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Formulation and Evaluation of Dolutegravir Sodium Controlled Release Tablets

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***Abstract*: The present of this research work to develop Dolutegravir sodium 200 mg controlled release tablets. This is a second-generation HIV drug and it is comes under anti-retroviral category. In this work six formulations are selected for design Dolutegravir sodium controlled release formulations by using direct compression method and then the formulations are prepared by using different concentrations hydrophobic polymer and different ingredients are used as fillers to develop the formula. The granules and tablets are evaluated by pre-compression, post-compression and In-vitro dissolution studies. Based on the dissolution studies F6 was selected as an optimized formula because of it gives best results in controlled by drug release manner and best fitted to order of kinetics.**

***Keywords*: Dolutegravir (DTG), HPMC K15M, Carbopol 971G, micro crystalline cellulose (MCC), controlled release tablets**

1. Introduction

A. Controlled Release Drug Therapy

For many decades treatment of acute diseases or chronic illnesses have been mostly accomplished by delivery of drugs to patients using various pharmaceutical dosage forms including tablets, capsules, suppositories, creams, ointments, liquids, aerosols and inject able. Present nova a day's these controlled release dosage forms most use full technology for the improve the release rate. In the oral route the control drug delivery drug delivery systems are well recognized to give on time release of the drug. So to achieve to maintain the drug concentration and therapeutically more effective. Different types of drug delivery systems are available now a days but the controlled drug delivery system is more affect for the compare the other drug delivery systems. This results in a significant fluctuation in drug levels often with a sub-therapeutic and or toxic levels and wastage of drug. Recently several technical advancements have resulted in the development of new systems of drug delivery capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and targeting the delivery of drug to a tissue. Dolutegravir is an HIV-1 antiviral agent. It inhibit HIV integrate by compulsory to the vigorous site and overcrowding the strand move step of retroviral DNA addition in the host cell. The thread conveys step is necessary in the HIV duplication cycle and results in the reserve of viral activity.

2. Materials and Methods

Dolutegravir sodium (Hetero Drugs Limited, Hyderabad), Carbopol (971G) (Chemiloids, Vijayawada), HPMC K15M (Chemiloids, Vijayawada), Micro crystalline cellulose (Chemiloids, Vijayawada) Sodium Stearyl Fumarate (S.D. Fine Chem limited, Mumbai), Talc (Reidel Chemicals, Hapur) and Magnesium stearate (S.D. Fine-Chem limited, Mumbai.)

A. Methods: Pre- formulation studies

1) Bulk Density (Db)

It is the ratio of the mass of powder to the bulk volume of powder. It was measured by pouring the weight powder into a measuring cylinder and the volume was noted. It is expressed in gm/ml and is given by

$$Db = M/Vb$$

Where, M= mass of powder. Vb=bulk volume of the powder.

2) Tapped density (Dt)

It is the ratio of total mass of powder to the tapped volume of powder. The tapped volume was measured by tapping the powder to constant volume. It is expressed in gm/ml and is given by

$$Dt = M/Vt$$

Where, M=mass of powder. Vt=tapped volume of the powder.

3) Carr's Index (I)

It in dictates the ease with which a material can be induced to flow. It is expressed in percentage and is given by

$$I= Dt-Db/Dt*100$$

Where, Dt = tapped density of the powder. Db = bulk density of the powder.

4) Angle of Repose (θ)

The friction force sin loose powder can be measured by the angle of repose θ.Itis side fine das maximum angle possible between the surface of a pile of powder and the horizontal plane.

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

Where θ = is the angle of repose, h = is the height, r = is the

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radius. The powder mixture was allowed to flow through the funnel fixed to a stand at definite height. The angle of repose was then calculated by measuring the height and radius of the heap of powder formed.

B. FT-IR Spectral studies

The IR spectra for the formulation excipients and pure drugs were recorded onJasco FT-Infrared spectrophotometer using KBr palette technique (1:100) at their solution rate of 4cm-1. Spectrum was integrated in transmittance mode at the wave number range 400-4000 cm-1utions were.

