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Formulation And Evaluation Of Rilpivirine Mouth Dissolving Thin Films

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Abstract

Rilpivirine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) employed in the treatment of HIV-1 infections in treatment-naive individuals. The objective of the current study was to develop mouth-dissolving films of Rilpivirine utilizing various polymers to achieve reduced disintegration time and enhanced drug release, thereby aiding patients with swallowing difficulties and improving the drug's bioavailability and onset of action. MDFs provide enhanced convenience for people with mental illness, as well as for juvenile, geriatric, and developmentally handicapped individuals. MDFs were prepared via a solvent casting method. The optimized MDF adheres to evaluation parameters including physical appearance, weight uniformity, drug content uniformity, thickness, folding endurance, surface pH, in vitro disintegration time, tensile strength, percent elongation, scanning electron microscopy, taste evaluation via spitting, in vitro dissolution study, comparison with marketed formulations, drug release kinetics, and stability studies. The improved MDF exhibited a % CDR of 99.16±1.35% after 10 minutes, whereas the market formulation demonstrated a % CDR of 79.48±1.82% in 12 minutes. The results validated the efficacy of the MDFs infused with Rilpivirine.

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

Introduction

The oral route of pharmaceutical administration is the most popular due to its convenience, non-invasiveness, flexibility, and high levels of patient compliance and acceptability. In terms of oral medicine delivery, new breakthrough technologies have continually presented many solutions for juvenile, elderly, nauseous, and noncompliant patients. Bioadhesive mucosal dosage forms, such as adhesive tablets, gels, and patches, are the result of technological innovation. Recent research has demonstrated that using polymeric films for medication administration in the buccal cavity has tremendous promise. Orally dissolving films (ODFs) rapidly hydrate when in contact with the tongue, absorbing saliva and facilitating disintegration and/or breakdown, therefore releasing the active medicinal substance from the dose form. ODFs are formulations made up of hydrophilic polymers that dissolve quickly when in contact with saliva. Oral disintegrating tablets (ODTs) and oral disintegrating films (ODFs) are examples of orally dissolving pharmaceutical delivery systems. These systems were developed in the late 1970s to provide alternatives to typical dosage forms, such as fast dissolving tablets and capsules, for elderly and pediatric patients who have difficulty swallowing conventional forms. An average ODF is around the size of a postage stamp. The introduction of ODT to the market was tightly tied to patient education for appropriate administration, which included recommendations like "do not chew/do not swallow." Nonetheless, despite these directions, events involving chewing and swallowing were frequently documented. [1]

The introduction of MDFs into the market was followed by patient education on correct administration, including advice like "do not chew/do not swallow." Despite these guidelines, occurrences linked to chewing and swallowing were often

documented. However, MDFs protected the population from these negative events. Mouth dissolving films can be made using either solvent casting or hot-melt extrusion procedures. The solvent casting technique has considerable downsides as compared to the hot melt extrusion method, mostly due to solvent residues in the film and the environmental dangers connected 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].

Rilpivirine (RPV) is commonly associated with CNS psychiatric effects such as depression/mood changes, metabolic effects, gastrointestinal effects, and in rare cases hepatic injury. In a systematic review/meta-analysis of 20 studies that included a total of 10 988 patients (majority male), the authors found the combination of DTG/RPV was associated with an increase in depressive symptoms when compared with DTG and RPV used alone[4] In a United Kingdom case report, a 27-year-old Mediterranean male who had been switched from RAL to RPV saw an increase in his LFTs approximately 14weeks later. The patient was switched to RAL on week 66, which showed an improvement in his liver function, however, that was changed to DRV/r on week 71 due to changes in the patient's mood. The patient was able to see a normalization of his LFTs and resolution of his nausea by week 92[5] Patients on RPV should be monitored for changes in mood/behavior as well as liver function tests.

Materials and methods

Materials Rilpivirine i.e "anti-retroviral agent" was obtained as a Gift sample. Propylene Glycol, Citric acid, Mannitol, PVA were obtained from S.D fine chemicals, Mumbai, Guar gum was obtained from INR chem. Mumbai, Lycoat 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 Rilpivirine By Using Solvent Casting Method:[6]
The Mouth Dissolving Films of Rilpivirine were prepared by solvent casting technique. The Mouth Dissolving Films were prepared using film forming agents like PVA and Guar Gum. Propylene glycol is used as a plasticizer, Citric acid as saliva stimulating agent and super disintegrant like Lycoat. 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 Rilpivirine 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 400c. The films were punched into size of 6cm2 containing 50mg of Rilpivirine. By carrying out the trial-and-error method different concentrations for a film forming polymers were used like PVA and Guar Gum . The concentrations of films were prepared by dissolving different quantities of film forming polymers in 20 ml of water.

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

Formulation Code / Ingredients	TF1	TF2	TF3	TF4	TF5
Rilpivirine (mg)	150	150	150	150	150
PVA	50	75	100	125	150
Guar gum	50	75	100	125	150

Lycoat	15	30	45	60	75
Citric acid	30	30	30	30	30
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 Rilpivirine Mouth Dissolving Films by using synthetic polymer

Formulation Code / Ingredients	**TF6**	**TF7**	**TF8**	**TF9**	**TF10**
Rilpivirine (mg)	150	150	150	150	150
PVA	100	150	200	250	300
Guar gum	-	-	-	-	
Lycoat	15	30	45	60	75
Citric acid	30	30	30	30	30
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 Rilpivirine Mouth Dissolving Films by using natural polymer

Formulation Code / Ingredients	**TF11**	**TF12**	**TF13**	**TF14**	**TF15**
Rilpivirine (mg)	150	150	150	150	150
PVA	-	-	-	-	-
Guar gum	100	150	200	250	300
Lycoat	15	30	45	60	75
Citric acid	30	30	30	30	30
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 Rilpivirine:

The dose of Rilpivirine is 150 mg. Therefore, amount of Rilpivirine required in 2cm*3cm=6 cm^2 film is 25 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 25 mg of drug
- 6 films contain 150 mg drug (6/150=25mg).
- So, the Labelled claim of drug = 25 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
Solubility study was conducted to determine the effect of different buffers on the drug. An excess amount of the drug was dispersed in 10 ml of distilled water, phosphate buffer solutions (pH 6.8, 7.4), 0.1N HCL in glass stoppered tubes, respectively. All flasks were closed with stopper and covered with cellophane membrane to avoid solvent loss for 24 hrs in water bath shaker at 37ºC. After reaching equilibrium, the samples were centrifuged (Hermle Z 200 A, Germany) at 3000 rpm for 5 min. Supernatant was filtered through 0.45 µm membrane filter. One ml sample of saturated solution was diluted with suitable solvents and then analyzed by UV spectrophotometer at 280.0 nm (Single Beam Spectrophotometer(YIS-294).

