FORMULATION AND EVALUATION OF TENOFOVIR DISOPROXIL FUMARATE MOUTH DISSOLVING THIN FILMS

Praneeth Rao Kakullamarri*, K Suresh Babu*

Lincoln University College, Faculty of Pharmacy, Malaysia

Corresponding author: K Suresh Babu, Lincoln University College, Faculty of Pharmacy, Malaysia. Email: babuiict@gmail.com

ABSTRACT

A nucleotide analogue reverse transcriptase inhibitor, tenofovir disoproxil fumarate is used for the treatment of hepatitis B and the management of HIV-1 infection. This study set out to develop Tenofovir mouth dissolving films using a variety of polymers in the hopes of helping patients who have trouble swallowing traditional dosage forms, increasing the drug's bioavailability and facilitating its rapid onset of action, and ultimately helping those patients. Additionally, children, the elderly, and patients with developmental disabilities, in addition to those with mental illness, benefit from the greater accessibility of MDFs. We used a solvent casting process to formulate the MDFs. The optimised MDF is subjected to a battery of tests, including those for uniformity of weight and drug content, thickness, folding endurance, surface pH, in vitro disintegration time, tensile strength and percent elongation, scanning electron microscopy, in vitro dissolution, stability, taste evaluation by spitting, comparison with marketed formulation, drug release kinetics, and optimisation. after contrast, the optimised MDF's % CDR was determined to be 99.37±2.06% after 10 minutes, whereas the market formulation reached 81.48±1.54% after 12 minutes. These results proved that the MDFs that were loaded with Tenofovir were effective.

Keywords: Mouth Dissolving Film, Tenofovir disoproxil fumarate, FTIR, XRD, DSC and SEM, Solvent casting method.

INTRODUCTION

Most patients prefer taking their medicine orally since it is the most convenient, least intrusive, and most well accepted manner. For patients who are too young, too old, too sick, or too disobedient to take their medication orally, new and improved delivery systems have provided a few viable options. Technology has led to the development of bio adhesive mucosal dosage forms, which include patches, gels, and tablets with an adhesive back. Recent advances have highlighted the promising use of polymeric films for buccal cavity medication administration. Quickly hydrating when touched to the tongue, orally disintegrating films (ODFs) absorb saliva, allowing for easier disintegration and/or breakdown and subsequent release of the active therapeutic component. One common component of ODFs is hydrophilic polymers, which allow for rapid dissolving when exposed to saliva. Oral disintegrating films (ODFs) and oral disintegrating tablets (ODTs) are two examples of methods for delivering medications in this way. For patients of all ages who have trouble swallowing regular pills, these systems were developed in the late 1970s as an alternative to fast-acting capsules and tablets. Typically, the dimensions of a postal stamp correspond to an average ODF. Patients were educated on how to properly administer ODT before it was available to the public, and this education included warnings like "do not chew/do not swallow." However, even with these instructions, it was common to record occurrences involving chewing and swallowing.

With the release of MDFs into the market came counselling for patients on how to take them, which included warnings like "do not chew/do not swallow." Still, several instances involving swallowing and chewing were documented, even when these instructions were given. But MDFs freed the people from these bad things that happened. Solvent casting and hot-melt extrusion are two methods for making films that dissolve in the mouth. Problems with solvent residues in the film and the environmental risks of organic solvents are the main reasons why the solvent casting technique is inferior to the hot melt extrusion method. These days, many people, even those with swallowing difficulties (e.g., youngsters and the elderly), can take their medications orally thanks to mouth dissolving films (MDF), which dissolve in the mouth. The hydrophilic polymers used to make MDF dissolve quickly in the mouth or on the tongue, allowing the medicine to be more easily absorbed into the bloodstream when it comes into touch with saliva. It is common practice to place the MDF strip on the inside of the cheek (buccal) or beneath the tongue (sublingual) for oral administration of these formulations. The drug may mainly enter the circulation via the buccal and sublingual pathways when the strip dissolves.

Headaches, reduced bone mineral density, and nephrotoxicity are typical side effects of Tenofovir Disoproxil Fumarate (TDF), much like TDF. A 49-year-old Thai lady was thought to have had a decline in renal function about three months after changing her antiretroviral treatment regimen from TDF/FTC/LPV/r to TAF/FTC/DTG, according to a recent case report. Her blood creatinine level was still climbing at her 6-month checkup, so her doctor ordered a kidney biopsy, which confirmed renal damage. The patient's renal 4 function improved after discontinuing the TAF/FTC/DTG. There were no alterations to the phosphate homeostasis in individuals with isolated hypophosphatemia when they switched from TDF to TAF, according to retrospective cohort research included 74 men and 28 females aged 30-82 years old. Patients with decreasing bone density may have reason to be concerned about the absence of change in phosphate levels. These side effects should be considered by medical experts before administering TDF5.

MATERIALS AND METHODS

Materials A gift sample of tenofovir disoproxil fumarate, a "anti-retroviral agent," was acquired. S.D. Fine Chemicals of Mumbai supplied the propylene glycol, citric acid, mannitol, and xanthan gum, while INR chem supplied the sodium alginate. Lycoat received in Mumbai from Signet Chemical Corp. in Mumbai International Flavours of Fragrances India Ltd. supplied the Trusil mixed flavour R.S.V. The remaining components were all of analytical quality and were not altered in any way.

PREPARATION METHOD

Formulation of Mouth Dissolving Films of Tenofovir disoproxil fumarate By Using Solvent Casting Method

The solvent casting process was used to manufacture the Tenofovir disoproxil fumarate mouth dissolving films. Sodium alginate and xanthan gum were used to create the mouth dissolving films. As a plasticiser, propylene glycol is useful, while citric acid stimulates saliva production and acts as a super disintegrant, similar to Lycoat. We used a magnetic stirrer to continuously stir the three-quarters volume of the polymer solution, and then we corrected the final volume with distilled water. Following levitation, the polymeric solutions were supplemented with the specified amounts of Tenofovir disoproxil fumarate, Mannitol, and Flavour. Cast onto a glass plate, the mixture was then placed in a hot air oven set at 400 degrees Celsius. The films, which contain 150 mg of Tenofovir disoproxil fumarate, were

punched to a size of 6 cm2. Xanthan Gum and Sodium Alginate, two film-forming polymers, were tested at varying concentrations using the trial-and-error technique. Dissolving varying amounts of film-forming polymers in 20 ml of water was used to produce the film concentrations.

Table.No.1 Formulation details of Tenofovir disoproxil fumarate Mouth Dissolving Films by using 2 different natural Polymer

Formulation Code / Ingredients	TF1	TF2	TF3	TF4	TF5
Tenofovir disoproxil fumarate (mg)	300	300	300	300	300
Xanthan Gum	100	150	200	250	300
Sodium Alginate	100	150	200	250	300
Lycoat	50	60	70	80	90
Citric acid	40	40	40	40	40
Mannitol	20	20	20	20	20
Trusil Flavor(mg)	10	10	10	10	10
Propylene Glycol(ml)	50	50	50	50	50
Distilled Water	Q.S	Q.S	Q.S	Q.S	Q.S

Table.No.2 Formulation details of Tenofovir disoproxil fumarate Mouth Dissolving Films by using Xanthan Gum

Formulation Code / Ingredients	TF6	TF7	TF8	TF9	TF10
Tenofovir disoproxil fumarate (mg)	300	300	300	300	300
Xanthan Gum	200	300	400	500	600
Sodium Alginate	-	-	-	-	
Lycoat	50	60	70	80	90
Citric acid	40	40	40	40	40
Mannitol	20	20	20	20	20
Trusil Flavor(mg)	10	10	10	10	10
Propylene Glycol(ml)	50	50	50	50	50
Distilled Water	Q.S	Q.S	Q.S	Q.S	Q.S

Table.No.3 Formulation details of Tenofovir disoproxil fumarate Mouth Dissolving Films by using Sodium Alginate

Formulation Code / Ingredients	TF11	TF12	TF13	TF14	TF15
Tenofovir disoproxil fumarate (mg)	300	300	300	300	300
Xanthan Gum	-	-	-	-	-
Sodium Alginate	200	300	400	500	600
Lycoat	50	60	70	80	90
Citric acid	40	40	40	40	40
Mannitol	20	20	20	20	20
Trusil Flavor(mg)	10	10	10	10	10
Propylene Glycol(ml)	50	50	50	50	50
Distilled Water	Q.S	Q.S	Q.S	Q.S	Q.S

Calculation of dose for Tenofovir disoproxil fumarate

The dose of Tenofovir disoproxil fumarate is 300 mg. Therefore, the amount of Tenofovir disoproxil fumarate required in 2cm*4cm=8 cm^2 film is 150 mg.