C. Differential scanning calorimetry

Conventional DSC and MTDSC experiments were performed using DSC Q200 (TA Instruments, NJ, USA) with a refrigerated cooling assembly (RCS) and a modulated capability. The DSC cell was purged with 50 ml/min dry nitrogen, and the RCS was purged with 150 ml/min nitrogen. The DSC cell was calibrated for baseline using empty pans of matched weight and for temperature using three temperature standards (cyclohexane, Tm = 279.54o K; indium, Tm = 429.61o K; tin Tm = 504.93o K). About 3-5 mg of samples was exposed to the desired heating rates from the desired starting temperature to above the melting point of Dolutegravir under dry nitrogen purging (50 ml/min) in hermetically sealed aluminum pans. The data was analyzed using Universal Analysis Software from TA Instruments

D. Analytical method development for Dolutegravir sodium

1) U. V Spectrophotometer

Calibration curve of the pure drug Dolutegravir sodium was prepared in the concentration range from 2-10 µg/ml at the wave length of 254 nm by using 6.8 phosphate buffer solutions. Based on the Beer' lamberts law the graph was plotted between the absorbance vs concentration. The calibration curve showed good linearity and regression coefficient (r^2) value is 0.999, and intercept 0.005.

2) Preparation of standard Stock solution of Dolutegravir sodium

100 mg of Dolutegravir sodium was dissolved in 100 ml of 6.8 phosphate buffer in a100 ml volumetric flask and made up to the volume with 6.8 phosphate buffer. From this 1 ml of solution was taken and made to 100 ml with 6.8 phosphate buffer.

3) Method

For the estimation of Dolutegravir sodium in 6.8 phosphate buffer the stock solution has to be diluted subsequently with 6.8 phosphate buffer to get a series of dilutions containing 2, 4, 6, 8, 10 µg/ml of solution. The absorbance of the drug solution was measured at 254 nm. The calibration curve was constructed.

4) Formulation of Dolutegravir sodium controlled release tablets

Dolutegravir sodium controlled release tablets were prepared by direct compression method. Six formulations of tablets each containing 200 mg dose of Dolutegravir sodium. Were prepared with different concentrations of various excipients which were shown in given below. Dolutegravir sodium and polymers such as Carbopol 971G, and HPMC k15 M were accurately weighed, mixed uniformly and passed through # 40 meshes. Microcrystalline Cellulose is used as diluents were weighed accurately and passed through #40 meshes. Both were mixed properly and the mixture of Talc and sodium Stearyl Fumarate and magnesium stearate 1:1 ratio was added and mix for few minutes. Then the above mixture was compressed in to tablets by using station rotary compressed machine with punch size of 8 mm.

E. Evaluation of Dolutegravir sodium controlled release tablets

1) Physical appearance

The Physical emergence of tablets is resolute by visual inspection by which involve the quantity of number of factors such as size, shape, colour, odour, taste, surface touch and recognition symbols there on the tablet.

2) Weight variation test

The weight variation test is performed by taking 20 tablets from each formulation and weighing the individual tablets by using electronic balance. Their average weight was calculated as

% weight variation = (WA- WI) ×100/ WI

Where,

WI = Individual weight of the tablets

WA = Average weight of the tablet

3) Thickness

The thickness of the tablets was calculated by vernier calipers. Take Five tablets from each batch and to evaluate average value are considered.

4) Hardness (kg/cm^2)

Hardness test was conducted by using a Monsanto hardness tester. Each batch contains Five tablets are selected and then find out each tablet hardness.

5) % Friability

The Roche friabilator is used for the determination of %friability. In this test Ten tablets were weighed initially (w1) and placed in the friabilator that revolves at a speed of 25 RPM, dropping those tablets at a distance of six inches height with each revolution and rotated in the friabilator for 100 revolutions. Behind achievement of rotations the tablets be dedusted and weighed (w^2).