Drug–polymer compatibility studies:
In the preparation of tablet formulation, drug and polymer may interact as they are in close contact with each other, which could lead to the instability of drug. Pre formulation studies regarding the drug-polymer interaction are therefore very critical in selecting appropriate polymers. FT-IR spectroscopy was employed to ascertain the compatibility between Rilpivirine, and the selected polymers. The pure drug and drug with excipient were scanned separately.

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 Rilpivirine
Preparation of Standard Calibration Curve of Rilpivirine in 7.4 pH Phosphate Buffer:
10mg of Rilpivirine was accurately weighed and transferred into 10ml volumetric flask. It was dissolved and diluted to volume with 7.4 pH Phosphate Buffer to give stock solution-II, containing 100µg/ml. Take 0.4 ml, 0.6 ml, 0.8 ml, 1.0 ml, 1.2ml and 1.4 ml from standard stock solution-II. The standard stock solution was then serially diluted with 7.4 pH Phosphate Buffer to get 4 to 14 µg/ml of Rilpivirine. The absorbance of the solution was measured against 7.4 pH Phosphate Buffer as blank at 280.0 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 cm2 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 280.0 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.
d) 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.

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

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 25 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 Rilpivirine Mouth Dissolving Films was studied in USP dissolution apparatus (Type II), 900ml 7.4 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, 12minutes) and analyzed for drug release by measuring the absorbance at 280.0 nm. The volume withdrawn at each time interval was replaced with the fresh quantity of dissolution medium. Cumulative percent Rilpivirine released was calculated and plotted against time.

Comparison of optimized formulation with marketed formulation:
The Comparative dissolution study of optimized TF15 formulation containing Rilpivirine was carried with Marketed Edurant Rilpivirine Tablet 25 mg. The results of in vitro drug release study of optimized Formulation (T15) of Rilpivirine with Marketed Edurant Rilpivirine Tablet 25 mg in 7.4 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:

$$Mt/M\infty = a t^{n}$$

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 aluminum foil and stored in a stability chamber for stability studies at 2-8°C (45% RH), 400C/75%RH, after a period of 1 Month and at 400C/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 Drug:

Discussion: 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 Rilpivirine pure drug was determined by using capillary method.

Discussion: The melting point of Rilpivirine pure drug was found to be 247.49 °C, which was determined by capillary method.

Solubility studies:

Solubility of Rilpivirine was carried out at 25°C using 6.8 pH phosphate buffer, 7.4 pH phosphate buffer and purified water.

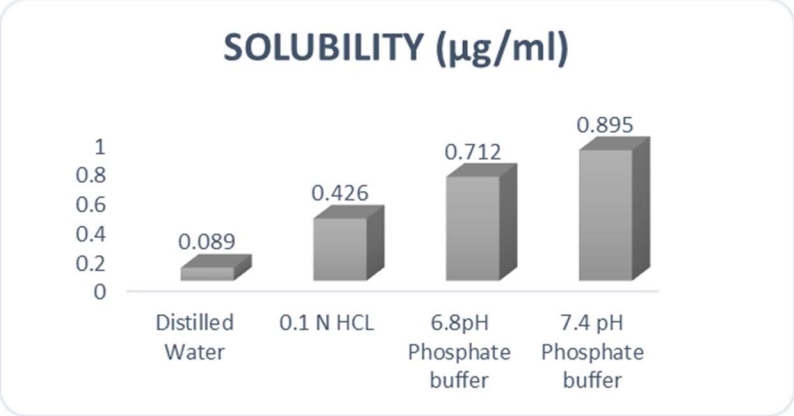

Figure No.1 Bar Graphs for Solubility studies

Discussion: The solubility studies were conducted by using various buffers like Acidic Buffer 0.1N HCL and basic buffers like 6.8pH 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 7.4 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:

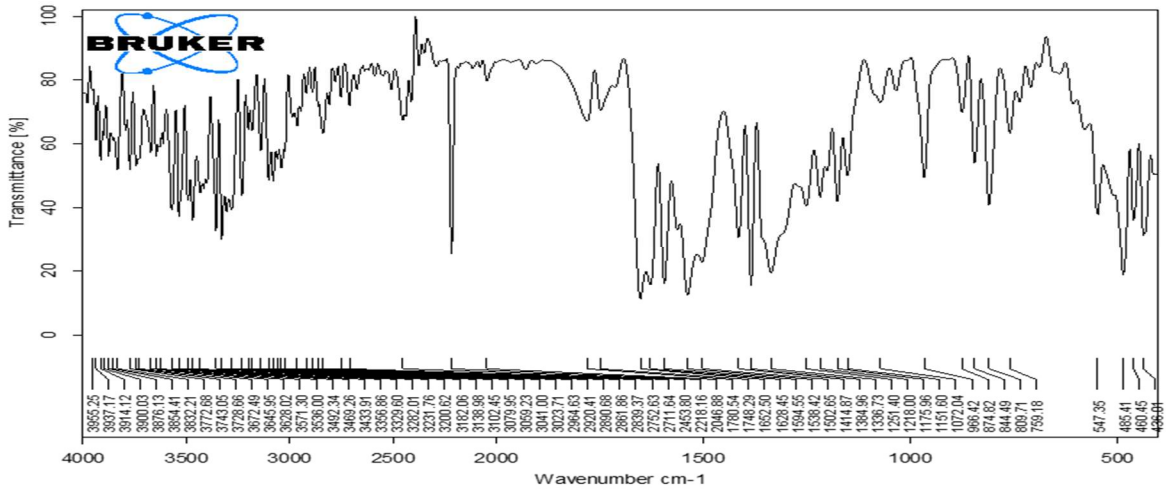

Figure No.2 IR spectrum of Rilpivirine

Optimized

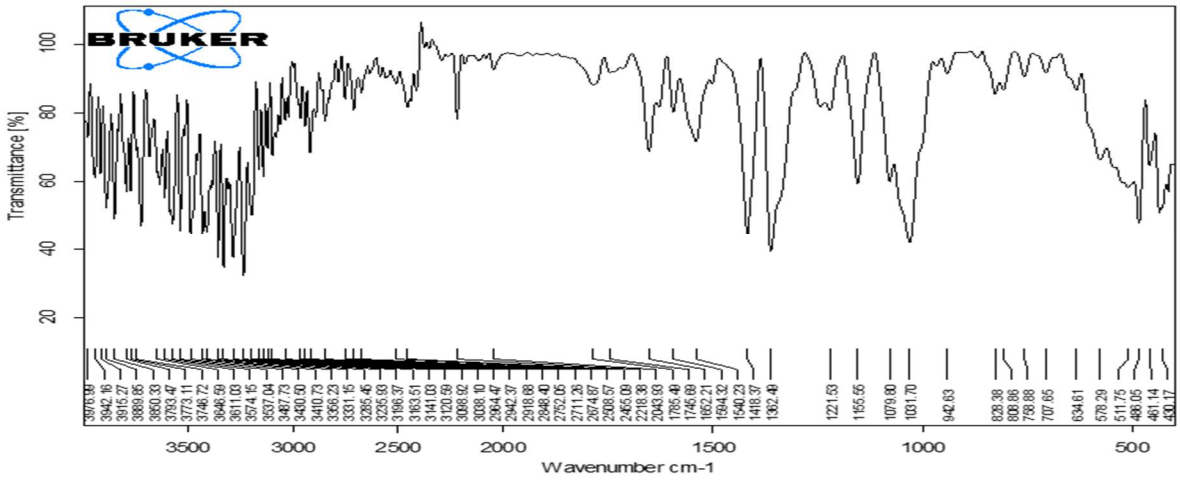

Figure No.3 IR spectrum of Rilpivirine & excipients

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

Pure Drug:

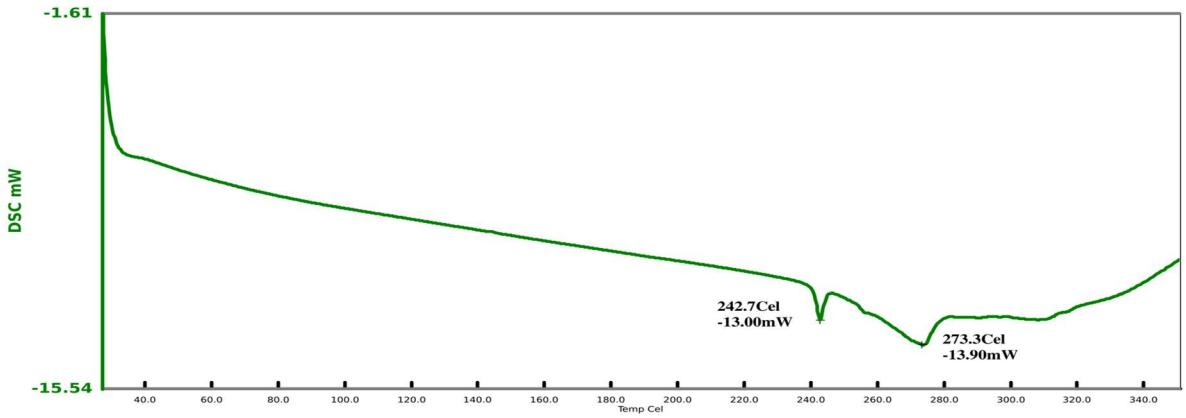

Figure No.4 DSC of the Pure Drug

Optimised :

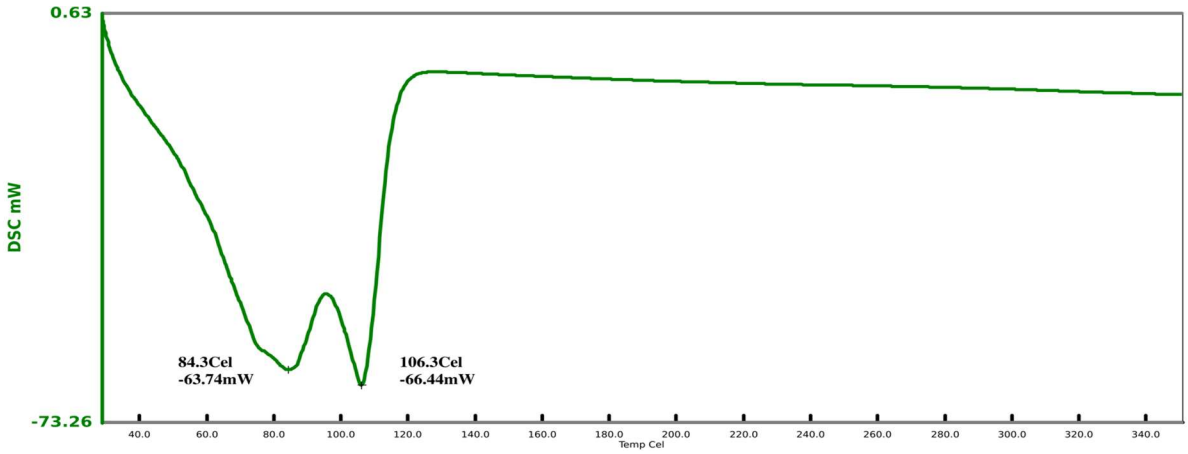

Figure No.5 DSC of the Optimized trail

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:

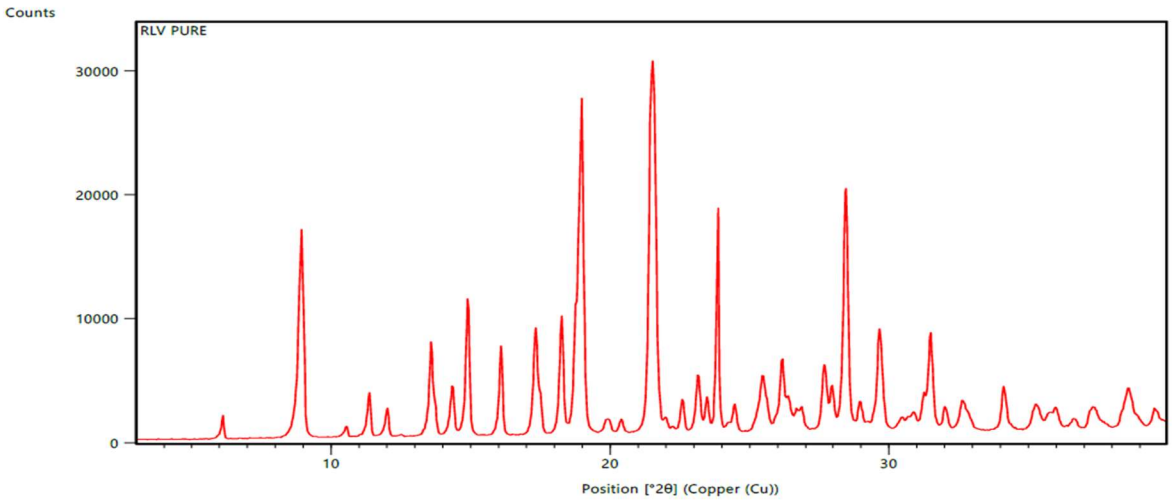

Figure No.6 XRD of Pure Drug

Optimized Trail:

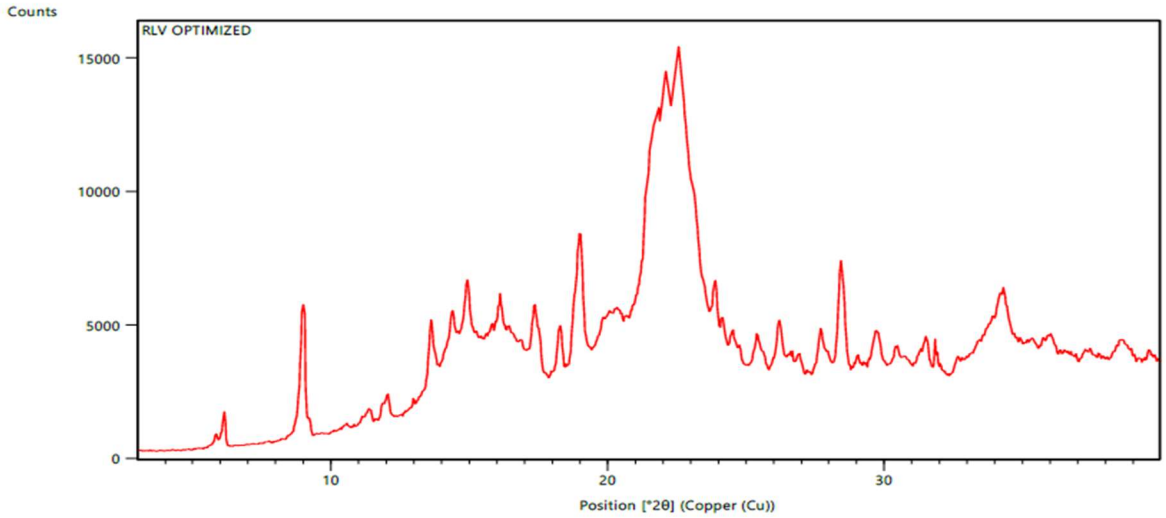

Figure No.7 XRD of Optimized Trail

Discussion:

FTIR: In the Pure Drug Rilpivirine, the absorption peaks observed at ~3743.05 cm-1 with the bond H-N (Stretching), 3182.06 cm-1 with the bond ≡ C- (Stretching), 2752.63 cm-1 with the bond C-H (Stretching), 2218.16 cm-1 with the bond -C≡N (Stretching), 1652.50 cm-1 with the bond C=C (Stretching), 1594.32 cm-1 with the bond N=C (Stretching), 1155.55 cm-1 with the bond N-C (Stretching) respectively In the Optimized Trail, the absorption peaks observed at ~3574.15 cm-1 with the bond H-N (Stretching), 3163.51 cm-1 with the bond ≡C- (Stretching), 2711.64 cm-1 with the bond C-H (Stretching), 2218.38 cm-1 with the bond -C≡N (Stretching), 1628.45 cm-1 with the bond C=C (Stretching), 1594.55 cm-1 with the bond N=C (Stretching), 1151.60 cm-1 with the bond N-C (Stretching). From the drug excipient compatibility studies we observe that there are no interactions between the pure drug (Rilpivirine) and optimized trail (Rilpivirine + excipients) which indicates there are no physical changes.

DSC studies were conducted on pure Rilpivirine and Optimized Trail. The melting point of pure Rilpivirine was found to be between 240 and 280 degrees Celsius. Pure Rilpivirine displays a distinct steep peak at 242.7 Cel and 273.3 Cel, which corresponds to its melting point. The peak vanished in the new trail, showing 84.3 Cel 106.3 Cel complete homogeneity with the film component and the formation of an amorphous form of Rilpivirine. The peaks in the DSC thermograms for Rilpivirine, Rilpivirine + Guar Gum, and disintegrate mixtures correlate to the drug's melting points. Thus, the DSC analysis discovered no interactions between the chosen pharmaceutical, Rilpivirine, and Guar Gum, or disintegrate combinations

XRD, Rilpivirine displayed sharp peaks at different diffraction angles indicating its crystalline shape. The major characteristic peaks of Rilpivirine drug , Guar gum and Lycoat polymer were observed in physical mixture with lower intensity, where the X-ray diffractogram of Optimized trail showed no obvious peaks of Rilpivirine. The X-ray diffraction pattern of Lycoat not showed any peaks which indicates that the structure is completely amorphous. As the Lycoat 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 Lycoat can be used as novel super disintegrant in the trail of mouth dissolving film.

Determination of λ_{max}: -

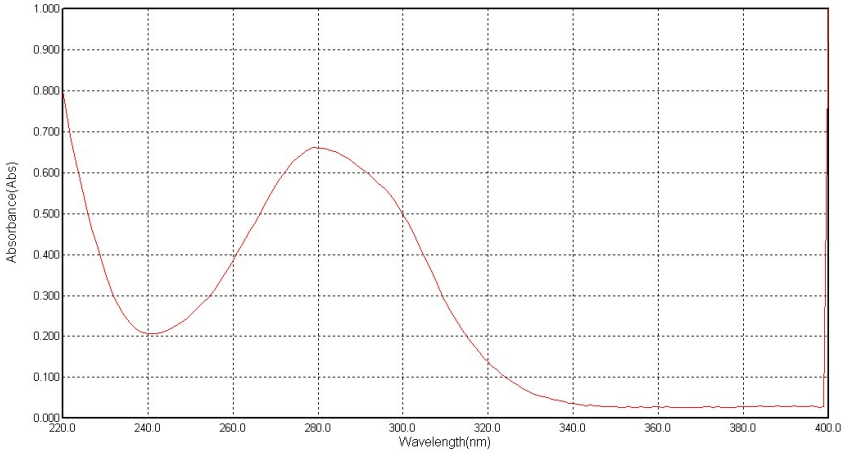

Figure No.8 UV Spectrum curve of Rilpivirine

Discussion: The lambda max of the Rilpivirine 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 Rilpivirine in 7.4 pH phopshate Buffer

