditions are not required in the tablet department.

1.2.2 Disadvantages

- Refuse to accept compression because amorphous nature & low density character.
- Drugs with poor wetting, slow dissolution property, large dosages or any grouping of these features may be not easy or impossible to formulate & manufacture as a tablet.
- Capsules having superior cost.
- The amount of liquid drug (e.g., vitamin E, Simethicone) that can be attentive onto a tablet is very less.
- Tricky to swallow for kids, terminally ill & elderly patients.
- Patients undergoing radiotherapy cannot gulp down tablet.

1.3 MANUFACTURING METHODS OF TABLETS: (F.A, 2005)

There are four wide-ranging methods of tablet preparation.

- Direct compression
- Wet granulation method
- Dry granulation method
- Fluidized bed granulation

The chief guideline in manufacture is to ensure that the apposite quantity of active ingredient is equal in each tablet so ingredients should be well-mixed. Compressed tablets are exert to enormous pressure in order to compact the material. If a sufficiently homogenous mix of the components cannot be obtained with uncomplicated mixing, the ingredients must be granulated prior to compression to pledge an even distribution of the active compound in the final tablet. into a tablet: wet granulation & dry granulation.

Direct Compression: This method is used when a cluster of ingredients can be blended & positioned in a tablet press to make a tablet devoid of any of the ingredients having to be changed. This is not very frequent because many tablets have active pharmaceutical ingredients which will not let for direct compression due to their concentration or the excipients used in formulation are not favorable to direct compression.

There are several different methods of granulation. The most well-liked, which is used by over 70% of formulation in tablet manufacture is wet granulation. Dry granulation is one more method used to form granules.

Wet granulation: Wet granulation is a procedure of using a liquid binder or adhesive to the powder mixture.

Procedure of Wet Granulation

Step 1: Weighing & Blending

Step 2: The wet granulate is equipped by adding the liquid binder/adhesive. Examples such as methyl cellulose, CMC, gelatin, & povidone.

Step 3: Screening the damp mass into pellets or granules

Step 4: Drying the granulation

Step 5: Dry screening: After the granules are dried, pass from side to side a screen of smaller size than the one used.

Step 6: Lubrication- It reduce friction flanked by the tablet & the walls of the die cavity.
Step7: Water form bonds between powder particles that are strong enough to lock them in together. However

Dry granulation: Dry granulation can be conducted on a press using slugging tooling or on a roller compactor commonly referred to as a chilsonator.

Dry granulation equipment offers a broad range ofpressure & roll types. Attain proper densification. Some granular chemicals are suitable fordirect compression (free flowing) e.g. potassium chloride.

Tableting excipients with good flow characteristics & compressibility allow for direct compression of a variety of drugs.

1.4 COATED TABLETS: Tablets covered with layers of mixture of various substances such as resins, gums sugar, plasticizer etc. (Hemchand P, 2017)

Coating composition is applied to a batch oftablets in tumbled coating pan sothat the tablet surfaces become covered with a tacky polymeric film. (Kamble ND, 2011)

1.4.1 OBJECTIVES OF COATING ((Basu A, 2013), (Pawar AS, 2010)
The objectives of tablet coating are as follows:

- Disagreeable odor, color or taste of the tablet & high patient compliance.
- Protect drug from air, moisture & light in order to improve stability.
- To extend the shelf life of the drug.
- To augment ease of swallowing large dose forms.
- To hold back loss of volatile ingredients.
- To incorporate incompatible drugs together in a single dosage form
- Rising the mechanical strength of the dosage form.
- Masking batch differences in the appearance of raw materials.
- In improving product robustness.

1.4.2 Types of coating

There are several types coatings are available, they are:

- Sugar coating

- Film coating
- Enteric coating
- Controlled release coating
- Specialized coating
- Compressed coating
- Electrostatic coating
- Dip coating
- Vacuum film coating

1.5 TABLET COATING DEFECTS

1.5.1 Picking & sticking: This is when the coating removes a piece of the tablet from the core. (Pole S, 2016)

1.5.2 Mottled color Happen when the coating solution is improperly prepared (Pole S, 2016).

1.5.3 Bridging: This happen when the coating fills in the lettering or logo on the tablet & is typicallyby imprper application of the solution, poor design of the tablet embossing. (OM Bagade, 2014)

1.5.4 Erosion: This can be the result ofsoft tablets, anover-wetted tablet surface, inadequate drying, or lack of tableturface strength. (OM Bagade, 2014)

1.5.5 Capping & lamination When the lower or upper portion of the tablet separates horizontally i.e. either partially or completely from the main body of a tablet & comes off as a cap, during ejection of the tablet press or during subsequent h&ling. (P. Mounica, 2018)

1.5.6 Twinning

Sticking of two tablets together is known as twinning & it is a common problem with capsule shaped tablets.

1.5.7 Peeling & frosting

This could be due to a defect in the coating solution, over-wetting, or high moisture content in the tablet core This is a defect where the coating peels away from the tablet surface in a sheet. Peeling indicates that the coating solution did not lock into the tablet surface.

1.5.9 Chipping

This is the result, In this the film becomes chipped, usually at the edges of the tablet. of high pan speed, a friable tablet core, or a coating solution that lacks a good plasticizer.

1.5.10 Orange peel It is defect where the film becomes chipped & dented, usually at the edges of the tablet. It is usually the result of high atomization pressure in combination with spray rates that are too high.

Blushing It is defect where the film becomes chipped & dented, usually at the edges of the tablet.

Blooming In this coating becomes dull immediately or after long time (Kamble ND, 2011).

FILM-COATING

Film coatings are an vital part of the dosage form development process. The process of film oating involve the application of a thin polymeric film onto the surface of a solid substrate. The substrate can be tablets, capsules, granules or particles. Typically, the coating is approximately 25 to 100 μm in thickness & is applied to get better the physical & chemical properties of the substrate. (D. Kablitz, 2009).

The coating solution or suspension contain polymers & conformist solvent-based film coating involves deposition of a thin polymer film on the surface of the tablet core, typically using a spray method. Other ingredients such as pigments & plasticizers, which is sprayed onto a rotating tablet bed inside a pan (Zhou, Porter, & Zhang, 2009). Plasticizers are also used to reduce the glass transition temperature (Tg) & increase flexibility to avoid cracking & subsequent peel of polymer films (Joshi & Petereit, 2013).

FILM COATING METHODS

Organic solvent-based film coating: The polymers are beneficial as moisture-protective coating polymers as reduce the water vapor permeability of the final film by preventing the movement of water molecules (Yang, et al., 2019).

Therefore, organic solvent-based coating is for moisture sensitive drugs. The evaporation of the solvent is crucial for the quality of final product(Yang, et al., 2019).

Despite of many critical limitations because of potential toxicity of residual solvents, flammability, & environmental safety issues (Kapoor D & Tekade, 2020). Eventilation facility, it is difficult to completely remove organic solvent vapors from the coating room, growing the risk of toxicity & explosion. Environmental & regulatory issues can increase the production costs.

Aqueous film coating: Film coating method Aqueous coating is a widely used in current pharmaceutical practice. It having advantages over organic solvent-based coatings in terms of operator safety, environmental pollution, & risk of explosion. (Bose & Bogner, 2017) In water-insoluble polymers addition, preparation of an aqueous coating solution with requires the addition of a suitable suspending agent or plasticizer for a homogeneous coating solution (Kapoor D & Tekade, 2020). Although aqueous film coating has a number of limitations, it can avoid organic solvent-based coating the safety issues associated with, & thus it is still widely used in the pharmaceutical industry. There are continuous efforts by process automation, process validation, to diminish the processing time & improve productivity & development of more efficient equipment. (Gaur P, 2014).

Solvent-free coating: solvent-free coating methods have been actively solvent-based coating pursued to overcome the drawbacks of. Solvent-freecoating time-consuming processecan reduce the process time & cost by avoiding expensive & s of solvent disposal (Bose & Bogner, 2017). Furthermore, since solvent-free coating is applicable it does not require drying in most cases, to heat-sensitive drugs (Bose & Bogner, 2017). Solvent-free coating includes various dry powder coating, electrostatic spray powder coating technologies such as compression coating & photocuring coating (Ki-Soo Seo, 2020).

Recently, injection molding coating also been proposed as dry coating processes that do not require solvent. & hot melt coating have.

In the injection molding coating process, using a vertical injection molding unit the upper & lower surfaces of tablets are coated in two steps. It is important to on workplace humidity & polymer properties choose the right polymer because quality varies depending. As it is important to examine the surface conditions of high temperature (over 80 ºC) is used for coating, coated tablets after cooling (Achanta A.S, 1997).

Hot-melt coating: In this a dry coating tablets to form a coherent coating layer method in which a lipid excipient is heated for melting & then sprayed onto the surface of. including a short process time & the tablet ingredients & the inert coating materials this method has advantages no chemical interactions between. However, the high process may affect the stability of the tablet ingredients temperatures depending on the melting point of coating materials (Achanta A.S, 1997).

Spray congealing or spray cooling: is also a melting-based transforms a melt into method that spherical solid particles. This method has compensationbsence of solvent including the, low cost, applicability water-sensitive substances to hygroscopic &, & the ability to obtain spherical free-flowing microparticles for tableting or capsule the need of filling without other downstream processes. Spray congealing technology includes three steps (feed, atomization, & solidification stages). The primary step involves the preparation molten carrier & drugs. As drugs it is important to keep the fluid homogeneous may be dissolved or dispersed into the molten carrier, for a uniform drug loading.

During the fluid stream breaks up atomization step, the molten into tiny droplets that are quickly solidified upon solid microparticles cooling to produce the. In this procedure, viscosity is factor deciding the viability a critical of spray congealing & the size of produced microparticles. In universal, for highly viscous molten mixtures pray congealing is not suitable that may clog the feed tube or atomizer. Although some issues associated solvent-free coating may overcome with solvent-based coating, solvent-free coating in the pharmaceutical industry (Bertoni S, 2018).the requirements for specific coating conditions, equipment, & coating materials limit wide application of

PROCESS PARAMETERS & FACTORS AFFECTING FILM COATING QUALITY

In the conventional the batch size is determined by the solvent-based pan coating process, tablets are filled into the coater that is generally operated in batch mode & mass of tablets from the compression unit operation. During, the rotating pan allows tablets the process operation to the coater walls circulate along. When tablets the droplets of coating pass the spray zone, solution are surface of tablets deposited on the to form a coating film. At each orientation & thus cycle, tablets pass the spray zone with different the surfaces of tablets facing to the spray gun are frequently to the entire changed, leading surface coating of tablets. After drying by a combination of the upper region of hot airflow supplied from the coater & conduction from the heated tablet be smooth bed, the obtained film must & uniform.

complexity of the However, the coatingleads to the coatin process often g defects including bridging, cracking, & orange-peel roughness (Christodoulou C, 2020).

These defects because process are mainly parameters are not satisfactory. Therefore, optimization of (compositions), process variables, & coating formulations equipment parameters are critical the uniform to obtain & smooth coating layer. Some of process parameters & factors affecting are discussed below. Film coating quality

Spray air flow rate: An important step in is spraying the coating the coating process solution. High-pressure atomization coating solution into air disintegrates the droplets that are pushed through the spray nozzle. With atomization air If spraying only, coating solution droplets may move directly into a narrow area which may cause problems of the tablet surface, with coating uniformity. Therefore, both atomization multaneously & pattern air must act sito spray droplets homogeneously & widely The ratio pattern air is between atomization air & an important parameter for coating efficiency. Atomization pattern air & air ratios closer to 1:1 correlate to smaller mean droplet sie & better coating efficiency (Wang J, 2012).