- Length of glass plate =4 cm.
- Width of glass plate =4 cm.
- Area of the plate =16 cm^2.
- No. of 8 cm^2 films present whole plate =16/8 =2 films.
- Therefore, each films contains 150 mg of drug

- 2 films contain 300 mg drug (2/300=150mg).

So, the Labelled claim of drug = 150 mg.

Evaluation Parameters of Mouth Dissolving Film

Organoleptic Properties of Pure Drug

The organoleptic characters like color, odor, taste and texture of the pure drug have been identified.

Determination of melting point

The capillary glass method was used to determine the drug's melting point. By sealing one end of a capillary tube and inserting a little amount of the drug inside, its melting point may be determined. The temperature at which the medicine melted was measured after positioning the capillary tube in the thermionic melting point apparatus. Thermodynamic melting point measurements compared to literature

Solubility studies of pure drug

The drug's solubility was investigated by testing it with various buffers. The following solutions were prepared in glass-capped tubes: 10 millilitres of distilled water, phosphate buffer solutions with pH 6.8, and 0.1N hydrochloric acid. The medication was distributed in each of these solutions. To prevent solvent loss, all flasks were sealed with stoppers and wrapped with cellophane membranes. They were then shaken in a water bath at 37ºC for 24 hours. The samples were centrifuged at 3000 rpm for 5 minutes after they reached equilibrium using a Hermle Z 200 A from Germany. Using a 0.45 µm membrane filter, the liquid above was strained out. After diluting a one millilitre sample of the saturated solution with appropriate solvents, it was examined using a UV spectrophotometer set at 259.0 nanometres (YIS-294).

Drug-polymer compatibility studies

Because the medicine and polymer are in such close proximity during tablet manufacturing, there is a risk that they may interact, rendering the drug unstable. Consequently, choosing the right polymers requires thorough pre-formulation research on the drug-polymer interaction. To determine if the chosen polymers were compatible with Tenofovir disoproxil fumarate, FT-IR spectroscopy was used. Two distinct batches of medication, one without an excipient and one with it, were scanned.

FT-IR studies

Sample/KBr ratio

It is recommended that the sample be concentrated in KBr between 0.2% and 1%. Due to the fact that the pellet is much thicker than a liquid film, Beer's Law states that a lower concentration in the sample is necessary. Typically, getting clear pellets becomes challenging at concentrations that are too high. Extremely noisy spectra are produced when the infrared beam is either entirely absorbed or dispersed by the material.

Differential scanning calorimetry (DSC)

TA Instruments' DSC Q20 Universal V4.5A was used for DSC. After the samples had equilibrated for 1 minute, they were subjected to temperatures ranging from 0 to 300°C in a nitrogen environment. We used the 2000 universal analysis program from TA Instruments

to get the thermograms.

X-Ray diffraction (XRD)

To document the samples, the XRD (PW 1729, Philips, Amsterdam, Netherlands) was used. The XRD patterns were recorded by using a Ni filter in conjunction with monochromatic Cu Kα radiation. The experiments were conducted at 2θ values ranging from 10° to 80° using a 40 kV voltage and 30 mA current. The data was processed using Diffrac Plus V1.01.

EXPERIMENTAL METHODS

Analytical method development by U.V. Spectroscopy

One of the most common methods used for analysing pharmaceuticals is ultraviolet-visible spectrophotometry. It is a method for determining how much light, either UV or visible, material in a solution can absorb. Spectrophotometers that measure the ratio of two U.V.-visible light beam intensities are known as ultraviolet-visible spectrophotometers. Quantitative spectrophotometric analysis determines the number of molecular species absorbing the light, whereas qualitative analysis uses a spectrophotometer to identify organic substances (if any recorded data is available). When working with low concentrations of substances, the spectrophotometric method is ideal since it is quick, easy, and somewhat selective. In quantitative spectrophotometric analysis, the Beer-Lambert law is the guiding principle.

Calibration curve of Tenofovir disoproxil fumarate

Preparation of Standard Calibration Curve of Tenofovir disoproxil fumarate in 7.4 pH Phosphate Buffer: A 10-millilitre volumetric flask was used to transfer 10 milligrammes of tenofovir disoproxil fumarate. To create stock solution-II, which has 100µg/ml, it was dissolved and then diluted to volume using 7.4 pH Phosphate Buffer. Sampling from the second standard stock solution, take 0.25 ml, 0.50 ml, 0.75 ml, 1.0 ml, 1.25 ml, and 1.50 m1. Tenofovir disoproxil fumarate, ranging from 2.5 to 15 ug/ml, was obtained by serially diluting the standard stock solution with 7.4 pH Phosphate Buffer. The solution's absorbance was measured at 259.0 nm using a UV visible spectrophotometer Single Beam Spectrophotometer (YIS-294), with a 7.4 pH Phosphate Buffer serving as a blank. The standard calibration curve was obtained by plotting the absorbance readings against the concentration (µg/ml).

Physical appearance and surface texture of film[7]

Film visual assessment and tack evaluation by feel or touch were the only methods used to verify this criterion.

Weight uniformity of films

A digital scale was used to measure each of the three films, which had a dimension of 2x4 cm^2 = 8 cm square, before averaging their weights.

Drug content uniformity study of films

Using a UV-Spectrophotometric technique, the films were examined for homogeneity drug

content. Three separate locations on the cast films were used to cut films with a diameter of 2×4 cm2. After dissolving the films in a 7.4 pH Phosphate Buffer solution, 0.2 ml was taken and diluted with buffer until it reached a volume of 10 ml. The solution was then added to a 100 ml volumetric flask. The solution's absorbance was measured at 259.0 nm using a UV-Visible Single Beam Spectrophotometer (YIS-294). For all three films, we used the same method to calculate the drug content % using the standard graph.

Moisture content of film

To guarantee dryness, testing was conducted on the moisture content. Before being placed in the desiccators with the calcium chloride, the prepared films were weighed. To find the percentage of moisture loss, the films were reweighed after 3 days. For this experiment, we employed three different formula films.

$$\%\ \textbf{Moisture content} = \frac{\boldsymbol{initial\ weight - final\ weight}}{\boldsymbol{initial\ weight}} * \mathbf{100}$$

The thickness of films[8,9,10]

We used a calibrated vernier calliper (Mitutoyo, Japan) to measure the film's thickness. A dosage-equivalent sample was collected. The film was inserted after the anvil of the thickness gauge was raised and the pointer was adjusted to zero. We measured the dial reading while the film was resting on the anvil. We took thickness readings at three separate locations. Average thickness was determined by averaging the results of six measurements.

Folding endurance of films[11]

One way to measure the pliability of films is by looking at their folding durability. To test the films' capacity to withstand repeated folding, a small (8 cm2) section was bent in the same direction until it snapped. The number of rip-free folds in a given area is one indicator of a film's folding endurance.

Surface pH of films[12,13]

The films were let to come into contact with 1ml of distilled water to ascertain the surface pH. To measure the surface pH, we brought a glass electrode and pH paper next to the films' surfaces and let them equilibrate for one minute.

In vitro disintegration time of films[14,15]

The disintegration test was conducted using a 7.4 pH phosphate buffer solution, which is the recommended medium according to the USP disintegration time testing device. The disintegration time of the films was measured after placing them in the container's tubes.