% Friability = (IW-FW)/ IW × 100

6) Drug content

Ten tablets were taken and amount of drug present in each tablet was determined as follows: Tablet was crushed in mortar and transferred to a 100 ml flask. The powder was dissolved buffer medium. The sample was mixed by using Sonicated for 5 minutes, after which it was filtered through what man's filter paper. The filtered solutions after appropriate dilution (1to10 ml) with PH 6.8 phosphate buffer were analyzed by the validated UV Spectrophotometric method at λmax 254 nm.

7) In-vitro dissolution studies

In-vitro dissolution study was performed by using USP type II dissolution test apparatus (paddle type) [Lab, India (DS-8000, Mumbai)] at 100 RPM. 900ml of phosphate buffer of pH 6.8was used as the dissolution medium which was maintained

Table 1
Formulation of Dolutegravir sodium controlled release tablets

Ingredients mg/tab	Formulation					
	F1	F2	F3	F4	F5	F6
API (Dolutegravir sodium)	100	100	100	100	100	100
Carbopol 971G	30	40	50	---	---	---
HPMC k15 M	---	---	---	30	40	50
Microcrystalline Cellulose	64	54	44	64	54	44
Talc	2	2	2	2	2	2
sodium Stearyl Fumarate	2	2	2	2	2	2
Mg stearate	2	2	2	2	2	2
Total weight (mg)	200	200	200	200	200	200

Table 2
Weight variation specifications (B.P)

Average Wt of the Tablets	Maximum difference allowed
Less than 130	5
130-324	7.5
More than 324	10

Table 3
Weight variation specifications (I.P)

Average weight of tablet(mg)	Percentage deviation
130 or less	10
130 to 324	7.5
More than 324	5

Table 4
Micromeritic properties of the granules of Dolutegravir Sodium formulation

Formulation code	Bulk density (g/ml)	Tapped density (g/ml)	Hausner's ratio	Angle of repose(o)	Compressibility
F1	0.510	0.634	1.31	23.01	18.20
F2	0.491	0.626	1.32	24.18	18.30
F3	0.500	0.622	1.29	25.11	20.57
F4	0.510	0.632	1.28	23.23	21.42
F5	0.508	0..640	1.27	25.17	22.80
F6	0.509	0..636	1.22	23.15	23.75

at 37±0.5ºC. Aliquots of dissolution medium (5mL) were withdrawn at specific time intervals (1hr, 2hr, 4hr, 8hr, 12hr, 16hrand 20 hr) and were filtered. The amount of drug dissolved was determined by UV spectrophotometer by measuring the absorbance of the sample at 254 nm.

3. Results and Discussion

Formulations of sustained release tablets of Dolutegravir sodium are prepared by using hydrophobic polymers like HPMCK15and Carbopol 971G was impact on In- Vitro dissolution rate.

Pre-formulation studies: The Active pharmaceutical ingredient and excipients were blended and evaluated for different parameters as clarified before. Bulk density was found in the limit of 0.491-0.510 g/cm3 and the tapped density between 0.622 -0.640 g/cm3. By using both density data Carr's compressibility was determined. The compressibility record was found between 18.20 -23.75 % and the Hausner's ratio were found to be 1.22-1.32. The result shows good flow properties of blend. The good flow properties of powder were also evident from angle of repose that range from 27.56-30.21°. In the present examination all powder mixes indicated excellent flow property. The outcomes are appeared in Table no 2.

A. Pre – compression parameters: FT-IR Spectral studies

1) FT-IR studies

From the FT-IR spectra, it was concluded that similar characteristic peaks with minor difference for the drug and the FT-IR formulation. Hence, it appears that there was no chemical interaction between the drugs and excipients used. The IR Spectra of with, HPMCK15, Carbopol 971G shown. The following peaks were observed in as well as Dolutegravir Sodium with excipients.

