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Formulation And Evaluation Of Dolutegravir Mouth Dissolving Thin Films

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Abstract

Dolutegravir is an HIV-1 integrase inhibitor that blocks the strand transfer step of the integration of the viral genome into the host cell (INSTI). The aim of present study was to develop mouth dissolving films Dolutegravir by using various polymers with shorter disintegration time and greater drug release with a prospect of assisting various patients who have difficulty in swallowing conventional dosage forms & enhance bioavailability of drug and quick onset of action. MDFs also offer better convenience to patients with mental illness, as well as pediatrics, elderly, and developmentally disabled patients. MDFs were formulated using a solvent casting technique. The optimized MDF follows the evaluation parameters like Physical appearance, weight uniformity, drug content uniformity, Thickness, Folding endurance, Surface pH, In vitro disintegration time, Tensile Strength and Percent Elongation, Scanning electron microscope, Taste Evaluation Study by Spitting, In-vitro Dissolution study, Comparison of optimized formulation with marketed formulation, Drug release kinetic studies and Stability Studies. The % CDR of the optimized MDF in comparison, the market formulation was found to be 69.41±1.16% in 12 mins and optimized formulation yield 99.75±1.48% within 10 minutes.

Keywords: Mouth Dissolving Film, Dolutegravir, FTIR, XRD, DSC and SEM, Solvent casting method.

Introduction

The oral route of medication administration is the most favoured method due to its ease of use, non-invasiveness, flexibility, and high levels of patient compliance and acceptance. Concerning the oral administration of drugs, several alternatives have been consistently introduced by recent innovative technologies for juvenile, elderly, nauseated, and non-compliant patients. Bioadhesive mucosal dosage forms, such as adhesive tablets, gels, and patches, are products of technical advancement. The utilization of polymeric films for drug delivery in the buccal cavity has shown significant potential in recent developments. Orally disintegrating films (ODFs) rapidly hydrate upon contact with the tongue, absorbing saliva, which facilitates disintegration and/or breakdown, hence releasing the active medicinal ingredient from the dosage form. ODFs are formulations typically composed of hydrophilic polymers that facilitate fast dissolving upon contact with saliva. Oral disintegrating tablets (ODTs) and oral disintegrating films (ODFs) exemplify orally disintegrating medication delivery techniques. These systems were created in the late 1970s as alternatives to traditional dose forms, such as rapidly dissolving tablets and capsules, for elderly and pediatric patients who experience difficulties ingesting conventional forms. An average ODF typically corresponds to the dimensions of a postage stamp. The debut of ODT in the marketplace was closely linked to patient education for proper administration, including instructions such as "do not chew/do not swallow." Nonetheless, despite these directives, events related to chewing and swallowing were often recorded. [1]

The intro of MDFs in the marketplace was accompanied by patient counseling regarding proper administration, including instructions such as "do not chew/do not swallow." Nevertheless, despite these directives, events related to chewing and swallowing were often recorded. However, MDFs liberated the populace from these detrimental occurrences. Mouth dissolving films can be manufactured using either solvent casting processes or hot-melt extrusion technologies. The solvent casting process has significant drawbacks compared to the hot melt extrusion method, mostly owing to solvent residues in the film and the environmental hazards associated with organic solvents [2]. Mouth dissolving films (MDF) disintegrate or dissolve in the oral cavity and have developed as a practical method for administering pharmaceuticals, not just for certain populations with swallowing issues, such as children and the elderly, but also for the general public. MDF are formulated with hydrophilic polymers that swiftly dissolve on the tongue or within the buccal cavity, facilitating medication delivery to systemic circulation by dissolving upon contact with saliva. MDF are often formulated for oral delivery, requiring the user to position the strip on or behind the tongue (sublingual) or on the inner cheek (buccal). As the strip dissolves, the medication can enter the bloodstream predominantly via buccal and sublingual routes [3].

Dolutegravir (DTG) is mostly linked to sleeplessness and minor elevations in serum creatinine, akin to cobicistat. For a period, it was believed that the administration of dolutegravir in pregnant women led to congenital anomalies, hence restricting its application in this demographic. A recent retrospective cohort research involving 1,427 women in Brazil shown that neonates exposed to dolutegravir during pregnancy had no occurrences of neural tube abnormalities. DTG is generally well tolerated by most patients; however, new studies indicate that its usage may be linked to increases in BMI [4]. A retrospective cohort study involving 211 females and 249 males, all virally suppressed teenagers, demonstrated an increase in BMI from around 0.3 kg/m² per year to 1.2 kg/m² per year following the transfer to DTG, with the most significant rise observed in female patients. Medical providers must be aware of these possible alterations while administering DTG. [5]

Materials and methods

Materials Dolutegravir i.e "anti-retroviral agent" was obtained as a Gift sample. Propylene Glycol, Citric acid, Mannitol, HPMC E5 were obtained from S.D fine chemicals, Mumbai, Xanthan Gum was obtained from INR chem. Mumbai, Crospovidone obtained from Signet Chemical Corp., Mumbai Trusil mixed flavor R.S.V obtained from International flavours of fragnance India Ltd. All other ingredients were used of analytical grade without any further modification.

Preparation Method:

Formulation of Mouth Dissolving Films of Dolutegravir By Using Solvent Casting Method:[6]
The Mouth Dissolving Films of Dolutegravir were prepared by solvent casting technique. The Mouth Dissolving Films were prepared using film forming agents like HPMC E5 and Xanthan Gum. Propylene glycol is used as a plasticizer, Citric acid as saliva stimulating agent and super disintegrant like Crospovidone. The calculated amount of polymer was dispersed in the three-fourth volume of with continuous stirring using magnetic stirrer and the final volume was adjusted with distilled water. The calculated amount of Dolutegravir was incorporated in the polymeric solutions after levitation with required volume of Propylene Glycol and Mannitol and Flavor. The solution was cast onto Glass Plate then kept in hot air oven at 40^0c. The films were punched into size of $6cm^2$ containing 50mg of Dolutegravir. By carrying out the trial-and-error method different concentrations for a film forming polymers were used like HPMC E5 and Xanthan Gum. The concentrations of films were prepared by dissolving different quantities of film forming polymers in 30 ml of distilled water.

Table.No.1 Formulation details of Dolutegravir Mouth Dissolving Films by using synthetic and natural Polymer

Formulation Code / Ingredients	T1	T2	T3	T4	T5
Dolutegravir (mg)	300	300	300	300	300
HPMC E5	125	150	175	200	225
Xanthan Gum	125	150	175	200	225
Crospovidone	25	50	75	100	125
Citric acid	50	50	50	50	50
Mannitol	10	10	10	10	10
Trusil Flavor(mg)	10	10	10	10	10
Propylene Glycol(ml)	20	20	20	20	20
Distilled Water	Q.S	Q.S	Q.S	Q.S	Q.S

Table.No 2 Formulation details of Dolutegravir Mouth Dissolving Films by using synthetic polymer

Formulation Code / Ingredients	T6	T7	T8	T9	T10
Dolutegravir (mg)	300	300	300	300	300
HPMC E5	250	300	350	400	450
Xanthan Gum	-	-	-	-	
Crospovidone	25	50	75	100	125
Citric acid	50	50	50	50	50
Mannitol	10	10	10	10	10

Trusil Flavor(mg)	10	10	10	10	10
Propylene Glycol(ml)	20	20	20	20	20
Distilled Water	Q.S	Q.S	Q.S	Q.S	Q.S

Table.No 3 Formulation details of Dolutegravir Mouth Dissolving Films by using natural polymer

Formulation Code / Ingredients	T11	T12	T13	T14	T15
Dolutegravir (mg)	300	300	300	300	300
HPMC E5	-	-	-	-	-
Xanthan Gum	250	300	350	400	450
Crospovidone	25	50	75	100	125
Citric acid	50	50	50	50	50
Mannitol	10	10	10	10	10
Trusil Flavor(mg)	10	10	10	10	10
Propylene Glycol(ml)	20	20	20	20	20
Distilled Water	Q.S	Q.S	Q.S	Q.S	Q.S

Calculation of dose for Dolutegravir:

The dose of Dolutegravir is 300 mg. Therefore, amount of Dolutegravir required in 2cm*3cm=6 cm^2 film is 50 mg.

