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Research Article

**FORMULATION AND *IN VITRO* CHARACTERIZATION OF
DOLUTEGRAVIR SUSTAINED RELEASE MATRIX TABLETS****Pravat Ranjan Guru, Sachidananda Satapathy, Sujit Kumar Mohanty, Somnath
Behera, Rajat Kumar Kar**Department Of Pharmaceutics, Dadhichi College Of Pharmacy,
Vidya- Vihar, Sundargram, Odisha 754002.**Abstract:**

The present study aimed to develop and in vitro characterize sustained-release matrix tablets of dolutegravir to achieve prolonged plasma levels and improve patient adherence. Dolutegravir matrix tablets were prepared by direct compression using hydrophilic and hydrophobic polymers (selected polymer(s) specified in the main text) to modulate drug release. Pre-compression evaluation of powder blends, including bulk density, tapped density, compressibility index, Hausner ratio, and angle of repose, demonstrated acceptable flow and compressibility consistent with Indian Pharmacopoeia (IP) specifications. Post-compression quality attributes—weight variation, hardness, thickness, friability, assay, and content uniformity—also complied with IP limits, confirming reproducible tableting and mechanical robustness. In vitro dissolution studies performed in simulated gastrointestinal media showed sustained release of dolutegravir over the targeted time period, with the optimized formulation exhibiting a controlled release profile and fitting the (specify: Higuchi/Korsmeyer–Peppas/zero-order) kinetic model, indicating release predominantly by (diffusion/erosion/swelling) mechanisms. Stability-indicating assessments under accelerated and short-term conditions revealed no significant deviations in drug content, physical appearance, or release behaviour. Collectively, the results indicate that the optimized dolutegravir sustained-release matrix tablets meet pharmacopeial quality criteria and demonstrate predictable in vitro performance.

Keywords : Dolutegravir; sustained-release matrix tablet**Corresponding author:****Pravat Ranjan Guru,**Department Of Pharmaceutics, Dadhichi College Of Pharmacy,
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INTRODUCTION¹⁻⁹:

Sustained release tablets are commonly taken only once or twice daily, compared with counterpart conventional forms that may have to take three or four times daily to achieve the same therapeutic effect. The advantage of administering a single dose of a drug that is released over an extended period of time to maintain a near-constant or uniform blood level of a drug often translates into better patient compliance, as well as enhanced clinical efficacy of the drug for its intended use. The first sustained release tablets were made by Howard Press in New Jersey in the early 1950's. The first tablets released under his process patent were called 'Nitroglyn' and made under license by Key Corp. in Florida. Sustained release, prolonged release, modified release, extended release or depot formulations are terms used to identify drug delivery systems that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. The goal in designing sustained or sustained delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. So, sustained release dosage form is a dosage form that release one or more drugs continuously in predetermined pattern for a fixed period of time, either systemically or to a specified target organ. Sustained release dosage forms provide a better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery. There are certain considerations for the preparation of extended release formulations:

- ✓ If the active compound has a long half-life, it is sustained on its own,
- ✓ If the pharmacological activity of the active is not directly related to its blood levels,
- ✓ If the absorption of the drug involves an active transport and
- ✓ If the active compound has very short half-life then it would require a large amount of drug to maintain a prolonged effective dose.

The above factors need serious review prior to design.

Introduction of matrix tablet as sustained release (SR) has given a new breakthrough for novel drug delivery system in the field of Pharmaceutical technology. It excludes complex production procedures such as coating and Pelletization during manufacturing and drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the preparations. Hydrophilic polymer matrix is widely used for formulating an SR dosage form. Because of increased complication and expense involved in marketing of new drug entities, has focused greater attention on development of

sustained release or controlled release drug delivery systems. Matrix systems are widely used for the purpose of sustained release. It is the release system which prolongs and controls the release of the drug that is dissolved or dispersed.

In fact, a matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers. By the sustained release method therapeutically effective concentration can be achieved in the systemic circulation over an extended period of time, thus achieving better compliance of patients. Numerous SR oral dosage forms such as membrane controlled system, matrices with water soluble/insoluble polymers or waxes and osmotic systems have been developed, intense research has recently focused on the designation of SR systems for poorly water soluble drugs.

1.1. RATIONALE FOR EXTENDED RELEASE DOSAGE FORMS¹⁰⁻¹²:

Some drugs are inherently long lasting and require only once-a-day oral dosing to sustain adequate drug blood levels and the desired therapeutic effect. These drugs are formulated in the conventional manner in immediate release dosage forms. However, many other drugs are not inherently long lasting and require multiple daily dosing to achieve the desired therapeutic results. Multiple daily dosing is inconvenient for the patient and can result in missed doses, made up doses, and noncompliance with the regimen. When conventional immediate-release dosage forms are taken on schedule and more than once daily, they cause sequential therapeutic blood level peaks and valleys (troughs) associated with the taking of each dose. However, when doses are not administered on schedule, the resulting peaks and valleys reflect less than optimum drug therapy. For example, if doses are administered too frequently, minimum toxic concentrations of drug may be reached, with toxic side effects resulting. If doses are missed, periods of sub therapeutic drug blood levels or those below the minimum effective concentration may result, with no benefit to the patient. Extended-release tablets and capsules are commonly taken only once or twice daily, compared with counterpart conventional forms that may have to be taken three or four times daily to achieve the same therapeutic effect. Typically, extended-release products provide an immediate release of drug that promptly produces the desired therapeutic effect, followed by gradual release of additional amounts of drug to maintain this effect over a predetermined period (Fig.1).

The sustained plasma drug levels provided by extended-release products oftentimes eliminate the need for night dosing, which benefits not only the patient but the caregiver as well.

