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Research Article

Solubility Enhancement, Formulation And Evaluation Of Dolutegravir

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ABSTRACT

Dolutegravir is an HIV-1 antiviral agent used to control HIV/AIDS. In the present study, Dolutegravir inclusion complexes have been subjected to improvement in solubility and dissolution rate performance by being formulated as immediate release tablets, in which β- CD were used as polymers. Inclusion complexes of dolutegravir were prepared with different ratios of dolutegravir and β-CD (1:0.5, 1:1, and 1:2) by the kneading method. The pre-compression and post-evaluation parameters were studied, and the results were shown. All the results were within acceptable IP limits. Finally, by comparing all the dissolution profiles of the inclusion complex, Formulation F2 containing Dolutegravir + β- CD (1:2) showed better results by the kneading method at the end of 45 min with maximum drug release; hence, it is selected as the best formulation. From the obtained optimized inclusion complex formulation, the Immediate release tablets were prepared by using different concentrations of various solubility enhancers and super disintegrants. The in-vitro drug releases of the formulated Dolutegravir tablets were performed using a 6.8 pH Phosphate buffer as a dissolution medium. The optimized F2 formulation contained Sodium starch glycolate (SSG) (6% w/w) as a super disintegrant, and it showed 99.75% drug release at 45 min. Characterization in the solid-state was done by analytical methods such as UV-visible and FT-IR studies.

INTRODUCTION

Solubility is a major physicochemical factor that affects drug absorption and its therapeutic efficiency. Solubility enhancement is the main area on which researchers have been focusing in recent days. Several methods, like the usage of polymers, super disintegrants, and formulations like inclusion and immediate release tablets, have been employed in solubility enhancement. Of all these, the preparation of inclusion complexes is the best choice for researchers, as they are easy to prepare, economical, and timesaving. They can be prepared by a simple kneading method. The miscibility of polymers with the drug plays a key role in the solubility enhancement of poorly soluble drugs. The present study aimed to

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formulate a dolutegravir inclusion complex using various polymers to improve its solubility and dissolution rate. Dolutegravir, an antiretroviral agent, mainly acts by inhibiting the enzyme HIV integrase, which is needed for the viral replication process. According to the Biopharmaceutical Classification Scheme, dolutegravir is considered a class II drug, i.e., a lipophilic and highly permeable compound. Therefore, it is possible to improve its bioavailability by increasing its apparent solubility in water through inclusion complex technology [5, 6]. The bioavailability of dolutegravir is approximately 34%. It is highly bound to plasma proteins. It has an approximate elimination half-life of 14 hours. Based on pharmacokinetic and pharmacodynamic parameters, Dolutegravir is selected as the drug of choice for the present study. The current study focused on the solubility enhancement of dolutegravir using inclusion complex technology.

MATERIAL AND METHODS

The following materials were used: Dolutegravir-API (B.M.R. Chemicals, Hyderabad) Sodium Starch Glycolate, Cross Carmellose Sodium, Microcrystalline Cellulose, Talc, and Magnesium Stearate (Modern Science, Nashik)

2.1 PREFORMULATION STUDIES

Pre-formulation studies were performed on the drug (API), which included solubility, melting point determination, and compatibility studies.

Solubility

The Solubility of Dolutegravir was observed in different solvents such as water, methanol, and **DMSO.**

Melting point Determination

The Melting point of the drug was determined by a melting point apparatus.

IR Spectroscopy

FTIR spectral analysis of pure drugs and polymers was carried out as physical mixtures. An observation was made to determine whether changes in the chemical constitution of the drug occurred after combining it with the polymer. The absorption maxima in the spectrum were compared with the reference spectrum.

2.2 PREPARATION OF INCLUSION COMPLEXATION

Kneading Method

The inclusion complex of Dolutegravir and Beta-cyclodextrins was prepared by the kneading method. In which distilled water was used to prepare drug: carrier complex in a mortar by grinding ingredients for half an hour. After grinding, the wet was mass left to air dry at room temperature for 48 hours with intermittent mixing and agitation. The complexes were made in different ratios with respect to drugs and carriers.