- Length of glass plate =6 cm.
- Width of glass plate =6 cm.
- Area of the plate =36 cm^2.
- No. of 6 cm^2 films present whole plate =36/6 =6 films.
- Therefore, each films contains 50 mg of drug
- 6 films contain 300 mg drug (6/300=50mg).
- So, the Labelled claim of drug = 50 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 were been identified.

Determination of melting point

The drug's melting point was ascertained using the capillary glass technique. The melting point of the medicine was ascertained by placing a tiny quantity of the substance in a capillary tube sealed at one end. The capillary tube was positioned in the thermionic melting point equipment, and the temperature at which the medication melted was recorded. Comparison of observed melting point values with published values

Solubility studies of pure drug

A solubility study was performed to assess the influence of various buffers on the medication. An excessive quantity of the medication was distributed in 10 ml of distilled water, phosphate buffer solutions (pH 6.8, 7.4), and 0.1N HCl in glass stoppered tubes, respectively. All flasks were sealed with stoppers and coated with cellophane membranes to prevent solvent evaporation for 24 hours in a water bath shaker at 37ºC. Upon achieving equilibrium, the samples were subjected to centrifugation (Hermle Z 200 A, Germany) at 3000 rpm for 5 minutes. The supernatant was filtered using a 0.45 µm membrane filter. A one milliliter sample of saturated solution was diluted with appropriate solvents and thereafter examined using a UV spectrophotometer at 257.0 nm (Single Beam Spectrophotometer YIS-294).

Drug–polymer compatibility studies:

During tablet formation, the proximity of the medication and polymer may result in interactions that might compromise the drug's stability. Pre-formulation investigations concerning drug-polymer interactions are essential for identifying suitable polymers. FT-IR spectroscopy was utilized to determine the compatibility between Dolutegravir and the chosen polymers. The pure drug and the medication with excipient were scanned individually.

FT-IR studies

Sample/KBr ratio:

The sample concentration in KBr must vary from 0.2% to 1%. The pellet is significantly thicker than a liquid layer, necessitating a reduced concentration in the sample (Beer's Law). An excessive concentration typically impedes the acquisition of clear pellets. The infrared beam is either fully absorbed or dispersed by the material, leading to highly noisy spectra.

Differential scanning calorimetry (DSC):
DSC was conducted using the DSC Q20 Universal V4.5A from TA Instruments. Samples were permitted to equilibrate for 1 minute and subsequently heated in a nitrogen environment throughout a temperature range of 0 to 300°C. Thermograms were acquired with TA Instruments Universal Analysis Software 2000.

X-Ray diffraction (XRD)
The samples were analyzed using XRD (PW 1729, Philips, Amsterdam, Netherlands). XRD patterns were recorded using monochromatic Cu Kα radiation with Ni filter at a voltage of 40 kV and a current of 30 mA between 10° and 80° 2θ values. The data were analyzed using Diffrac Plus V1.01 software.

Experimental Methods
Analytical method development by U.V. Spectroscopy
UV-Visible spectrophotometry is a commonly utilized technology in pharmaceutical analysis. This entails quantifying the quantity of UV or visible radiation absorbed by a material in solution. Devices that quantify the ratio, or function of the ratio, of the intensity of two light beams in the ultraviolet-visible spectrum are referred to as ultraviolet-visible spectrophotometers. In qualitative analysis, organic substances can be recognized using a spectrophotometer, provided that recorded data is available, whereas quantitative spectrophotometric analysis is employed to determine the concentration of molecular species that absorb radiation. The spectrophotometric approach is straightforward, quick, fairly selective, and suitable for tiny amounts of chemicals. The primary principle that regulates quantitative spectrophotometric analysis is the Beer-Lambert law.

Calibration curve of Dolutegravir

Preparation of Standard Calibration Curve of Dolutegravir in 6.8 pH Phosphate Buffer:
10mg of Dolutegravir was accurately weighed and transferred into 10ml volumetric flask. It was dissolved and diluted to volume with 6.8 pH Phosphate Buffer to give stock solution-II, containing 100µg/ml. Take 1 ml, 1.2ml 1.4ml, 1.6ml, 1.8ml and 2.0ml from standard stock solution-II. The standard stock solution was then serially diluted with 6.8 pH Phosphate Buffer to get 10 to 20 µg/ml of Dolutegravir. The absorbance of the solution was measured against 6.8 pH Phosphate Buffer as blank at 257.0 nm using UV visible spectrophotometer Single Beam Spectrophotometer (YIS-294). The absorbance values were plotted against concentration (µg/ml) to obtain the standard calibration curve.

Physical appearance and surface texture of film:[7]
This parameter was checked simply with visual inspection of films and evaluation of tack by feel or touch.

Weight uniformity of films
Three films of the size 2*3cm^2=6cm square were weighed individually using digital balance and the average weights were calculated.

Drug content uniformity study of films
The films were tested for drug content uniformity by a UV-Spectrophotometric method. Films of 2× 3 cm^2 diameter were cut from three different places from the casted films. Each film was placed in 100 ml volumetric flask and dissolved in 6.8 pH Phosphate Buffer solution and 0.2 ml is taken and diluted with Buffer up to 10 ml. The absorbance of the solution was measured at 257 nm using UV-Visible Single Beam Spectrophotometer (YIS-294). The percentage drug content was determined using the standard graph and the same procedure was repeated for three films.

Moisture content of film
Moisture content tests were performed to ensure dryness. The prepared films were initially weighed and located in the desiccators containing calcium chloride. After 3 days the films were reweighed to obtain the percentage of moisture loss. Three films of each formula were used in this test.

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

The thickness of films[8,9,10]
The thickness of the film was evaluated using calibrated Vernier caliper (Mitutoyo, Japan). The sample equivalent to dose

of the drug was taken. Anvil of the thickness gage was lifted and the film was inserted after making sure that pointer was set to zero. The film was held on the anvil and the reading on the dial was noted down. The thickness was measured at three different positions. The average of six readings was taken as mean thickness.

Folding endurance of films[11]

The flexibility of films can be measured quantitatively in terms of folding endurance. Folding endurance of the films was determined by repeatedly folding a small strip of the films (6 cm^2) at the same place till it broke. The number of times films could be folded at the same place, without breaking gives the value of folding endurance.

Surface pH of films[12,13]

Surface pH was determined by the films were allowed in contact with 1ml of distilled water. The surface pH was noted by bringing a combined glass electrode or pH paper near the surface of films and allowing equilibrate for 1 min.

In vitro disintegration time of films[14,15]

Disintegration test was performed in the USP disintegration time testing apparatus 6.8 pH phosphate buffer solution used as a medium. The films were placed in the tubes of the container and disintegration time was recorded.

Tensile strength and Percentage elongation

The tensile strength of the films was evaluated by using a TAXT Plus Texture Analyzer (Texture Technologies, Scarsdale, NY) and miniature tensile grips TA-96B according to the procedure described below: A 2x3 cm^2 film free from air bubbles or physical imperfections was held longitudinally in the tensile grip on texture analyzer. The test was performed at 6 mm of initial grip separation from both sides at a crosshead speed of 2 mm/sec till the film broke. All measurements were conducted in triplicate for each film. [16,17]

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

Percentage elongation was calculated by the following equation

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

Scanning electron microscopy (SEM):

The surface characteristics of formulations were examined by means of a scanning electron microscope(Quanta-200, Thermo Fischer Scientific, USA). The double-sided carbon tape was placed on aluminum stab. The stab was dipped in the sample and with the help of air blower, loose particles were removed. The sample was coated with gold particles by using bio-radpolaran sputter coater. The sample was placed in an evacuated chamber and was scanned in a controlled pattern by electron beam. Images of plain KCl and that of the coated ones were compared with each other.[18]

Taste Evaluation Study by Spitting:[19]

Taste acceptability was measured by a taste panel (n=5) with 5 mg drug and subsequently film sample containing 50 mg drug held in mouth until disintegration, then spat out and the bitterness level was then recorded. The volunteers were asked to gargle with distilled water between the drug and film sample administration. The scale for the bitterness study was as follows:

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

In-vitro Dissolution Study[20]

In vitro dissolution of Dolutegravir Mouth Dissolving Films was studied in USP dissolution apparatus (Type II), 900ml 6.8 pH phosphate Buffer solution was used as dissolution medium. The stirrer was adjusted to rotate at 50rpm.The temperature of dissolution medium was maintained at 37±0.5ºC throughout the experiment. One film was used in each test. Samples of dissolution medium (5ml) were withdrawn by means of a syringe fitted with pre-filter at known intervals of time (1, 3, 5, 7, 10, 12 minutes) and analysed for drug release by measuring the absorbance at 257 nm. The volume withdrawn at each time interval was replaced with the fresh quantity of dissolution medium. Cumulative percent Dolutegravir released was calculated and plotted against time.

