FORMULATION DEVELOPMENT AND EVALUATION OF DOLUTEGRAVIR ORAL DISINTEGRATION TABLETS USING THE STARCH PHTHALATE

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Abstract

Objective: The rationale of the current work was to formulate and evaluate Oral disintegrating tablets of Dolutegravir by direct compression technique with a vision to augment patient compliance and rapid onset of action.
Methods: Elven oral disintegrating formulations of Dolutegravir were formulated by direct compression method using starch phthalate, Microcrystalline cellulose and starch glycolate sodium as the super disintegrants. The prepared formulations were evaluated for wetting time, drug content, *in vitro* disintegration time, dissolution time and also projected to kinetic treatment to know the pattern of drug release. Further, the discovered promising formulation was subjected to stability studies.
Results: Based on the results obtained, formulation F10 containing 20 mg of starch Phthalate and 100 mg of Micro crystalline cellulose exhibited good wetting time, dispersion time, and disintegration time and drug release compared to Oral disintegrating tablets prepared with other super disintegrants. The stability studies piloted as per International Conference on Harmonisation guidelines on the promising formulation F10 disclosed no significant changes in the drug content at 30±2°C and 75% RH 40±2°C with 75% RH was found to be 98.68 ±0.87 and 98.28 ±0.37 after 1 and 6 months respectively , and drug release after 6 months After 5 min, the percentage drug release of F10 was found to be 30±2°C and 75% RH 40±2°C with 75% RH Were found to be 96.14 ± 0.42 and 96.24 ± 0.42respectively after 1 and 6 months , respectively.
Conclusion: Oral disintegrating tablets of Dolutegravir sodium were formulated successfully by employing direct compression technique. From the investigation, it can be reasonably concluded that F10 batch Oral disintegrating tablets of propranolol with 20 mg of starch Phthalate and 100 mg of Micro crystalline cellulose exhibited maximum cumulative drug release in 5 min.

Keywords: Dolutegravir, Oral disintegrating tablets, Direct compression technique, Super disintegrants

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1. INTRODUCTION

The global landscape of healthcare has been profoundly impacted by viral infections, ranging from the common cold to formidable pandemics. As viral outbreaks continue to challenge public health systems worldwide, the development of effective antiviral medications remains a cornerstone of disease management and prevention. In this context, the formulation and advancement of antiviral drugs have taken a pivotal role in addressing these persistent healthcare needs.[1]

Traditionally, antiviral medications have been available in various forms, including tablets, capsules, and injectables. While effective, these conventional dosage forms may not always align with the preferences and practicalities of diverse patient populations. Moreover, antiviral drugs often require rapid and precise administration to exert their maximum therapeutic effect, especially during outbreaks or in cases of viral emergencies.[2]

Enter the era of orally disintegrating tablets (ODTs) of antiviral drugs—a groundbreaking innovation poised to redefine the landscape of antiviral therapy. ODTs represent a dynamic convergence of pharmaceutical science, patient-centricity, and clinical efficacy. Unlike their conventional counterparts, ODTs are designed to dissolve or disintegrate rapidly within the oral cavity, negating the need for water or additional aids for ingestion. [3-4]

The advantages of ODTs in the context of antiviral therapy are multifaceted. First and foremost, they offer a user-friendly, patient-centric approach to medication administration. This is particularly vital in scenarios where rapid antiviral treatment initiation is paramount, such as in the early stages of a viral infection or for post-exposure prophylaxis. The swift disintegration of ODTs not only expedites drug absorption but also enhances patient adherence, reducing the risk of treatment interruption and potential viral resistance.

Furthermore, the formulation of ODTs introduces an element of taste-masking and flavor enhancement, ensuring that the experience of taking antiviral medications is as palatable as possible. This aspect can be crucial, especially in pediatric and geriatric patient populations, where medication aversion can be a significant barrier to effective treatment.

In the development of ODTs of antiviral drugs, formulation strategies, excipient selection, and regulatory considerations converge to create a dosage form that not only meets stringent quality and safety standards but also addresses the unique challenges posed by antiviral agents.[5]

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 effect of this drug has no homology in human host cells, which gives it excellent tolerability and minimal toxicity. Dolutegravir was developed by ViiV Healthcare and FDA-approved on August 12, 2013 On November 21, 2017, dolutegravir, in combination with rilpivirine, was approved as part of the first complete treatment regimen with only two drugs for the treatment of adults with HIV-1 named Juluca. [6]

Figure1: Chemical structure of Dolutegravir

2. EXPERIMENTAL WORK

Materials and Methods:

MATERIALS:

The following materials of Pharma grade or the best possible Laboratory Reagent (LR) were used as supplied by the manufacturer. Distilled water was used in all experiments.

Dolutegravir API Pharma grade was Purchased from Arene Life Sciences Ltd, Hyderabad. Micro crystalline cellulose, INDION 414,SSG, Lycoat, Sodium saccharin, Talc, Magnesium stearate Laboraotry reagent grade purchased from

Pre formulation studies [7]

Solubility

Solubility of Dolutegravir was determined in pH 1.2, pH 7.4, and 6.8 phosphate buffers. Solubility studies were performed by taking excess amount of Dolutegravir in beakers containing the solvents. The mixtures were shaken for 24 hrs at regular intervals. The solutions were filtered by using whattmann's filter paper grade no.41. The filtered solutions are analyzed by spectrophotometrically.

Determination of λ_{max}: -

From stock solution (SS-II), 1 ml was withdrawn and the volume was made up to 10 ml with 6.8 pH HCL to get a concentration of 10 µg/ml. UV scan range was taken between the wavelengths 200-400 nm.

Calibration Curve for Dolutegravir In 6.8 pH Buffer

Preparation of Standard Stock Solution: -

10 mg of Dolutegravir was accurately weighed into 10 ml volumetric flask and dissolved in small quantity of 6.8pH Buffer. The volume was made up to 10 ml with the 6.8pH Buffer to get a concentration of (1000 µg/ml) SS-I. From this, 1 ml was withdrawn and diluted to 10 ml with distilled water to get a concentration of (100 µg/ml) SS-II and from SS-II withdrawn 1ml solution into VF and make upto 10ml this was the SS-III.

Calibration Curve in 6.8 pH Buffer: -

From the standard stock solution (SS-II), 0,0.2,0.4,0.6,0.8,1.0 and 1.2ml were withdrawn and volume was made up to 10 ml with 6.8pH Buffer to give a concentration of 2, 4, 6,8 ,10 and 12µg/ml. Absorbance of these solutions was measured against a blank of 6.8pH Buffer at 257 nm for Dolutegravir and the absorbance values are summarized in Table.4 Calibration curve was plotted, drug concentrations versus absorbance was given in the Figure.3

Preparation of starch phthalate:

Procedure

Step-1: 3 parts of phthalic anhydrous was dissolved in 2 parts of dimethyl sulphoxide (DMSO). Then, pH of the solution was adjusted to pH 3.5 using 10M NAOH and finally made up to 50ml.