Spray rate: Along with the, another important parameter aforementioned spray air that affects the coating process is spray rate. As droplet size increases spray rate increases, & droplet velocity decreases. Spray rate affects coating quality no air & pattern air. Because mean droplet size does not change as an individual parameter significantly when the ratio t only but also as a composite parameter with atomization of atomization air & spray rate is fixed, the atomization air/spray most important rate ratio is one of the parameters that affect droplet size & coating quality.

In addition, by spray rate droplet size determined & atomization air is an important factor that determines the drying capacity in the coating process (Wang J, 2012).

Inlet air/Outlet air: Sprayed droplets are transferred to the tablet surface of coating solution & dried to form a coating film. Heat energy must coating pan via be supplied to dry the heated inlet air flow. The relative humidity can have a significant of supplied inlet air impact on the related humidity of the coating pan & outlet air, affects drying which in turn effciency. In cases of over-drying due to excessive coating droplet may inlet air supply, the be dried before it adheres to the tablet surface. generate a large number This may of polymer particles,

resulting in a rough surface of the coated tablet. Conversely not supplied , if suffcient inlet air is for drying, twinning & tablet may occur due to the viscosity agglomeration of droplets on the wet tablet surface. Outlet air (exhausted air) indicate the temperature temperature can indirectly of the coating pan or tablet during the coating process. Generally, the coating pan is ~2–3 tablet temperature inside ºC lower than the outlet air temperature. Changed Outlet air temperature should be according to the characteristics of the solvent or spray rate. Inlet & outlet air temperature can be controlled according to the coating machine br&. (Aliseda A, 2010).

Droplet size: Droplet size is highly affected by coating solution characteristics of the & process conditions. It also has a high correlation with coating e_ciency. Conversely, if the size of the droplet in contact with the tablet surface is Droplet size is highly dependent on process too large, tablet surface roughness may increase. conditions & requires (spray air flow rate, spray rate, gun-to-bed distance, viscosity, etc.) careful control. (Aliseda A, 2010).

Solid content & viscosity: The amount coating solution is important of polymers in the in determining the viscosity of coating solution. The coating solution is viscosity of increased by using a high polymer content ihigh molecular weight polymer or n coating solution. In coating solution increases tablet High solid content weight faster but can lead to diffculty transferring a viscous coating liquid. If necessary, raise the temperature the coating solution may be heated to & lower he viscosity. Conversely, content contains more coating solution with low solid moisture, the coating pan & resulting in increasing the relative humidity inside poor drying effciency. In this case, inlet air flow rate or inlet air temperature must be optimized. (Aliseda A, 2010).

Gun-to-bed distance: Gun-to-bed distance between the represents the distance virtual plane of the tablet mass & the inside the coating pan tip of the, which can often spray gun nozzle be changed by an perator's subjectivity As the droplets of coating solution move away from the nozzle tip, droplet velocity decreases & agglomeration occurs, resulting in increased droplet size (diameter). coating process efficiency decreases As the gun-to-bed distance increases,. Droplets may be dried resulting in a rough tablet surface before they reach the tablet surface,. Conversely, if the gun-to-bed distance is short, sprayed droplets adhere to the tablet surface before they are dried & the tablet surface gets wet. Twinning or coating surface wet tablet surfaces can cause dissolution. Tablet surface moisture should be controlled by considering the aforementioned factors including coating machine size. (Aliseda A, 2010).

Curing time: Finished when the coating Coating process is not necessarily solution sprayed onto the tablet reaches the target tablet weight the coating layer contains a small amount of undried solvent. After the the polymer coalesces to form solvent evaporates, a dense structure. Post-coating thermal treatment (curing) induces residual solvent Curing time usually lasts from 1 to drying & polymer coalescence. several hours. The dissolution profile may change with curing because the coating layer hardens. (Gendre, et al., 2012).

Equipments: Pharmaceutical processes take place in coating coating pans or fluid bed apparatuses. Most coated in tablets are (perforated) pans or drums but also fluid bed equipment is in is typically performed in a fluid bed use. Pellet coating. (C.D. Kablitz, 2006) various examples of coating pan includes:

ACCELA COTA

HI-COATER\

DRIAM

FLUID BED COATERS

The **Accela Cota** has cylindrical drum a horizontal rotating, the curved surface of which is uniformly perforated. The are conically dished ends of the cylinder, so that tablets in the drum are inverted & also mixed laterally during the coating operation. There are baffles to assist the mixing process. Drying air perforations on the enters the drum through the side remote from the tablet bed, & is drawn through the bed by the exhaust fan located in the exhaust duct connected to the plenum positioned under the tablet bed.

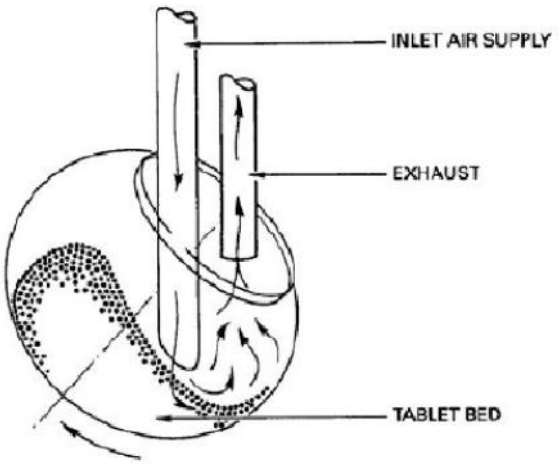
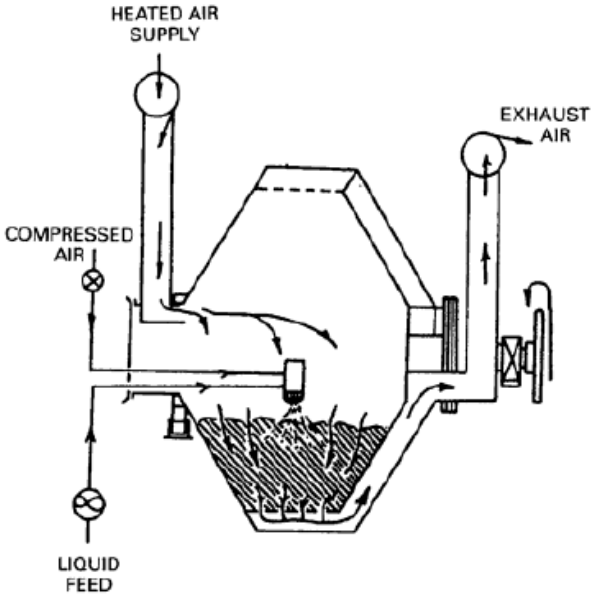


Figure 1: Simplified diagram of Accela Cota (Cole, 1995).

Hi-Coater has four perforated panels linked to air ducts that are in constant contact with the exhaust ducts. Capacities range from 500 g load up to the HCF 200, claimed to hold 700 kg. Loading & unloading can be achieved through the front of the unit & by a flap in the pan which discharges into a mobile container under the machine or onto a conveyor (Cole, 1995).



Simplified diagram of Hi- Coater (Cole, 1995)

The **Driam** differs from the Accela Cota coaters in the shape of the coating pan & the way the air is utilized in the drying process. On the outside of the drum covering the perforated areas, there are the air flow channels with removable covers. At the rear of the pan the air channels are connected to the air distributor. This distributor guides the drying air through the air channels & the perforations into the product. The direction of air flow is reversible.

Direct Air Flow: air is supplied through the perforated areas at the top of the pan & through the product bed, & the air exhausted through the perforated areas under the product.

Reverse Air Flow: air is supplied through the perforated areas at the bottom of the pan & through the product bed. It is exhausted through the perforated areas at the top of the pan or through the hollow shaft at the rear.

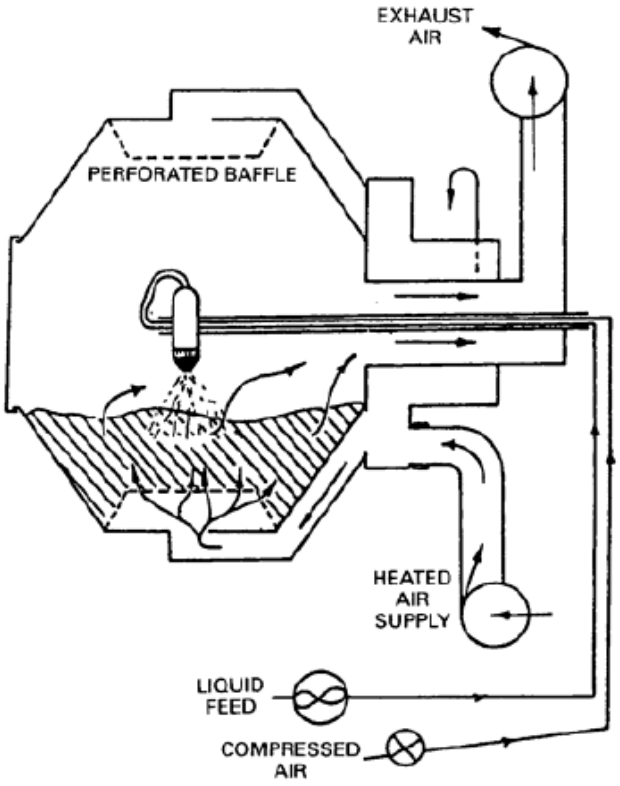


Diagram of Driam (Cole, 1995)

2. COMPOSITION OF FILM COATING FORMULA

Pharmaceutically acceptable film coating forms are primarily of solid dosage based on acrylic or cellulosic polymers. Many of these formulated into polymers have dispersions been aqueous colloidal (e.g., latexes or pseudolatexes) in order overcome the to high costs, potential toxicities & environmental with the use of organic concerns associated polymer solutions.

Film coating to control the has been successfully utilized release of active ingredients, prevent interaction increase the strength between ingredients, of the dosage form to maintain product integrity during shipping & protect the dosage form from the environment.

Most formulations that impart flexibility to the contain plasticizers films & reduce the incidence of crack formation. Usually contain Coating formulations many additives, in addition to the polymer, appearance & product performance that aid in processing. The amount & type of plasticizer in the film & the p dded to alter the appearance of the final product & lubricants may be resence of other additives in the coating can significantly impact the film's mechanical properties. Pigments may be a required to prevent agglomeration of the coated substrates.

Polymers

The film ingredient in a coating former is the major formulation. For aqueous-based coating systems be divided into two essential, the polymers can classes: aqueous soluble polymer & water insoluble or pH dependent soluble polymers.

The most commonly used ***aqueous sol***primarily of *polye**uble polymers*** consist *thylene glycols, polyvinyl pyrrolidone* (povidone) & cellulosic polymers (*Carboxymethyl cellulose sodium, Hydroxypropyl cellulose, Hydroxypropyl methylcellulose & Methylcellulose*) (L.A. Felton, 2008).

The ***water insoluble polymers*** are used enteric coating or when an a special controlled release delivery system is desired. Enteric coatings constitute the major portion of the pH dependent polymers. These polymers can be solubilized by adjusting the pH of the coating or they can be formulated to be suspended in aqueous media & applied as insoluble polymer particles.

Some of the most common polymer with pH-dependent solubility are *cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose phthalate (HPMCP), polyvinyl acetate phthalate* (PVAP), (meth)acrylic acid copolymer (*Eudragit® E, Eudragit® L, Eudragit® S*). Among water insoluble coating polymers, *Eudragit® RL, Eudragit® RS, polyvinyl acetate & ethylcellulose* are included (L.A. Felton, 2008).

Plasticizer

Films prepared from pure polymers frequently are brittle & crack on drying. To correct this deficiency, the polymer can be chemically modified or other excipients can be added to make the film more pliable (L.A. Felton, 2008).