Comparison of optimized formulation with marketed formulation:

The Comparative dissolution study of optimized T15 formulation containing Dolutegravir was carried with Marketed Dolutegravir Tablets 50mg. The results of in vitro drug release study of optimized Formulation (T15) of Dolutegravir with

Marketed Dolutegravir Tablets 50mg in 6.8 pH Phosphate Buffer.

Drug Release Kinetics[21,22]

To analyze the mechanism of the drug release rate kinetics of the dosage form, the data obtained were plotted as:

Zero order model:

The pharmaceutical dosage forms following this profiles release the same amount of drug by unit of time and it is the ideal method of drug release in order to achieve a pharmacological prolonged action.

$$Qt = Q0 + K0t$$

First order model:

The application of this model to drug dissolution studies was first proposed by Gibaldi and Feldman (1967) and later by Wagner (1969).

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

Higuchi model:

This is the first mathematical model that describes drug release from a matrix system, proposed by Higuchi in 1961.

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

Korsemeyer- peppas model:

Korsemeyer et al. (1983) derived a simple relationship which described drug release from a polymeric system equation. Under some experimental situations the release mechanism deviates from the Ficks equation, following an anomalous behavior (non-Fickian)**.** In these cases a more generic equation can be used:

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

Stability studies[23]

The stability study of the formulated Mouth dissolving films were carried out under different environmental conditions. The film was packed in the aluminium foil and stored in a stability chamber for stability studies at 2-8°C (45% RH), 40^0C/75%RH, after a period of 1 Month and at 40^0C/75%RH after a period of 3 Months. The patches were characterized for the visual appearance, drug content uniformity, surface pH, tensile strength and In-vitro dissolution study parameters during the stability study period.

Results and DiscussionOrganoleptic Properties of Pure DrugDiscussion: The Pure drug was a pure white and smooth in texture. It was amorphous in nature and have unpleasant taste and characteristic odor.

Determination of Melting Point

The melting point of Dolutegravir pure drug was determined by using capillary method.

Discussion: The melting point of Dolutegravir pure drug was found to be 191°C, which was determined by capillary method.

Solubility studies:

Solubility of Dolutegravir was carried out at 250C using 6.8 pH phosphate buffer, 7.4 pH phosphate buffer and purified water.

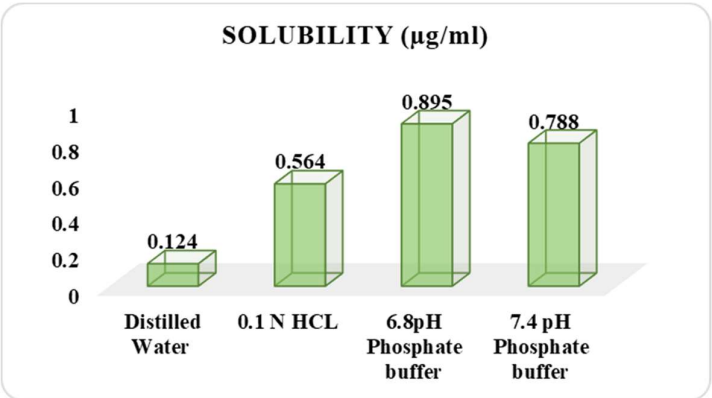


Figure No.1 Bar Graphs for Solubility studies

Discussion: The solubility studies were conducted by using various buffers like Acidic Buffer 0.1N HCL and basic buffers like 6.8 pH phosphate Buffer and 7.4 pH Phosphate buffer and also in water. So based on the above solubility data which was conducted in various buffers, we can say the drug was more soluble in 6.8 pH phosphate Buffer when compared to other buffer solutions.

Drug excipient compatibility: Drug and excipient compatibility was confirmed by comparing spectra of FT-IR analysis of pure drug with that of various excipients used in the trail.

FTIR Studies

Pure Drug:

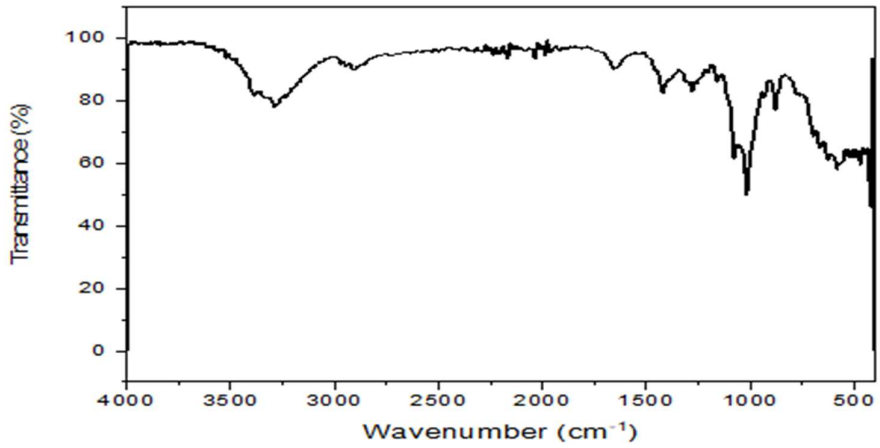


Figure No.2 IR spectrum of Dolutegravir

Optimized

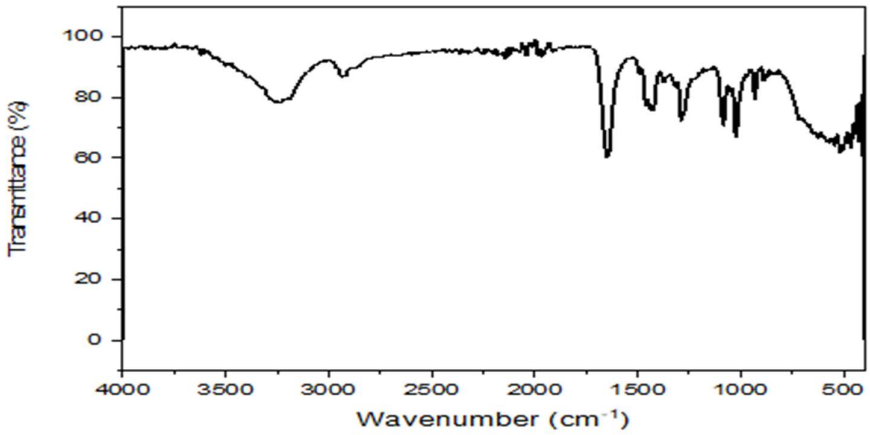


Figure No.3 IR spectrum of Dolutegravir & excipients

Differential scanning calorimetry: The DSC curves of pure drug, and optimized trail were obtained using differential scanning calorimeter.