Tensile strength and Percentage elongation

Following the steps outlined below, the films' tensile strengths were measured using a TAXT Plus Texture Analyser (Texture Technologies, Scarsdale, NY) in conjunction with micro tensile grips TA-96B. In the tensile grasp of the texture analyser, a 2 × 4 cm^2 sheet devoid of air bubbles or physical flaws was held longitudinally. At an initial grip separation of 6 mm from both sides, the test was run at a crosshead speed of 2 mm/sec until the film broke. For every film, the measurements were taken three times.

$$\boldsymbol{Tensile\ strength} = \frac{\textbf{Force at break (N)}}{\textbf{Initial cross sectional area of the film (mm2)}}$$

Percentage elongation was calculated by the following equation

$$\% \boldsymbol{Elongation} = \frac{\textbf{Increase in length}}{\textbf{Original length}} * \textbf{100}$$

Scanning electron microscopy (SEM)

A scanning electron microscope (Quanta-200, Thermo Fischer Scientific, USA) was used to test the formulations' surface properties. Carbon tape with two sides was applied to an aluminium stick. We dipped the stab in the sample and used an air blower to get rid of any loose particles. A bio-radpolaran sputter coater was used to apply a layer of gold particles on the sample. After positioning the sample in an evacuated chamber, an electron beam was used to scan it in a regulated pattern. Comparisons were made between images of uncoated KCl and those of the coated ones.

Taste Evaluation Study by Spitting:[19]

A taste panel (n=5) was used to test the acceptability of the medication's flavour. A film sample containing 150 mg of the drug was kept in the mouth until it disintegrated, then spit out and the amount of bitterness was recorded. Gargling with distilled water was instructed by the participants in between the delivery of the medicine and the film samples. Here is the scale that was used for the bitter study:

- → + = very bitter
- → ++ = moderate to bitter
- → +++ = slightly bitter
- → ++++ = tasteless/taste masked
- → +++++ = excellent taste masking

In-vitro Dissolution Study[20]

Using a USP dissolving device (Type II) and a 900 ml 7.4 pH phosphate buffer solution, the in vitro dissolution of Tenofovir disoproxil fumarate mouth solvating films was investigated. We set the stirrer to spin at 50 revolutions per minute.Throughout the experiment, the dissolving medium's temperature was kept at 37±0.5ºC. Every test made use of a single film. Using a syringe equipped with a pre-filter, 5 ml of dissolving media were taken at 1, 3, 5-, 7-, 10- and 12-minute intervals. The absorbance at 259.0 nm was measured to determine the drug release. Every time a volume was removed, the same number of dissolving media was added to replace it. Tenofovir disoproxil fumarate release percentage over time was determined and shown graphically.

Comparison of optimized formulation with marketed formulation

Using commercially available 300 mg Tenofovir disoproxil fumarate tablets, researchers compared the solubility of an optimised T15 formulation containing the drug. Here are the findings of an in vitro drug release research comparing the market-ready 300 mg Tenofovir disoproxil fumarate tablets in a 7.4 pH phosphate buffer to the optimised formulation (T15) of this medicine.

Drug Release Kinetics[21,22]

A kinetic analysis of the dosage form's drug release rate was performed by plotting the

acquired data as:

Zero order model:

The optimal way to accomplish a pharmacological extended effect is using pharmaceutical dose forms that follow these characteristics, as they release the same quantity of medication per unit of time.

$$Qt = Q0 + K0t$$

First order model:

In 1967, Gibaldi and Feldman were the first to suggest using this model in drug dissolution investigations, and Wagner followed suit in 1969.

$$\log Qt = \log Q0 + (K1/2.303)$$

Higuchi model:

In 1961, Higuchi put forth the first mathematical model that explains the release of drugs from a matrix system.

$$f\,t = Q = KH \sqrt{t}$$

Korsemeyer- peppas model:

A straightforward equation describing drug release was developed by Korsemeyer et al. (1983) from a polymeric system. In some experimental settings, the releasing mechanism acts in a way that is not consistent with Ficks equation. It is possible to apply a more general equation in these instances:

$$Mt/M\infty = at^{n}$$

Stability studies[23]

Various environmental conditions were used to conduct the stability investigation of the mouth dissolving films that were developed. For the stability investigations, the film was packaged in aluminium foil and kept in a stability chamber at 2-8°C (45% RH), 400C/75% RH after one month, and 400C/75% RH after three months. During the stability investigation, the patches were examined for characteristics such as their appearance, drug content homogeneity, surface pH, tensile strength, and In-vitro dissolution studies.

RESULTS AND DISCUSSION

Organoleptic Properties of Pure Drug

Discussion: The drug's texture was silky smooth, and its colour was pure white. It had an awful taste and a distinct aroma, and it was amorphous in shape.

Determination of Melting Point: Tenofovir disoproxil fumarate's pure medication melting point was confirmed by the capillary technique.

Discussion: By using the capillary technique, the melting point of the pure medication Tenofovir disoproxil fumarate was discovered to be 112oC.

Solubility studies: Purified water, 0.1 N hydrochloric acid, 6.8 pH phosphate buffer, and 7.4 pH phosphate buffer were used to determine the solubility of tenofovir disoproxil fumarate at 250C.

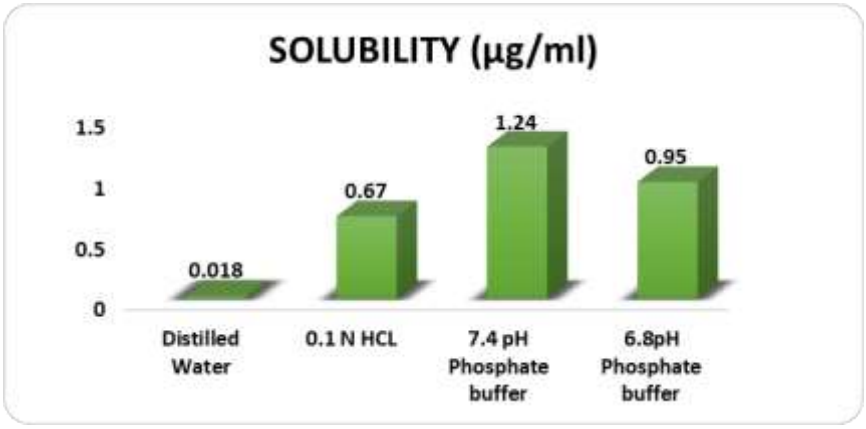

Figure No.1 Bar Graphs for Solubility studies

Discussion: A variety of buffers, including acidic (0.1N HCL) and basic (6.8pH phosphate buffer, 7.4pH phosphate buffer, and water), were used to perform the solubility investigations. According to the solubility tests that were performed in different buffers, it was found that the medication was more soluble in a 7.4 pH phosphate buffer than in the other solutions.

Drug excipient compatibility: This trial's excipient compatibility was confirmed by comparing the spectra of the pure drug's FT-IR analysis with those of the various excipients utilised.