Plasticizers are added to polymeric solutions or dispersions to increase workability or flexibility of the polymer, reduce its brittleness, improve flowability, increase toughness & tear resistance of the films. These effects are the result of the plasticizer's ability to weaken intermolecular attractions & allow the polymeric molecules to move more easily (L.A. Felton, 2008).

Thus, plasticizers can be classified into two general categories

Internal & external plasticizers.

Internal plasticizing involves the chemical modification of a basic polymer to alter the physical properties of the polymer. Changes both in degree & type of substitution or in polymer chain length could influence the physical characteristic of the polymeric film.

Generally, the formulator must work with polymers that are available & the film properties are altered by the addition of external plasticizers.

The **external plasticizer** can be another polymer, a nonvolatile liquid or even the aqueous solvent. The plasticizer alters the polymer – polymer interactions to improve the flexibility of the film by relieving molecular rigidity. As general rule, the film will become more flexible & more resistant to mechanical stress when a plasticizer is added to a coating composition Plasticizer acts by interposing itself between the polymer chains to decrease the degree of interaction between the polymer molecules thereby enhancing chain mobility & the dissipation of internal stresses that lead to bridging & cracking of film (K. Nollenberger, 2013).

Moreover, plasticizers alter the thermo- mechanical properties of film forming polymers owering its softening temperature of the polymer (MST).

PLASTICIZERS
Castor oil, USP
Propylene glycol, USP
Glycerin, USP
Polyethylene glycols (PEG), NF, low molecular weights (200 – 400 series)
Polysorbates NF (Tweens)
Sorbitans NF (Spans)
Polyoxyl derivatives NF
Diethyl Phthalate
Acetylated monoglycerides
Triacetin
Triethyl citrate (TEC)
Dibutyl sebacate (DBS)

Dyes & Pigments: Often a distinctive color is desired to give the product a unique identity. It is a GMP requirement that products must be differentiated at all stages during the manufacturing & distribution cycle. The colorant can be either solubilized in the solvent system or suspended as insoluble particles. The addition of pigments into a coating

formulation may improve the esthetic appearance of the final product, providing distinctive color & pharmaceutical elegance to the coated substrates (L.A. Felton, 2008).

COLORANTS and OPAQUANTS	
Colorants	Opaquants
FD&C dyes	**Silicates**
FD&C lakes	Talc
Iron oxides	Aluminium silicate
Titanium dioxide	**Magnesium carbonate**
Natural colorants	**Calcium sulfate**
Anthocyanins	**Magnesium oxide**
Caramel	**Aluminium hydroxide**
Carotenoids	
Flavones	
Tumeric	
Carmine	
Annatto	
Amaranth	

Glossing & Polishing Agents: At the end of the coating process, some gloss is developed directly from the polymers, especially with poly(meth)acrylates. Gloss could be improved by polyethylene glycols solutions sprayed on the film coating at the end of the process or by the application of an additional layer of wax dissolved in an organic solvent.

Antiadherents: Fillers are mainly powder materials which are insoluble in coating solvents & reduce the ticking effects on the binder. If the binder is sugar, the fillers are mainly calcium carbonate, calcium phosphate, starch & titanium dioxide which, additionally, is a white pigment.

Surfactants: As mentioned above, incorporating water-insoluble plasticizers into an aqueous polymeric dispersions requires that the plasticizer first be emulsified in water with an appropriate surfactant. The addition of these compounds to film coating formulations has been shown to influence the mechanical properties of the films. Sorbitan mono- oleate & polysorbate 80 are the most commonly employed surfactants in films coating based on Eudragit® L 30 D-55 plasticized with the hydrophobic tributyl citrate, while no significant benefits were noted when the polymeric dispersion was plasticized with the water-soluble triethyl citrate. Moreover, surfactants should be added to the film coating formulation in order to improve the spreadability of the coating material across the core surfaces &, thus, modulate drug release (L.A. Felton, 2008).

Pharmaceutical Application of Film Coating

Modified Drug Release: (Shah & Prajapati, 2019) Therefore, tablet film coating with various polymers is actively drug release by controlling pursued to achieve modified the rate &/or sites of drug release. Representative film coating approaches for modified drug release are discussed below.

Delayed Drug Release: (Moroz E & Leroux, 2016) **t**he main advantage of enteric coating is increasing environment &/or reducing drug stability in the harsh gastric undesirable gastric irritation caused by drugs. To prevent premature drug dependent solubility release in the stomach & ensure drug release mainly in the small intestine, polymers with pH- or water-insoluble polymers are applied to enteric film coating. These polymers can be used alone, in combination, or one after the other to ensure delayed drug release.

Physicochemical the gastrointestinal (GI) tract instability & low permeability in limit oral delivery of macromolecules, such as proteins & peptides. Among these absorption barriers & various strategies to overcome low bioavailability of macromolecules, enteric coating is the most actively pursued strategy alone or in combination with other approaches.

Colon-targeted drug release: (Dodoo C.C, 2017) Colon-targeted drug delivery systems are required for local treatment specific diseases such as Crohn's of colon- disease, irritable bowel syndrome (IBS), & colon cancer. In addition, there is great interest in colonic drug release as an effective approach for improving the bioavailability of peptides & protein drugs.

Chronotherapeutic drug release: (Thapaliya R, 2019) Release of APIs can be delayed for a the chronotherapeutic needs, in particular programmable period of time to meet for circadian symptoms. Chronic iseases with circadian symptoms that likely recur in the night or early morning include cardiovascular disease, bronchial asthma, rheumatoid arthritis, & sleep disorders. At bedtime, Although drugs are administered pulsatile drug release matched with the circadian rhythms of the disease can cover the critical period of the selectively disease without requiring the patient to wake up for drug intake. Chronotherapeutic drug release can be achieved by enteric film coating.

Sustained Drug Release: (Felton L.A, 2013) Drug release rate can be controlled by physicochemical properties amount of polymers used & the for surface coating. It is also controlled by altering the thickness, tortuosity, & permeability of the coating layer Coating

materials release are usually water-insoluble for sustained drug & pH-independent, & are exemplified by ethyl cellulose, polyvinyl acetate, & polymethacrylate copolymers. These polymers have good film, making forming properties & mechanical strength them suitable for sustained drug release coating.

Improved Drug Stability: (Odani, et al., 2019) Tablets containing light sensitive drugs (e.g., sorivudine, nifedipine, sulfisomidine, & molsidomine) undergo film coating for photostabilization. Film coating of core tablets Photostability mainly depends on the thickness of coating layers & can also be affected by concentration of the opacifier. has also been attempted to improve the product stability of moisture-sensitive drugs using various water-proof coating agents The effectiveness of moisture protective film coating including polyvinyl alcohol (PVA), Eudragit® EPO, hydroxypropyl methyl cellulose (HPMC), hydroxyethyl cellulose (HEC), & polyvinyl alcohol-polyethylene glycol (PVA-PEG copolymer). depends on the type of polymers used & coating conditions. Combined use of different coating polymers at different proportions is also promising for improving the stability of moisture sensitive drugs.

Taste Masking: (Odani, et al., 2019) Among various tastes, bitterness is the most repellent Unpleasant taste is a major hurdle to ensure patient compliance, particularly in pediatric & geriatric populations. Thus, masking bitter taste in oral dosage forms is a key parameter to improve patient compliance & therapeutic effciency. Taste masking should not negatively affecOptimized oral dosage forms should reliably hinder the release of bitter drug molecules in the mouth. However, tt the bioavailability of drugs, or sensory awareness including mucosa irritation, roughness in the mouth, or hindered swallowing. A variety of methods have been used for taste masking, such as chemical modification (prodrug approach), salt formation, interaction with ionogenic polymers (methacrylates), complexation, incorporation of flavor enhancers (e.g., sweeteners) in the formulation, & surface coating. Among these methods, film coating is the most effective & commonly used approach for taste masking & is particularly suitable for microencapsulation of small particles to form taste masked multi-unit dosage forms.

Many a bitter drug in the oral cavity different polymers are available for taste masking, including natural or synthetic polymers that hinder fast release of & its contact with taste receptors in the tongue. In including starch derivatives addition to water-soluble polymers, , cellulose ethers, & hydrophilic block copolymers, water-insoluble polymers & gel-forming

polymers can be also used to mask the taste. These polymers are used alone or in combination with different polymers, preferably in combination with water-soluble & insoluble polymers at various ratios.

EVALUATION OF TABLET: (Chugh Isha, 2012)

Thickness & Diameter

Hardness & thickness of tablet is important for the weight uniformity. Thickness & diameter is measured using venire caliper.

Tablet Hardness

The resistance of breakage under conditions of storage tablets to shipping or or transportation & h&ling of drug before on its hardness. The hardness usage depends of tablet is measured by Monsanto hardness tester. The hardness of tablet is measured in kg/cm2.

Friability

Friability is the measurement tablet by using the following procedure of tablet strength. Electro lab EF-2 friabilator (USP) is used for testing the friability of. Twenty tablets are weighed accurately & the tablets through a distance placed in the apparatusat 25 rpm dropping of six inches with each revolution. After 4 min the tablets weighed are measured & the percentage loss in tablet weight is determined by the following formula.

% Friability = Initial weight of tablets –Final weight of tablets / Initial wt. of tablets ×100

Uniformity of weight

Twenty tablets selected r&omly & their average weight is calculated & Weight Variation is calculated & compared with I. P. st&ards.

Dissolution Studies (Singh B. N., 2000)

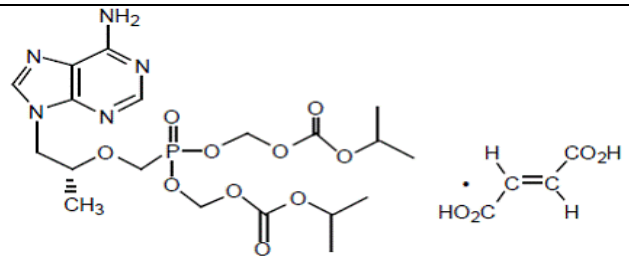
For the in vitro providing the desired controlled release drug release studies of Bilayer tablets in simulated gastric & intestinal fluids to assess their ability to of drug delivery. Drug release studies are carried out using the USP dissolution test apparatus I at 100 rpm, 37±0.5°C, & pH 1.2 buffer (900 ml) (i.e. 0.1 N HCl) or pH 6.8 buffer(i.e. simulated intestinal fluid). 5ml of the samples The sampling is carried out at different time intervals, was withdrawn & 5ml of drug-free dissolution medium added. The samples withdrawn are analyzed by UV spectrophotometer.

Stability studies (Balaji G, 2013)

The satisfactory formulation sealed in aluminum packaging The stability studies are conducted of best formulation for 3 month. & store the formulation at 30±2°C with 65±5% RH for 3months.Samples are analyzed for physical parameters & drug content.

DRUG PROFILE

Tenofovir Disoproxil Fumarate

S. No.	Parameters	Details
1.	Nomenclature	9-[(R)-2 [[bis [[(isopropoxycarbonyl) oxy]methoxy]phosphinyl]methoxy]propyl]adenine fumarate (1:1)
2.	Empirical Formula	$C_{19}H_{30}N_5O_{10}P \bullet C_4H_4O_4$
3.	Chemical Structure	
4.	Molecular Weight	635.5
5.	Shelf Life	2 years
6.	Storage Conditions	Store under tightly closed container, protected from light and store at a temperature between 2-8°C.