Pure Drug:

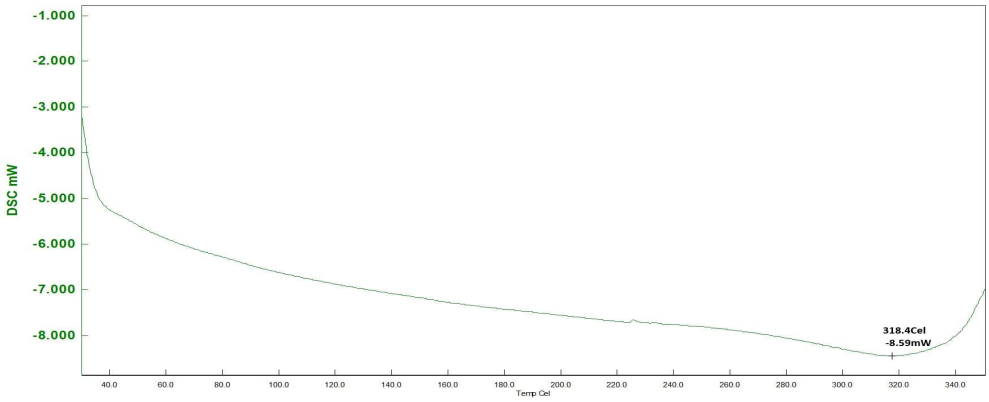


Figure No.4 DSC of the Pure Drug

Optimised :

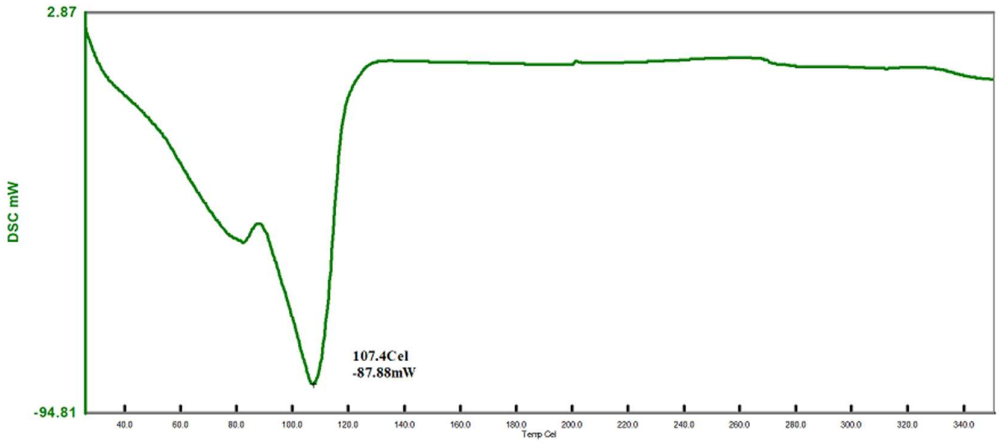


Figure No.5 DSC of the Optimized trail

X-Ray diffraction: The degree of crystallinity of pure drug does not change in its mixture form. The peak intensity however decreased due to lesser fraction of pure drug in its mixture form with excipients.

Pure Drug:

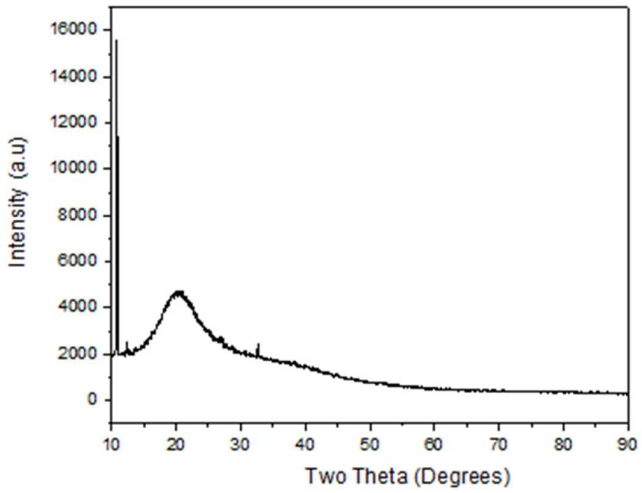


Figure No.6 XRD of Pure Drug

Optimized Trail:

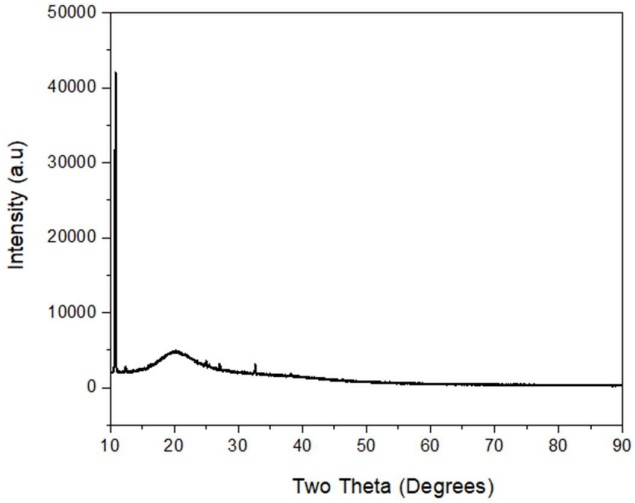


Figure No.7 XRD of Optimized Trail

Discussion:

FTIR, In the Pure Drug Dolutegravir, the absorption peaks observed at ~3251.24 cm-1 with the bond N-H (Stretching), 2913.46 cm-1 with the bond C-H (aliphatic) (Stretching), 1623.24 cm-1 with the bond C=C (Stretching), 1293.11 cm-1 with the bond C-O (Stretching), 1102.45 cm-1 with the bond C-F (Stretching), 1000.71 cm-1 with the bond N-C (Stretching), respectively. In the Optimized Trail, the absorption peaks observed at ~3253.46 cm-1 with the bond N-H (Stretching), 3000.71 cm-1 with the bond C-H (aliphatic) (Stretching),1643.57 cm-1 with the bond C=C (Stretching), 1302.48 cm-1 with the bond C-O (Stretching), 1150.21 cm-1 with the bond C-F (Stretching), 1012.45 cm-1 with the bond N-C (Stretching), respectively. From the drug excipient compatibility studies we observe that there are no interactions between the pure drug (Dolutegravir) and optimized trail (Dolutegravir + excipients) which indicates there are no physical changes.

DSC experiments were carried out on pure Dolutegravir and Optimized Trail. The melting point of pure drug dolutegravir was determined to be between 300 and 350 degrees Celsius. The DSC thermograms are shown Pure Dolutegravir has a noticeable sharp peak at 318.4Cel, matching to its melting point. The peak disappeared in the improved trail, indicating 107.4 Cel perfect homogeneity with the film component and the development of an amorphous form of Dolutegravir. The peaks in the DSC thermograms of Dolutegravir, Dolutegravir + Xanthan Gum, and disintegrate mixes correspond to the drug's melting points. Thus, the DSC investigation found no interactions between the chosen medication Dolutegravir and Xanthan Gum or disintegrate combinations.

XRD, Dolutegravir displayed sharp peaks at different diffraction angles indicating its crystalline shape. The major characteristic peaks of Dolutegravir drug, Xanthan Gum and Crospovidone polymer were observed in physical mixture with lower intensity, where the X-ray diffractogram of Optimized trail showed no obvious peaks of Dolutegravir. The X-ray diffraction pattern of Crospovidone not showed any peaks which indicates

that the structure is completely amorphous. As the Crospovidone was amorphous, smooth, and free flowing powder and it had got all the characteristics of film forming agent and super disintegrant, it was concluded that Crospovidone can be used as novel super disintegrant in the trail of mouth dissolving film.