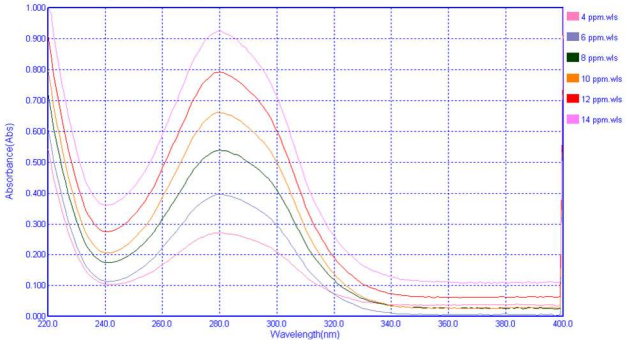

Figure No.9 Spectrum comparison for linearity ppms

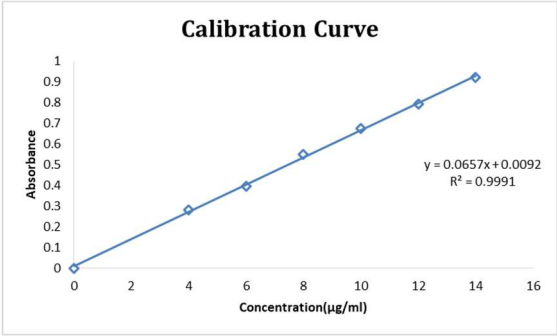

Figure No.10 Standard graph of Rilpivirine Discussion: The calibration curve of Rilpivirine show absorption maxima at 280.0 nm, in phosphate buffer of pH 7.4 Phosphate Buffer. The UV spectrophotometric exhibited a linearity range of 4-14 µg/ml the absorption data points were considered for linear regression analysis by Microprocessor UV Visible single beam spectrophotometer. The equation of straight-line, y= 0.0657x+0.0092, was generated for the calculation of amount of drug. The coefficient of determination (R2) was found to be 0.9991 as illustrated in Figure No.

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:

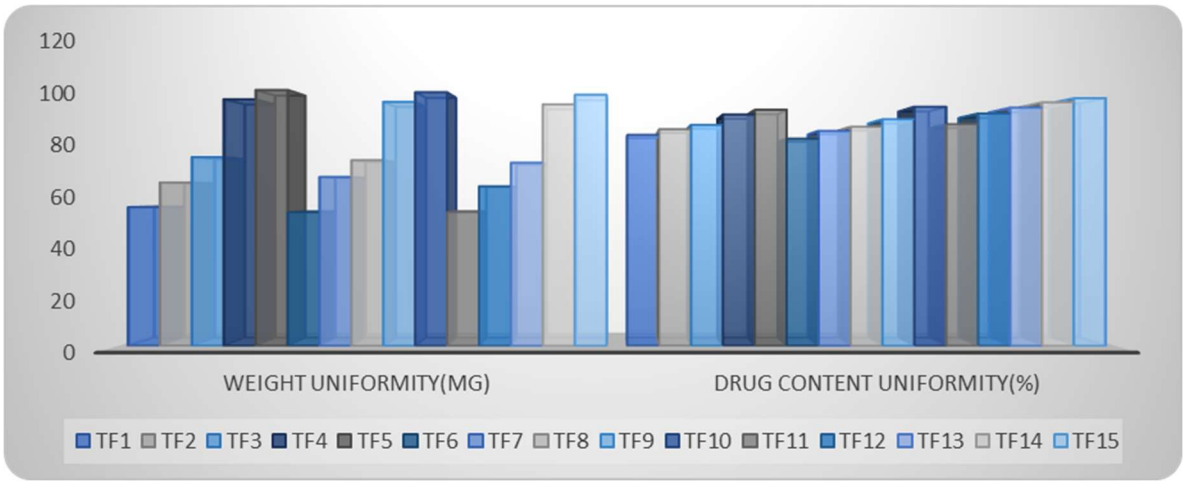

Figure No.11 Graphs of weight uniformity and drug content uniformity

Determination of Moisture content of film

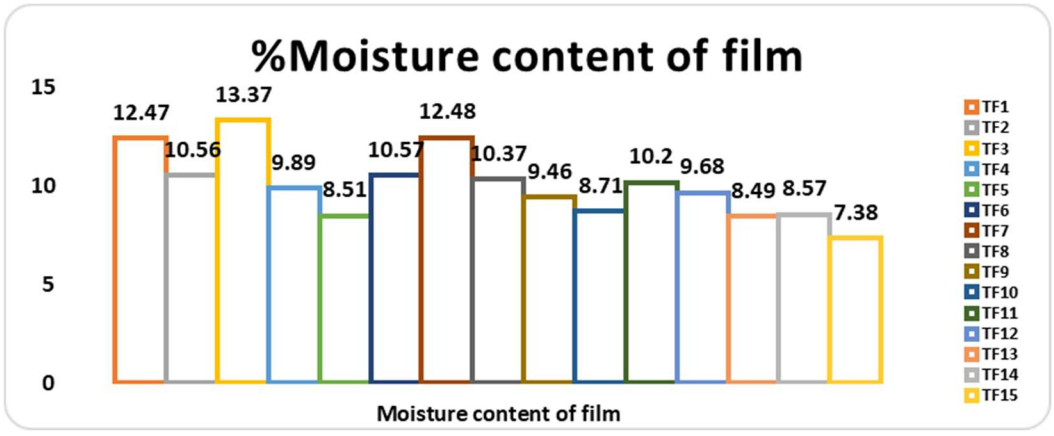

Figure No.12 % Moisture content of films

Determination of Thickness:

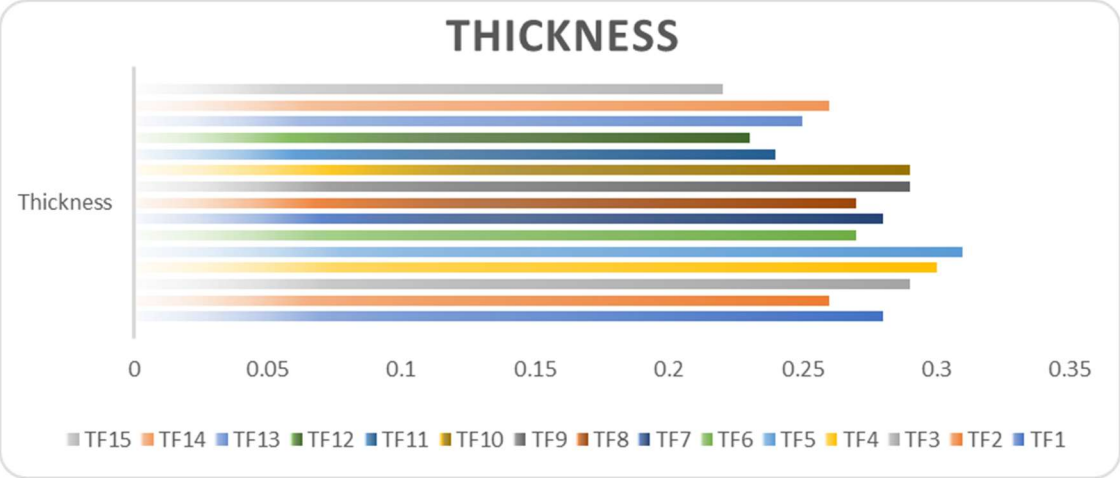

Figure No.13 Thickness of Films

Determination of folding endurance:

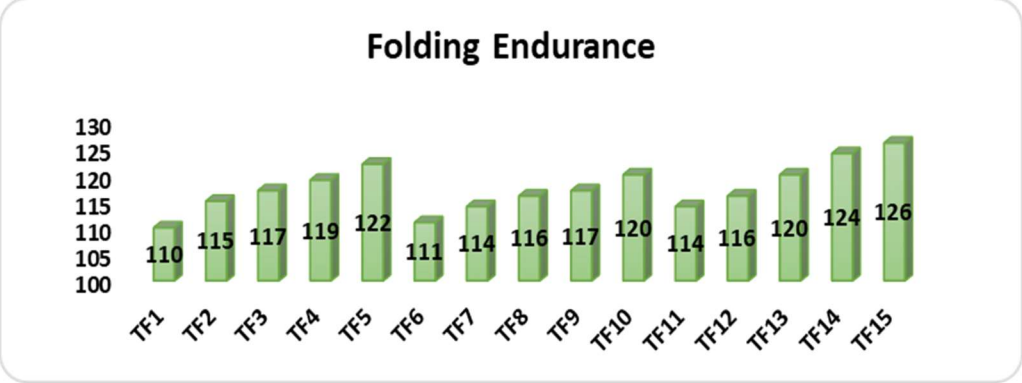

Figure No.14 Folding endurance of the films

Discussions: All batches were uniform in weight, with no significant deviation across trails from the average. Weight consistency ranged from 53.48±1.69 mg to 102.17±1.38 mg for films manufactured. Drug content uniformity was tested for all prepared films and found to be between 82.75±2.20% and 98.87±2.20%, indicating homogeneous mixing. According to IP specifications, drug content readings were between 85 and 110%.

The percentage moisture Content test was carried out to check the physical stability or integrity of the film at the humid condition. The moisture uptake by the films is used to inspect the physical strength of Mouth Dissolving films under high moisture conditions, and results range from 13.37±1.47% to 7.38±1.74%.

It is critical to ensure consistency in the thickness of the film since it is directly connected to the precision of dosage distribution. The thickness of the films steadily grew as the amount of polymer increased, and it was determined to be between 0.22±0.02mm and 0.30±0.02 mm.

Folding endurance gives an indication of brittleness of the film. A result showed that as the concentration of polymer and plasticizer increases, folding endurance of mouth dissolving film increases. Folding endurance was determined by repeatedly folding a film at the same place till it breaks. The folding endurance values of the prepared films were in range of 110±2-126±. The values comply with in the limit 100-150.

Determination of Surface pH:

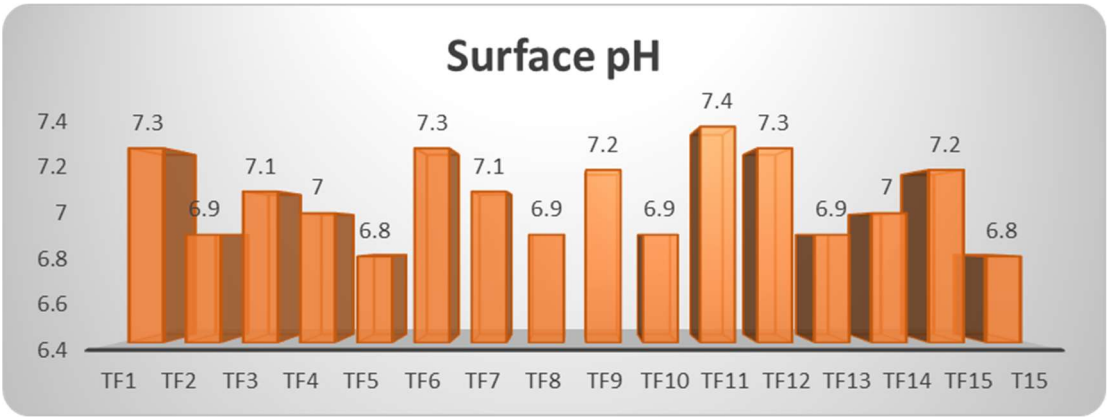

Figure No.15 Graphs of Surface pH

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 6.8±0.4 to 7.4±0.1 pH which comply within the limits 6.8pH-7.4 pH, 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 29±1.24 to 13±1.47 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:

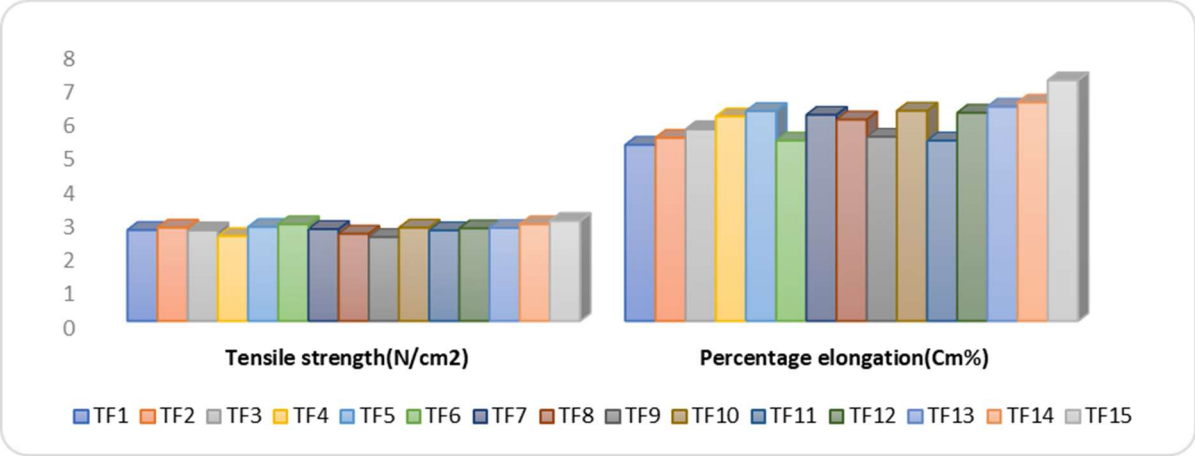

Figure No.16 Tensile strength and percentage elongation of films

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 5.21±0.2 cm%- 7.12±0.7 cm%.