FTIR Studies

Pure Drug

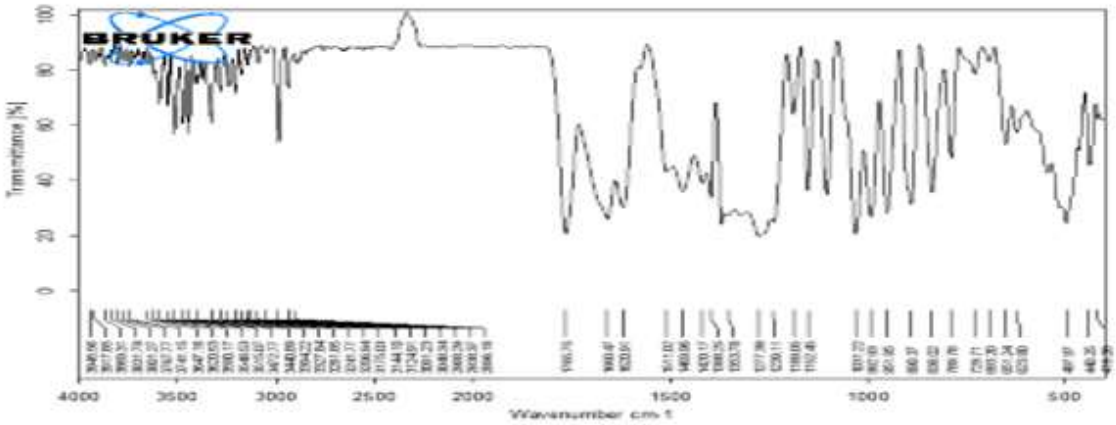

Figure No.2 IR spectrum of Tenofovir disoproxil fumarate

Optimized

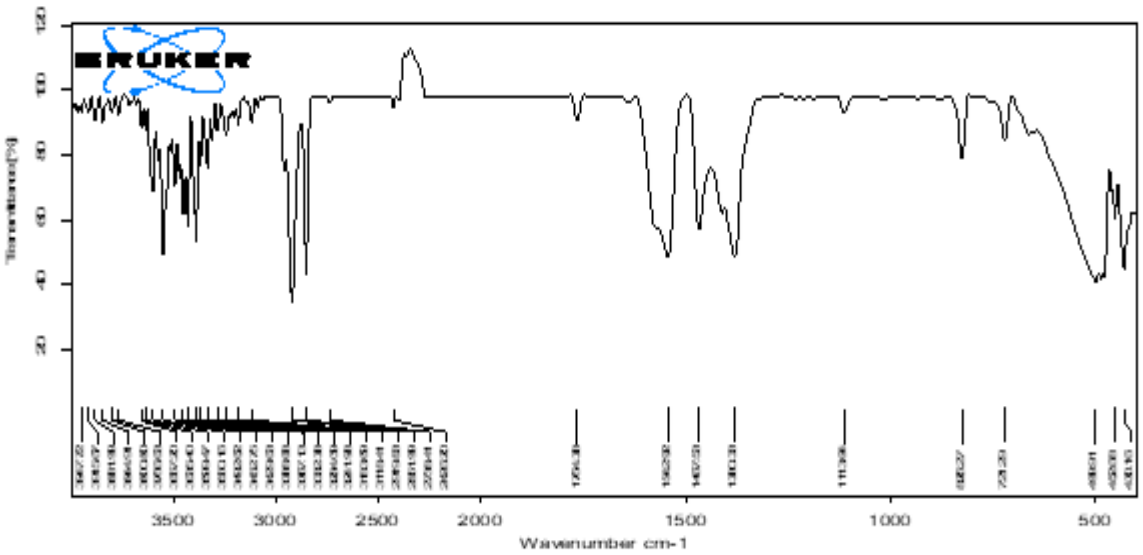

Figure No.3 IR spectrum of Tenofovir disoproxil fumarate & excipients

Differential scanning calorimetry

By use of a differential scanning calorimeter, the pure medication and optimised trail DSC curves were acquired.

Pure Drug

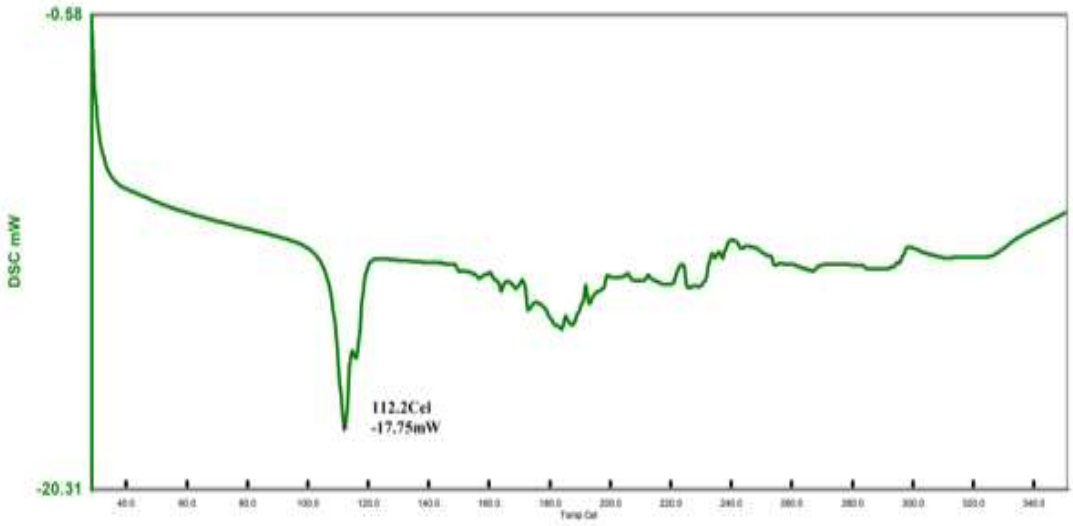

Figure No.4 DSC of the Pure Drug

Optimised :

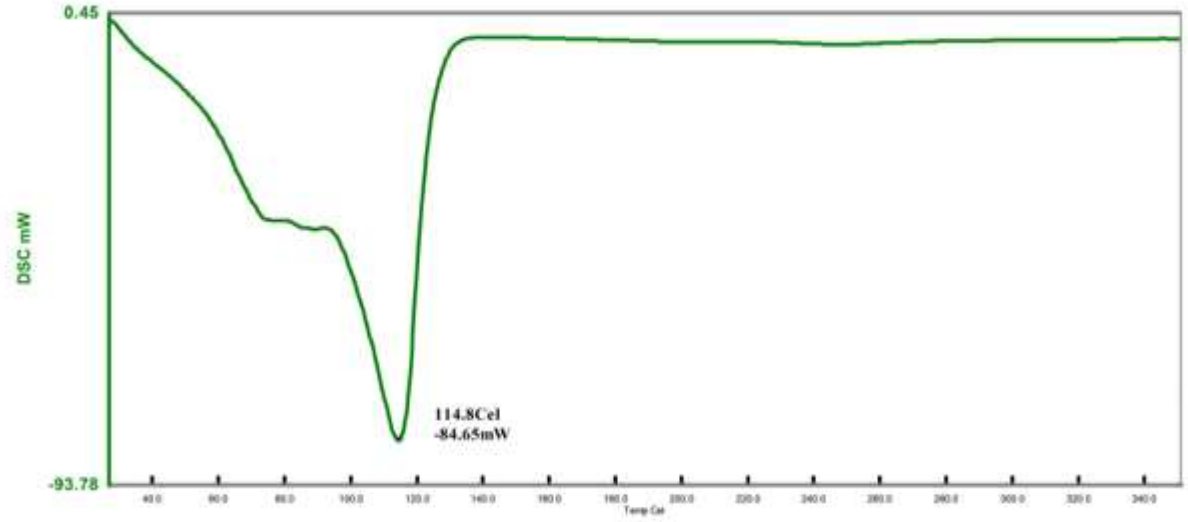

Figure No.5 DSC of the Optimized trail

X-Ray diffraction: Even when mixed, the level of crystallinity of the pure medicine remains constant. On the other hand, the peak intensity was lower since there was less pure drug in the combination compared to the pure version.