Determination of λ_{max}: -

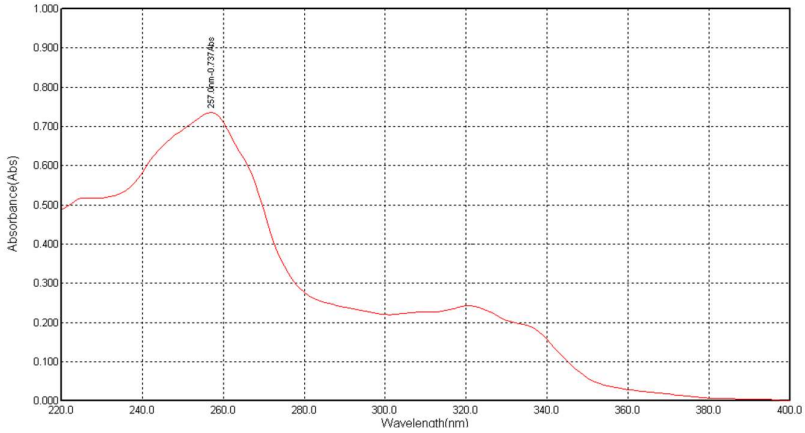
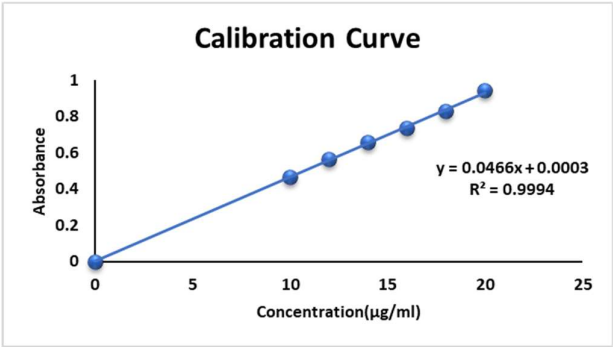


Figure No.8 UV Spectrum curve of Dolutegravir

Discussion: The lambda max of the dolutegravir for the standard dissolution i.e 100% concentration solution of 16 ppm (i.e 16µg/ml) was found to be at 257 nm with the absorbances shows 0.735 Abs by using Microprocessor UV visible single beam spectrophotometer.

Calibration curve of Dolutegravir in 6.8pH phopshate Buffer



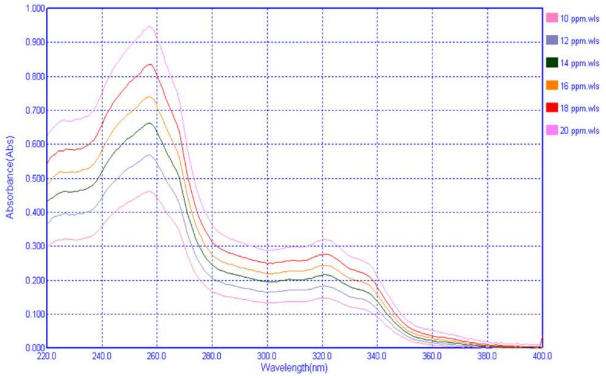


Figure No.9 Spectrum comparison for linearity ppms

Figure No.10 Standard graph of Dolutegravir Discussion: The calibration curve of Dolutegravir show absorption maxima at 257.0 nm, in phosphate buffer of pH 6.8 Phosphate Buffer. The UV spectrophotometric exhibited a linearity range of 10-20 µg/ml the absorption data points were considered for linear regression analysis by Microprocessor UV Visible single beam spectrophotometer. The equation of straight-line, y= 0.0466x+0.0003, was generated for the calculation of amount of drug. The coefficient of determination (R^2) was found to be 0.9994 as illustrated in Figure No. The present analytical method was found to obey beers lambert's law in concentration range of 10 - 20 µg/ml and it is found suitable for estimation of Dolutegravir.

Physical appearance and surface texture

Discussion: By the Physical appearance and surface texture all the trails were appeared as semi transparent with flexible and smooth in structure and Non-tacky in nature

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

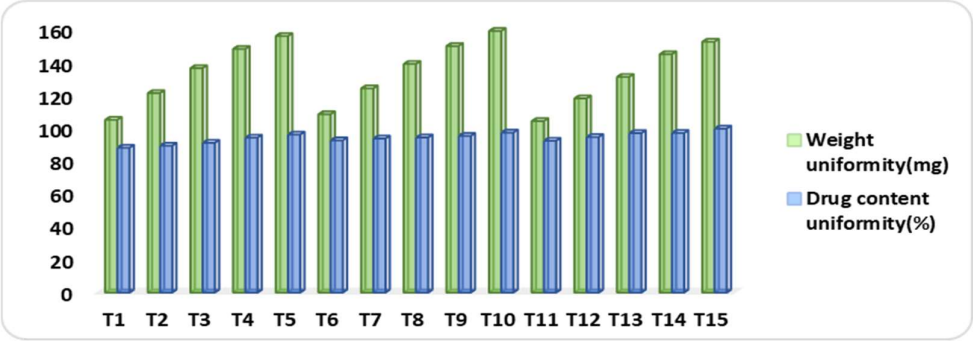


Figure No.11 Graphs of weight uniformity and drug content uniformity

Determination of Moisture content of film

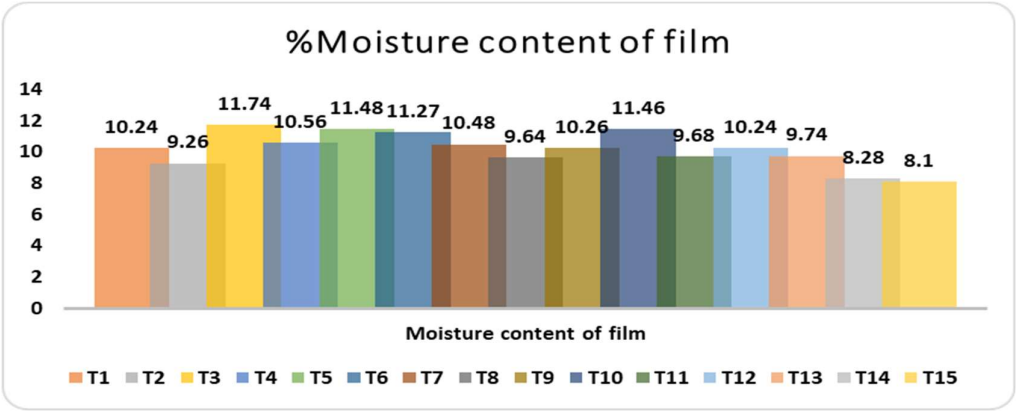


Figure No.12 % Moisture content of films

Determination of Thickness:

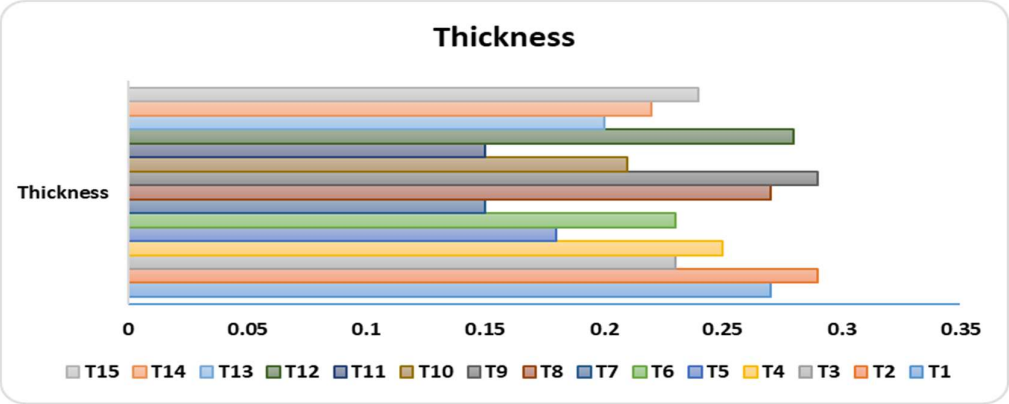


Figure No.13 Thickness of Films

Determination of folding endurance:

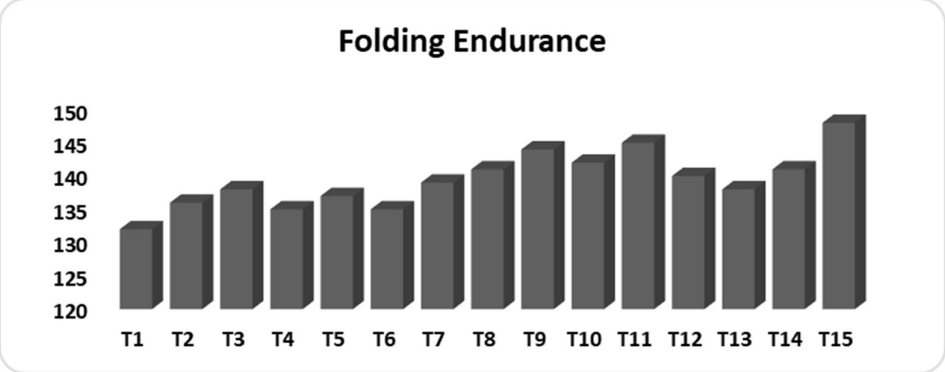


Figure No.14 Folding endurance of the films

Discussions: All batches exhibited uniformity in weight, with no substantial variance from the average among trials. The weight consistency of the produced films varied from 105.26±1.24 mg to 152.84±1.15 mg. The drug content uniformity of all manufactured films was assessed and ranged from 88.24±1.45% to 99.87±1.29%, demonstrating homogenous mixing. Per IP requirements, drug content measurements ranged from 85% to 110%.