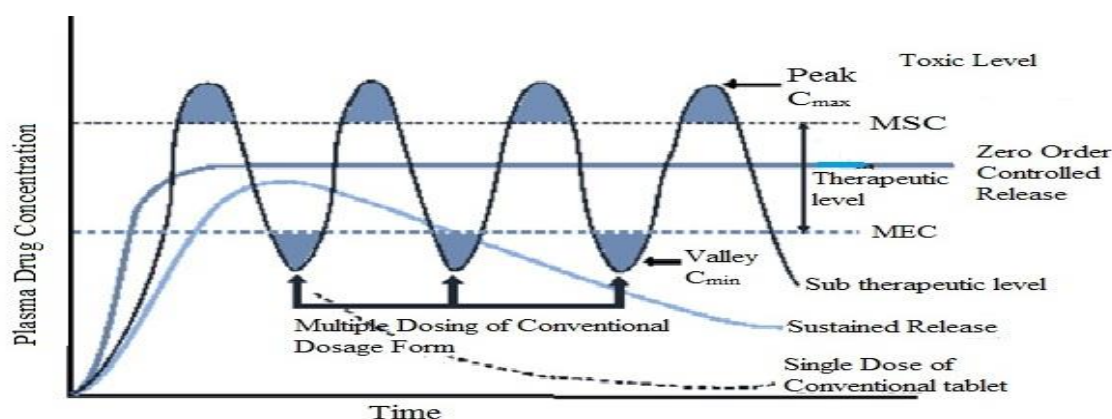


Figure 1.1: Hypothetical plasma concentration-time profile from conventional multiple dosing and single doses of sustained and controlled delivery formulations.

1.2. Drawbacks of Conventional Dosage Forms¹³:

1. Poor patient compliance, increased chances of missing the dose of a drug with short half-life for which frequent administration is necessary.
2. A typical peak-valley plasma concentration time profile is obtained which makes attainment of steady-state condition difficult.
3. The fluctuations in drug levels may lead to precipitation of adverse effects especially of a drug with small Therapeutic Index (TI) whenever over medication occur.

METHODOLOGY:

Analytical method development:

Determination of λ_{max} :

100mg of pure drug was dissolved in 10ml methanol (primary stock solution - 1000 $\mu\text{g/ml}$). From this primary stock solution 1 ml was pipette out into 100 ml volumetric flask and made it up to 100ml with the media (Secondary stock solution-100 $\mu\text{g/ml}$). From secondary stock solution again 1ml was taken it in to another volumetric flask and made it up to 10 ml with media (working solution - 10 $\mu\text{g/ml}$). The working solution was taken for determining the wavelength.

Determination of calibration curve:

100mg of pure drug was dissolved in 10ml methanol (Primary stock solution - 1000 $\mu\text{g/ml}$). From this primary stock solution 10 ml was pipette out into 100 ml volumetric flask and made it up to 10ml with the media (Secondary stock solution - 100 $\mu\text{g/ml}$). From secondary stock solution required

concentrations were prepared (shown in Table 8.1 and 8.2) and those concentrations absorbance were found out at required wavelength.

Preformulation parameters

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Indian Pharmacopoeia.

Angle of repose:

The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose was calculated using the following formula:

$$\tan \theta = h / r$$

$\tan \theta$ = Angle of repose

h = Height of the cone,

r = Radius of the cone base

Table 7.1: Angle of Repose values (as per USP)

Angle of Repose	Nature of Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Bulk density:

Density is defined as weight per unit volume. Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm³. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment. 10 gm powder blend was sieved and introduced into a dry 20 ml cylinder, without compacting. The powder was carefully leveled without compacting and the unsettled apparent volume, V_o, was read.

The bulk density was calculated using the formula:

$$\text{Bulk Density} = M / V_o$$

Where, M = weight of sample

V_o = apparent volume of powder

Tapped density:

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this was repeated until difference between succeeding measurement is less than 2 % and then tapped volume, V measured, to the

nearest graduated unit. The tapped density was calculated, in gm per L, using the formula:

$$\text{Tap} = M / V$$

Where, Tap= Tapped Density

M = Weight of sample

V= Tapped volume of powder

Measures of powder compressibility:

The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it is measures of the relative importance of interparticulate interactions. In a free- flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value.

For poorer flowing materials, there are frequently greater interparticle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index which is calculated using the following formulas:

$$\text{Carr's Index} = [(\text{tap} - b) / \text{tap}] \times 100$$

Where, b = Bulk Density

Tap = Tapped Density

Table 7.2: Carr's index value (as per USP)

Carr's index	Properties
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair to Passable
2 – 35	Poor
33 – 38	Very Poor
>40	Very Very Poor

Formulation development of Tablets:

All the formulations were compress by direct compression. The compositions of different formulations are given in Table 7.4. The tablets were prepared as per the procedure given below and aim is to prolong the release of Dolutegravir. Total weight of the tablet was considered as 300mg.

Procedure:

- 1) Dolutegravir and all other ingredients were individually passed through sieve no ≠ 60.
- 2) All the ingredients were mixed thoroughly by triturating up to 15 min.
- 3) The powder mixture was lubricated with talc.
- 4) The tablets were prepared by using direct compression method.