Step-2: To the above solution 5 parts of potato starch was added and conditioned for 16hrs. After conditioning the dispersion was kept in an oven at 60^{o} C for one hour.

Step-3: Then the product was mixed with acetone for 15min and then washed with isopropanol to remove any unwanted phthalic anhydride if present.

Step-4: After washing the resultant starch phthalate was kept in oven at 60^{o}C until it

gets dried. The Product obtained was Griend and sieved through #120.

Drug-excipient compatibility studies by FTIR:

Excipients are integral components of almost all pharmaceutical dosage forms. The successful formulation of a stable and effective solid dosage form depends on the careful selection of the excipients, which are added to facilitate administration, promote the consistent release and bioavailability of the drug and protect it from degradation. Infra Red spectroscopy is one of the most powerful analytical techniques to identify functional groups of a drug.

The drug and excipient compatibility was observed using Fourier Transform – Infra Red spectroscopy (FT-IR). The FT-IR spectra obtained from Bruker FT-IR Germany (Alpha T) was utilized in determining any possible interaction between the pure drug and the excipients in the solid state. The potassium bromide pellets were prepared on KBr press by grounding the solid powder sample with 100 times the quantity of KBr in a mortar. The finely grounded powder was then introduced into a stainless steel die and was compressed between polished steel anvils at a pressure of about 8t/in^2. The spectra were recorded over the wave number of 4000 to 400cm^{-1}.

Differential scanning calorimetry (DSC)

DSC was performed utilizing DSC Q20 Universal V4.5A TA Instruments. Samples were allowed to equilibrate for 1 min and then heated in an atmosphere of nitrogen over a temperature range from 0 to 300°C. Thermograms were obtained using TA Instruments universal analysis software 2000.

X-Ray diffraction (XRD)

The samples were recorded on 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 processed with the software Diffrac Plus V1.01.

Formulation Of Orally Disintegrating Tablets of Dolutegravir: [8-11]

In the present study Direct Compression technique was employed for the preparation of disintegrating tablets.

Direct compression is widely used in tableting because it requires fewer processing steps. Direct compression also eliminates exposure to heat and moisture during processing and is a more economical process. However, the majority of active pharmaceutical ingredients exhibit poor compressibility. Therefore, the addition of directly compressible adjuvant is mandatory in such cases.

Directly compressible filler should exhibit good flowability and compatibility. Good flowability is necessary to ensure rapid and uniform die filling, whereas high compatibility is necessary to produce tablets having sufficient mechanical strength.

Precautions:

1. Inspection of cleanliness of the compression machine.
2. Inspection of cleanliness of storage container.
3. Inspection of cleanliness of all the Mechanical stirrers and weighing balance.

MANUFACTURING PROCEDURE:

Step 1: Optimized batch of drug polymer complex equivalent to 50 mg of Dolutegravir was
used for the ODT preparation.

Step 2: INDION 414/ SSG/ Lycoat and aspartame were weighed individually and passed through #40 mesh.

Step 3: All the above sifted excipients were mixed with the Micro crystalline cellulose, Povidone K30 and Starch Phthalate mixer properly for 3 min and Sodium saccharin was added and mixed properly.

Step 4: Finally, magnesium stearate and talc were added to the mixture thoroughly for 2 min.

Step 5: The powder blend was compressed by using 6 mm concave punch.

Table No.1 Formulation table for Dolutegravir Oral Disintegrating tablets

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Dolutegravir	50	50	50	50	50	50	50	50	50	**50**	50
Micro crystalline cellulose	130	120	120	100	110	100	120	100	100	**100**	100
Starch Phthalate	10	20	10	20	10	20	10	20	20	**20**	20
INDION 414	--	--	10	10	--	--	--	--	5	--	5
SSG	--	--	--	--	10	10	--	--	5	**5**	--
Lycoat	--	--	--	--	--	--	10	10	--	**5**	5
Sodium saccharin	6	6	6	6	6	6	6	6	6	**6**	6
Talc	2	2	2	2	2	2	2	2	2	**2**	2
Magnesium stearate	2	2	2	2	2	2	2	2	2	**2**	2
Total	200	200	200	200	200	200	200	200	200	**200**	200

EVALUATION PARAMETERS OF POWDER BLEND

Precompression Parameters [12-16]

Method Preparation of Mixed Blend of Drug and Excipients

All the materials were passed through sieve no. 80. Required quantity of each ingredient was taken for each specified formulation and all the ingredients were subjected to grinding to a required degree of fineness (except magnesium stearate and talc). The powdered blend was evaluated for flow properties as follows.

Angle of repose

Angle of repose is determined by using funnel method. The accurately weighed blend is taken in a funnel. The height of the funnel is adjusted in such a way that the tip of the funnel just touches the apex of the heap of blend. The drug-excipient blend is allowed to flow through the funnel freely on to the surface. The diameter of the powder cone is measured and angle of repose is calculated using the following equation. Angle of Repose less than 30 ° shows the free flowing of the material.

$$\theta = \tan^{-1} (h / r)$$

Bulk density

Apparent bulk density is determined by pouring a weighed quantity of blend into graduated cylinder and measuring the volume and weight.

The bulk density was calculated by using the below mentioned formula

$$D_b = \frac{M}{Vo}$$

Where, **M** is the mass of powder, **V0** is the bulk volume of the powder

Tapped density

It is determined by placing a graduated cylinder, containing a known mass of drug-excipients blend. The cylinder is allowed to fall under its own weight onto a hard surface from the height of 10 cm at 2 second intervals. The tapping is continued until no further change in volume is noted.

The tapped density was calculated using the following formula,

$$D_T = \frac{M}{Vt}$$

Where, **M** is the mass of powder, $\mathbf{V_T}$ is the tapped volume of the powder

Compressibility index

The simplest way for measurement of free flow of powder is compressibility, an indication of the ease with which a material can be induced to flow is given by compressibility index(I) which is calculated as follows,

Carr's Index (I) = (Tapped Density-Bulk Density)/(Tapped Density) x100

The value between 13-19% indicates a powder with usually good flow characteristics, whereas above 21% indicate poor flowability.

Hausner's Ratio

Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula

$$\textbf{Hausner's Ratio} = \frac{\textbf{BulkDensity}}{\textbf{Tapped Density}}$$

Where $\mathbf{D_t}$ is tapped density and $\mathbf{D_b}$ is bulk density

Lower Hausner‟sratio (<1.25) indicates better flow properties and higher Hausner‟s ratio (>1.25) indicates poor flow properties.