Physicochemical Properties of Active

S. No.	Parameters	Details
1.	Description	White to off white crystalline powder
2.	Solubility	Slightly soluble in water, soluble in methanol, very slightly soluble in dichloromethane.
3.	Identification test by IR	The infrared spectrum of sample in potassium bromide dispersion should be concordant with the spectrum obtained from the similar preparation of Tenofovir Disoproxil Fumarate working standard.
4.	Water content (By KF)	Not more than 1.0% w/w
5.	Sulphated ash	Not more than 0.10% w/w
6.	Heavy metals	Not more than 20 ppm
7.	Clarity and color of the solution	Not more intense than the reference solution B9 and reference suspension
8.	Enantiomeric purity by HPLC	Not more than 1.0% of S-isomer
9.	Related substance by HPLC	
	Impurity A (Monoproxil impurity)	Not more than 1.0%
	PMPA	Not more than 0.15%
	Unspecified impurity	Not more than 0.20%
	Total Impurities	Not more than 2.5%
10.	Fumaric acid content by	Between 17.5% and 19.0% w/w

	potentiomentry (on anhydrous basis)	
11.	Impurity K by HPLC	Not more than 5.0 ppm.
12.	Assay by potentiometry (on anhydrous basis)	Between 98.5% and 101.0% w/w
13.	Residual solvents by GC	
	Method –I	
	Isopropyl alcohol	Not more than 3000 ppm
	Dichloromethane	Not more than 300 ppm
	Isopropyl acetate	Not more than 4000 ppm
	Method –II	
	Content of N-methyl Pyrrolidone	Not more than 480 ppm
	Method –III	
	Content of chloromethyl isopropyl carbonate	Not more than 0.15% ppm

Biological Properties of Active

S. No.	Parameters	Details
1	Absorption site	Intestine
2	% Absorption	Approximately 25%
3	Effect of Food on absorption	Increase with co-administration with food
4	Apparent volume of distribution	more than 1.0 l/kg
5	C_{max}	14%
6	t_{max}	0.5-1.0 hours
7	Half-life ($t_{1/2}$)	When a single oral dose is given, the terminal elimination half-life is approximately 17 hour
8	Protein binding	Very low: < 0.7% to human plasma proteins and < 7.2% to serum proteins
9	Metabolism	The cytochrome P450 enzyme system is not involved with the metabolism of Tenofovir Disoproxil or Tenofovir.
10	Excretion	When Tenofovir is given IV, 70-80% of the dose is recovered in the urine as unchanged drug within 72 hours of administration. Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion. There may be competition for elimination with other compounds that are also renally eliminated.
11	Dose	75 mg, 150 mg, 300 mg, or 600 mg
12	Side Effects	liver damage - nausea, stomach pain, low fever, loss of appetite, dark urine, clay-colored stools, jaundice (yellowing of the skin or eyes); kidney problems - increased thirst and urination, loss of appetite, weakness, constipation, urinating less than usual or not at all fever, chills, body aches, flu symptoms; or any other signs of new infection. *Less serious side effects may include:* sleep problems (insomnia), strange dreams; depression, headache, dizziness; diarrhea, bloating, gas;

		Muscle or joint pain; skin rash.
13	Contraindication	None
14	Mechanism of action	Tenofovir inhibits the activity of HIV reverse transcriptase by competing with the natural substrate deoxyadenosine 5'-triphosphate and, after incorporation into DNA, by DNA chain termination. Specifically, the drugs are analogues of the naturally occurring deoxynucleotides needed to synthesize the viral DNA and they compete with the natural deoxynucleotides for incorporation into the growing viral DNA chain. However, unlike the natural deoxynucleotides substrates, NRTIs and NTRTIs (nucleoside/tide reverse transcriptase inhibitors) lack a 3'-hydroxyl group on the deoxyribose moiety. As a result, following incorporation of an NRTI or an NtRTI, the next incoming deoxynucleotide cannot form the next 5'-3' phosphodiester bond needed to extend the DNA chain. Thus, when an NRTI or NtRTI is incorporated, viral DNA synthesis is halted, a process known as chain termination. All NRTIs and NtRTIs are classified as competitive substrate inhibitors

MATERIALS AND METHODOLOGY

Material Used: Tenofovir Disoproxil Fumarate bought from Acebright is used as active pharmaceutical ingredient whose specification is set as per In house specification. Excipients used in formulation were carefully chosen and adequate compatibility test performed to determine that no interactions are present between drug and excipient.

Excipients used in the formulation of tablet core include Lactose Monohydrate, Croscarmellose Sodium, Polyethylene Glycol 400, Pre-gelatinized Starch 1500, and Magnesium Stearate. None of the excipients is of human or animal origin.

Table 4: 1 list of material used in formulation of tablet.

S. No.	Ingredients	Pharmacopoeial Status	Source
1.	Lactose monohydrate	BP	Lactose India ltd
2.	Croscarmellose sodium	USP-NF	Mingtai
3.	Polyethylene glycol 400	BP	Clariant chemicals (India) ltd
4.	Pre-gelatinized starch	USP-NF	Colorcon Asia Pvt Ltd
5.	Magnesium stearate	BP	Amishi Drugs Chemicals Ltd
6.	Opadry white Y-1-7000	IH	Colorcon Asia Pvt Ltd

Equipment used (laboratory scale)

S. No.	Equipment/ Instrument ID	Name of Equipments/ Instrument	Capacity/Model
1.	RDE005	Rapid mixer granulator	10L/GMP
2.	RDE004	Fluid Bed Processor	5L
3.	RDE006	Vibrosifter	12''
4.	RDE007	Multimill	GMP
5.	RDE008	Cage Blender	10L
6.	RDE002	Mini Press	10 station
7.	RDE009	Tablet Friabilator	EF-1W
8.	RDE010	Tap Density Tester	ETD1020
9.	RDE011	Tablet Disintegration Tester	ED2AL
10.	RDE012	Electromagnetic Sieve shaker	EMS-8
11.	RDE014	Vernier Caliper	0 -210 mm/standard
12.	RDE017	Balance	0.5 g – 496 g
13.	RDE018	Balance	10 g – 4800 g
14.	RDE019	Magnetic stirrer	-
15.	RDE003	Becoater	12"/18"

PREFORMULATION STUDIES

Preformulation is the first step in the rational formulation of an active pharmaceutical ingredient (API).preformulation studies is an investigation of the physio-chemical properties of the drug substance, alone and in combination of excipients. Estimation of possible incompatibilities between the drug and different excipients is an important part of preformulation.

Identification test: The drug sample was authenticated using FT-IR and Melting Point test apparatus. Organoleptic characteristics of the drug was observed and recorded by using descriptive terminology.

a. Physical Appearance:
b. Solubility
c. Melting Point test
d. FT- IR Characterization
e. Determination of analytical wavelength
f. Drug- excipient Compatibility study

Physical appearance[97,98]

Physical appearance of drug was examined by organoleptic properties, colour, odour, taste, state.

Solubility[97]

Small amount of the drug was mixed with solvent in screw capped glass tube. The solution was examined physically for the absence or presence of drug particles.

Melting Point test[97,98,99]

Melting point of Tenofovir was determined by using digital auto melting point apparatus. A capillary fused at one end was taken and a small quantity of Tenofovir was pushed in through the free end of capillary. The capillary was then placed in the well provided space in digital melting point apparatus. The temperature at which the drug started to melt was noted.

FT- IR Characterization

The infrared spectrum of sample in potassium bromide dispersion should be concordant with the spectrum obtained from the similar preparation of Tenofovir Disoproxil Fumarate working standard.

Drug- excipient Compatibility study

Compatibility studies

Drug-excipient compatibility study

The active pharmaceutical ingredient was found to be compatible with other excipients used in the formulation of Tablet.

During development of finished pharmaceutical product the following compatibility studies were performed. Change in appearance of the drug substance when mixed with the excipients and stored at accelerated condition (40^{o}C & RH 75 %) for 21days.

UV-visible Spectrophotometric study: Standard stock solution containing 100 µg/ml of TDF was prepared by dissolving in 1ml methanol and the volume was made up to 100 ml with distilled water. From the stock, different aliquots were taken and diluted to 10 ml mark with same solvent to obtain series of concentrations. The solutions were scanned on spectrophotometer in the UV range 200-400 nm. Linearity, accuracy and precision were determined.

Preparation of 0.1N HCL

To prepare 0.1N HCL, 8.5 ml of concentrated HCL was taken and it was diluted up to 1000 ml in distilled water.

Stock solution

100 mg of drug was dissolved in sufficient amount of 0.1N HCl in a 100 ml volumetric flask and the solution was made up to the mark with 0.1N HCl.

Standard solution

The stock solution was diluted subsequently with 0.1N HCl to get a series of dilutions containing 2, 4, 6, 8 and 10 mg/ml. One single dilution was selected and scanned in the wavelength range 200- 400 nm to get the UV spectrum and record the characteristic peak, λmax. All other dilutions were then analysed at that particular λmax to determine their absorbance for the preparation of calibration curve of famotidine in 0.1 N HCl. Linearity, accuracy and precision were determined.

IDENTIFICATION BY HPLC: High performance liquid chromatographic system consisting of a pump, an injector, a Column (Hyper ODS2 C18) equipped with UV - Visible detector and A2000 data system software was used. Ultrasonic cleanser was used for sonication and pH meter was used for adjusting the pH of the buffer.

Preparation of Tenofovir solution: Weighed accurately about 100 mg of Tenofovir into 100 ml volumetric flask, added with a minimum quantity of methanol, sonicated to dissolve and further diluted to 100ml with methanol.1ml of this solution was diluted to 10 ml with methanol(100 µg ml). Then it was filtered through 0.45µ PVDF membrane filter by discarding the first 5 ml of the filtrate.

Mobile phase: Mobile phase, HPLC Methanol: Phosphate buffer of pH-5 (90:10)

An accurately weighed portion of 100mg of TDF was dissolved in 50mL of methanol into a 100 ml volumetric flask by sonication for 30 min with intermittent vigorous shaking. The final volume was made up to the mark with methanol to get a stock solution of 1mg/ml. This solution was filtered through 0.45 µm filter. Aliquots of (0.3 -0.7ml) the standard drug stock solutions (1mg/ml) were transferred into series of 10 ml volumetric flasks and the volume was made up to the mark with methanol. All the concentrations were sonicated, filtered and 20µl of each solution was injected into the column.

Column temperature : 300C

Injection volume : 10µl

Run time : 12 min.

FORMULATION METHODOLOGY: Tenofovir Disoproxil Fumarate is used as active pharmaceutical ingredient whose specification is set as per In house specification. Excipients used in formulation were carefully chosen and adequate compatibility test performed to determine that no interactions are present between drug and excipient.

Excipients used in the formulation of tablet core include Lactose Monohydrate, Croscarmellose Sodium, Polyethylene Glycol 400, Pre-gelatinized Starch 1500, and Magnesium Stearate.

The manufacturing process involves wet granulation followed by compression and film coating. The critical process parameters of the manufacturing method were identified and the process was validated.

Composition

Each film coated tablet contains:

Tenofovir Disoproxil Fumarate 300mg

Excipients q.s.

Colour: Titanium Dioxide

Unit Composition

S. No.	Ingredients	Label claim (mg)	Specification	Quantity/Tablet (mg)	Quantity/ Batch (kg)
Active ingredients					
1	Tenofovir Disoproxil Fumarate*	300.0	IH	300.0	30.0
Inactive ingredients					
2	Lactose Monohydrate**	--	BP	175.0	17.5
3	Croscarmellose Sodium	--	USP/NF	7.0	0.7
4	Polyethylene Glycol 400	--	BP	1.0	0.1
5	Purified Water@	--	IH	140.0	14.0
6	Croscarmellose Sodium	--	USP/NF	25.0	2.5
7	Pregelatinized starch 1500	--	USP/NF	12.0	1.2
8	Magnesium Stearate	--	BP	10.0	1.0
9	Opadry White Y-1-7000	--	IH	15.0	1.5
10	Purified Water@	--	IH	85.0	8.5

Average weight of tablet: 545.0mg ± 5.0% / tablet

*Quantity to be taken according to 100% assay on as such basis

**Quantity of Lactose Monohydrate to be taken per batch =

Std. qty. of the Lactose Monohydrate - Excess qty. of drug taken to get 100% assay

@ Does not contribute to final mass of tablet

Composition of coating material involves

All the ingredients of the coating agent are well known and traditionally used in coating of tablets.