Table 7.3: Ingredients and Uses

Ingredients	Uses
Dolutegravir	API
Tragacanth	Binding Agent
Acacia gum	Binding Agent
Xanthan gum	Binding Agent
PVP-K 30	Binding Agent
Aerosil	Diluent
Magnesium Stearate	Lubricant
Lactose	Anticaking agent

Table 7.4: Formulation composition for tablets

INGREDIENTS (MG)	FORMULATION								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Dolutegravir	50	50	50	50	50	50	50	50	50
Tragacanth	50	100	150	-	-	-	-	-	-
Acacia gum	-	-	-	50	100	150	-	-	-
Xanthan gum	-	-	-	-	-	-	50	100	150
PVP-K 30	10	10	10	10	10	10	10	10	10
Aerosil	5	5	5	5	5	5	5	5	5
Magnesium Stearate	4	4	4	4	4	4	4	4	4
Lactose	181	131	81	181	131	81	181	131	81
Total Weight	300	300	300	300	300	300	300	300	300

Evaluation of post compression parameters for prepared Tablets

The designed formulation tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

sustained release tablets of Dolutegravir using various polymers. All the formulations were evaluated for physicochemical properties and *in vitro* drug release study.

Analytical method

Graphs of Dolutegravir were taken in 0.1N HCL and in pH 6.8 phosphate buffer at 259 nm and 263 nm respectively.

RESULTS & DISCUSSION:

The present study was aimed to developing

Table 8.1: Observations for graph of Dolutegravir in 0.1N HCL

Concentration (µg/ml)	Absorbance
0	0
5	0.155
10	0.302
15	0.439
20	0.576
25	0.698

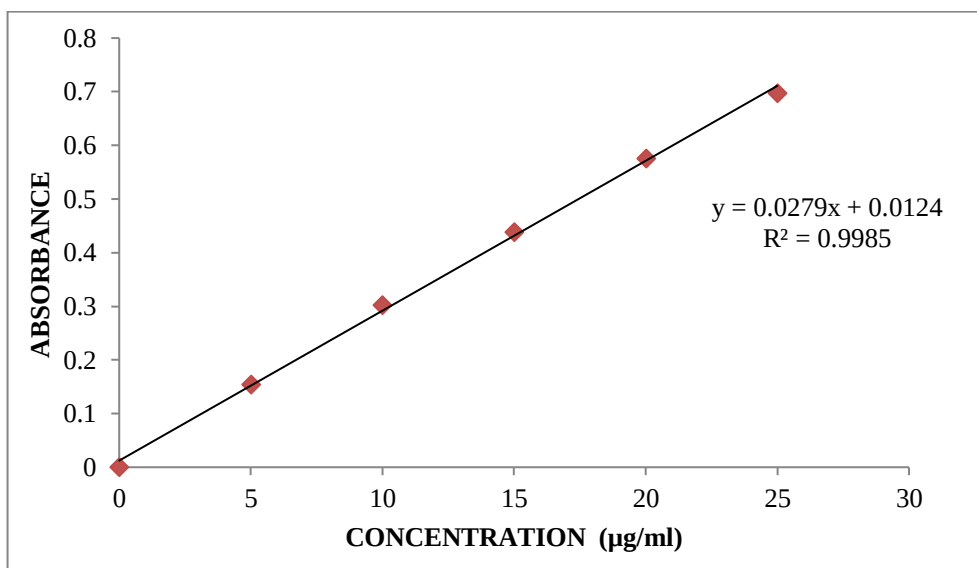
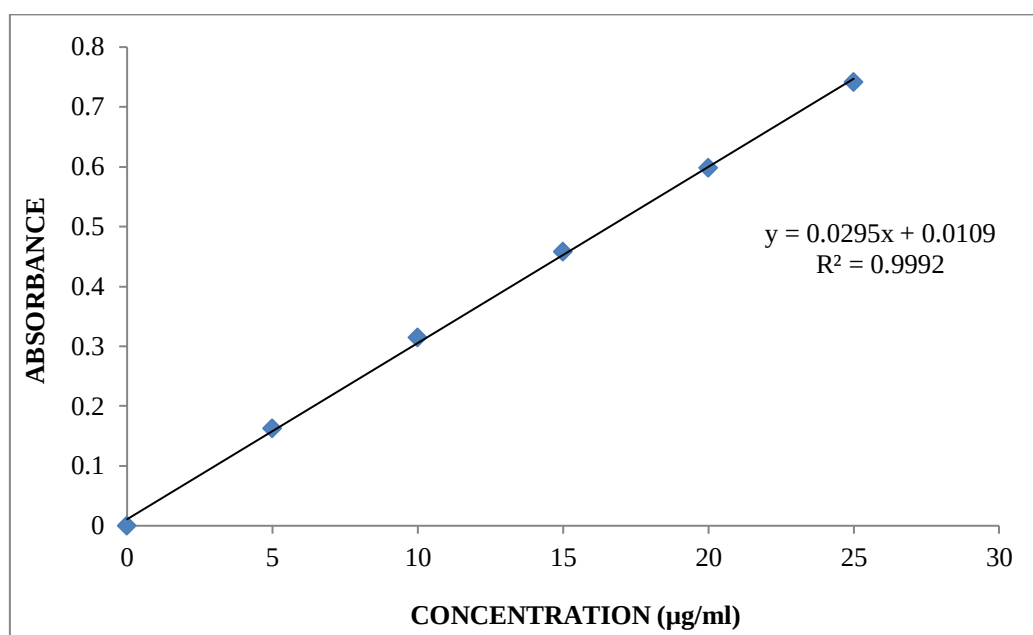


Fig 8.1: Standard curve of Dolutegravir

Table 8.2: Standard graph values of Dolutegravir at 263 nm in pH 6.8 phosphate buffer

Concentration (µg/ml)	Absorbance
0	0
5	0.163
10	0.314
15	0.458
20	0.598
25	0.741

**Fig 8.2: Standard curve of Dolutegravir****Preformulation parameters of powder blend****Table 8.3: Pre-formulation parameters of Core blend**