Pure Drug

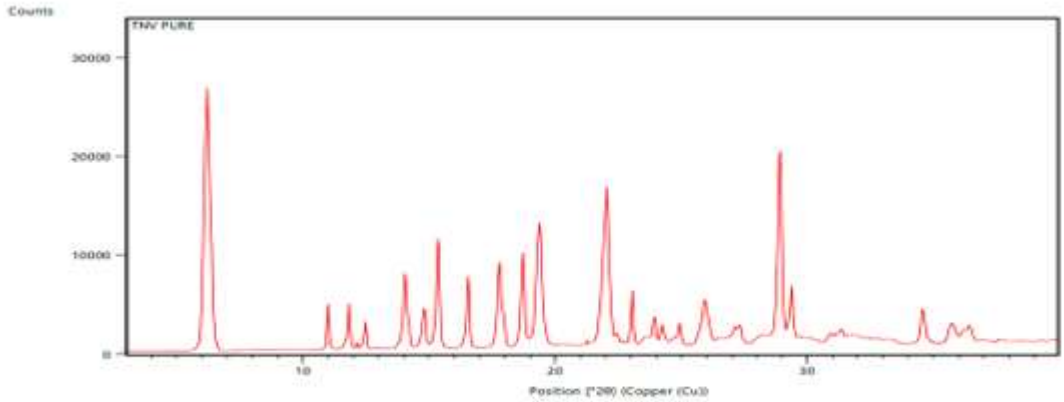

Figure No.6 XRD of Pure Drug

Optimized Trail

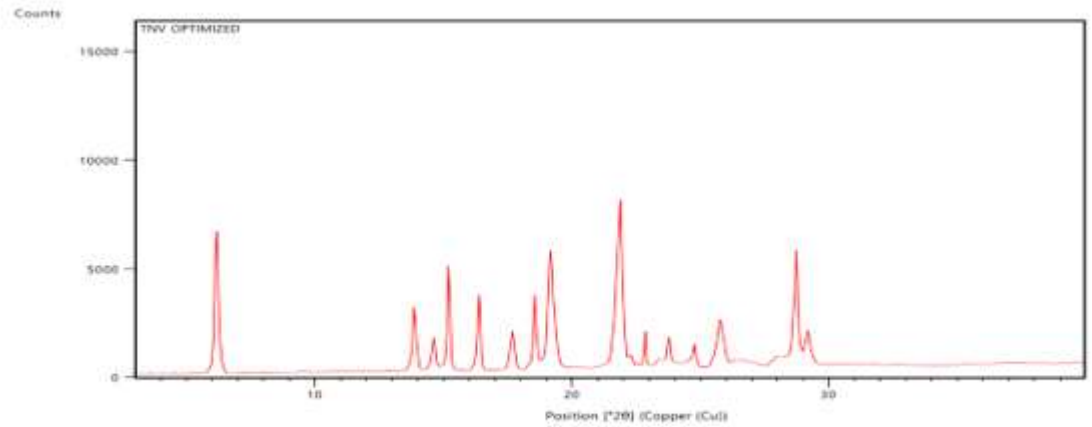

Figure No.7 XRD of Optimized Trail

DISCUSSION

FTIR The absorption peaks in the pure drug tenofovir disoproxil fumarate were observed at approximately 3515.07 cm-1 for the stretching bond H-O, 3394.22 cm-1 for the N-H bond, 1765.75 cm-1 for the C=O bond, 1660.47 cm-1 for the C=C bond, 1620.91 cm-1 for the C-N bond, 1353.78 cm-1 for the P=O bond, 1239.11 cm- 1 for the N-C bond, 1031.22 cm-1 for the C-O bond, and 992.93 cm-1 for the P-O bond, respectively. The absorption peaks in the Optimised Trail were observed at approximately 3599.47 cm-1 for the H-O bond (Stretching), 3492.62 cm-1 for the N-H bond (Stretching), 1764.38 cm-1 for the C=O bond, 1542.92 cm-1 for the C=C bond, 1467.53 cm-1 for the C-N bond, 1380.73 cm-1 for the P=O bond, 1113.64 cm-1 for the N-C bond, 826.27 cm-1 for the C-O bond, and 726.29 cm-1 for the P-O bond, respectively. Research on the drug-excipient compatibility has shown that the active ingredient, tenofovir disoproxil fumarate, does not interact with the optimised trail mixture, tenofovir disoproxil fumarate + excipients. This means that no physical changes have occurred.

DSC investigations were carried out on Optimised Trail and pure Tenofovir disoproxil fumarate. It was discovered that pure Tenofovir disoproxil fumarate has a melting point ranging from 110 to 120 degrees Celsius. The melting point of pure Tenofovir disoproxil fumarate, 112.2 Cel, is accompanied by a clear and sharp rise. An amorphous Rilpivirine form was formed, and the peak disappeared in the new trail, which demonstrated 114.8 Cel perfect homogeneity with the film component. The melting points of Tenofovir disoproxil fumarate, Tenofovir disoproxil fumarate + Sodium Alginate, and combination formulations of the medicine are correlated with the peaks seen in differential scanning calorimetry (DSC) thermograms. Therefore, there were no interactions found in the DSC study between the selected medication, Tenofovir disoproxil fumarate, and Sodium Alginate or any combinations thereof.

XRD, the crystalline structure of tenofovir disoproxil fumarate was revealed by its strong peaks seen at various diffraction angles. In the physical mixing, the X-ray diffractogram of Optimised trail exhibited no conspicuous peaks of Tenofovir disoproxil fumarate, whereas the primary characteristic peaks of Tenofovir disoproxil fumarate rug, Sodium Alginate, and Lycoat polymer were seen with reduced intensity. Lycoat is an amorphous structure as its X-ray diffraction pattern does not exhibit any peaks. Lycoat was determined to be a unique super disintegrant for use in trailing mouth dissolving films since it exhibited all the properties of a film producing agent and a free-flowing, amorphous powder.

Determination of λ_{max}: -

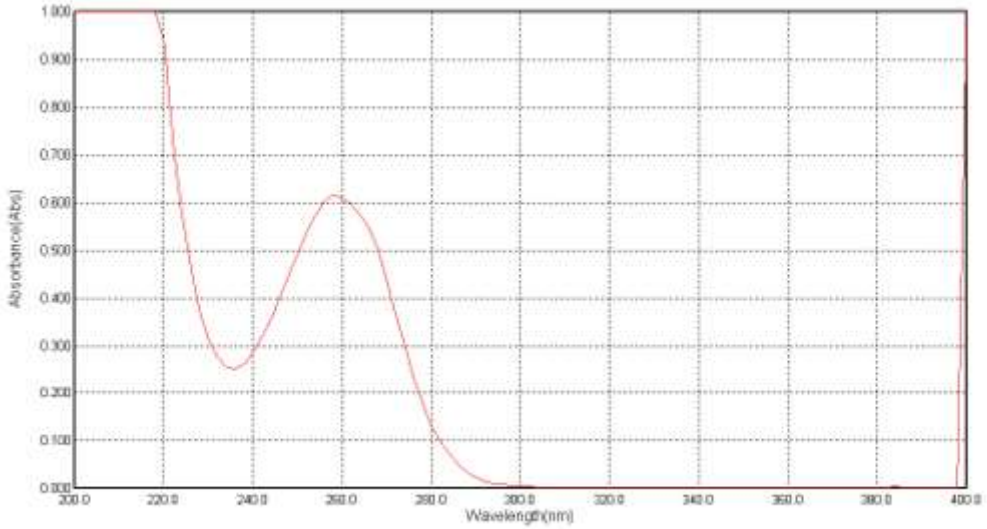

Figure No.8 UV Spectrum curve of Rilpivirine

Discussion: Using a microprocessor-based UV visible single beam spectrophotometer, the maximum absorption peak (abbreviated as 0.615 Abs) at 259.0 nm was recorded for the standard dissolving solution of Tenofovir disoproxil fumarate, which is a 100% concentration solution with a concentration of 10 ppm (10 µg/ml).

Calibration curve of Rilpivirine in 7.4 pH phopshate Buffer

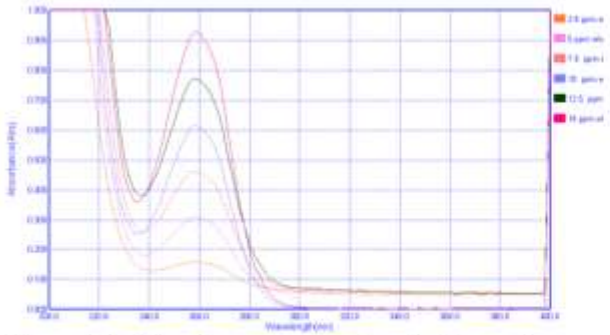

Figure No.9 Spectrum comparison for linearity ppms

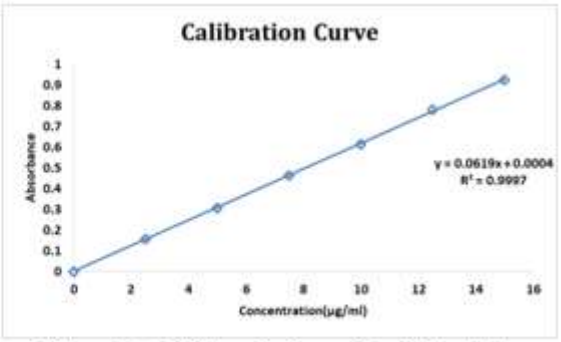

Figure No.10 Standard graph of Rilpivirine

Discussion: In a phosphate buffer with a pH of 7.4, the absorption maxima of tenofovir disoproxil fumarate are seen at 259.0 nm, according to the calibration curve. The absorption data points were used for linear regression analysis using the Microprocessor UV Visible single beam spectrophotometer, since the UV spectrophotometric showed a linearity range of 2.5-15 µg/ml. The quantity of medication was calculated using the straight-line equation y= 0.0619x + 0.0004. Relative significance (R2) was determined to be 0.9997.

Physical appearance and surface texture

Discussion: All the trails seemed semi-transparent, flexible, and smooth in structure, and non-tacky in nature based on physical appearance and surface texture.