Characterization and Control of Excipients

S. No.	Ingredients	Pharmacopoeial Status	Source
1.	Lactose monohydrate	BP	Lactose India ltd
2.	Croscarmellose sodium	USP-NF	Mingtai
3.	Polyethylene glycol 400	BP	Clariant chemicals (India) ltd
4.	Pre-gelatinized starch	USP-NF	Colorcon Asia Pvt Ltd
5.	Magnesium stearate	BP	Amishi Drugs Chemicals Ltd
6.	Opadry white Y-1-7000	IH	Colorcon Asia Pvt Ltd

Functionality and safety of excipient

S. No.	Ingredients	Category	Qty. (As per IIG limits)
1.	Lactose monohydrate	Diluent	346.5mg
2.	Croscarmellose sodium	Disintegrant	165.0mg
3.	Polyethylene glycol 400	Surfactant	5.91mg
4.	Pre-gelatinized starch	Binder	180.0mg
5.	Magnesium stearate	Lubricant	28.31 mg

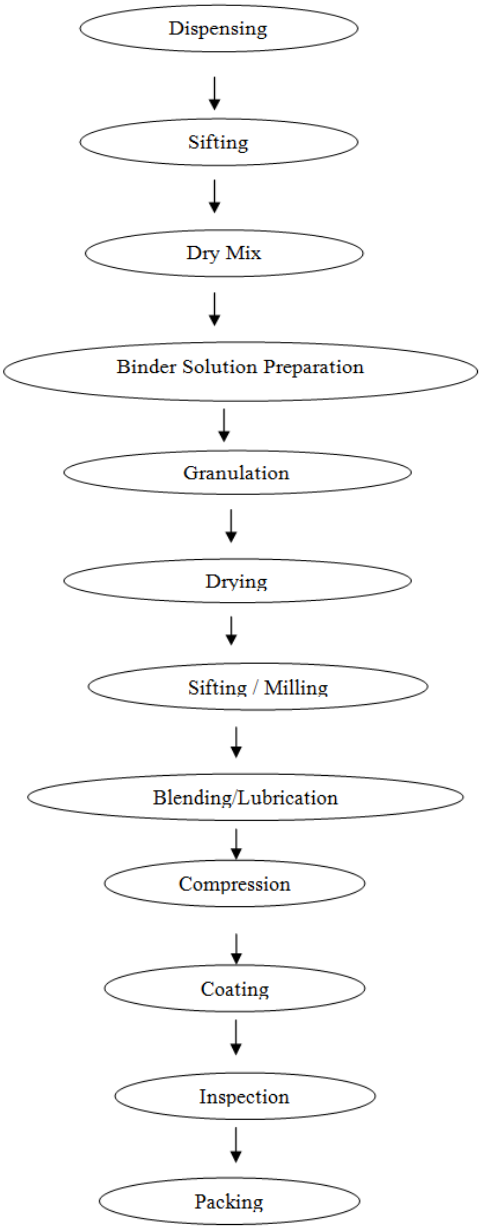
Manufacturing process development

Manufacturing procedure

Step No.	STAGE	PROCESS
1	Dispensing	Dispense the materials as per formulation order and kept in separate double polybag tightly sealed with appropriate label.
2	Sifting	Sift intra-granular Tenofovir Disoproxil Fumarate through 60# sieve and Lactose Monohydrate, Croscarmellose sodium through 40# sieve and collect in polybag.
3	Dry mix	Mix the sifted Tenofovir Disoproxil Fumarate, Lactose Monohydrate & Croscarmellose sodium for 7 minutes in RMG with slow speed of impeller.
4	Binder solution preparation	Take Purified water in to appropriate container and then add PEG 400 with stirring to form homogenous binder solution.
5	Granulation	Add binder solution to the dry mix over a period of 3 minutes with slow speed of impeller. After complete addition of binder solution continue mixing at slow/fast speed of impeller /chopper for 3 minutes or more till proper granulation end point is achieved. If necessary add extra quantity of Purified water to get proper granular mass.
6	Drying	Dry the material in FBD by keeping the inlet temperature at 50°C to 60°C Check the LOD at 80°C (Limit: - NMT 2%)
7	Sifting & milling	Sift the dried mass through 20# sieve. Mill the retained granules through 2.0 mm screen in knife forward direction. Sift the milled granules again through 20 # sieve.
8	Blending	Sift extra granular Croscarmellose sodium and Pre-gelatinized starch 1500 through 40# sieve and magnesium stearate through 80# sieve Blend the dried sifted granules with extra-granular ingredients except magnesium stearate and mix for 5 minutes.
9	Lubrication	Lubricate the above blend with Magnesium stearate for 3 minutes in a blender
10	Compression	Compress the lubricated granules into tablet using 12.0 mm round shaped standard concave punches.

		Upper punch: Plain Lower punch: Plain
11	Coating	Weigh specified quantity of Opadry white Y-1-7000; pour it gradually in stepwise manner into a beaker containing weighed qty of Purified water. Stir the suspension for 45 minutes to form homogenous solution. Filter the above solution through 100# sieve. Load the recipe of Tenofovir Disoproxil Fumarate tablets from HMI. Recipe contains data like inlet & Exhaust temperature, spray on/ off time, Pan RPM etc. Set the Inlet air temperature to 40–60o C. Maintain Exhaust temperature at 35 to 45°C and Warm the tablets 10 min. to 15 min. Press the Film start button from HMI. Film coating will start with the set Parameter loaded in the recipe. Check the coating Parameters and record in the record sheet. After completion of film coating dry the tablets in Coating Pan for 10 to 15 min at 50°C - 55° C. temperature and then cool it down to room temperature. Check and record net weight of the batch.

Flow Chart of Manufacturing Process



FORMULATION EVALUATION

Flow Properties

a. Angle of repose
b. Bulk density
c. Hausner's ratio
d. Compressibility index

POST COMPRESSION PROPERTIES

a. Hardness test
b. Friability test
c. Weight variation test
d. Drug content
e. *In-vitro* Dissolution test

PRE-COMPRESSION PROPERTIES-Most of the formulation include one or more combination of chemicals that are effect the preformulation property of active ingredient that are needed for compression. That's why the precompressionparametes evaluation is needed before final compression according to the standard procedure.

Flow Properties

For the determination of frictional force, bulk density, tapped density, Measures of Powder Compressibility (cars index or Hauser's Ratio) or measurement of flow ability the Preformulation Parameters are needed before formulation.

a. Angle of repose

The angle of repose of the powdered blend was determined by the funnel method. The accurately weight granules were taken in a funnel. The granules were allowed to flow freely through the funnel onto the surface. And the angle of repose measured using the following equitation.

$$Ø = \tan^{-1} (h/r)$$

Table 4.5 Shown the value of Ɵ equal their flow property.

Angle of repose(Ɵ)	Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Where, h and r are the height and radius of the powder pile respectively.

b. Bulk density

Both loose bulk density (LBD) and tapped density were determined, A quantity of the powder from each formula, previously lightly shaken for breaking the any agglomerates formed in the powder than introduced into a 10 ml measuring cylinder, After the initial volume was absorbed, the cylinder was allowed to fall under its one weight onto a hard surface. From the height of the 2.5 cm. LBD and TBD were calculated using the following formulas.

LBD = weight of powder / volume of the packing.

TBD = weight of powder / tapped volume of the packing.

c. Compressibility index

The compressibility of the powder blend was determined by Carr's compressibility index.

Carr's index (%) = (TBD - LBD) / TBD × 100

d. Hausner's Ratio

The hausner's ratio of the powder blend was determined by following formula.

HR = TBD / LBD

Table 4.6: Shows the value of compressibility index and Hausner Ratio equal to flow property.

Compressibility Index (%)	Flow character	Hausner Ratio
≤10	Excellent	1.0-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very Poor	1.46-1.59
>38	Very, Very Poor	>1.60

Post Compression Properties- For ensuring the tablet strength or uniformity in weight, uniformity in thickness of the tablet or various parameters such as drug dissolution rate and amount of drug present in a single tablet (drug content) or dispersion time of tablet, swelling property the post compression parameters evaluation are require and their procedure and equipment used in evaluation are given below.

a. Hardness

The strength of tablet is expressed as tensile (Kg/cm^2). The tablet crushing load is the force required to break a tablet in to pieces by compression. The hardness was measured by a tablet hardness tester (Monsanto hardness tester).

b. Thickness

Thickness of the tablet in mm was studied with the help of Vernier Calliper.

c. Friability

The friability of the tablets was determined using Roche friabilater. Pre-weighted tablets for taste were placed in the friabilaterand subjected to 100 revolutions. Tablets were degusted using a soft muslin cloth and reweighted. The friability (F) is measure by the formula.

$$F = (1\text{-}w_0/w) \times 100$$

Where,

$W_0$is the weight of the tablets before the test and w is the weight of the tablets after the test.

d. Weight Variation Test

20 tablets were randomly selected andweighed individually and together in a single pan balance. The average weight was notedand weight variation calculated using following formula.

$$PD= (W_{avg}) – (W_{initial}) / (W_{avg}) \text{ x } 100$$

Where PD= Percentage deviation,

W_{avg}= Average weight of tablet,

$W_{initial}$ = Individual weight of tablet.

Table 4.7: Shown the average weight of tablet and acceptable range.

Average Weight of A Tablet	Percentage Deviation
125 mg or less	10
More than 125 mg and less than 300 mg	7.5
300 mg or more	5

Drug content

Ten randomly selected tablets were weight and average weight was calculated, then tablet were crushed and 10mg weight and dissolve in 10ml of 0.1NHCL with the help of magnetic stirrer. This was the stock solution. From the stock solution 1ml of sample was withdrawn

and diluted. The content of each formulation was determined by spectrophotometry at 265 nm.[100]

e. *In- vitro* Dissolution Study

The drug dissolution studies were carriedout using the USP dissolution apparatus at 100 rpm and maintained temperature 37^0 C $\pm 0.5^0$ C in 0.1 N HCL for 8-10 hrs. At different time interval 5 ml of sample were withdrawn and replaced with 5 ml of drug free dissolution medium. The sample withdrawn and analyzedat 260 nm using UV-VIS spectrophotometry.[100]

Assay: High performance liquid chromatographic system consisting of a pump, an injector, a Column (Hyper ODS2 C18) equipped with UV - Visible detector and A2000 data system software was used. Ultrasonic cleanser was used for sonication and pH meter was used for adjusting the pH of the buffer.

Preparation of Tenofovir solution: Weighed accurately about 100 mg of Tenofovir into 100 ml volumetric flask, added with a minimum quantity of methanol, sonicated to dissolve and further diluted to 100ml with methanol.1ml of this solution was diluted to 10 ml with methanol(100 µg ml). Then it was filtered through 0.45µ PVDF membrane filter by discarding the first 5 ml of the filtrate.

Mobile phase: mobile phase, HPLC Methanol: Phosphate buffer of pH-5 (90:10) An accurately weighed portion of 100mg of TDF was dissolved in 50mL of methanol into a 100 ml volumetric flask by sonication for 30 min with intermittent vigorous shaking. The final volume was made up to the mark with methanol to get a stock solution of 1mg/ml. This solution was filtered through 0.45 µm filter. Aliquots of (0.3 -0.7ml) the standard drug stock solutions (1mg/ml) were transferred into series of 10 ml volumetric flasks and the volume was made up to the mark with methanol. All the concentrations were sonicated, filtered and 20µl of each solution was injected into the column.