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	25.56±0.3	0.57±0.01	0.61±0.01	10.11±0.8	1.13±0.02
F2	24.67±0.3	0.53±0.01	0.68±0.03	10.23±0.5	1.12±0.03
F3	25.56±0.2	0.52±0.06	0.64±0.03	10.34±1.0	1.14±0.06
F4	23.30±0.1	0.50±0.21	0.66±0.12	10.23±0.5	1.12±0.06
F5	22.56±0.1	0.65±0.02	0.59±0.02	11.23±0.8	1.11±0.05
F6	23.89±0.2	0.50±0.04	0.68±0.04	11.34±0.6	1.14±0.03
F7	26.54±0.1	0.59±0.04	0.64±0.05	10.12±0.7	1.13±0.09
F8	23.67±0.3	0.58±0.12	0.58±0.04	10.23±1.0	1.11±0.07
F9	24.34±0.4	0.56±0.02	0.54±0.01	10.23±0.8	1.13±0.02

All the values represent n=3

Tablet powder blend was subjected to various preformulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range showing that the powder has good flow properties. The tapped density of all the formulations powders has good flow properties. The compressibility index of all the formulations was found to be 10.11 to 11.34 which

show that the powder has good flow properties. All the formulations have shown the hausner ratio 1.11 to 1.14 indicating the powder has good flow properties.

Quality control parameters for tablets:

Tablet quality control tests such as weight variation, hardness, friability, thickness, and drug release studies in different media were performed on the compression tablet.

Table 8.4: Quality control parameters for tablets

Formulation codes	Weight variation (mg)	Hardness (kg/cm ²)	Friability (% loss)	Thickness (mm)	Drug content (%)
F1	299.85	5.1	0.58	3.21	98.12
F2	300.05	5.6	0.42	3.69	99.27
F3	297.61	5.8	0.36	3.47	100.00
F4	298.47	6.1	0.34	3.22	95.34
F5	299.83	5.0	0.29	3.98	96.87
F6	300.02	6.3	0.20	3.45	99.31
F7	299.87	5.0	0.41	3.28	97.24
F8	296.50	5.2	0.52	3.11	98.62
F9	299.75	5.8	0.44	3.72	95.40

Weight variation test:

Tablets of each batch were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet. The average weight of the tablet is approximately in range of 296.50 to 300.05 mg, so the permissible limit is $\pm 7.5\%$ (>300 mg). The results of the test showed that, the tablet weights were within the limit.

Hardness test:

Hardness of the five tablets of each batch was checked by using Pfizer hardness tester and the data's were shown in Table 8.4. The results showed that the hardness of the tablets is in range of 5.0 to 6.3 kg/cm², which was within IP limits.

Thickness:

Thickness of five tablets of each batch was checked by using Micrometer and data shown in

Table-8.4. The result showed that thickness of the tablet is ranging from 3.11 to 3.98 mm.

Friability:

Tablets of each batch were evaluated for percentage friability and the data were shown in the Table-8.4. The average friability of all the formulations was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets.

Drug content:

Drug content studies were performed for the prepared formulations. From the drug content studies it was concluded that all the formulations were showing the % drug content values within 95.40 – 100.00 %.

All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

IN VITRO DRUG RELEASE STUDIES

Table 8.5: Dissolution data of Dolutegravir tablets F1-F9

Time (H)	% OF DRUG RELEASE								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.5	20.62	18.38	16.23	14.97	11.82	15.31	11.22	13.49	9.07
1	35.81	30.14	24.38	20.65	16.31	18.38	17.38	15.21	13.31
2	42.20	36.63	35.79	28.16	21.23	24.43	22.45	19.07	21.03
3	46.39	42.82	40.88	36.98	26.96	31.86	29.59	26.17	24.12
4	53.85	50.40	47.54	43.29	34.35	39.75	37.83	35.56	31.13
5	60.34	58.09	58.17	52.73	42.02	48.46	43.26	42.58	39.09
6	67.13	65.46	64.62	65.22	50.75	55.13	53.15	51.27	48.17
7	78.91	71.02	73.93	72.73	58.13	60.16	61.29	59.68	55.24
8	82.28	78.59	78.87	78.40	63.84	67.77	66.76	67.37	64.36
9	90.96	82.36	82.26	85.01	71.22	73.85	73.27	71.77	68.81
10	96.21	88.11	87.15	88.58	81.09	80.49	78.19	77.42	75.63
11	98.56	95.78	91.02	92.96	87.56	85.88	84.64	82.12	79.43
12		99.19	95.14	95.63	93.75	92.16	95.49	89.28	87.19