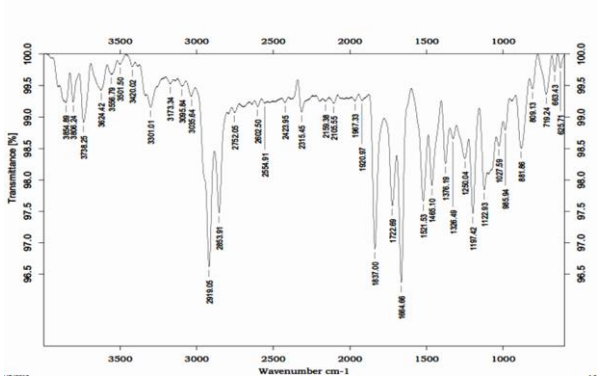

Fig. 1. FT-IR Reports of Dolutegravir Sodium

Table 6
Post compression parameters of Dolutegravir Sodium controlled release tablets

Formula	Weight Variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	% Friability (% loss)	Drug content
F1	203.1	2.00	3.6	0.352	99.3 ± 0.65
F2	204.1	2.10	3.9	0.172	98.2 ± 0.65
F3	202.1	2.35	3.8	0.101	99.6 ± 0.65
F4	199.5	2.21	3.7	0.132	99.5 ± 0.65
F5	198.3	2.13	3.2	0.142	99.4 ± 0.65
F6	202.3	2.28	3.3	0.122	99.3 ± 0.65

Table 7
Dissolution studies for Dolutegravir Sodium controlled release tablets

Dissolution with pH 6.8 phosphate buffer, 900ml, RPM 100, λ max 254 nm							
% Cumulative Drug Release							
S. no	Time (hr)	F1	F2	F3	F4	F5	F6
1.	0	0	0	0	0	0	0
2.	1hr	10.79	14.07	16.43	25.05	18.15	12.20
3.	2hr	15.50	25.24	28.14	36.24	40.20	36.21
4	3hr	28.39	31.55	36.40	51.33	53.35	58.36
5	4hr	41.35	39.57	42.50	63.21	65.57	69.61
6	8hr	59.63	48.96	51.82	78.90	71.96	78.83
7	12hr	65.89	56.02	62.98	82.32	79.46	85.39
8	16hr	72.28	69.19	70.34	89.81	84.76	93.88
9	20 hr	82.71	73.61	76.77	94.23	92.30	100.35

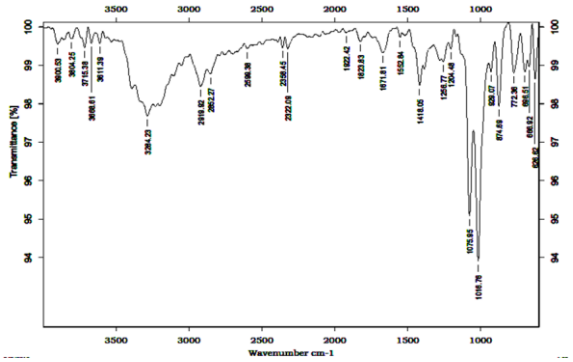

Fig. 2. FT-IR Reports for optimized formula

2) Differential scanning calorimetry

DSC indicated better drug stability presence of hydrophobic polymers. A stronger drug amorphization and entrapment in hydrophobic polymers was observed.