EVALUATION PARAMETERS OF TABLETS

Post compression parameters[17-20]

Weight variation test

The weight variation test is carried out in order to ensure uniformity in the weight of tablets in a batch. First the total weight of 20 tablets from each formulation is determined and the average is calculated. The individual weight of the each tablet is also determined to find out the weight variation.

Thickness

Tablet thickness can be measured using a simple procedure. Five tablets are taken and their thickness is measured using Vernier calipers. The thickness is measured by placing tablet between two arms of the Vernier calipers.

Tablet hardness

The hardness of tablet is an indication of its strength. It is the force required to break a tablet by compression in the radial direction. The force is measured in kg and the hardness of about 3-5 kg/cm^2 is considered to be satisfactory for uncoated tablets. Hardness of 10 tablets from each formulation is determined by Monsanto hardness tester, Pfizer hardness tester etc. Excessive hardness significantly reduces the disintegration time.

Tablet friability

Friability is the loss of weight of tablet in the container due to removal of fine particles from the surface. Friability test is carried out to access the ability of the tablet to withstand abrasion in packaging, handling and transport. Roche friabilator is employed for finding the friability of the tablets. Weigh the 20 tablets from each batch and place in Roche friabilator that will rotate at 25 rpm for 4 minutes. All the tablets are dedusted and weighed again. The percentage of friability can be calculated using the formula.

% Friability = [(W1-W2)100]/W1

Where, W1= Weight of tablet before test, W2 = Weight of tablet after test

The pharmacopoeial limit of friability test for a tablet is not more than 1%. This test is not applicable for lyophilized and flash dose tablets, but is done for tablets prepared by direct compression and moulding. It is a difficult to achieve friability within this limit for MDT and to keep hardness to the lowest to achieve a minimum possible disintegration time.

In-Vitro Disintegration time

Tablet disintegration is an important step in drug absorption. The test for disintegration was carried out in Electro lab USP disintegration test apparatus. It consists of 6 glass tubes which are 3 inches long, open at the top, and held against a 10 mesh screen, at the bottom end of the basket rack assembly. To test the disintegration time of tablets, one tablet was placed in each tube and the basket rack was positioned in a 1 liter beaker containing pH 6.8 buffer solution at 37°C ± 1°C such that the tablet remains

2.5 cm below the surface of the liquid. The time taken for the complete disintegration of the tablets was noted.

Wetting time:

The wetting time of the tablets is measure by using a simple procedure. Place the five circular tissue papers of 10 cm diameter in a petridish containing 0.2% w/v solution (3ml). A tablet is carefully placed on the surface of the tissue paper. The time require for develop blue color on the upper surface of the tablet is noted as the wetting time.

Drug content uniformity

The tablets were tested for their drug content uniformity. At random 20 tablets were weighed, powdered & dissolved in 100ml of 6.8pH. The solution was shaken thoroughly. The undissolved matter was removed by filtration through Whatman No.41 filter paper. Then the dilute the solution to obtain 10µg solution. The absorbance of the diluted solutions was measured at 257 nm.

Dissolution studies

In-vitro dissolution study is performed by using USP Type II Apparatus (Paddle type) at 50 rpm. 6.8 pH buffer 900 ml is used as dissolution medium which is maintained at 37±0.5°C. Aliquots of dissolution medium (10 ml) are withdrawn at specific time intervals and filter. An equal amount of fresh dissolution medium is replaced immediately following withdrawal of test sample. The percentage of drug released at various intervals is calculated using beer-lamberts law.

Data Analysis (Curve fitting analysis):

To analyze the mechanism of the drug release rate kinetics of the dosage form, the data obtained were plotted as [21-22]

Kinetics of drug release:

To examine the drug release kinetics and mechanism, the cumulative release data were fitted to models representing zero order (Q v/s t), first order [Log(Q_0-Q) v/s t.

In short, the results obtained from *in vitro* release studies were plotted in four kinetics models of data treatment as follows.

- **Zero-order kinetic model** – Cumulative % drug released Vs time.
- **First-order kinetic model** – log cumulative % drug remaining Vs time.
- **Higuchi model** - Cumulative % drug released Vs square root of time.
- **Korsmeyer-Peppas model** - log cumulative % drug released Vs log time.

Table 2: Release kinetics data

S. No	Release exponent	Drug transport mechanism	Rate as a function of time
1	0.5	Fickian diffusion	$t^{-0.5}$
2	0.45 < n = 0.89	Non -Fickian transport	t^{n-1}
3	0.89	Case II transport	Zero order release
4	Higher than 0.89	Super case II transport	t^{n-1}

Stability studies:[23]

As per International Council for harmonization stability, guidelines stability studies are performed to check the changes in the quality of a drug substance or drug product by the effect of temperature, humidity, and light with time. Stability studies of F10 formulation were carried out. Tablets were packed in high-density polyethylene bottles and stored at 30±2°C and 75% RH and 40±2°C with 75% RH for 6 months. By evaluating the stored tablets for drug content and drug release, tablet stability was determined after 6 months.

3. RESULTS AND DISCUSSION:

Solubility studies:

Solubility of Dolutegravir was carried out at 25^0C using methanol, ethanol, 6.8 phosphate buffer, 7.4pH buffer and purified water. From solubility studies in various buffers, we can say 6.8 pH Buffer has more solubility when compared to other buffer solutions.

Table 3: Solubility studies

MEDIUM	**SOLUBILITY (µg/ml)**
Water	0.042±0.047
0.1 N HCl	0.564±0.068
6.8 pH buffer	1.221±0.075
7.4 pH buffer	0.788±0.057

Determination of λ_{max}: -

λ_{max} of Dolutegravir was found to be 257 nm for the 8ppm (µg/ml) concentration in the 6.8 pH buffer solution.