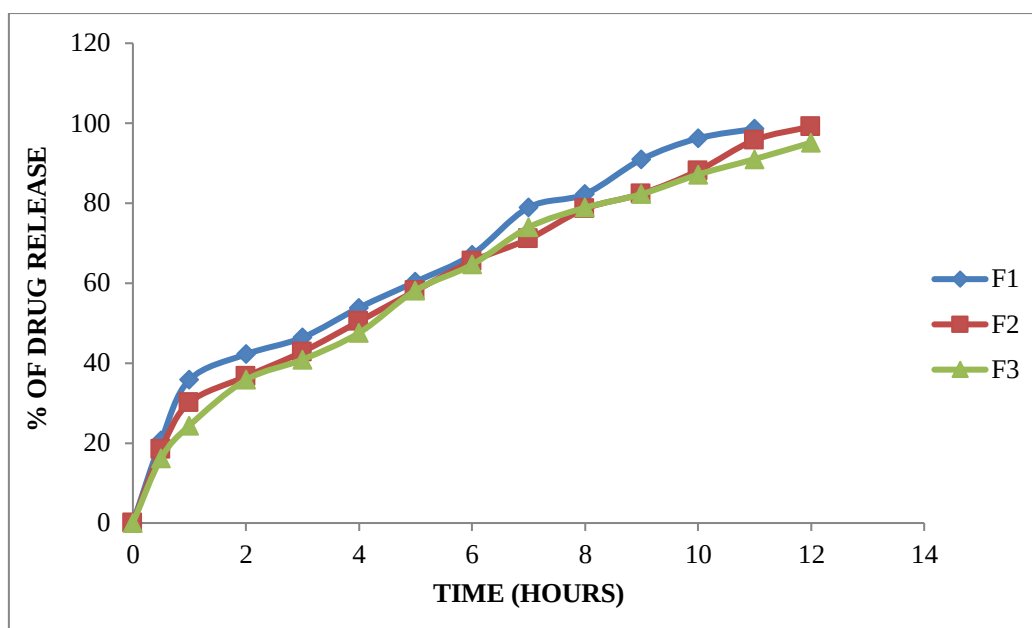


Fig 8.3: Dissolution profile of Dolutegravir (F1, F2 and F3 formulations)

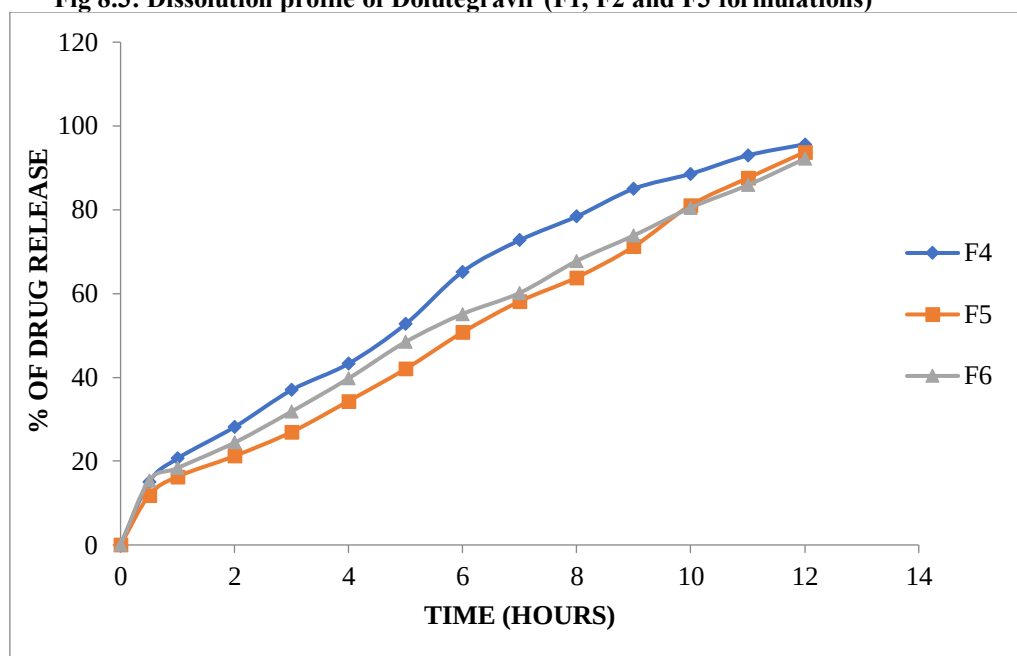


Fig 8.4: Dissolution profile of Dolutegravir (F4, F5 and F6 formulations)

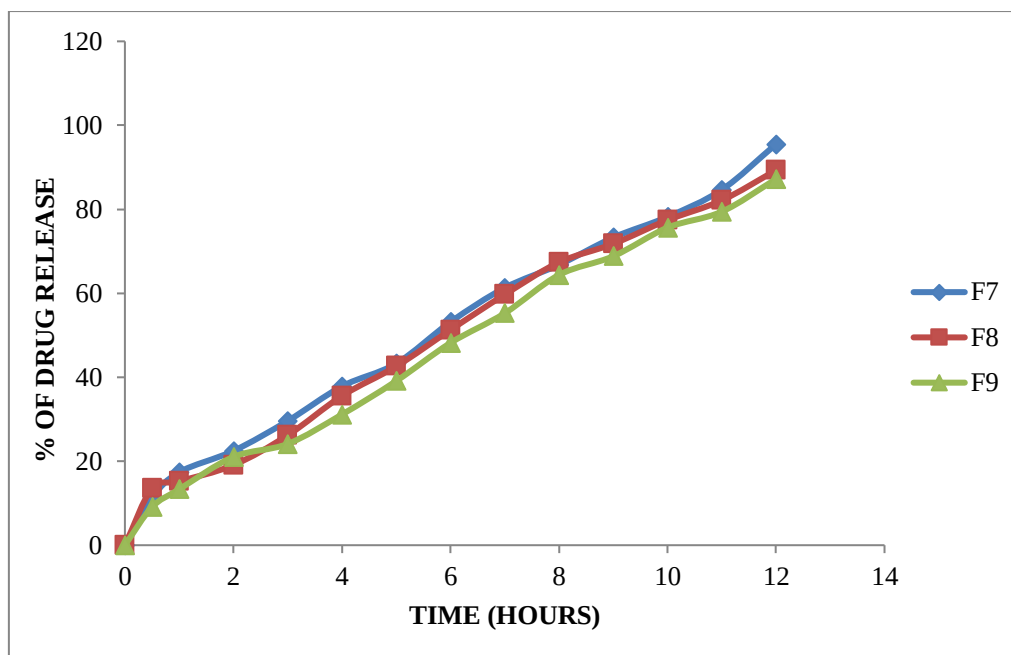


Fig 8.5: Dissolution profile of Dolutegravir (F7, F8 and F9 formulations)

Different formulations (F1-F9) were prepared using different polymers like Tragacanth, Acacia gum and Xanthan gum alone at different ratios. Formulations F1-I3 were prepared using Tragacanth at the ratio of 1:1, 1:2 and 1:3 which showed the drug release about 98.56% at 11h, 99.19% at 12h and 95.14 at 12h %.