Column temperature: 300C

Injection volume : 10µl

Run time : 12 min.

5.7 MATHEMATICAL MODELLING

The data obtained from *in-vitro* release studies was treated by various conventional mathematical models (zero-order, first- order, higuchi, hixon-crowell model and korsmeyer-

peppas) to determine the release mechanism from the designed double layer formulation. Selection of a suitable release model was based on the values of R (correlation coefficient), k (release constant) and n (diffusion exponent) obtained from the curve fitting of release data.

ZERO ORDER MODELS

Drug dissolution from dosage form that do not disaggregate and release the drug slowly can be represented by the equation:

$$Q_0 - Q_t = K_0 t$$

Rearrangement of the equation yields:

$$Q_t = Q_0 + K_0 t$$

Where

Q_t is the amount of drug dissolved in time t

Q_0 is the initial amount of drug in the solution

K_0 is the zero order release constant expressed in units of concentration/time.

First Order Model

This model has been used to describe absorption and elimination of some drugs, although it is difficult to conceptualize this mechanism on a theoretical basis. This release of the drug which followed first order kinetics can be expressed by the equation:

$$LogC = \log C_0 - Kt/2.303$$

Where, C0 is the initial concentration of drug.

K is the first order rate constant, and t is the time.

The data obtained are plotted as log cumulative percentage of drug remaining vs. time which would be straight line with a slope of –K/2.303.

Korsmeyer-Peppas Model

Korsmeyer derived a simple relationship which described drug release from a polymeric system equation to find out the mechanism of drug release, first 60% drug release data were fitted in korsmeyer-peppas model.

$$M_t/M_\infty = Kt^n$$

Where, M_t/M_∞ is a fraction of drug released at time t,

K is the release rate constant and n is the release exponent.

Then n value is used to characterize the release mechanism of drug.

Table 4.8: Diffusion exponent n and mechanism of diffusional Release from Swellable controlled-release System[104].

Slab	Cylinder	Sphere	Drug release Mechanism
0.5	0.45	0.43	Fickian diffusion
>0.5-<1.0	>0.45-<0.89	>0.43-<0.85	Non Fickian
1.0	0.89	0.85	Zero-order release
>1.0	>0.89	>0.85	Case II transport
>>1.0	>1.0	>1.0	Super Case II transport

Type of container and closure used

10 tablets packed in an Alu-PVDC blister further 3 blisters packed in a carton along with package insert.

STABILITY STUDIES

The film coated tablets are packed in commercial packaging and stability studies were carried out under accelerated conditions(40^{o}C ± 2°C & 75 % RH ± 5 % for 6 months) and shelf life conditions (Real time) (30^{o}C±2°C & 75% RH ± 5 %). Tablets were stable & complied with established specification. Samples were analyzed for physical parameters and drug content.

RESULT

Description of Medicinal Product

White to off white colored round shaped biconvex film coated tablets plain on both sides were formulated.

Tenofovir Disoproxil Fumarate is used as active pharmaceutical ingredient whose specification is set as per In house specification. Excipients used in formulation were carefully chosen and adequate compatibility test performed to determine that no interactions are present between drug and excipient.

Excipients used in the formulation of tablet core include Lactose Monohydrate, Croscarmellose Sodium, Polyethylene Glycol 400, Pre-gelatinized Starch 1500, and Magnesium Stearate.

The manufacturing process involves wet granulation followed by compression and film coating. The critical process parameters of the manufacturing method were identified and the process was validated.

Preformulation studies of Tenofovir Disoproxil Fumarate

Physicochemical Properties of Active

Physical appearance: White to off white crystalline powder

Solubility: Slightly soluble in water, soluble in methanol, very slightly soluble in dichloromethane.

Identification test by IR: The infrared spectrum of sample in potassium bromide dispersion was concordant with the spectrum obtained from the similar preparation of Tenofovir Disoproxil Fumarate working standard.

Melting point determination: The melting point range of famotidine was found to be in the range between 277-279. and matched with reference result. Thus melting point of drug indicates purity of drug sample.

Sample no.	Melting Point (^{0}c)	Average Melting Point(^{0}c)
1	277	278
2	278	
3	278	

Drug- excipient Compatibility study

Different excipients were studied & tested for compatibility with Active Ingredient and only those found to be compatible were used in the formulation of Tenofovir tablet.

Formulation does not contain any Excipient of Human or Animal Origin. The excipients used are of Pharmacopoeial grade, mainly complying with the United States Pharmacopoeia-National Formulary (USP-NF), British Pharmacopoeia (BP) and are frequently used in the solid oral dosage forms. The results showed that the excipients had no interaction with the drug substance. The colour remains unchanged of samples.

Samples prepared for compatibility assessment were as follows

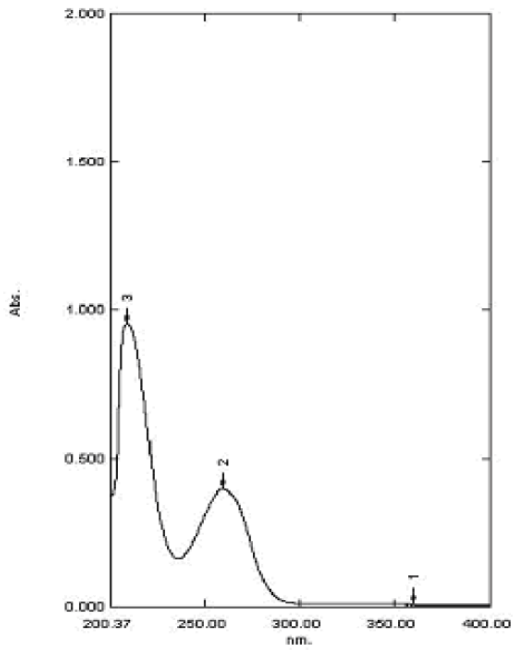
Compatibility samples	Preformulation Details	D:E ratio	25°C / 60% RH	40°C / 75% RH
F-1	Tenofovir: Lactose monohydrate	1:1	o.k.	o.k.
F-2	Tenofovir: PG Starch 1500	1:1	o.k.	o.k.
F-3	Tenofovir: Croscarmellose sodium	1:05	o.k.	o.k.
F-4	Tenofovir: Magnesium stearate	1:0.5	o.k.	o.k.
F-5	Tenofovir: PEG 400	1:0.25	o.k.	o.k.
F-6	Tenofovir: Coating agent	1:0.5	o.k.	o.k.
F-7	Composite in same ratio as of formulation	-	o.k.	o.k.

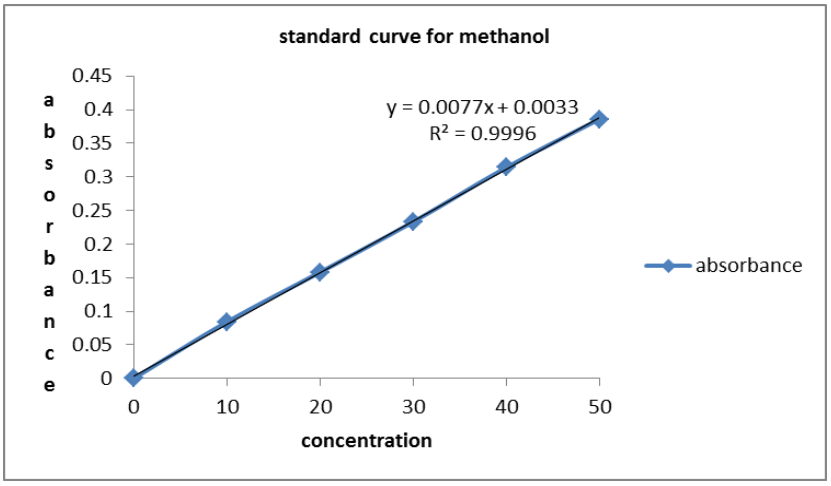
UV-visible Spectrophotometric study: Standard stock solution containing 100 µg/ml of TDF was prepared by dissolving in 1ml methanol and 0.1 N HCL the volume was made up to 100 ml with distilled water. From the stock, different aliquots were taken and diluted to 10 ml mark with same solvent to obtain series of concentrations. The solutions were scanned on spectrophotometer in the UV range 200-400 nm.

TDF showed absorption maxima at 260 nm (fig. In the method, drug follows linearity in the concentration range of 10 – 50 µg/ml.

In case of HCL max TDF showed absorption maxima at 255 nm (fig. In the method, drug follows linearity in the concentration range of 2– 10 µg/ml.

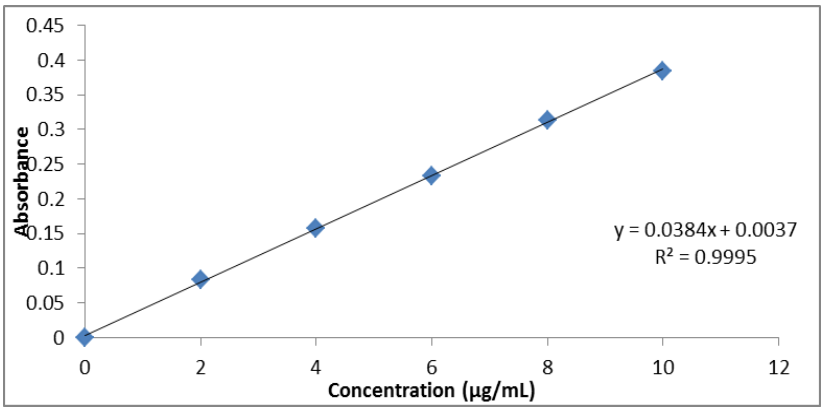
Figure 1: UV Spectrum of Tenofovir





Values of straight line equation

STRAIGHT LINE EQUATION(Y=mx+c)	VALUE
GRADIENT (m)	0.007x
INTERCEPT(c)	0.003
REGRESSION COEFFICIENT(R^2)	0.999



Standard curve of tenofovir in 0.1 N HCL

values of straight line equation

STRAIGHT LINE EQUATION(Y=mx+c)	VALUE
GRADIENT (m)	0.0384x
INTERCEPT(c)	0.0037
REGRESSION COEFFICIENT(R^2)	0.9995

EVALUATION OF various formulations

FLOW PROPRTIES

Pre-compression Parameters of Designed Formulations

S.N.	Formulation Code	Bulk Density	Tapped Density	Carr's Index	Hausner's Ratio	Angle Of Repose
1	**Trial 1**	0.60	0.72	26.66	1.40	43.60
2	**Trial 2**	0.58	0.71	28.42	1.32	42.90
3	**Trial 3**	0.60	0.72	16.66	1.20	23.58
4	**Trial 4**	0.57	0.68	16.17	1.19	24.20
5	**Trial 5**	0.56	0.66	15.15	1.17	22.50
6	**Trial 6**	0.61	0.71	14.08	1.16	24
7	**Trial 7**	0.69	0.79	27.16	1.48	44.10
8	**Trial 8**	0.59	0.81	28.42	1.32	40.99
9	**Trial 9**	0.60	0.73	26.06	1.40	41.68
10	**Trial 10**	0.60	0.72	16.66	1.20	23.58
11	**Trial 11**	0.59	0.73	29.46	1.48	41.93
12	**Trial 12**	0.56	0.73	28.12	1.42	42.80
13	**Trial 13**	0.60	0.72	16.66	1.20	23.58

Preliminary trials on the basis of literature survey: Various trials of about 13 formulations were done based on literature survey and various evaluation studies were performed. Based on evaluation parameters the best formulation was optimized and compared with the marketed formula.