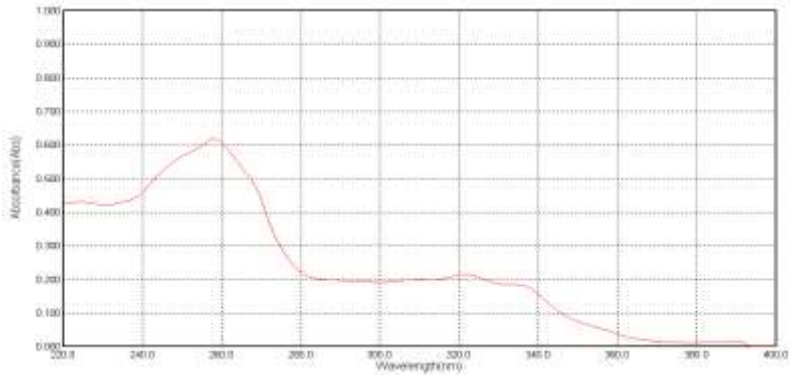
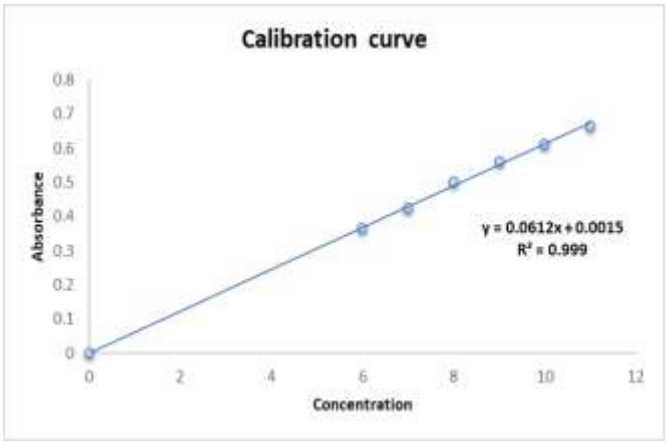


Figure 2: UV Spectrum curve of Dolutegravir

Calibration curve of Dolutegravir in 6.8pH Buffer

Table 4: Calibration curve of Dolutegravir in 6.8pH buffer



Concentration (µg/ml)	Absorbance
0	0
2	0.366±0.074
4	0.426±0.057
6	0.501±0.084
8	0.562±0.056
10	0.612±0.041
12	0.665±0.026

Figure 3 Standard graph of Dolutegravir

The calibration curve of Dolutegravir show absorption maxima at 257 nm in phosphate buffer of pH 6.8. The UV spectrophotometric exhibited a linearity range of 2-12 µg/ml the absorption data points were considered for linear regression analysis. The equation of straight-line y= 0.0612x+0.0015 was generated for the calculation of amount of drug. The coefficient of determination (R2) was found to be 0.999 as illustrated in Figure 3. The present analytical method was found to obey beers lambert's law in concentration range of 2 - 12 µg/ml and its found suitable for estimation of Dolutegravir as given in table 4.

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 formulation.

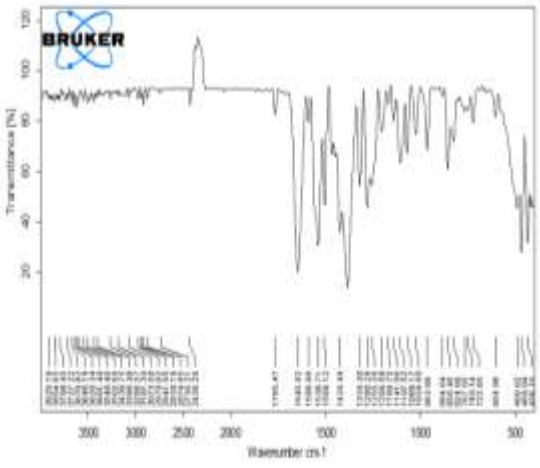


Figure. 4 IR spectrum of Dolutegravir

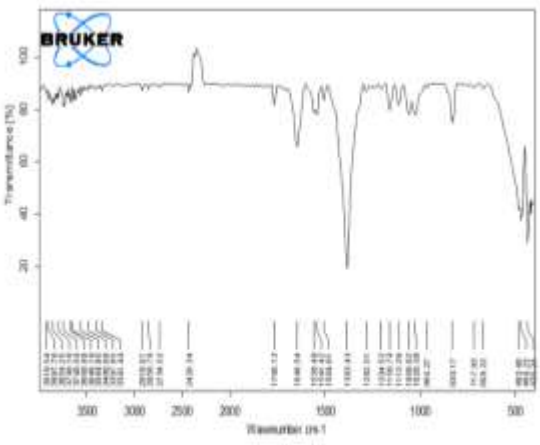


Figure. No. 5 IR spectrum of Dolutegravir & excipients

Table 5: FTIR Interpretation Table for Pure and Optimized Drug

Functional	Stretching/deformation	Pure drug (cm-1)	Drug + polymers (cm-1)

groups			
O-H	Stretching	3601.40 cm-1	3740.54 cm-1
C=O	Stretching	1645.92 cm-1	1646.54 cm-1
N-H	Deforming	1538.71 cm-1	1541.42 cm-1
C-N (Aromatic)	Stretching	1379.45 cm-1	1383.43 cm-1
C-O-C	Stretching	1255.26 cm-1	1204.52 cm-1
C-F	Stretching	1024.60 cm-1	1028.38 cm-1

Form the drug excipient compatibility studies we observe that there are no interactions between the pure drug (Dolutegravir) and optimized formulation (Dolutegravir + excipients) which indicates there are no physical changes.

Differential scanning calorimetry:

The DSC curves of pure drug, and optimized formulation were obtained using differential scanning calorimeter.

Table 6: Results of Differential scanning calorimetry

Component	**Endothermic peak**
Pure Dolutegravir	318.4 Cel
Optimized Formulation	79.8 Cel and 129.7 Cel

DSC studies were performed for pure Dolutegravir and Optimized Formulation. The melting of Pure Drug Dolutegravir was found in between 300 to 350^{O}C.The DSC thermogram are presented in Fig.13 and 14 of Pure Dolutegravir and optimized formulation shows distinct sharp peak at 318.4Cel corresponding to its melting point. The peak was disappeared in optimized formulation indicate 79.8Cel and 129.7Cel complete homogeneity with the tablet component and formation amorphous form of Dolutegravir. The peaks observed in the DSC thermograms of Dolutegravir and Dolutegravir -starch phthalate mixtures correspond to the melting points of the respective drug. Thus, DSC study indicating no interactions between the selected drug Dolutegravir and starch phthalate.

X-Ray diffraction:

The powder XRD pattern of pure drug and with the excipients Starch Phthalate, SSG and Lycoat showed that drug was highly crystalline in nature as indicated by the distinctive peaks. 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.

As shown in Figure 14 and 15 Dolutegravir displayed sharp peaks at different diffraction angles indicating its crystalline shape. The major characteristic peaks of Dolutegravir drug and Starch Phthalate polymer were observed in physical mixture with lower intensity, where the X-ray diffractiogram of Optimized formulation showed no obvious peaks of Dolutegravir. The X-ray diffraction pattern of starch phthalate not showed any peaks which indicates that the structure is completely amorphous. As the starch phthalate was amorphous, smooth, and free flowing powder and it had got all the characteristics of super disintegrants, it was concluded that starch phthalate can be used as novel super disintegrant in the formulation of fast dissolving tablets.