Scanning electron microscopy (SEM):

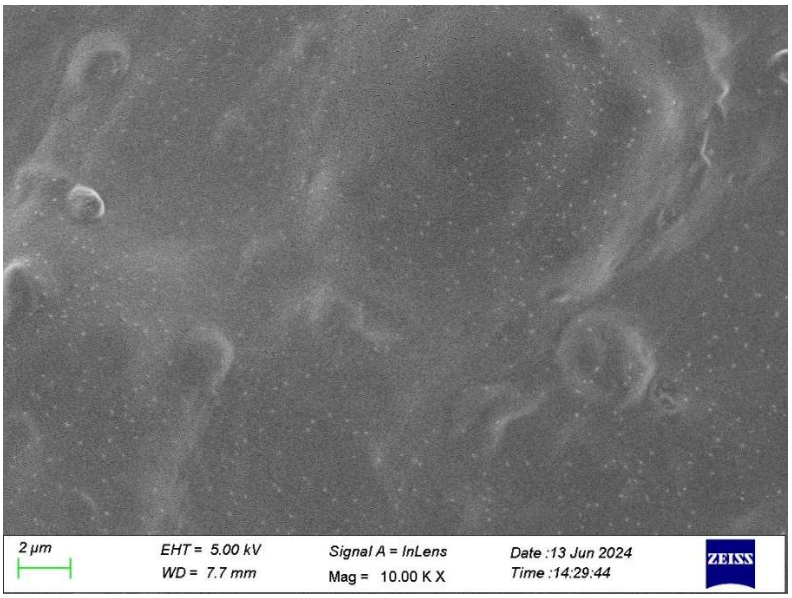

Figure No.17 SEM image of Optimized Trail

Discussion: The surface of the optimized Rilpivirine trail is homogeneous and smooth, as evidenced by the SEM. It also demonstrates the substance particles' hardness and thickness. In contrast, the Rilpivirine-Guar Gum complex that was observed by SEM is narrow and pliable. The optimized trail was demonstrated by the reduction in particle size. The SEM image of Rilpivirine MDF reveals a smooth and irregular surface, which is devoid of particulates, indicating that the drug

is present in a dissolved state within the polymer Guar 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 except some trails which shows taste masked of drug bitter taste only.

In-vitro Dissolution Studies:

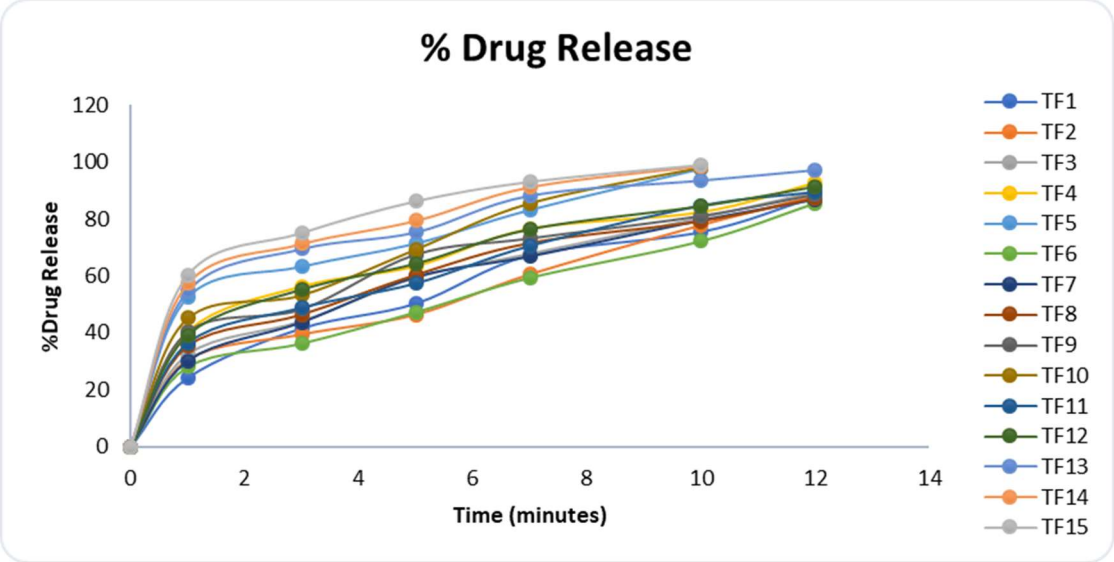

Figure No.7.18 %Drug Release of Trails from T1 to T15

Discussions: In-vitro drug release of Rilpivirine Mouth Dissolving Films with PVA and Guar gum as polymers in various ratios were observed which shows at the end of 12 mins , the Trail TF1 shows 87.79±1.48%, TF2 shows 87.97±1.54%, TF3 show 89.54±1.19%, TF4 shows 92.45±1.18%, T5 shows 97.69±1.24% at the end of 10 minutes. In-vitro drug release of Rilpivirine Mouth Dissolving Films with PVA as polymer in various ratios was observed. At the end of 12 minutes, the Trail TF6 shows 85.58±1.47%, TF7 shows 86.75±1.23%, TF8 shows 87.24±1.19%, TF9 shows 88.69±1.72%, and TF10 shows 98.25±1.48% at the end of 10 minutes. In-vitro drug release of Rilpivirine Mouth Dissolving Films with Guar Gum as polymer in various ratios was observed. At the end of 12 minutes, the Trail TF11 shows 89.38±1.10%, TF12 shows 91.46±1.27%, TF13 shows 97.25±1.37%, and TF14 shows 98.75±1.28%, TF15 shows 99.16±1.35% at the end of 10 minutes. Among all Trails, TF15 shows maximum drug release at the end of 10 minutes. So, it was chosen as optimized trail.