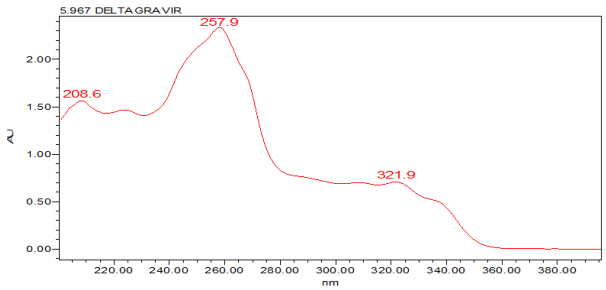

Fig. 3. DSC Reports for Dolutegravir Sodium

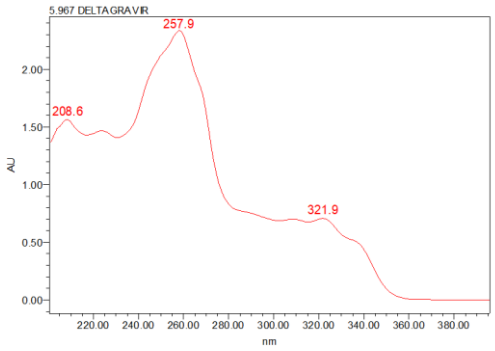

Fig. 4. DSC Reports for Dolutegravir Sodium Optimized Formula

3) Analytical method development

Dolutegravir Sodium was estimation using UV/VIS spectrophotometer method. It was found that under UV/VIS spectrophotometer standard absorbance of the peak of Dolutegravir Sodium was 0.311 µg/ml.

Table 5
Standard Calibration Curve for the Dolutegravir Sodium in 6.8 pH phosphate buffer

S. No	Concentration (µg/ml)	Absorbance(nm)
1	2(µg/ml)	0.102
2	4(µg/ml)	0.206
3	6(µg/ml)	0.311
4	8(µg/ml)	0.424
5	10(µg/ml)	0.538

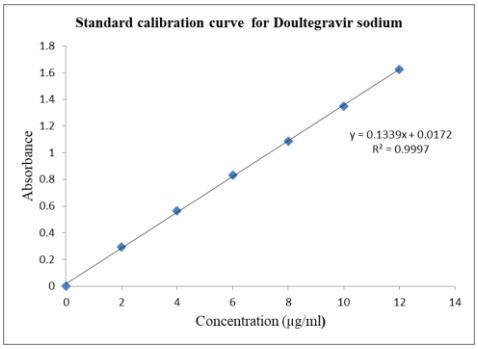

Fig. 5. Standard Calibration Curve for the Dolutegravir Sodium in 6.8 pH phosphate buffer

4) Post – compression parameters

The preliminary studies were carried out by preparing various formulations with different process variable and subjecting the formulation to all post-compression parameters has fulfilled according to IP standards.

5) Weight variation

Average weight of 20 tablets of Dolutegravir Sodium was calculated for each formulation which varied from mg 203±1to 198±3 mg the complied the official requirements as per IP.

6) Tablet thickness

The thickness of the Dolutegravir Sodium formulation varied from 2.00±0.06 mm to 2.28±0.06mm

7) Tablet hardness (kg/cm^2)

The hardness of the tablet developed formulation shows 3.6. ±1.0 kg/cm^2.

8) %Friability

The friability of the developed formulation varied from 0.352±0.1% to 0.101±0.01% loss which was less than 1% as per official requirement of IP.

B. Drug content

The drug content of the developed formulation shows 93.5%

1) Post – compression parameters: In-Vitro Dissolution studies of Dolutegravir Sodium controlled release tablets

In-vitro dissolution study was performed by using USP type II dissolution test apparatus (paddle type) [Lab, India (DS-8000, Mumbai)] at 100 RPM. 900ml of phosphate buffer of pH 6.8was used as the dissolution medium which was maintained at 37±0.5oC. Aliquots of dissolution medium (5mL) were withdrawn at specific time intervals (1hr, 2hr, 4hr, 8hr, 12hr, 16hr and 20hr) and were filtered. The amount of drug dissolved was determined by UV- spectrophotometer by measuring the absorbance of the sample at 254 nm. The formulation F1,F2 and F3 contains the Carbopol (970G) was prepared in Dolutegravir Sodium controlled release tablets the drug released in formulation f1 is 82 % in 20hr, f2 formulation drug released is 73.61% in 20hr,F3 formulation drug released is 76 % in 20hr.