The moisture content test was conducted to assess the physical stability of the film under humid conditions. The moisture absorption by the films is utilized to evaluate the mechanical integrity of Mouth Dissolving films in high humidity circumstances, with findings varying from 8.10±1.43% to 11.74±1.06%. Ensuring uniformity in film thickness is essential, since it directly impacts the accuracy of dose distribution. The film thickness consistently rose with the polymer quantity, measured between 0.15±0.02 mm and 0.29±0.03 mm.

Folding endurance indicates the film's brittleness. The results indicated that an increase in the concentration of polymer and plasticizer enhances the folding durability of mouth-dissolving film. The folding endurance was assessed by repeatedly folding a film at the same location until it fractures. The folding endurance values of the fabricated films ranged from 132±1 to 148±2. The values adhere to the range of 100-150.

Determination of Surface pH:

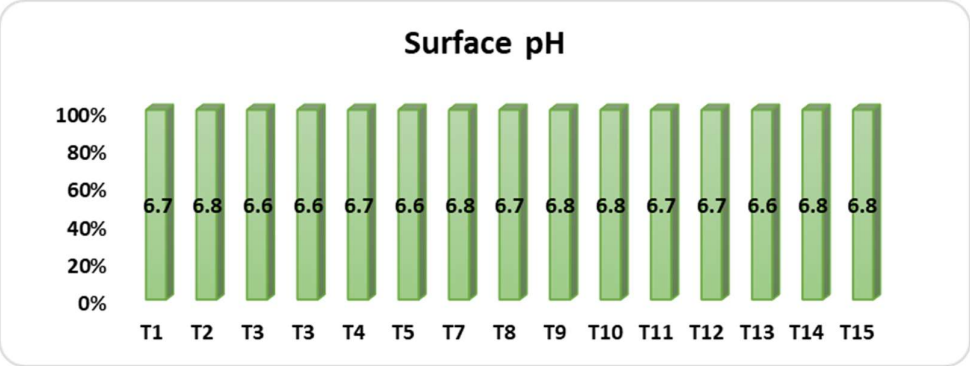


Figure No.15 Graphs of Surface pH

Discussion: Surface pH of the films was determined to investigate any side effects because any changes in pH in vivo, an acidic or alkaline pH may cause irritation to the oral mucosa. The surface pH of the films was found to be in a range of 6.5±0.2 to 6.8±0.4, which comply within the limits 6-7. which indicated that the formulated Mouth Dissolving Films were in the neutral pH range and would not cause any irritation after placing in the oral cavity.

Determination of Disintegration Time of Films:

Discussion: Disintegration times for all trails ranged from 15±1.47 to 28±1.24 seconds. It was discovered that as the polymer content grew, so did the thickness of the film, and therefore the time required for the film to dissolve increased. The quick disintegration of Mouth Dissolving Films owing to a rise in the concentration of plasticizer was caused by the rapid absorption of water by the hydrophilic plasticizer, followed by swelling and immediate breakage of H-bonds.

Determination of Tensile strength and Percentage elongation:

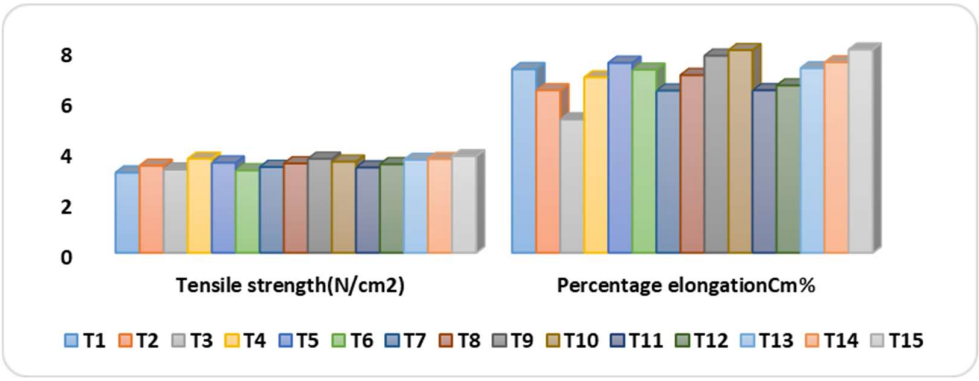


Figure No.16 Tensile strength and percentage elongation of films

Discussion: By using a TAXT Plus Texture Analyzer (Texture Technologies, Scarsdale, NY) the tensile strength also increased. The Trail T15 showed the maximum tensile strength and T1 minimum. This was probably due to the presence of plasticizer that imparts flexibility to the polymer due to the formation of strong hydrogen bonds between the polymer and the plasticizer. The Percentage elongation of films was found in between 5.24±0.9cm%- 7.98±0.7cm%.

Scanning electron microscopy (SEM)

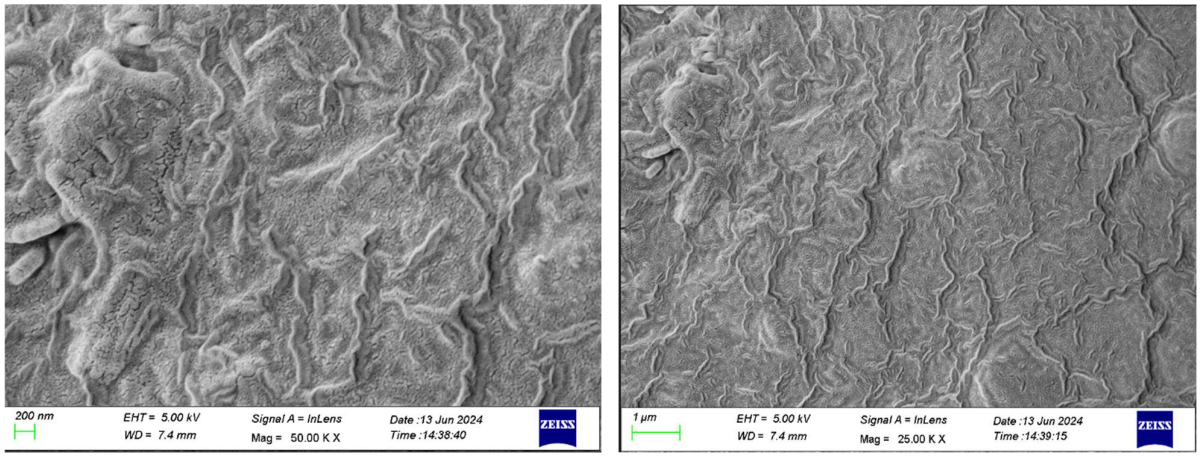


Figure No.17 Morphology of Mouth dissolving film at 200 nm resolutions and at 1 µm resolutions

Discussion: SEM of dolutegravir exposes discrete, elongated flake-like structures with edges covered on their surfaces by fine particles. It also reveals the hard and thick nature of the drug particles. In contrast, dolutegravir –Xanthan Gum complex observed by SEM is soft and thin. Agglomerates of particles clumping to each other was present. The optimized trail was shown as reduced particles size. SEM of dolutegravir MDF shows the rough and uneven surface with the absence of particles suggesting the presence of the drug in dissolved state in the polymer Xanthan Gum.

Taste Evaluation Study by Spitting

Discussions: Taste masking was evaluated by human panel volunteers. The taste masking of all trail was evaluated by human panel volunteers. A result shows that excellent taste masking was found in all trails.