Determination of Weight uniformity and Drug content uniformity of the Trails:

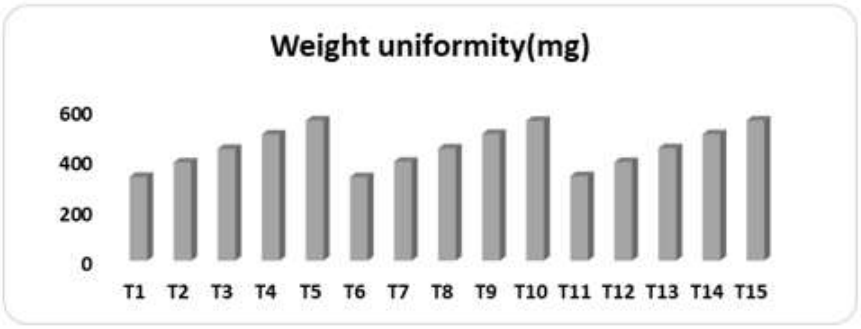

Figure No.11 Graphs of weight uniformity

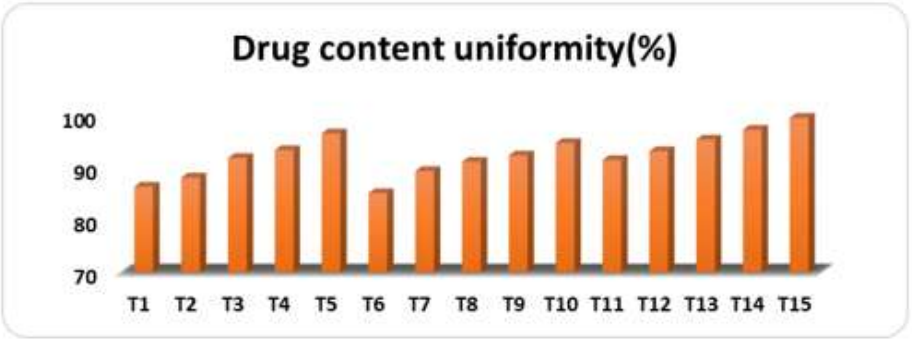

Figure No.12 Graphs of Drug content uniformity

Determination of Moisture content of film

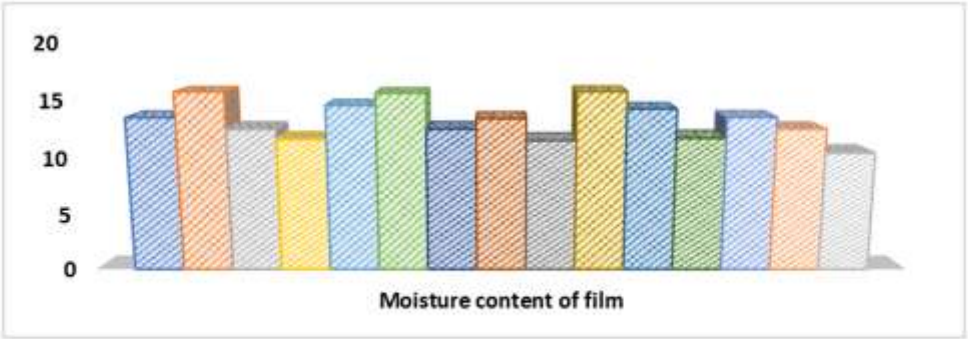

Figure No.13 % Moisture content of films

Determination of Thickness:

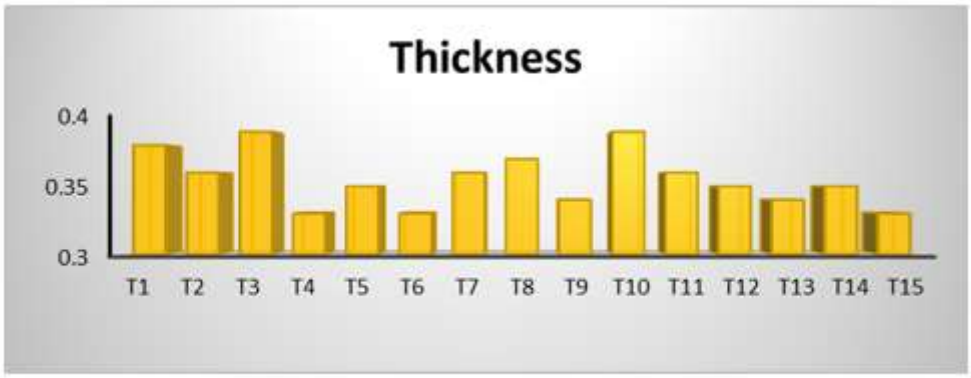

Figure No.14 Thickness of Films

Determination of folding endurance:

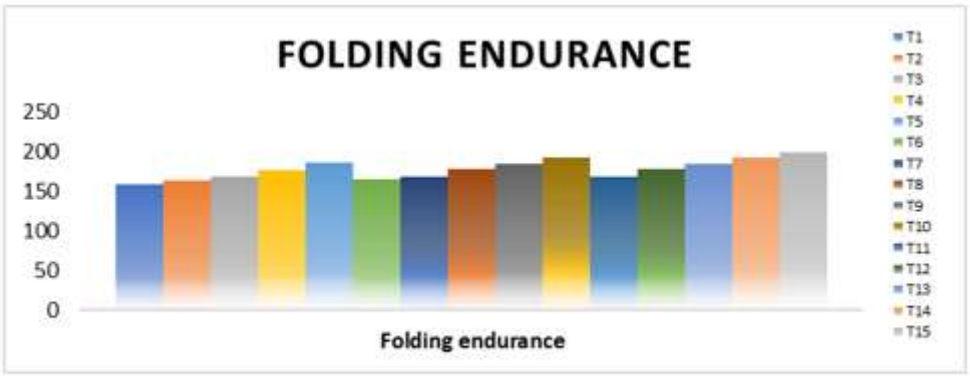

Figure No.15 Folding endurance of the films

Discussions: No substantial difference from the average was seen among trails, and all batches were of equal weight. The films that were made had weight consistency ranging from 331.75±2.48 mg to 554.85±1.12 mg. A test was conducted to ensure that all of the films were homogeneously mixed with drug content, and the results showed that it ranged from 85.20±1.58% to 99.67±1.58%. The drug content values ranged from 85 to 110%, as per the criteria provided by IP. The physical stability or integrity of the film was checked in humid conditions by conducting the % moisture content test. The physical strength of Mouth Dissolving films is evaluated by measuring their moisture absorption in high moisture circumstances; the findings vary between 15.67±1.16% and 10.38±1.74%. Because it is directly related to the accuracy of dose distribution, maintaining a constant film thickness is of the utmost importance. With increasing amounts of polymer, the films' thickness rose continuously and was found to range from 0.39±0.06 to 0.33±0.01 mm. The film's brittleness can be determined by its folding endurance. The results shown that the folding durability of the oral dissolving film increased with increasing concentrations of polymer and plasticiser. To test folding endurance, a film was folded in the same spot until it snapped. The prepared films had folding endurance values ranging from 159±1 to 199±2. Because acidic or alkaline pH variations in vivo might irritate the oral mucosa, we measured the films' surface pH to evaluate potential negative effects. Based on the results, the mouth dissolving films were determined to have a neutral pH range and would not irritate the oral cavity when placed there. This was due to the fact that the films' surface pH fell within the specified parameters of 6.8 to 7.4.

Determination of Surface pH:

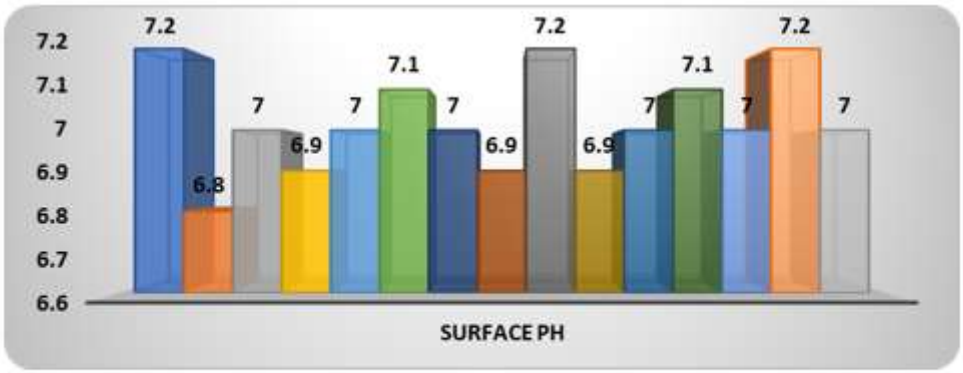

Figure No.16 Graphs of Surface pH

Discussion: Because acidic or alkaline pH variations in vivo might irritate the oral mucosa, we measured the films' surface pH to evaluate potential negative effects. Based on the results, the mouth dissolving films were determined to have a neutral pH range and would not irritate the oral cavity when placed there. This was due to the fact that the film's surface pH fell within the specified parameters of 6.8 to 7.4.