⟶ Trials Batch Number	Trial -1	Trial-2	Trial -3
Ingredients	**Dry Mix**		
MCC PH101	103.0	40.0	28.0
Lactose monohydrate	100.0	225.0	-
Tenofovir Disoproxil Fumarate	-	-	300.0
Maize starch	-	-	171.0
Binder			
Maize starch	7.0	7.0	14.0
Purified water	q.s.	q.s.	q.s.
Extra Granular			
Tenofovir Disoproxil Fumarate	300.0	300.0	-
Pre-gelatinized starch	10.0	15.0	-
Croscarmellose	5.0	20.0	-
Maize starch	-	-	18.5
Magnesium stearate	5.0	15.0	7.0
Core Tablet Weight (in mg)	**530.0mg**		
Opadry white 21K580010	--	--	15
Purified Water	--	--	q.s.
Coated Tablet Weight (in mg)	**530.0mg**		

PHYSICOCHEMICAL PARAMETERS OF CORE TABLETS			
⟶ Trials Batch no.	**Trial -1**	**Trial -2**	**Trial-3**
Punch details	12.0 mm round standard concave punch		
Hardness (Kg/cm^2)	5-7 kg/cm^2	6-7 kg/cm^2	6-7 kg/cm^2
Thickness (mm)	5.1mm-5.2mm	5.2mm-5.3mm	4.9mm-5.0mm
Friability (%)	0.2%	0.3%	0.12%
Disintegration time (minutes) at 37±5°C Temperature	4-5 minutes	4-5 minutes	4-5 minutes
Remark	Flow poor and sticking observed	Flow poor and sticking observed	Uncoated tablets o.k.

PHYSICOCHEMICAL PARAMETERS OF COATED TABLETS			
Parameters	**Trial-1**	**Trial-2**	**Trial-3**
D.T.	-		5-6 minutes
Dissolution			92.08%
Related substance	-	-	-
Assay	-	-	-
Remark	-	-	CDP not O.k. with innovator

⟶ Trials Batch Number	Trial -4	Trial-5	Trial -6
Ingredients	**Dry Mix**		
MCC PH101	29.0	29.0	30.0
Lactose monohydrate	164.0	164.0	164
Tenofovir Disoproxil Fumarate	300.0	300.0	300.0
Maize starch	-	-	171.0
Pre-gelatinized starch	-	7.0	-
BINDER			
Maize starch	7.0	-	10.0
Pre-gelatinized starch	7.0	-	-
Purified water	q.s.	q.s.	q.s.
EXTRAGRANULAR			
Tenofovir Disoproxil Fumarate	-	-	-
Pre-gelatinized starch	4.0	4.0	-
Croscarmellose sodium	12.0	12.0	12.0
Maize starch	-	-	1.0
Magnesium stearate	4.0	4.0	2.0
Core Tablet Weight (in mg)	**520.0mg**	**520.0**	**520.0**
Opadry white 21K580010	-	-	15
Purified Water	-	-	q.s.
Coated Tablet Weight (in mg)			

PHYSICOCHEMICAL PARAMETERS OF CORE TABLETS			
⟶ Trials Batch no.	**Trial -4**	**Trial -5**	**Trial-6**
Punch details	12.0 mm round standard concave punch		
Hardness(Kg/cm^2)	7-8 kg/cm^2	5-6 kg/cm^2	6-7 kg/cm^2
Thickness (mm)	4.8mm-5.2mm	5.0mm-5.1mm	4.9mm-5.0mm
Friability (%)	0.1%	0.13%	0.12%
Disintegration time (minutes) at 37 ± 5°C Temperature	More than 30 minutes	More than 15 minutes	More than 20 minutes
Remark	Tablets failed in disintegration	Tablets failed in disintegration	Tablets failed in disintegration

⟶ Trials Batch Number	Trial -7	Trial-8	Trial -9
Ingredients	**DRY MIX**		
MCC PH101	28.0	-	-
Lactose spray dried	-	130	-
Lactose monohydrate	-	-	179.0
Tenofovir Disoproxil Fumarate	300.0	300.0	300.0
Maize starch	171.0	-	-
MCC 302	-	103	-
Croscarmellose sodium	-	15.0	-
Pre-gelatinized starch	-	65.0	-
Binder			
Maize starch	14	-	14.0
Purified water	q.s.	-	q.s.
Extra granular			
Tenofovir Disoproxil Fumarate	-	-	-

Pre-gelatinized starch	-	-	-
Croscarmellose sodium	-	-	20.0
Maize starch	-	-	--
Magnesium stearate	7.0	7.0	7.0
Core Tablet Weight (in mg)	**520.0mg**	**620.0**	**520.0**
Opadry white 21K580010	--	--	---
Purified Water	--	--	q.s.
Coated Tablet Weight (in mg)			

PHYSICOCHEMICAL PARAMETERS OF CORE TABLETS			
⟶Trials Batch no.	**Trial -7**	**Trial -8**	**Trial-9**
Punch details	12.0 mm round standard concave punch		
Hardness(Kg/cm^2)	5-7 kg/cm^2	5-6 kg/cm^2	5-7 kg/cm^2
Thickness (mm)	4.9mm-5.0mm	5.5mm-5.6mm	5.1mm-5.2mm
Friability (%)	0.3%	0.11%	0.12%
Disintegration time (minutes) at 37 ± 5°C Temperature	1 minute	1-2 minutes	1-2 minutes
Remark		Powder flow poor	Sticking observed

⟶Trials Batch Number	**Trial -10**	**Trial-11**	**Trial -12**
Ingredients	**Dry Mix**		
MCC PH101	-	-	
Lactose spray dried	25.0	225.0	-
Lactose monohydrate	-	-	175.0
Tenofovir Disoproxil Fumarate	300.0	300.0	300.0
Maize starch	-	-	-
MCC 302	278.0	35	-
Croscarmellose sodium	-	-	7.0
Pre-gelatinized starch	-	-	-
Binder			
Maize starch	-	-	14.0
Purified water	-	-	q.s.
Extra Granular			
Pre-gelatinized starch	20.0	65.0	-
Croscarmellose sodium	15.0	30.0	20.0
Maize starch	-	-	12.0
Colloidal anhydrous silica	4.0	4.0	-
Magnesium stearate	15.0	15.0	10.0
Core Tablet Weight (in mg)	**657.0mg**	**674.0**	**525.0**
Opadry white Y-1-7000	19.0	-	-
Purified Water	q.s.	-	-
Coated Tablet Weight (in mg)			

PHYSICOCHEMICAL PARAMETERS OF CORE TABLETS			
⟶Trials Batch no.	**Trial -10**	**Trial -11**	**Trial-12**
Punch details	16.5 x 8.5 elongated standard concave(for trial No.10 and 11) and 12.0 mm round standard concave punch		
Hardness(Kg/cm^2)	12-13 kg/cm^2	7-8 kg/cm^2	5-6 kg/cm^2
Thickness (mm)	4.6 mm - 4.7 mm	4.7 mm - 4.8 mm	4.8 mm - 4.9 mm
Friability (%)	0.23%	0.1%	0.2%
Disintegration time (minutes) at 37 ± 5°C Temperature	1-2 minutes	1-2 minutes	1-2 minutes
Remark	-	Powder flow poor and sticking observed	Sticking observed

PHYSICOCHEMICAL PARAMETERS OF COATED TABLETS			
Parameters	**Trial-10**	**Trial-11**	**Trial-12**
D.T.	-	-	-
Dissolution	92.0%--94.0%		92.40%--99.59
Related substance	-	-	-
Assay	-	-	-
Remark	Fail in CDP	--	Fail in CDP

Trials Batch Number ⟶ Trial -13	
Ingredients	**Mg/tab.**
Dry Mix	
Tenofovir Disoproxil Fumarate	300.0
Lactose monohydrate	175.0
Croscarmellose sodium	7.0
Binder	
PEG 400	1.0
Purified water	q.s.
Extra granular	
Pre-gelatinized starch	12.0
Croscarmellose sodium	25.0
Magnesium stearate	10.0
Core Tablet Weight (in mg)	**530.0mg**
Opadry white Y-1-7000	15
Purified Water	--
Coated Tablet Weight (in mg)	**545.0 mg**

Physicochemical Parameters of Core Tablets	
⟶Trials Batch no.	**Trial -13**
Punch details	12.0 mm round standard concave punch
Hardness(Kg/cm^2)	5-6 kg/cm^2
Thickness (mm)	4.9mm-5.0mm
Friability (%)	0.32%
Disintegration time (minutes) at 37 ± 5°C Temperature	1-2 minutes
Remark	uncoated tablets ok in physicochemical parameters

Physicochemical parameters of coated tablets	
Parameters	**Trial-13**
D.T.	2-3 min
Dissolution	95.18% to 97.88
Related substance	IMPA=0.68%, PMPA = Not Detected Single Unidentified0.13%, Total imp= 0.81%
Assay	97.5%
Remark	Pass in CDP analysis

Criteria for selection of punches, packing material etc

S. No.	Selection	Criteria
1	12.0 mm Round shape Standard concave	Concave shape punches used for film coating, 12.0 mm size is suitable for desired weight of tablets.
2	Tablet packed in Alu/PVDC blister pack (3 x 10)	As per comparator pack style

Finished pharmaceutical product

Formulation development

Market product study

Market Product Study-Label Details

S. No.	Parameters	Details
1.	Brand Name	Viread
2.	Manufacturer	Gilead
	Marketed By	Gilead
3.	Generic Name	Tenofovir Disoproxil Fumarate tablets
4.	Batch No. / Lot No.	13VR025D
5.	Expiry Date	02/2022
6.	Manufacturer's Label Claim	Tenofovir Disoproxil Fumarate 300mg
7.	Storage	At a temperature not more than 30°C
8.	Pack Details	Mono pack carton with HDPE bottle containing 30 tablets along with cotton plug and desiccant

Market Product Study-Physicochemical Parameters:

S. No.	Parameters		Observations
1.	Description		Blue coloured almond shaped biconvex film coated tablets debossed with "GILEAD" and "4331" on one side and with "300" on the other side
2.	Average weight		700.0 mg
3.	Diameter		17.1± 0.1mm
4.	Width		NA
5.	Thickness		5.2 mm ± 0.2 mm
6.	Disintegration time		2- 3 minutes
7.	In-Vitro Dissolution:		
8.	Dissolution Parameters	Media	0.1 M hydrochloric acid
		Volume	900ml

		Apparatus	Paddle mixer
		RPM	50
		Temperature	37°C ±0.5°C
		Sampling Time	30 minutes
	Dissolution Observed		96%-101%
9.	Assay		99.5%

Stability Batches

Three stability batches were manufactured using the lead formula to confirm the reproducibility of batches & to understand the stability attributes of the formulation.