The formulation F4, F5, and F6 contains the HPMCK15 as a polymer in different concentration prepared by matrix coating techniques. The dissolution with the pH 6.8 phosphate buffers, F4 formulation the drug released was 94.23 % in 20 hr. F5 formulation the drug released was 92.30 % in 20 hr. F6 formulations the drug released was 100.35 % in 20hr. The optimized formulation F5 the prepared with HPMCK15 the dissolution medium was the PH 6.8 phosphate buffer the drug released in formulation F6 is 100.35 % in 20hr.

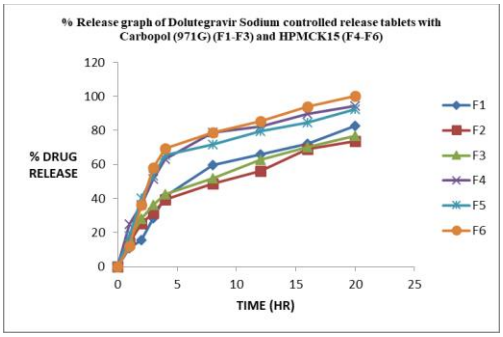

Fig. 6. %Release graph of Dolutegravir Sodium controlled release tablets with Carbopol 971G (F1-F3) and HPMCK15 (F4-F6)

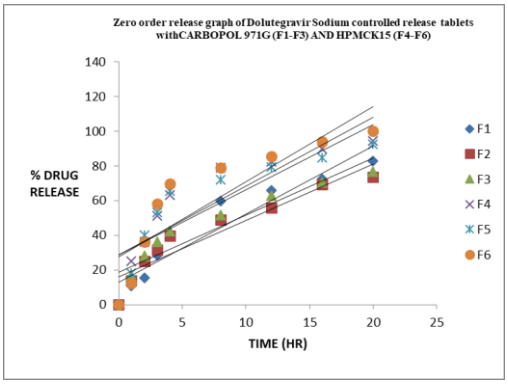

Fig. 7. Zero order release graph of Dolutegravir Sodium controlled release tablets with Carbopol 971G (F1-F3) and HPMCK15 (F4-F6)

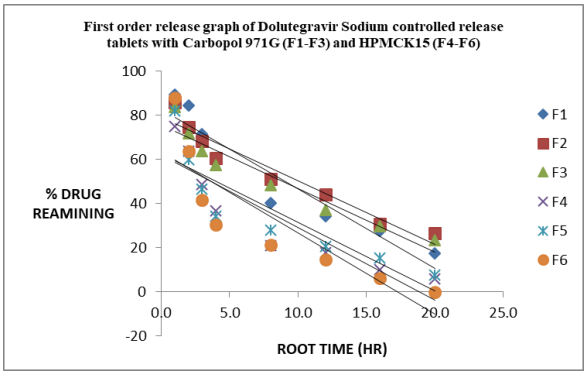

Fig. 8. First order release graph of Dolutegravir Sodium controlled release tablets with Carbopol 971G (F1-F3) and HPMCK15 (F4-F6)

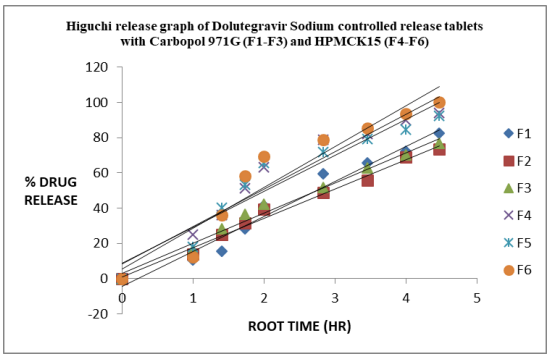

Fig. 9. Higuchi release graph of Dolutegravir Sodium controlled release tablets with Carbopol 971G (F1-F3) and HPMCK15 (F4-F6)