In-vitro Dissolution Studies

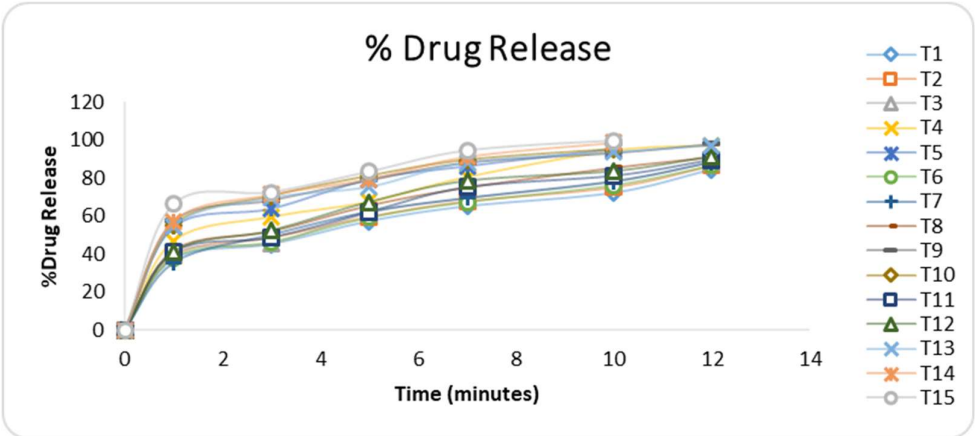


Figure No.7.18 % Drug Release of Trails from T1 to T15

Discussions: *In-vitro* drug release of Dolutegravir Mouth Dissolving Films with HPMC E5 and Xanthan Gum as polymers in various ratios were observed which shows at the end of 12 minutes , the Trail T1 shows 84.49±1.79%, T2 shows 86.57±1.69%, T3 show 88.35±1.09%, T4 shows 97.24±1.26%, T5 shows 98.28±1.20% at the end of 10 minutes.

In-vitro drug release of Dolutegravir Mouth Dissolving Films with HPMC E5 as polymer in various ratios was observed. At the end of 12 minutes, the Trail T6 shows 86.58±1.67%, T7 shows 88.24±1.45%, T8 shows 91.24±1.28%, T9 shows 98.26±1.75%, and T10 shows 98.75±1.28% at the end of 10 minutes. In-vitro drug release of Dolutegravir Mouth Dissolving Films with Xanthan Gum as polymer in various ratios was observed. At the end of 12 minutes, the Trail T11 shows 89.65±1.66%, T12 shows 91.48±1.54%, T13 shows 97.25±1.26%, and T14 shows 98.75±1.79%, T115 shows 99.75±1.48% at the end of 10 minutes. Among all Trails, T15 shows maximum drug release at the end of 10 minutes. So, it was chosen as optimized trail.

Comparison of optimized trail with marketed trail

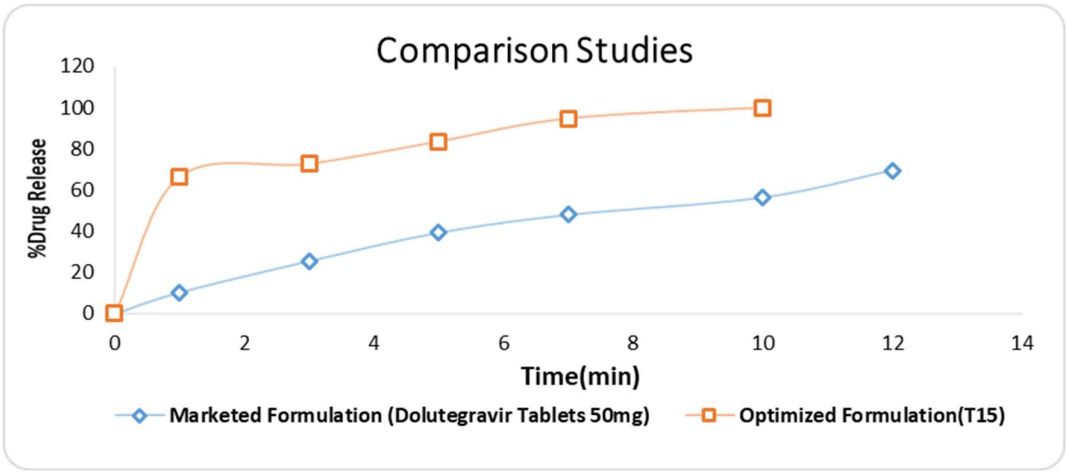


Figure No.19 In vitro Comparison studies of Optimized trail with Marketed Trails

Discussion: The comparison studies for in vitro drug release of Optimized trail with Marketed Trails. The Comparison studies shows the Optimized trail was show 99.75±1.48% of drug release at the end of 10 minutes and the marketed trail shows the 69.41±1.16% of drug release at the end of 12 minutes. Based on comparison The Optimized trail T15 having best release than marketed trail.

Drug release kinetics studiesZero order:

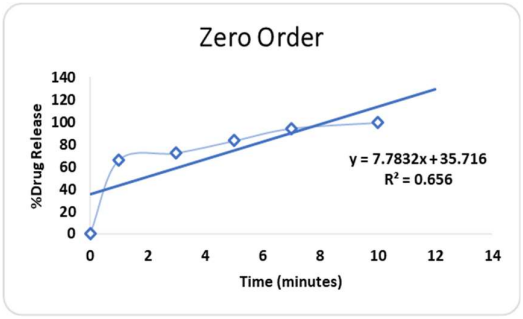


Figure No.20 zero order plot of dolutegravir t15 trail (time vs % drug release)

First order:

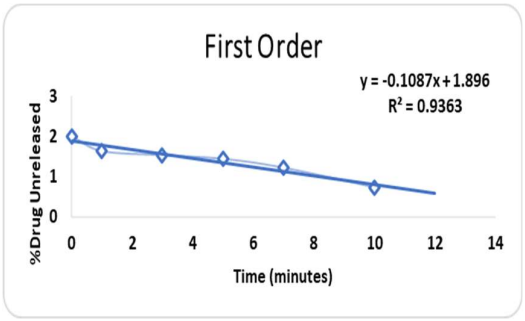


Figure No.22 First order plot of Dolutegravir T15 Trail (Time Vs Log% ARA)

Higuchi plot:

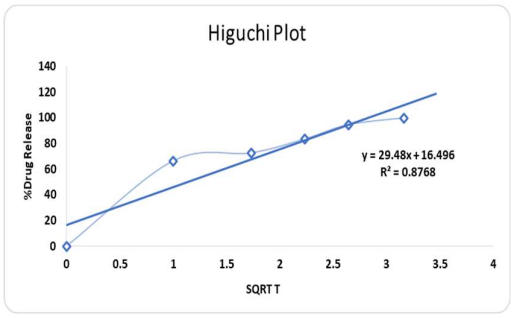
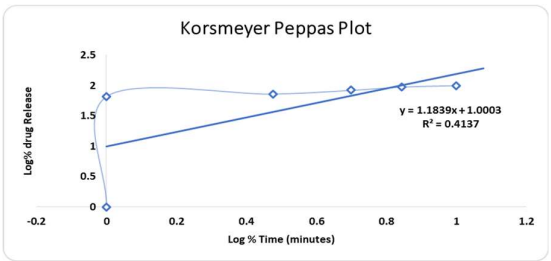


Figure No.21 Higuchi plot of Dolutegravir T15 Trail (%Drug Release vs Root Time)



Korsmeyer -peppas plot:

Figure No.23 Korsmeyer -Peppas plot of Dolutegravir T15 Trail (Log%Drug Release vs Log % Time

Discussion:

The drug release from the Mouth Dissolving Films was explained by the using mathematical model equations such as zero order, first order methods. Based on the regression values it was concluded that the optimized trail T15 follows first order drug release with super case-II transport mechanism.

Stability Studies:

Stability study was conducted on optimized trail (T15). The trails were packed in an airtight container and stored in stability chamber at 40 ± 2°C and 75 ± 5% RH for a period of 1st month and 3rd month. The samples were then withdrawn at interval of 30, 90 days and were evaluated for visual appearance, drug content uniformity, surface pH, tensile strength and In-vitro dissolution studies.