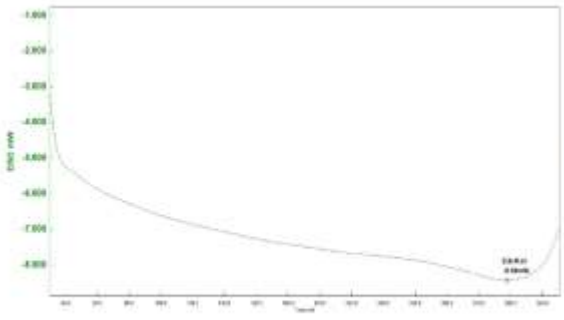


Figure. 13 DSC of the Pure Drug

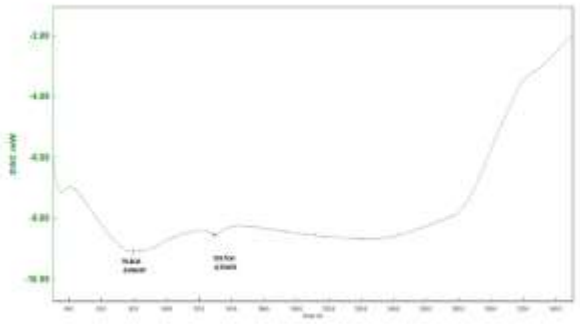


Figure. 14 DSC of the Optimized formulation

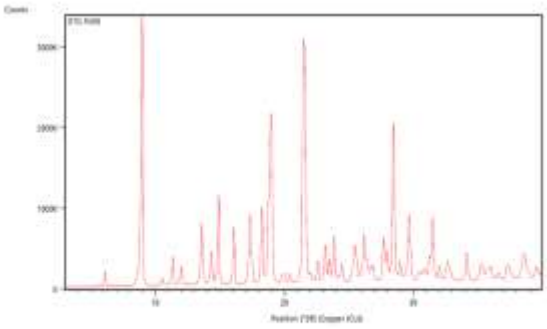


Figure 15 XRD of Pure Drug

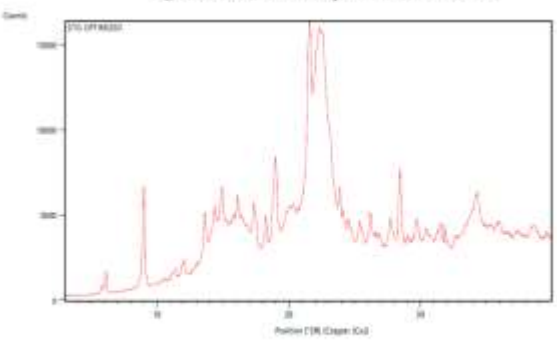


Figure 16 XRD of Optimized Formulation

Characterization of blend:

Pre-Compression parameters:

All the granules prepared by wet-granulation were evaluated for precompression parameters. All the prepared granules exhibited excellent flow properties. The bulk density of prepared granules was in the range of $0.509\pm0.02 g/cm^3$ to $0.648\pm0.07 g/cm^3$. Tapped density was in the range of $0.589\pm0.05 g/cm^3$ to $0.715\pm0.08 g/cm^3$. Carr's compressibility index and hausner's ratio of prepared granules indicated good flow properties. The data is tabulated in table.

Table 7 : Pre-Compression parameters:

Formulation Code	Flow properties				
	Bulk density (mean±SD)	Tapped density	Angle of repose	Carr's index	Hausner's ratio

		(mean±SD)	(mean±SD)	(mean±SD)	(mean±SD)
F1	0.543±0.09	0.621±0.08	29.17±0.24	11.12±1.09	1.12±0.08
F2	0.585±0.05	0.642±0.08	27.34±0.19	09.34±1.21	1.14±0.09
F3	0.673±0.07	0.686±0.04	31.48±0.34	11.45±1.46	1.11±0.07
F4	0.529±0.06	0.695±0.06	29.24±0.62	10.79±1.84	1.16±0.05
F5	0.624±0.05	0.625±0.03	27.19±0.24	13.18±1.26	1.15±0.03
F6	0.526±0.03	0.642±0.06	31.48±0.19	08.24±1.45	1.13±0.06
F7	0.509±0.02	0.596±0.05	32.26±0.37	13.19±1.61	1.17±0.07
F8	0.638±0.03	0.678±0.07	29.18±0.16	11.38±1.49	1.10±0.02
F9	0.576±0.06	0.665±0.01	26.16±0.22	14.47±1.25	1.16±0.04
F10	0.648±0.07	0.715±0.08	29.34±0.24	14.21±1.71	1.18±0.04
F11	0.628±0.05	0.698±0.02	27.34±0.85	11.19±1.16	1.11±0.09

The angle of repose of different formulations was ≤ 29.34 which indicates that material had good flow property. So, it was confirmed that the flow property of blends were free flowing. The bulk density of blend was found between 0.509±0.02g/cm^3 to 0.648±0.07g/cm^3. Tapped density was found between 0.596±0.05g/cm^3 to 0.715±0.08 g/cm^3.These values indicate that the blends had good flow property. Carr's index for all the formulations was found to be between 08.24±1.45-14.21±1.71 and Hausner's ratio from 1.11±0.09-1.18±0.04 which reveals that the blends have good flow character.

Characterization of tablets

Post Compression parameters

The prepared tablets were evaluated for post compression parameters such as hardness (kg/cm2), weight variation (%), disintegration time (sec), wetting time (sec) and the data is given in Table The hardness of prepared tablets were found to be 4.5±0.15–5.7±0.22kg/cm^2. The weight variation was in the range of 198.3±204.8±0.02 units, the % friability was in the range of 0.21±0.08-0.39±0.02 the disintegration time and wetting time of formulations F1-F11 were in the range of 09±1.67-18±1.65 and 15±1.01-26±1.39 seconds respectively.