Determination of Disintegration Time of Films:

Discussion: The durations of disintegration for each trail varied between 49±1.08 and 22±1.25 seconds. It was found that the film's thickness and, by extension, the time needed for the film to dissolve, were both affected by the amount of polymer used. Because the hydrophilic plasticiser quickly absorbed water, swelled, and immediately broke down H-bonds, Mouth Dissolving Films disintegrated rapidly as the plasticiser concentration rose.

Determination of Tensile strength and Percentage elongation:

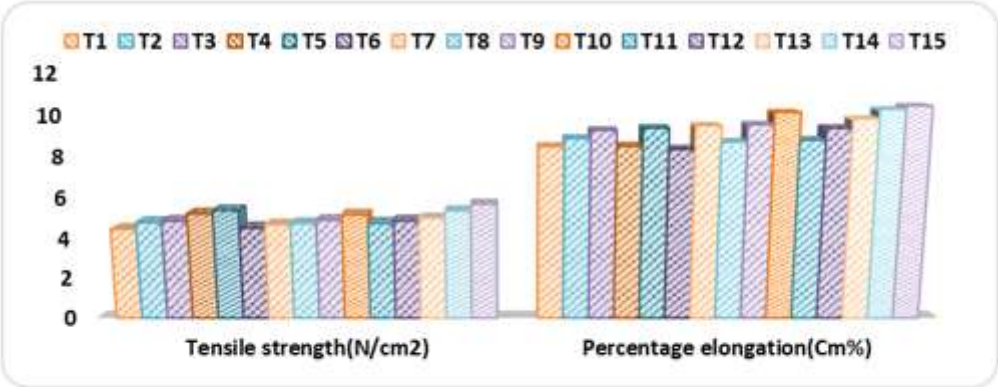

Figure No.17 Tensile strength and percentage elongation of films

Discussion: There was an increase in tensile strength as well when a TAXT Plus Texture Analyser (Texture Technologies, Scarsdale, NY) was used. T1 had the lowest tensile strength and Trail T15 had the highest. The addition of a plasticiser, which forms strong hydrogen bonds with the polymer, likely contributed to this by making the polymer more flexible. The films' percentage elongation ranged from 5.21±0.2 cm% to 7.12±0.7 cm%.

Scanning electron microscopy (SEM)

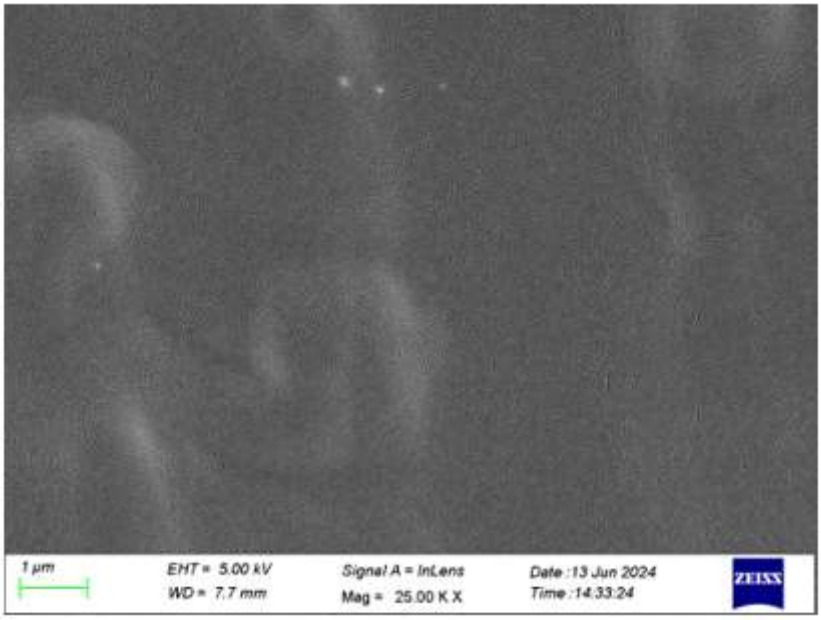

Figure No.18 SEM image of Optimized Trail

Discussion: Upon scanning electron microscopy (SEM), the combination of tenofovir disoproxil fumarate and sodium alginate appears to be thin and soft. The decreased particle size indicated the optimised trail. Sodium alginate, a polymer, contains the tenofovir disoproxil fumarate medicine, and scanning electron microscopy (SEM) reveals that the medication is present in a dissolved form on the drug's uneven and rough surface.

Taste Evaluation Study by Spitting

Discussions: Volunteers from a human panel assessed the effectiveness of taste masking. On this study, human panel participants assessed the efficacy of each trail's flavour masking. All trials demonstrated great taste masking.

In-vitro Dissolution Studies:

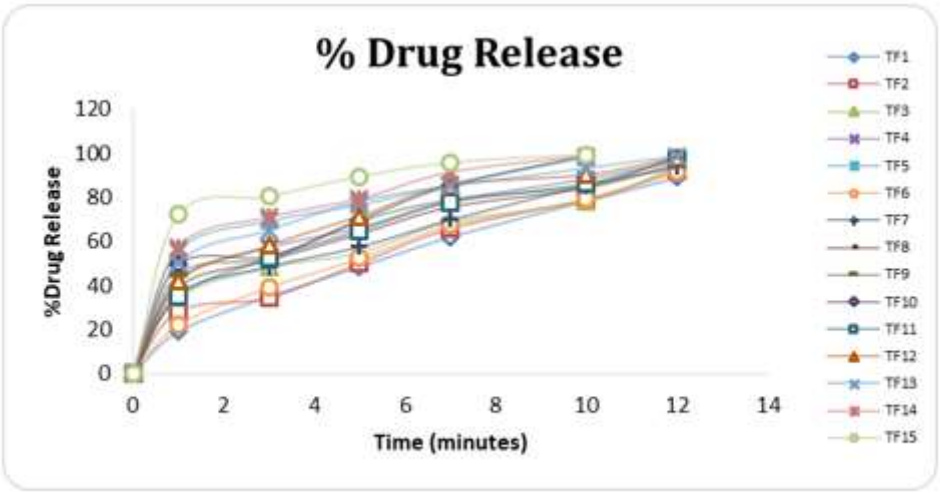

Figure No..19 % Drug Release of Trails from T1 to T15

Discussions:

Tenofovir disoproxil fumarate mouth dissolving films containing Xanthan gum and sodium alginate were tested for in vitro drug release in different ratios. After 12 minutes, the results showed that Trail TF1 had an efficacy of 89.21±1.48%, TF2 of 92.44±1.54%, TF3 of

94.51±1.19%, TF4 of 96.45±1.18%, and T5 of 98.26±1.24%. Researchers studied the in vitro drug release of mouth dissolving films containing tenofovir disoproxil fumarate and guar gum in different ratios. After 12 minutes, the results for Trail TF6, TF7, TF8, TF9, and TF10 are as follows: 91.58±1.47%, 93.75±1.23%, 95.24±1.19%, 98.16±1.72%, and 98.75±1.48%, respectively. Films containing tenofovir disoproxil fumarate and sodium alginate were tested for in vitro drug release in a range of ratios. The following results are shown by the various time series: TF11 at 12 minutes, TF12 at 1.47%, TF13 at 1.02%, TF14 at 1.84%, and TF15 at 2.06%. At the end of 10 minutes, TF15 demonstrates the highest drug release compared to other Trials. Consequently, it was selected as the optimal route.