Batch No.	Batch size	Mfg. Date	Exp. Date
TEN-S-001	1.0 Lac	02/2021	01/2023
TEN-S-002	1.0 Lac	02/2021	01/2023
TEN-S-003	1.0 Lac	02/2021	01/2023

Solubility and dissolution study

Solubility study in different solvents and buffer media

Solubility Study	Highest Dose in 250 ml (Highest dose 600 mg taken in 250 ml solvent/ Buffer media)
0.1N HCl	Soluble
pH 4.5 Acetate Buffer	Not Soluble
pH 6.8 Phosphate Buffer	Soluble
Purified Water	Soluble

Multi-Media Comparative Dissolution Study

(RLD Vs Optimized Formula)

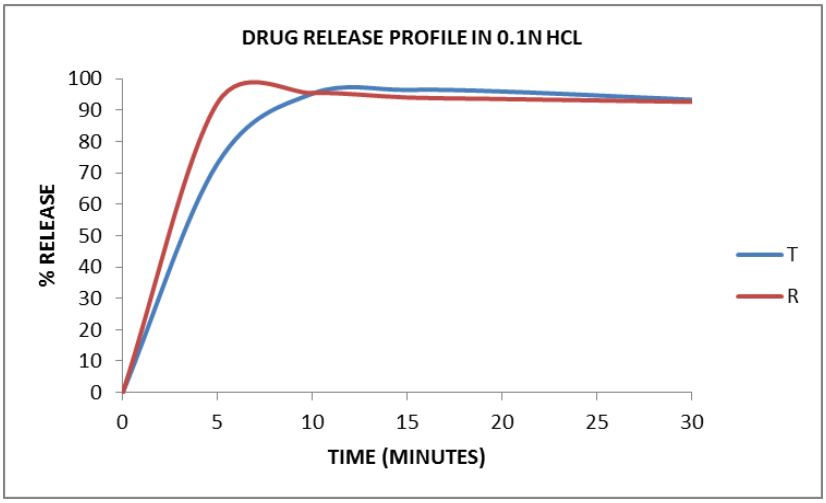
Details of Batches of Reference vs. Test sample

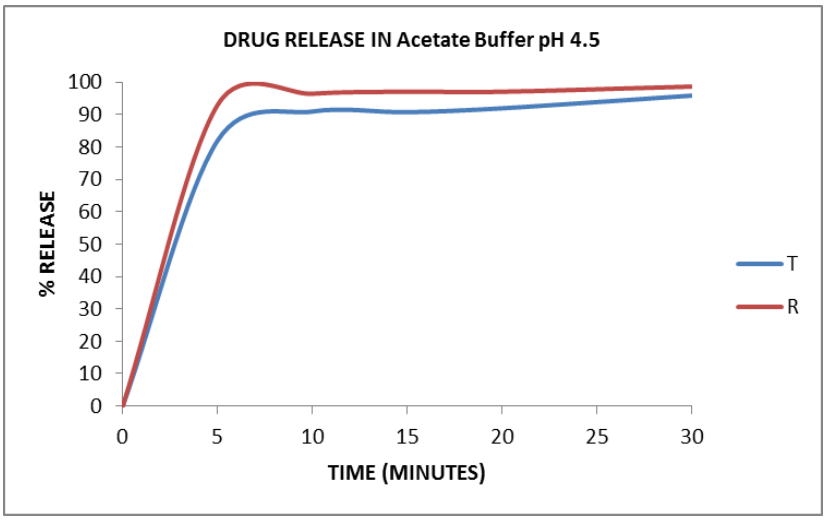
Reference	Viread (Mfd. By Gilead)	Test Sample	Tenofovir disoproxil fumarate tablets 300 mg
B. No.	20VR02SD	B. No.	TNT2-S-001
Mfg. Date	02/2020	Mfg. Date	02/2021

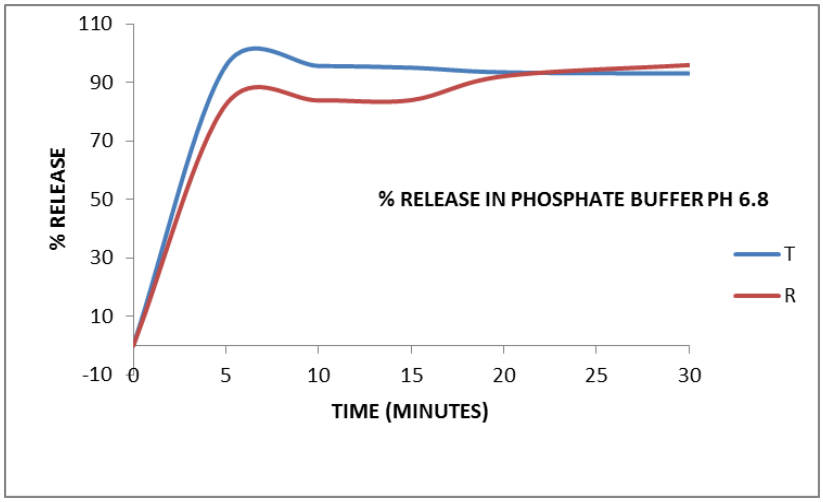
	Medium 0.1 M HCl	
	Mean of release of 12 tablets	
Time (min)	Test Sample	Reference
5	73.1	92.4
10	95.3	95.5
15	96.5	94.1
20	96.0	93.6
30	93.4	92.7
Similarity Factor	52.7	

	Medium Acetate Buffer pH 4.5	
	Mean of release of 12 tablets	
Time (min)	**Test Sample**	**Reference**
5	82	93
10	91	96.5
15	90.8	97.1
20	92	97.1
30	95.9	98.7
Similarity Factor	60.4	

	Medium Phosphate Buffer pH 6.8	
	Mean of release of 12 tablets	
Time (min)	**Test Sample**	**Reference**
5	95.8	82.5
10	95.7	83.9
15	95.1	84.0
20	93.5	92.2
30	93.1	96.0
Similarity Factor	53	







***In vitro* Release Profile of Optimized Formulation ForStudying the Release Kinetics**

ACCELERATED STABILITY STUDY: The optimised formulation of three batches stored under accelerated conditions(40^{o}C ± 2°C & 75 % RH ± 5 % for 6 months) and shelf life conditions (Real time) (30^{o}C±2°C & 75% RH ± 5%). After storage all evaluation parameters were nearly similar to the initial results. So, it was clear that the drug and the formulation were thermally stable as well as not affected by the high humidity at 40 ± 2°C/75 ± 5%.

ACCELERATED STABILITY STUDY OF TENOFOVIR TABLETS						
S. No.	**Parameters**	**B. No.**	**Specification**	**Initial**	**3 M**	**6 M**
1.	Description	TEN-S-001	White to off white colored round shaped biconvex film coated tablets plain on both side.	Complies	Complies	Complies
		TEN-S-002		Complies	Complies	Complies
		TEN-S-003		Complies	Complies	Complies
2.	Authenticity By HPLC	TEN-S-001	The retention time of the main peak in chromatogram of the test solution should correspond with the retention time of the main peak in chromatogram of standard solution. UV-spectrum of the test solution in the range from 200 to400 nm should correspond to UV – spectrum of the standard solution of Tenofovir Disoproxil Fumarate.	Complies	Complies	Complies
		TEN-S-002		Complies	Complies	Complies
	By UV Spectro-photometry	TEN-S-003		Complies	Complies	Complies
3.	Average Weight	TEN-S-001	545.0 mg ± 5.0%	545.5 mg	544.8 mg	551.0 mg
		TEN-S-002		544.7 mg	544.8 mg	548.7 mg
		TEN-S-003		545.7 mg	545.4 mg	548.6 mg
4.	Disintegration	TEN-S-001	Not more than 30min	3 min 25 sec	3 min 50 sec	4 min 40 sec
		TEN-S-002		3 min 30 sec	4 min 10 sec	5 min 05 sec

		TEN-S-003		3 min 50 sec	4 min 40 sec	5 min 35 sec
5.	Water content	TEN-S-001	Not more than 5.5%	2.82%	2.96%	3.05%
		TEN-S-002		2.64%	2.96%	3.05%
		TEN-S-003		2.74%	2.95%	3.12%
6.		TEN-S-002	Impurity A (Monoproxil impurity): NMT 1.50%	0.342%	0.624%	0.758%
			PMPA: NMT 0.30%	Not Detected	0.025%	0.038%
			Unspecified impurity: NMT 0.20%	0.024%	0.032%	0.051%
			Total impurities: NMT 3.00%	0.649%	0.895%	1.122%
		TEN-S-003	Impurity A (Monoproxil impurity) NMT 1.50%	0.349%	0.598%	0.724%
			PMPA: NMT 0.30%	Not Detected	0.022%	0.034%
			Unspecified impurity: NMT 0.20%	0.026%	0.035%	0.057%
			Total impurities: NMT 3.00%	0.670%	0.924%	1.119%
7.	Dissolution	TEN-S-001	Not less than 80% (Q) of claimed quantity of $C_{19}H_{30}N_5O_{10}P$, $C_4H_4O_4$ should pass in to the solution after 30 minutes	Min :98.7% Max: 102.5%	Min :97.3% Max: 100.8%	Min :96.2% Max: 99.6%
		TEN-S-002		Min :99.0% Max: 101.5%	Min :97.3% Max: 100.8%	Min :96.2% Max: 99.6%
		TEN-S-003		Min. 99.3% Max 101.4%	Min 98.4% Max 100.6%	Min96.8% Max: 99.7%
8.	Assay	TEN-S-001	Between 285 mg and 315 mg of Tenofovir Disoproxil Fumarate in a tablet (between 95% -105% of label claim)	98.5%	97.9%	97.1%
		TEN-S-002		99.2%	97.9%	97.1%
		TEN-S-003		99.5%	98.8%	98.1%
9.	Microbiological Impurity	TEN-S-001	a) Total aerobic microbial count: NMT 1000 cfu/g	<10 cfu/g	NA	<10 cfu/g
			b) Total fungal count: NMT 100 cfu/g	<10 cfu/g	NA	<10 cfu/g
			c) Pathogens *E. coli*: Absent/g	Absent/ g	NA	Absent/ g
		TEN-S-002	a) Total aerobic microbial count: NMT 1000 cfu/g	<10 cfu/g	NA	<10 cfu/g
			b) Total fungal count: NMT 100 cfu/g	<10 cfu/g	NA	<10 cfu/g
			c) Pathogens *E. coli*: Absent/g	Absent/ g	NA	Absent/ g
		TEN-S-003	a) Total aerobic microbial count: NMT 1000 cfu/g	<10 cfu/g	NA	<10 cfu/g
			b) Total fungal count: NMT 100 cfu/g	<10 cfu/g	NA	<10 cfu/g
			c) Pathogens *E. coli*: Absent/g	Absent/ g	NA	Absent/ g

CONCLUSION

Tenofovir Disoproxil Fumarate tablets 300 mg has been developed with an objective to formulate a finished pharmaceutical product, in order to attain physicochemical parameters equivalent to comparator product Viread.

Vendors were identified and the samples were analyzed from different vendors as per the specification. All the raw materials and packing materials were sourced from certified vendors and duly tested for integrity.

Tenofovir Disoproxil Fumarate is used as active pharmaceutical ingredient whose specification is set as per In house specification. Excipients used in formulation were carefully chosen and adequate compatibility test performed to determine that no interactions are present between drug and excipient.

Excipients used in the formulation of tablet core include Lactose Monohydrate, Croscarmellose Sodium, Polyethylene Glycol 400, Pre-gelatinized Starch 1500, and Magnesium Stearate.

The control of all excipients is described in respective pharmacopoeia. None of the excipients is of human or animal origin. Magnesium stearate is of plant origin.

Compatibility between drug and excipients used were determined studying change in the appearance of the drug product/mixture. Repeated experiments indicated very good compatibility of drug substance with excipients.

The manufacturing process involves wet granulation followed by compression and film coating. The critical process parameters of the manufacturing method were identified and the process was validated.

Based on literature review various trial batches were formulated and In process quality control studies were performed to the tablet batches. Finally trial 13 gave the best optimized formulation. Results of the evaluation test were compared to marketed formulation and comparable results were obtained.

The predevelopment study, stability study and compatibility study indicated and confirm the absence of any physical and chemical incompatibility between the excipients used and active.

The film coated tablets are packed in commercial packaging and stability studies were carried out under accelerated conditions(40^{o}C ± 2°C & 75 % RH ± 5 % for 6 months) and shelf life conditions (Real time) (30^{o}C±2°C & 75% RH ± 5 %). Tablets were stable & complied with established specification. Chemical and microbiological profile before and during stability was excellent.

No special or novel excipients were used in the formulation.