Table 8: Characterization Dolutegravir oral disintegrating tablets

Formulation	Average Weight (mg)	Thickness (mm)	Hardness (kp)	Friability (%)	Disintegrating time(sec)	Wetting Time

F1	202.2±0.02	3.9±0.16	5.6±0.12	0.25±0.02	15±1.01	10±1.21
F2	198.3±0.06	3.8±0.15	4.9±0.19	0.36±0.06	18±1.42	13±1.78
F3	201.4±0.07	3.6±0.18	4.5±0.15	0.21±0.08	26±1.36	18±1.32
F4	203.6±0.04	3.7±0.24	5.6±0.16	0.35±0.02	18±1.42	13±1.54
F5	201.2±0.03	3.6±0.26	5.6±0.18	0.26±0.08	26±1.39	18±1.65 98
F6	204.8±0.02	3.6±0.19	4.8±0.19	0.34±0.06	18±1.45	13±1.24
F7	202.3±0.01	3.7±0.15	5.5±0.21	0.38±0.04	15±1.60	12±1.84
F8	200.1±0.06	3.6±0.19	4.8±0.19	0.29±0.08	18±1.52	18±1.52
F9	200.5±0.04	3.8±0.18	5.4±0.17	0.31±0.02	24±1.34	17±1.25
F10	200.0±0.52	3.5±0.12	5.7±0.22	0.39±0.02	12±1.20	09±1.67
F11	199.9±0.23	3.2±0.11	4.7±0.28	0.25±0.06	24±1.26	17±1.98

Hardness of the tablet was acceptable and uniform from batch to batch variation, which was found to be 4.5±0.15–5.7±0.22kg/cm^2. All the formulations passed the weight variation test as the % weight variation was within the pharmacopoeia limits of the tablet weight. Friability values were found to be less than 1% in all the formulations F1 – F11 and considered to be satisfactory ensuring that all the formulations are mechanically stable. Disintegration time, Wetting time as per IP, for all the formulations was found to be within 12 seconds and 9 seconds, which was well within IP limit. Formulations with Starch Phthalate (20mg) & Lycoat (5mg), SSG(5mg) as super disintegrants shows quicker disintegration among all the formulations.

Drug content uniformity of formulations:

The prepared formulations were analyzed for drug content and the data is reported in below Table. The drug content was found to be within the limits which show that the drug was uniformly distributed in all the formulations.

Table 9 Drug content uniformity of formulations F1-F11

Tablet formulation	**% Drug Content**
F1	86.45±1.75
F2	91.16±1.84
F3	94.74±1.36
F4	88.36±1.75

F5	94.64±1.94
F6	96.27±1.08
F7	88.29±1.36
F8	96.27±1.47
F9	95.45±1.24
F10	99.42±0.87
F11	88.45±1.21

The % drug content values of formulation F1 –F11 was found to be in the range of 86.45±1.75 to 99.42±0.87%.

Dissolution studies:

The prepared tablets were subjected to dissolution studies in order to know the amount drug release. As the concentration of super disintegrant increased, the drug release time decreased.

Table 10 Cumulative drug release of formulations F1-F11

Time (Min)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**
0	0	0	0	0	0	0	0	0	0	0	0
1	48.47 ±1.74	52.45 ±1.74	59.47 ±1.28	62.44 ±1.74	72.15 ±1.84	79.64 ±1.69	81.35 ±1.47	72.36 ±1.67	86.51 ±1.25	**86.87** ±1.85	87.74 ±1.69
3	55.78 ±1.86	59.61 ±1.85	76.84 ±1.36	78.49 ±1.25	81.59 ±1.24	85.19 ±1.75	85.36 ±1.14	84.36 ±1.57	92.26 ±1.69	**92.26** ±1.68	92.74 ±1.68
5	67.63 ±1.26	67.34 ±1.84	88.82 ±1.74	89.42 ±1.26	89.74 ±1.65	89.84 ±1.25	90.89 ±1.54	95.89 ±1.85	98.82 ±1.78	**99.24** ±1.85	98.73 ±1.75
8	78.61 ±1.39	78.46 ±1.67	93.12 ±1.48	96.72 ±1.24	95.75 ±1.25	98.84 ±1.69	97.58 ±1.68	98.92 ±1.68			
10	93.43 ±1.75	97.47 ±1.25									

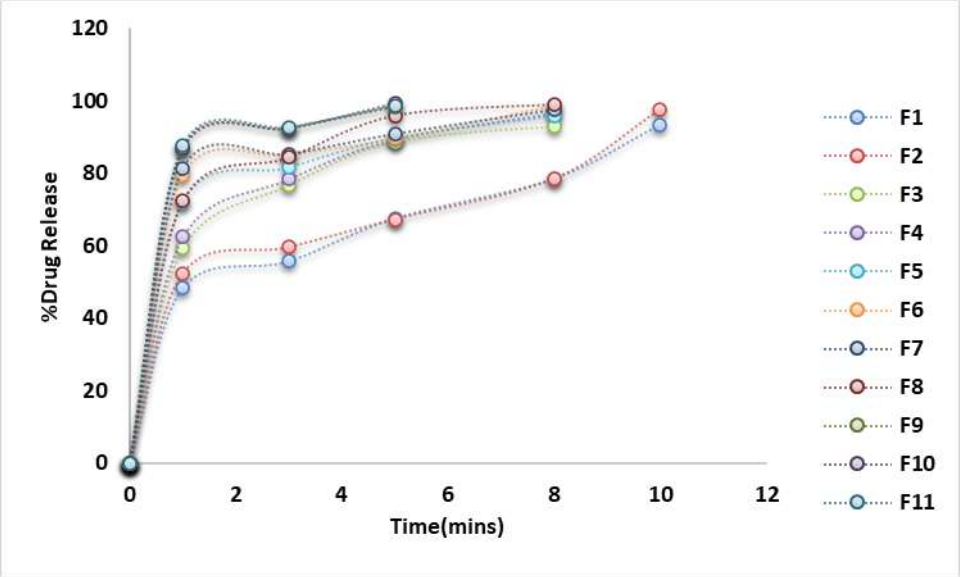


Figure 17 :%cumulative drug release of the formulations F1 to F11

From the invitro drug release studies it was observed that the formulations containing only Starch Phthalate (F1-F2) as super disintegrants in the concentrations of 10mg & 20 mg. The Formulation F1, F2, shows 93.43±1.75%, 97.47±1.25%, drug release at the end of 10minutes.

Whereas the formulations containing Starch Phthalate 10mg & 20 mg with INDION 414 (F3-F4) as super disintegrants in the concentrations of 10mg. So, Formulation F3 & F4 shows 93.12±1.48% & 96.72±1.24% drug release at the end of 8 minutes.

Whereas the formulations containing Starch Phthalate 10mg & 20 mg with SSG (F5-F6) as super disintegrants in the concentrations of 10mg (5%). So, Formulation F5 & F6 shows 95.75±1.25% & 98.84±1.69% drug release at the end of 8 minutes.

Whereas the formulations containing Starch Phthalate 10mg & 20 mg with Lycoat (F7-F8) as super disintegrants in the concentrations of 10mg. So, Formulation F7 & F8 shows 97.58±1.68% & 98.92±1.68% drug release at the end of 8 minutes.

And the Formulation containing 20 mg Starch Phthalate along with two Super disintegrants INDION 414, SSG (F9) in the concentrations of 5mg &5mg the formulations show 98.82±1.78% of drug release at the end of 5 minutes.