Formulations F4-F6 were prepared using Acacia gum at the ratio of 1:1, 1:2 and 1:3 with the drug release of 95.63%, 93.75 and 92.16 % and the formulations F7-F9 were prepared by using Xanthan gum polymer at the ratio of 1:1, 1:2 and 1:3. Showed the drug release of 95.49 %, 89.28 % and 87.19 % at the end of 12 h. Among all these formulations F2 was selected as the best ideal formulation which exhibited 99.19 % of drug release in 12 h.

Finally Concluded that F2 formulation was considered as optimized formulation.

Table 8.6: Release kinetics:

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
18.38	0.5	0.707	1.264	0.301	1.912	36.760	0.0544	-0.736	81.62	4.642	4.338	0.304
30.14	1	1.000	1.479	0.000	1.844	30.140	0.0332	-0.521	69.86	4.642	4.119	0.523
36.63	2	1.414	1.564	0.301	1.802	18.315	0.0273	-0.436	63.37	4.642	3.987	0.655
42.82	3	1.732	1.632	0.477	1.757	14.273	0.0234	-0.368	57.18	4.642	3.853	0.789
50.4	4	2.000	1.702	0.602	1.695	12.600	0.0198	-0.298	49.6	4.642	3.674	0.967
58.09	5	2.236	1.764	0.699	1.622	11.618	0.0172	-0.236	41.91	4.642	3.474	1.168
65.46	6	2.449	1.816	0.778	1.538	10.910	0.0153	-0.184	34.54	4.642	3.257	1.385
71.02	7	2.646	1.851	0.845	1.462	10.146	0.0141	-0.149	28.98	4.642	3.072	1.570
78.59	8	2.828	1.895	0.903	1.331	9.824	0.0127	-0.105	21.41	4.642	2.777	1.865
82.36	9	3.000	1.916	0.954	1.246	9.151	0.0121	-0.084	17.64	4.642	2.603	2.038
88.11	10	3.162	1.945	1.000	1.075	8.811	0.0113	-0.055	11.89	4.642	2.282	2.359
95.78	11	3.317	1.981	1.041	0.625	8.707	0.0104	-0.019	4.22	4.642	1.616	3.026
99.19	12	3.464	1.996	1.079	-0.092	8.266	0.0101	-0.004	0.81	4.642	0.932	3.709