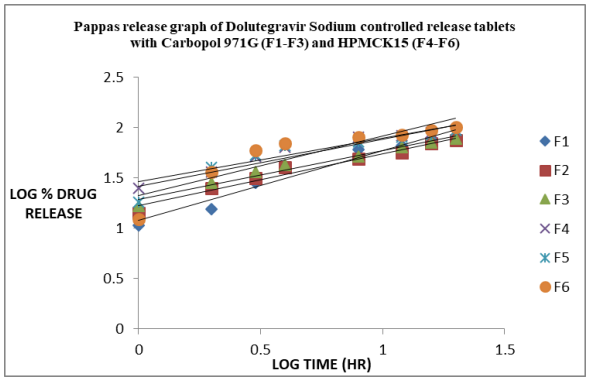

Fig. 10. Pappas release graph of Dolutegravir Sodium controlled release tablets with Carbopol 971G (F1-F3) and HPMCK15 (F4-F6)

C. Curve-Fitting Analysis

According to different kinetic models, the kinetics of the f1 and f6 drug release was evaluated by drug release rate models namely zero order, first order kinetics, and higuchi, papas mechanisms. The dissolution kinetics data was defected in table 8 and the comparative dissolution profile was given in the fig 6. The optimized formulation F4 showed highest R2 value i.e. 0.978 for zero order plots indicating that release of drug follows zero order kinetics, and mechanism of release was fitted to Korsmeyer peppas equation with the n value of 1.742 indicating anomalous non-fickian diffusion mechanisms and may indicate that the drug release is controlled by more than one process.

Table 8
Drug Release Rate Kinetics

	Correlation co-efficient			
Formulation	Zero order	First order	Higuchi	Pappas
F1 (C-917 G)	0.963	0.892	0.969	0.946
F2 (C-917 G)	0.981	0.889	0.988	0.969
F3 (C-917 G)	0.981	0.866	0.985	0.970
F4 (HPMC K15)	0.920	0.770	0.941	0.936
F5 (HPMC K15)	0.877	0.738	0.915	0.854
F6 (HPMC K15)	0.859	0.749	0.909	0.804

4. Conclusion

Dolutegravir Sodium was chosen as the model candidate for this study since it possess near ideal characteristics that a drug must have in formulating a controlled drug delivery system. It has high lipid solubility, effective in low plasma concentration and high degree of first pass metabolism. In this present study the tablets were prepared by using direct compression technique. All the formulations were evaluated for physical characteristics, pre-compression and post-compression, In-vitro dissolution studies. The pure drug Dolutegravir Sodium % drug release was found to be 100.35% at the end of 20th hour, when compared to pure drug release the F6 formulation showed 100.35 % drug release at the end of release time. Finally we have found that from all the formulations (F1-F6) only F6 formulation has successfully attained the sustained drug release for 20th hour. The optimized formulation F6 showed highest R2 value i.e. 0.978 for zero order plots indicating that release of drug follows zero order kinetics, and mechanism of release was fitted to higuchi equation with the n value of 1.742 indicating anomalous non-fickian diffusion mechanisms and may indicate that the drug release is controlled by more than one process.

Drug – excipients compatibility studies were conducted by FT-IR spectroscopy, results indicated that the Dolutegravir Sodium and polymers were found to be compatible. The micromeritic properties of granules were evaluated, all the formulations exhibited good flow properties. The evaluation parameters for the prepared tablets such as % weight variation, hardness, % friability, thickness and drug content were found to be in satisfactory limits. The maximum drug release was found to be 100.33% over a period of 20 hours in HPMC K15 M tablets. This indicates combination of HPMC K15M required preparing the controlled release tablets of Dolutegravir Sodium. All the formulations were also subjected to model fitting analysis to know the order and mechanism of drug release from the formulations by treating the data according to Zero order, First order, Higuchi and Peppas Equations, The data clearly shows that, the release kinetics revealed that the formulations containing HPMC K15M and Carbopol follows zero order release kinetics and release rate was controlled by Non-Fickian diffusion. Thus, in the present investigation, finally concluded that control release tablets of Dolutegravir Sodium were successfully designed by dry granulation method and evaluated. It can be concluded that HPMC K15M can be used as an effective former to control the release of Dolutegravir Sodium for the period of 20 Hours.

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