And the Formulation containing 20 mg Starch Phthalate along with two Super disintegrants SSG and Lycoat (F10) in the concentrations of 5mg & 5mg the formulations show 99.24±1.85% of drug release at the end of 5 minutes.

And the Formulation containing 20 mg Starch Phthalate along with two Super disintegrants INDION 414, Lycoat (F11) in the concentrations 5mg &5mg the formulations show 98.73±1.75% of drug release at the end of 5 minutes.

By comparing the dissolutions profiles of formulations F1-F11 contains super disintegrants in the concentrations, the super disintegrant ratio of Starch Phthalate along with Lycoat and SSG shows satisfactory drug release at the end of 5mins. Among all the formulations F10 containing 20mg of Starch Phthalate and 5mg & 5 mg of SSG & Lyocat shows 99.24±1.85% drug release at the end of 5min. So F10 formulation was as the optimized formulation.

DRUG RELEASE KINETICS STUDIES:

The invitro dissolution profile of all batches were fitted to Zero order, first order, Higuchi model and Koresmeyer-Peppas model to ascertain the kinetic modeling of drug release. Correlation coefficient (R^2) values were calculated for linear curves obtained by the regression analysis of the above plot.

- **Zero-order kinetic model** – Cumulative % drug released Vs time.
- **First-order kinetic model** – log cumulative % drug remaining Vs time.
- **Higuchi model** - Cumulative % drug released Vs square root of time.
- **Korsmeyer-Peppas model** - log cumulative % drug released Vs log time.

Table 11: **drug release kinetics studies of formulation F10**

Time (min)	cumulative % drug released	% drug remaining	Square root time	log Cumulative % drug remaining	log time	log Cumulative % drug released	% Drug released	Cube Root of % drug Remaining (Wt)
0	0	100	0.000	2.000	0.000	0.000	100	4.642
1	86.87	13.13	1.000	1.118	0.000	1.939	86.87	2.359
3	92.26	7.74	1.732	0.889	0.477	1.965	5.39	1.978
5	99.24	0.76	2.236	-0.119	0.699	1.997	6.98	0.913

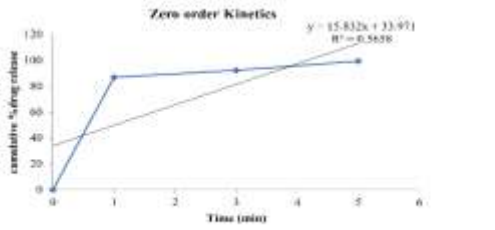


Figure.18 Zero order plot of Dolutegravir F10 Formulation

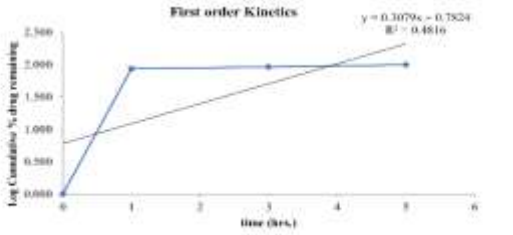


Figure 19 First order plot of Dolutegravir F10 Formulation

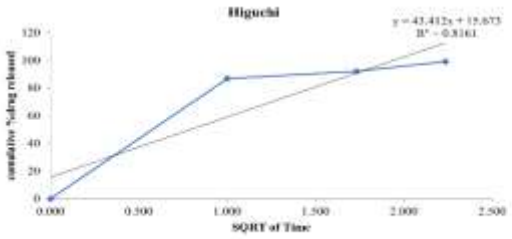


Figure .20 Higuchi plot of Dolutegravir F10 Formulation

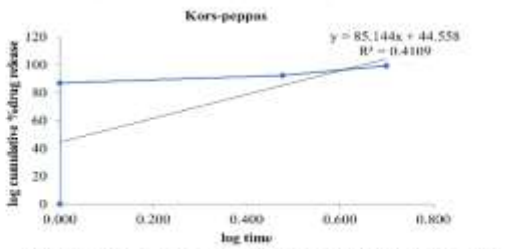


Figure .21 kors-peppas plot of Dolutegravir F10 Formulation

Table 12: **drug release kinetics studies of regression values of formulation F10**

Order of kinetics	Zero order	First order	Higuchi plot	Kors-peppas Model
Regression value(r2)	0.565	0.920	0.8161	0.4109

The drug release from the oral disintegrating tablets 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 formulation F_{10} follows First order drug release. The n value was found to be 0.482 is shows that drug release follows non-Fickian transport.

Stability studies

The stability studies if the formulation F10 was performed the drug content and drug release of the formulation F10 as follows

Table 13: **drug release kinetics studies of regression values of formulation F10**

Time in months	**Formulation F_{10}**			
	Drug Content		**Drug release**	
	30±2°C and 75% RH	**40±2°C with 75% RH**	**30±2°C and 75% RH**	**40±2°C with 75% RH**
1	99.42±0.87	99.39±0.27	99.24 ± 0.42	99.21 ± 0.52
2	99.38 ±0.25	99.34 ±0.25	99.22 ± 1.32	99.18 ± 0.82
3	99.25 ±0.57	99.21 ±0.87	98.89± 0.32	98.75± 0.22
4	99.01 ±0.67	99.03 ±0.47	98.19 ± 0.22	98.10 ± 0.32
5	98.68 ±0.87	98.28 ±0.37	97.24 ± 0.42	97.11 ± 0.62
6	97.38 ±0.57	97.18 ±0.27	96.14 ± 0.42	96.24 ± 0.42

The stability studies of the formulation F10 conducted at 30±2°C and 75% RH and 40±2°C with 75% RH revealed that no any significant changes in the drug content uniformity the values were ranging from 99.42±0.87 and 97.18 ±0.27 , % CDR the values were ranging from 99.24 ± 0.42 and 96.24 ± 0.42.

4. SUMMARY:

The present study is an attempt to select the best possible diluent - disintegrant combination to formulate Oral disintegrating tablets of Dolutegravir, which disintegrates in matter of seconds in the oral cavity, thereby reducing the time of onset of pharmacological action. In present research work, starch phthalate a novel super disintegrant was prepared using potato starch and phthalic anhydride. INDION 414, SSG and Lycoat, were used as disintegrants MCC used as Binder and Sodium saccharin is used as sweetener and Magnesium stearate and talc were used as lubricant and glidant respectively. The results of the drug – excipient compatibility studies i.e FTIR spectrum, DSC and XRD studies for Pure and Optimized formulation revealed that there was no chemical interaction between the pure drug and excipients. The precompression parameters like bulk density, tapped density, Carr's index and angle of repose were determined. All the formulations showed acceptable flow properties. The post compression parameters like the hardness, thickness, friability and weight variation, wetting time, disintegration time, and Invitro release were carried out and the values were found to be within IP limits. The percentage drug content of all the tablets was found to be between 86.45±1.75-99.42±0.87% of Dolutegravir, which was within the acceptable limits. Among all the formulations F10 shows 99.24±1.85% drug release within 5minutes. The Formulation F10 contains Starch Phthalate (20mg) and SSG (5mg), Lycoat(5mg) it shows better drug release when compared to other formulations. So, F10 was considered as the optimized formulation.