Discussion: The optimized trail (T15) was the subject of the stability experiments. The trails were stored in a stability laboratory at 40 ± 2°C and 75 ± 5% RH for the first and third months, after being packaged in an impermeable container. The samples were subsequently withdrawn at intervals of 30, 90, and were assessed for visual appearance, drug content uniformity, surface pH, tensile strength and In-vitro dissolution studies were done and the stability studies concluded that the optimized mouth dissolving films was stabled up to 3Months.

Summary and Conclusion:

In the present study Oral drug delivery system of Dolutegravir was successfully developed in the form of mouth dissolving films which offers a suitable and practical approach in serving the desired objective of faster disintegration and dissolution characteristics with increase bioavailability. Mouth dissolving films of Dolutegravir were prepared by using Crospovidone as super disintegrants, Xanthan Gum as Film Forming agent and Propylene Glycol as Plasticizer by using solvent casting method. Under the pre-formulation studies, API characterization and drug-excipient compatibility studies like FTIR, DSC and XRD were carried out. The API characterization showed compliance with the drug characteristics. The polymers, plasticizers and disintegrant were selected based on the satisfying results produced during drug- excipient compatibility studies to develop the final formulation.The Trails undergoes Evaluation parameters like Physical appearance, weight uniformity, drug content uniformity, Thickness, Folding endurance, Surface pH, In vitro disintegration time, Tensile Strength and Percent Elongation, Scanning electron microscopy, Taste Evaluation Study by Spitting, In-vitro Dissolution study, Comparison of optimized formulation with marketed formulation, Drug release kinetic studies and Stability Studies. The final suitable formulation **(T15)** was achieved fruitfully by the solvent casting method using Xanthan gum as Polymer and Crospovidone as disintegrant which exhibited a rapid disintegration time (15±1.47 sec) and in vitro drug release (99.75±1.48%) at the end of 10 minutes. The in vitro dissolution data for best trail T15 were fitted in different kinetic models i.e, zero order, first order, Higuchi and korsemeyer-peppas equation. Optimized trail T15 shows R^2 value 0.936. As its value nearer to the '1' it is conformed as it follows the first order release. The mechanism of drug release is further confirmed by the korsmeyer and peppas plot, the 'n' value is 1.183 for the optimized trail (T15) i.e., n value was >0.89 this indicates Super case-II transport mechanism. For the Stability Studies the Optimized Trail was were packed in an airtight container and stored in stability chamber at 40 ± 2°C and 75 ± 5% RH for a period of 1st month and 3rd month. The samples were then withdrawn at interval of 30, 90 days and were evaluated for visual appearance, drug content uniformity, surface pH, tensile strength and In-vitro dissolution studies. Considering the results of trails containing crospovidone as disintegrant 125mg and Xanthan Gum 450 mg as Film Forming agent and Propylene Glycol 20ml as Plasticizer. It can be concluded that the Trail **T15** was meeting the higher in-vitro correlation limits and in less instance of time when subjected to the comparison with other trails. It was also observed that solvent casting method was the best suitable method used for immediate drug release

References

1. Pawar Rajat*, Sharma Ravi, Sharma Pravin, Darwhekar G.N , A Review on Mouth Dissolving Film , Journal of Drug Delivery & Therapeutics. 2019; 9(6):206-210.
2. Kunte S., and Tandale, P. Fast dissolving strips: A novel approach for the delivery of verapamil. Journal of Pharmacy and Bioallied Sciences, 2010:2: 325–328.
3. Kulkarni P.K., Dixit M., Gunashekara K., and Kulkarni A. Formulation and Evaluation of Mouth dissolving film containing Rofecoxib. International Research Journal of Pharmacy, 2011:2: 273-278.
4. Pereira, G., Kim, A., et al. (2021). Dolutegravir and pregnancy outcomes in women on antiretroviral therapy in Brazil: A retrospective national cohort study. The Lancet. HIV, 8(1), e33–e41.
5. Thivalapill, N., Simelane, T., et al. (2021). Transition to dolutegravir is associated with an increase in the rate of body mass index change in a cohort of virally suppressed adolescents. Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America, 73(3), e580–e586.
6. Koland, M., Sundeep, V.P., Charyulu, N.R., "Fast Dissolving Sublingual Films of Ondansetron hydrochloride: Effect of additives on In-vitro drug release and mucosal permeation." J. y. pharma. 2010, 2(3), 216-222.
7. R.C. Mashru, V.B. Sutariya, M. G. Sankalia and P.P. Parikh; Development and evaluation of fast dissolving film of salbutamol sulphate, Drug development and industrial pharmacy (2005). Page no 25-34.
8. A. Arya, A. Chnadra, V. Sharma and K. Pathak; An innovative drug delivery system and dosage form, International Journal of Chemtech research, Volume 2 (2010). Page no 576-583.

9. 21.P.K. Kulkarni, Disit Mundit, Gunashekara K and Kulkarni Ajay; Formulation and evaluation of mouth dissolving film containing rofecoxib. International research journal of pharmacy, volume 2 (2011). Page no 273-278.
10. S Kunte, P Tandale; Fast dissolving strips a novel approach for the delivery of verapamil, Journal of pharmacy and bio-allide science, Volume 2 (2010). Page no 325-328.
11. Irfan M, Rabel S, Bukhtar Q, Qadir MI, Jabeen F and Khan A: Orally disintegrating films: a modern expansion in drug delivery system. Saudi Pharmaceutical Journal 2016; 24(5): 537-46.
12. Rana S, Raju L, Dhatwalia V, Yadav V. Formulation and evaluation of domperidone fast dissolving film by using different polymers. Int J Pharm Res Health Sci. 2014;2(5):374-8.
13. irfan M, Rabel S. Quratuain Bukhtar, Muhammad Imran Qadir, Farhat Jabeen and Ahmed Khan. Orally disintegrating films: A modern expansion in drug delivery System. Saudi Pharma J 2016;24(5):537-46.
14. Kai BL, Yvonne TFT and Kok KP: Characterization of oral disintegrating film containing donepezil for Alzheimer disease. AAPS Pharm Sci Tech 2012; 13(1): 134-42.
15. Takeuchi Y, Umemura K, Tahara K and Takeuchi: Formulation design of hydroxypropyl cellulose films for use as orally disintegrating dosage forms. Journal of Drug Delivery Science and Technology 2018; 46: 93-100.
16. Breitenbach, J., 2002. Melt extrusion: from process to drug delivery technology. Europ. J. Pharmaceut. Biopharmaceut., 54: 107-117.
17. Chokshi, R., and Hossein, Z., 2004. Hot Melt Extrusion Technique: A Review. Int. J. Pharmaceut. Res., 3: 3-16.
18. K.M. Maheshwari, P.K. Devineni, Sarasvati Deekandu, Salma Shaik and Buchi N Nalluri; Development and evaluation of mouth dissolving film of amlodipine besylate for enhance therapeutic efficacy, Journal of pharmaceutics (2014). Page no 170.
19. Sayed HA, Mahmoud EB and Mohamed AI: Design, formulation and characterization of fast dissolving films containing dextromethorphan. Digest Journal of Nanomaterials & Biostructures 2014; 9(1): 133-141
20. Mishra, R. and Amin, A., "Formulation Development of Taste-Masked Rapidly Dissolving Films of Cetirizine Hydrochloride" Pharma. Techn. 2009, 48-56.
21. Francesco C, Irma EC, Paola M, Francesca S and Luisa M: Fast dissolving films made of maltodextrins. European Journal of Pharmaceutics and Biopharmaceutics 2008; 70(3): 895-900.
22. Sarfaraz Md*, Sushil Kumar, H. Doddayya, Fabrication And Evaluation Of Mouth-Dissolving Films Of Domperidone, 15, Issue 2, 2023.
23. Ahmed A, Ehab RB, Afaf AR and Dalia AM: Pharmaceutical and pharmacokinetic evaluation of a novel fast dissolving film formulation of flupentixol dihydrochloride. AAPS Pharm Sci Tech 2014; 15(6): 1603-10.