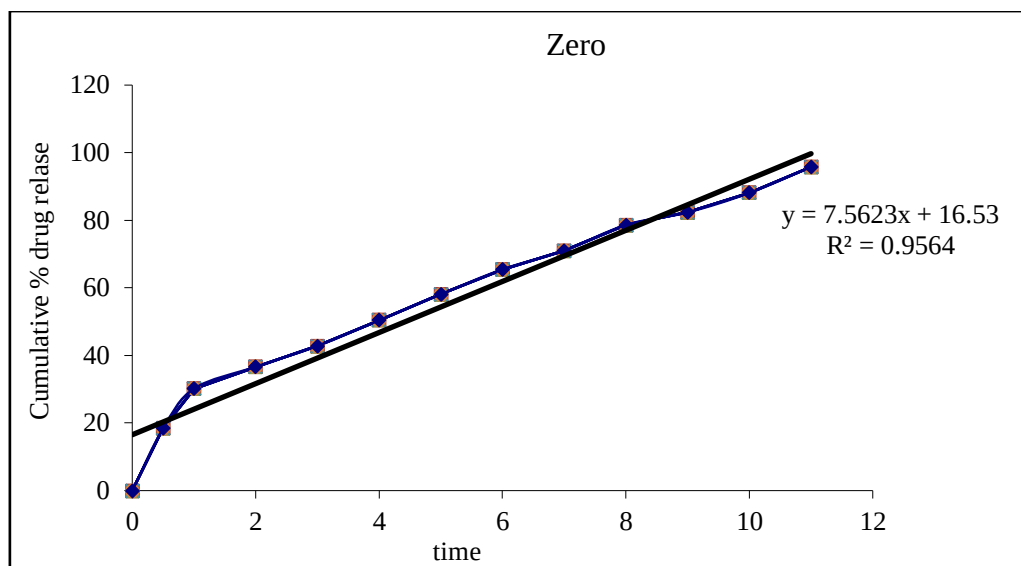


Figure 10.6: Zero order release kinetics graph

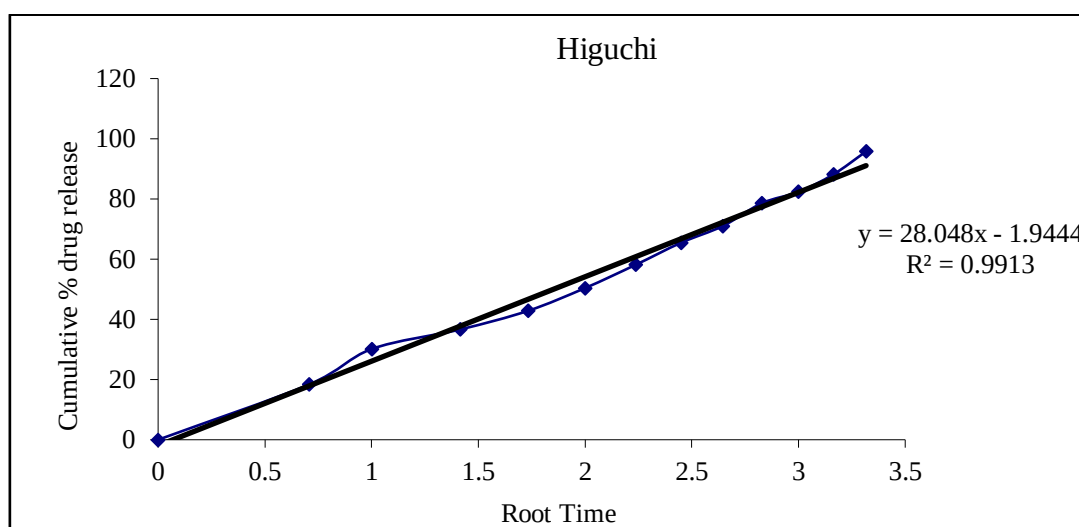


Figure 8.7: Higuchi release kinetics graph

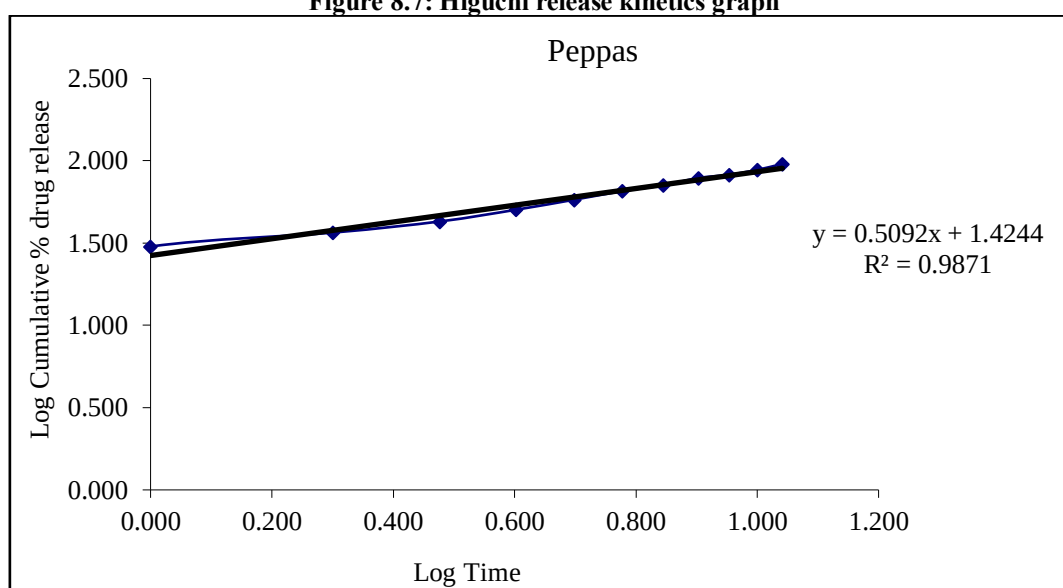


Figure 8.8: Peppas release kinetics graph

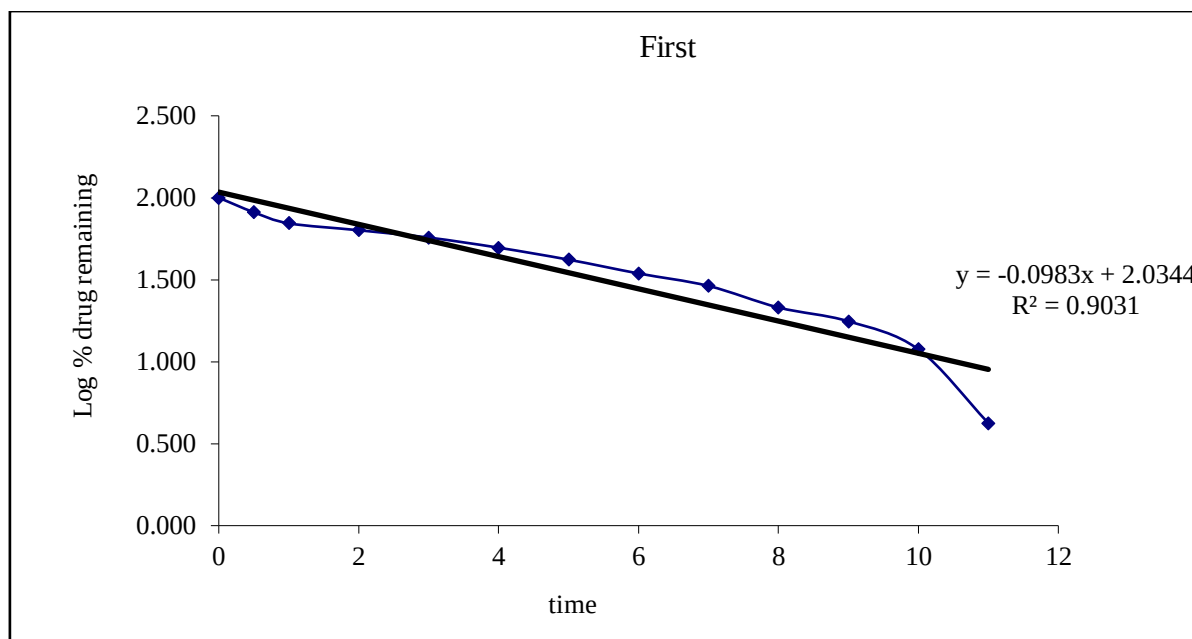


Figure 8.9: First order release kinetics graph

Table 8.7: kinetics Correlation coefficient values

Release kinetics	Correlation coefficient values
Zero order release kinetics	$R^2 = 0.956$
Higuchi release kinetics	$R^2 = 0.991$
Peppas release kinetics	$R^2 = 0.987$
First order release kinetics	$R^2 = 0.903$

From the above graphs it was evident that the formulation F2 was followed Higuchi release kinetics mechanism.