Thus, starch phthalate (10%) showed more dissolution efficiency in 5min. So, starch phthalate found to be an effective super disintegrant for the preparation of fast dissolving tablets. The drug release kinetics shows that the optimized formulation F10 follows First order kinetics. The n value was found to be 0.482 is shows that drug release follows non-Fickian transport.

5. CONCLUSION:

In the current efforts have been made to formulate and evaluate Oral disintegrating tablets of Dolutegravir using Starch phthalate as super disintegrant by a direct compression method. The results disclosed that increased amount of various super disintegrants were associated with an increase in overall rate of cumulative drug release. Of all 11 formulations, F10 formulation with 20 mg of Starch Phthalate exhibited maximum cumulative drug release in 5 min. In addition, formulation F10 also showed, short wetting time good drug content, fast disintegration and fast dissolution rate and followed first order as an ideal fitting model. Stability studies conducted also revealed no any significant changes in the drug content uniformity, % CDR. Henceforth, we concluded that formulated Dolutegravir sodium ODTs can be one of the better choices for the management of HIV-1 infection with enhanced patient compliance and rapid onset of action.

Conflicts of Interest

The authors declare no conflicts of interest.

6. REFERENCES:

1. Jaysukh J Hirani, Dhaval A Rathod, Kantilal R Vadalia. Tropical Journal of Pharmaceutical Research, April 2009; 8 (2), 161-172.
2. RakeshPahwa, Mona Piplani, Prabodh C Sharma, Dhirender Kaushik, SanjuNanda.Orally disintegrating tablets- Friendly to Pediatrics and gediatrics.Arch. Apll. Sci. Res., 2010; 2(2), 35-48.
3. Dhandapani N.V., El-gied A.A. Solid dispersions of cefixime using β-cyclodextrin: Characterization and in vitro evaluation. Int. J. Pharmacol. Pharm. Sci. 2016;10:1523–1527
4. Chaturvedi S., Alim M., Agrawal V.K. Solubility and dissolution enhancement of domperidone using 2-hydroxypropyl- β - cyclodextrin by kneading method. Asian J. Pharm. 2017;11:168–175.
5. Sekiguchi K., Obi N. Studies on absorption of eutectic mixture. I. A comparison of the behavior of eutectic mixture of sulfathiazole and that of ordinary sulfathiazole in man. Chem. Pharm. Bull. (Tokyo) 1961;9:866–872. doi: 10.1248/cpb.9.866.
6. https://go.drugbank.com/drugs/DB08930
7. Nagarajan J. S. K., Muralidharan S. A validated RP-HPLC method for estimation of Domperidone in pharmaceutical formulation. Der Pharmacia Lettre, 2009, 1(1):162-168.
8. Jabbaribar F, Mortazavi A, Jalali-Milani A, Jouyban A. Analysis of Domperidone in Tamiflu® Capsules Using Micellar Electrokinetic Chromatography. Chem Pharm Bull., 2008, 56:1639-1644.
9. Validation of Analytical Procedures, Methodoly, ICH Harmonised tripartite guidelines; 1996:1.
10. V. Metker, A. Kumar, N. Pathak, K. Padhee, and S. Sahoo, "Formulation and evaluation of orodispersible tablets of lornoxicam," International Journal of Drug Development and Research, vol. 3, no. 1, pp. 281–285, 2011.
11. A. Arya, S. Sharma, J. Kumar, A. Chandra, and P. Jaiswal, "Formulation and evaluation of mouth dissolving tablets of ranitidine

HCL," International Journal of Pharm Tech Research, vol. 2, no. 2, pp. 1574–1577, 2010.
12. R. B. Parmar, A. H. Baria, H. M. Tank, and S. D. Faldu, "Formulation and evaluation of domperidone fast dissolving tablets," International Journal of PharmTech Research, vol. 1, no. 3, pp. 483–487, 2009.
13. B. Senthilnathan and A. Rupenagunta, "Formulation development and evaluation of venlafaxine hydrochloride orodispersible tablets," International Journal of Pharmaceutical Sciences and Research, vol. 2, no. 4, pp. 913–921, 2011.
14. P. B. Anjankumar, M. Nazmuddin, U. Kulkarni, and R. C. Hariprasanna, "Formulation and evaluation of lornoxicam fast dissolving tablet," International Research Journal of Pharmacy, vol. 2, no. 4, pp. 130–133, 2011.
15. Setty CM, Prasad DVK, Gupta VRM. Development of fast dispersible aceclofenac tablets: Effect of functionality of superdisintegrants. Indian Journal of Pharmaceutical Sciences, 70, 2008, 180–185.
16. Yang S, Fu Y, Jeong SH, Park K. Application of poly (acrylicacid) superporous hydrogel microparticles as asuperdisintegrant in fast disintegrating tablets. Journal of Pharmacology 2004;56:429-36.
17. Ozeki T, Yasuzawa Y, Katsuyama H, Takshima Y, Kasai T, Eguchi T. Design of rapidly disintegrating oral tablets using acid-treated yeast cell wall: A technical note. AAPS Pharm Sci Tech 2003;4.
18. Bhagwati ST, Hiremath SN, Sreenivas SA. Comparative evaluation of disintegrants by formulating cefixime dispersible tablets. Indian J Pharm Edu Res 2005; 39(4): 194- 7.
19. Raghavendra Rao NG, Patel T, Gandhi S. Development and evaluation of Carbamazepine fast dissolving tablets prepared with a complex by direct compression technique. Asian J Pharm 2009; 97-103.
20. Higuchi T. Mechanism of sustained action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J PharmSci 1963; 51: 1145-9.
21. Peppas NA. Analysis of Fickian and non-fickian drug release from polymer. PharmActaHelv 1985; 60: 110-11.
22. Kumari A, Kumar RS. Synthesis and characterization of starch malonate: development of fast dissolving tablets of aceclofenac by 23 factorial designs. International journal of applied pharmaceutics. 2021 may 7:87-102.
23. Umalkar DG, Shinde GV, Bangale GS, KS R, Murthy RS. Design and Evaluation of Orodispersible Tablet of Aceclofenac Using Different Superdisintegrants by 2 3 Factorial Designs. Magnesium. 2010 Apr 28;50(50):50.