Comparison of optimized trail with marketed trail:

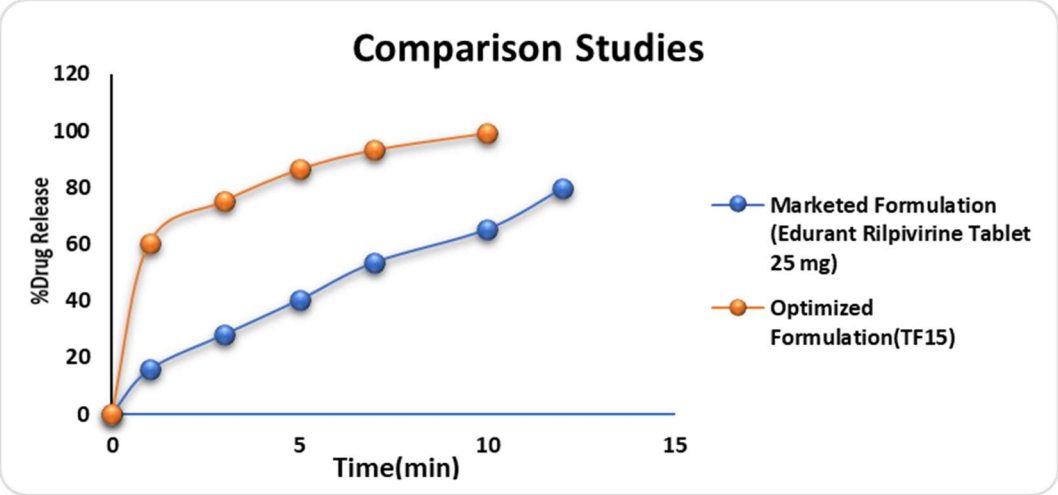

Figure No.19 In vitro Comparison studies of Optimized trail with Marketed Trails

Discussion: The comparison studies for in vitro drug release of Optimized trail with Marketed Trails. The Comparison studies shows the Optimized trail was show 99.16±1.35% of drug release at the end of 10 minutes and the marketed trail shows the 79.48±1.82% of drug release at the end of 12 minutes. Based on comparison The Optimized trail TF15 having best release than marketed trail.

Drug release kinetics studies:
Zero order:

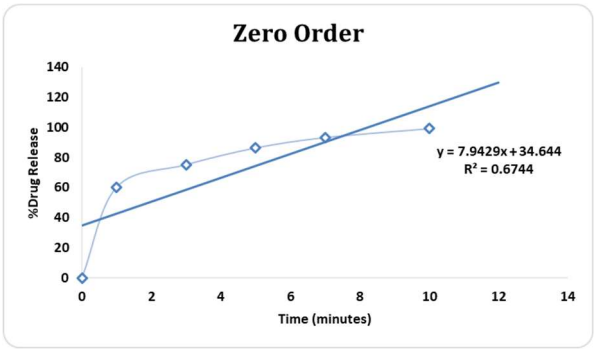

Figure no.20 zero order plot of Rilpivirine TF15 trail (time vs % drug release)

First order:

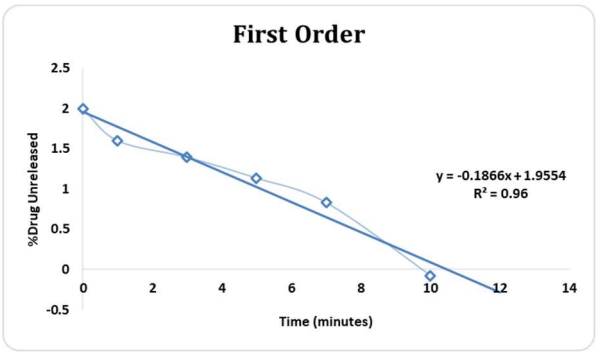

Figure No.22 First order plot of Rilpivirine TF15 Trail (Time Vs Log% ARA)

Higuchi plot:

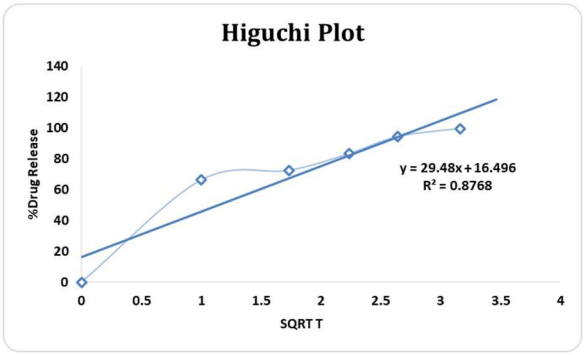

Figure No.21 Higuchi plot of Rilpivirine TF15 Trail (%Drug Release vs Root Time)

Korsmeyer -peppas plot:

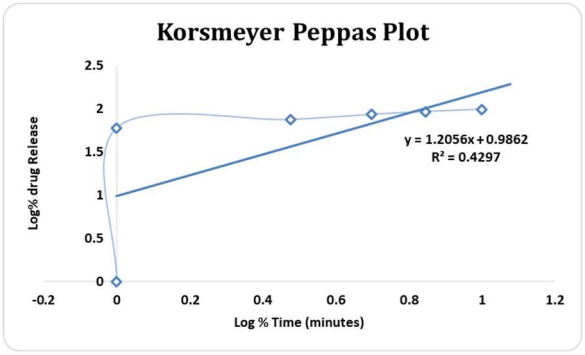

Figure No.23 Korsmeyer -Peppas plot of Rilpivirine TF15 Trail (Log%Drug Release vs Log % Time**Discussion:**
The drug release from the Mouth Dissolving Films was explained by the using mathematical model equations such as zero order, first order methods. Based on the regression values it was concluded that the optimized trail TF15 follows first order drug release with super case-II transport mechanism.

Stability Studies:

Stability study was conducted on optimized trail (TF15). 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, and tensile strength and In-vitro dissolution studies.

Discussion: The optimized trail (TF15) 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 3 Months.

Summary and Conclusion:

In the present study Oral drug delivery system of Rilpivirine 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 Rilpivirine were prepared by using Lycoat as super disintegrants, Guar Gum and PVA 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 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 final suitable formulation (TF15) was achieved fruitfully by the solvent casting method using Guar Gum as Polymer and Lycoat as disintegrant which exhibited a rapid disintegration time (13±1.47 sec) and in vitro drug release (99.16±1.35%%) at the end of 10 minutes. The in vitro dissolution data for best trail TF15 were fitted in different kinetic models i.e, zero order, first order, Higuchi and korsemeyer-peppas equation. Optimized trail TF15 shows R2 value 0.960. 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 1.205 for the optimized trail (TF15) i.e., n value was >0.89 this indicates Super case-II transport mechanism. For the Stability Studies the Optimized Trail TF15 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, 60 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 Lycoat as disintegrant 75 mg and Guar Gum 300 mg as Film Forming agent and Propylene Glycol 20ml as Plasticizer. It can be concluded that the Trail TF15 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.

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