Drug – Excipient compatibility studies

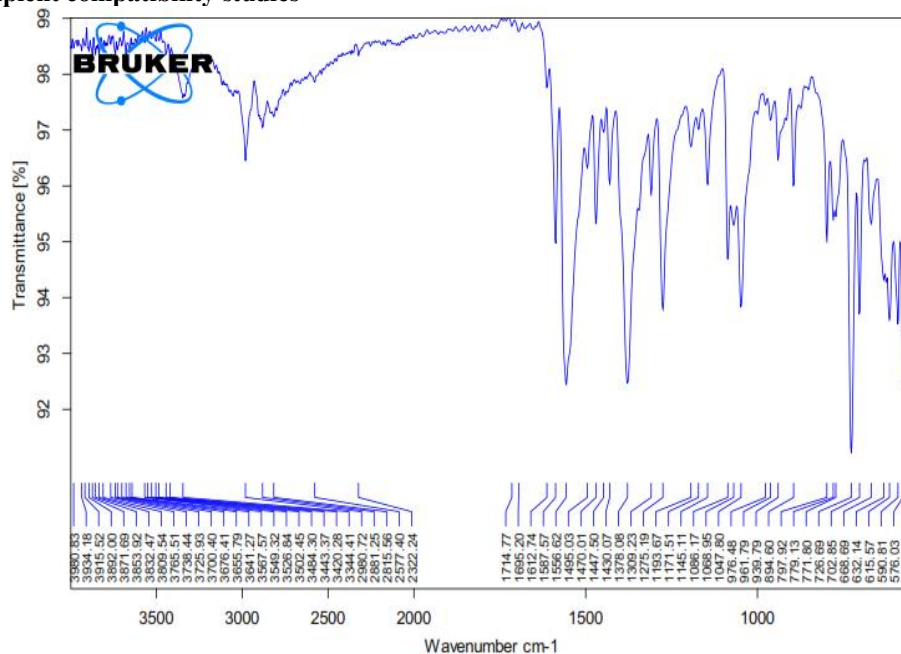


Figure 8.10: FT-TR Spectrum of Dolutegravir pure drug

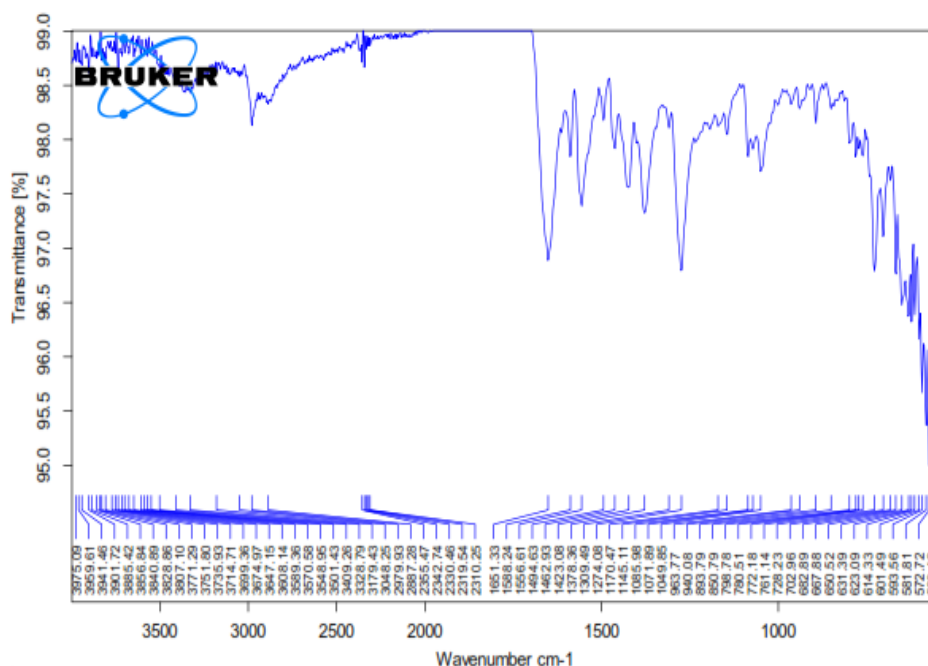


Figure 8.11: FT-IR Spectrum of Optimized Formulation

From the above studies it was found that there was no shifting in the major peaks which indicated that there were no significant interactions occurred between the Dolutegravir and excipients used in the preparation of different Dolutegravir Sustained release formulations. Therefore the drug and excipients are compatible to form stable.

Formulations under study, The FTIR spectra of Dolutegravir and physical mixture used for optimized formulation were obtained and these are depicted in above figures. From the FTIR data it was evident that the drug and excipients does not have any interactions. Hence they were compatible.

CONCLUSION:

In this study, sustained-release matrix tablets of dolutegravir were successfully formulated and characterized. All pre-compression parameters (flow properties, bulk and tapped densities, compressibility index, and angle of repose) and post-compression attributes (weight variation, hardness, friability, thickness, drug content, and uniformity) complied with Indian Pharmacopoeia specifications, indicating robust manufacturability and consistent tablet quality. In vitro dissolution testing demonstrated controlled and prolonged release of dolutegravir over the intended timeframe, with release kinetics best fitting (specify model—e.g., Korsmeyer–Peppas/ Higuchi/zero-order) suggesting that drug release is governed primarily by (diffusion/erosion/swelling) mechanisms. The optimized matrix composition provided desirable mechanical strength while maintaining sustained drug release, supporting its potential to improve dosing frequency and patient adherence. Stability-

indicating parameters remained acceptable under the tested conditions, further confirming the formulation's suitability for development.

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