Comparison of optimized trail with marketed trail:

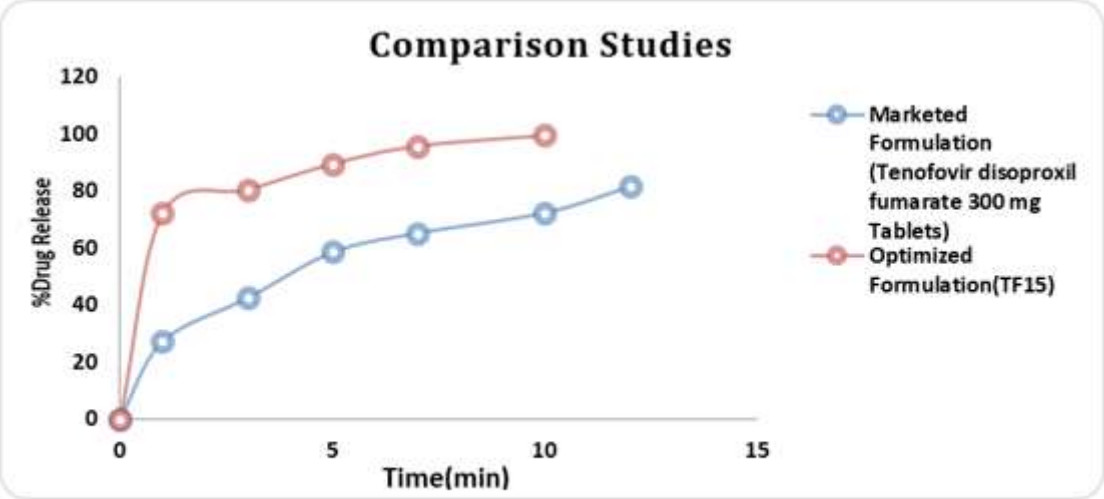

Figure No.20 In vitro Comparison studies of Optimized trail with Marketed Trails

Discussion: In vitro drug release studies comparing Optimised Trails to Marketed Trails. According to the comparison tests, the Optimised trail shown a drug release of 99.37±2.06% after 10 minutes, whereas the marketed trail had a drug release of 81.48±1.54% after 12 minutes. When compared to the advertised trail, the optimised mouth dissolving films provide the best release.

Drug release kinetics studies:

Zero order:

Figure No.21 Zero order plot of Tenofovir disoproxil fumarate TF15 Trail (Time Vs % Drug Release)

Higuchi plot:

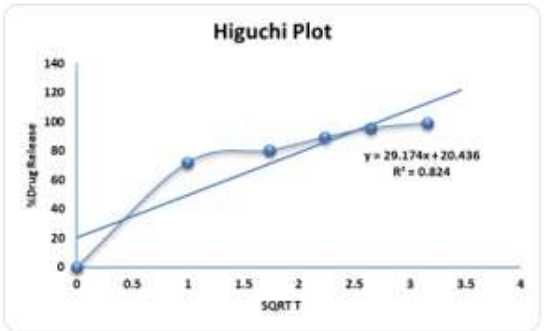

Figure No.22 Higuchi plot of Tenofovir disoproxil fumarate TF15 Trail (%Drug Release vs Root Time)

First order:

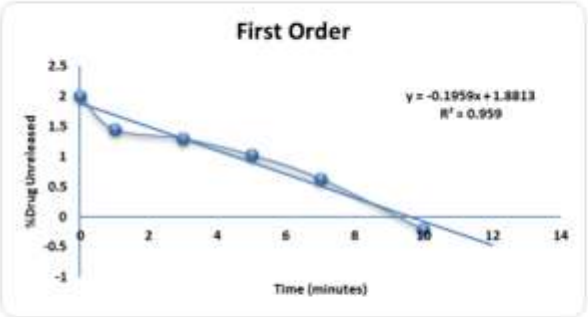

Figure No.23 First order plot of Tenofovir disoproxil fumarate TF15 Trail (Time Vs Log% ARA)

Korsmeyer -peppas plot:

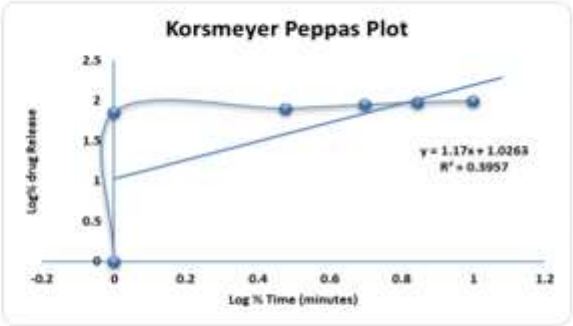

Figure No.24 Korsmeyer -Peppas plot of Tenofovir disoproxil fumarate TF15 Trail (Log%Drug Release vs Log % Time)

Discussion: Mathematical model equations, such as first-order and zero-order techniques, were used to explain the drug release from mouth dissolving films. The regression results led to the conclusion that the optimised trail TF15 uses a super case-II transport mechanism for first-order drug release.

Stability Studies:

The optimised trail (TF15) was the subject of a stability analysis. After being sealed in an airtight container, the trails were kept in a stability chamber for the first and third months at a temperature of 40 ± 2°C and relative humidity of 75 ± 5%. After that, at 30, and 60-day intervals, the samples were taken out and examined for things like surface pH, tensile strength, in-vitro dissolution tests, visual appearance, and drug content homogeneity.

Discussion: The stability studies were conducted on the optimised trail, which is TF15. After being sealed in an airtight container, the trails were kept in a controlled environment at a temperature of 40 ± 2°C and a relative humidity of 75 ± 5% for the first two months. Visual appearance, drug content uniformity, surface pH, tensile strength, and in-vitro dissolution studies were performed. The samples were subsequently withdrawn at 30, 90, and 36-hour intervals. Stability studies found that the optimised mouth dissolving films were stable for up to three months.

Summary and Conclusion:

Tenofovir disoproxil fumarate oral dissolving films were developed as a drug delivery system in this study. These films offer a practical and appropriate way to achieve the desired disintegration and dissolution characteristics, as well as increased bioavailability. Sodium alginate, propylene glycol, Lycoat (a super disintegrant), and Xanthan gum (a film forming ingredient) were used in the solvent casting process to create tenofovir disoproxil fumarate mouth dissolving films. Research such as FTIR, DSC, and XRD were conducted as part of the pre-formulation studies to characterise the API and determine if the medication and the excipient were compatible. The drug's properties were confirmed by the API characterisation. The final formulation's polymers, plasticisers, and disintegrant were chosen after drug-excipient compatibility experiments yielded satisfactory results. Physical appearance, weight uniformity, drug content uniformity, thickness, folding endurance, surface pH, in vitro disintegration time, tensile strength, percent elongation, scanning electron microscopy, in vitro dissolution, stability, stability, taste evaluation by spitting, evaluation of optimised formulation compared to marketed formulation, drug release kinetics, and stability studies are some of the evaluation parameters that the trials undergo.

The solvent casting process was used to successfully create the final formulation (TF15) using Sodium Alginate as the polymer and Lycoat as the disintegrant. The result was a quick disintegration time of 22±1.25 seconds and a drug release of 99.37±2.06% after 10 minutes in vitro. Various kinetic models, including the zero-order, first-order, Higuchi, and korsemeyer-peppas equations, were used to match the in vitro dissolving data of best trail TF15. R2 value of 0.959 is shown by optimised trail T15. It confirms to the first-order release as its value approaches 1. According to the korsmeyer and peppas plot, which further confirms the drug release mechanism, the optimised trail (TF15) has a 'n' value of 1.17 (n value >0.89), indicating the Super case-II transport mechanism. An airtight container was used to hold the Optimised Trail for the Stability Studies. The chamber was kept at 40 ± 2°C and 75 ± 5% RH during the first and third months. After that, at 30, and 60-day intervals, the samples were taken out and examined for things like surface pH, tensile strength, in-vitro dissolution tests, visual appearance, and drug content homogeneity. Trials using 90 mg of Lycoat disintegrant, 600 mg of Sodium Alginate film-forming agent, and 50 cc of Propylene Glycol plasticiser were considered. After comparing Trail TF15 to other trails, it was found that it met the higher in-vitro correlation limits in less time. Further research confirmed that the solvent casting approach provided the most effective means of rapid medication release.

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