2.3 EVALUATION OF INCLUSION COMPLEX

Inclusion Complexation was evaluated and characterized by the following methods.

Percentage Practical Yield

The percentage practical yield was calculated to know the percent yield or efficiency of any method, which helps in the selection of an appropriate method of production. CD complexes were collected and weighed to determine practical yield from the following equation.

% yield = (theoretical mass (Drug+Carrier) / Practical mass Complex) / ×100

Drug content:

An accurately weighed 100 mg of Inclusion complex formulations was taken into a 50 ml volumetric flask and dissolved in 40 ml of methanol. The solution was made up to volume with methanol. The solution was then suitably diluted with pH 6.8 buffer and assayed for drug content using the UV spectrophotometric method at 260nm.

% Drug Content = WA/WT × 100

WA: actual drug content: WT: theoretical drug content.

2.4 EVALUATION OF PRE-COMPRESSION PARAMETERS OF INCLUSION COMPLEX

Flow properties such as angle of repose, bulk density, tapped density, and compressibility Index, which showed better release and solubility enhancement, were evaluated to determine the suitability for tablet formulation.

Angle of repose

Angle of repose was determined by the funnel method. The powders were allowed to flow through the funnel fixed to a stand at a definite height (h). The angle of repose (θ) was then calculated by measuring the height (h) and radius (r) of the heap of granules formed.

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

Bulk Density

Apparent bulk density was determined by pouring a weighed quantity of powder into a graduated cylinder and measuring the volume of packing.

$$\rho b = M / V$$

Tapped Density

Tapped density was determined by the tapping method. A weighed quantity of powder was placed in a graduated cylinder and tapped until no further change in volume of powder was noted and the volume of the tapped packing was noted.

$$\text{Tapped density} = \frac{\text{weight of the powder}}{\text{volume of the tapped packing}}$$

Compressibility Index

The compressibility of the powder was calculated by determining Carr's index and Hausner's ratio.

% Compressibility: tapped density-bulk density/tapped density× 100

Hausner's ratio= tapped density/bulk density

2.5 PREPARATION OF TABLET WITH DOLUTEGRAVIR COMPLEXATION

Direct Compression Method

Complexations were prepared by kneading method formulated into tablets by direct compression. In the case of direct compression, Sodium starch glycolate, Cross-carmallose sodium (5%), Microcrystalline Cellulose (5%), Talc (2%), and magnesium stearate (2%) were incorporated, respectively, as disintegrants and lubricants. All ingredients were thoroughly blended in a closed, dry plastic container. The blend of powders was compressed into tablets to a hardness of 4-5 kg/ sq.cm on a single-punch tablet machine (Rimek Mini Press 10STN, Karnavati).

2.6 EVALUATION OF TABLETS PHYSICO-CHEMICAL PROPERTIES

Thickness:

The tablet thickness was calculated using Vernier calipers. It is expressed as mm.

Hardness:

The hardness of the prepared tablets was estimated using a Monsanto hardness tester. Three tablets from each formulation batch were selected, and force is applied diametrically. It is expressed in kg/cm2.

Friability:

Roche friabilator was used for testing the friability of prepared fast dissolving tablets. It subjects the tablet to the combined effects of abrasion and shock in a plastic chamber revolving at 25 rpm for 4 minutes, or 100 revolutions. A preweighed sample (Wi) of tablets was placed in the friabilator and subjected to 100 revolutions. Tablets were dedusted using a soft muslin cloth and reweighed (Wf). The friability (F) is given by the formula.

% friability = (initial weight – weight after 100 revolutions) / initial weight x 100

Weight Variation:

Test Twenty tablets were selected randomly, and the average weight was determined. Then individual tablets were weighed and compared with the average weight. The comparison variation was within the I.P. limits; it passed the weight variation test.

Disintegration Time:

The disintegration time of the tablets was determined as per the Indian pharmacopoeia. The test was carried out using a tablet disintegration apparatus. Distilled water was used as a disintegrating medium at 37±0.2°C. The time required to obtain complete disintegration of all the tablets was noted.

Drug Content:

Five tablets were weighed and powdered using a glass mortar and pestle. An accurately weighed 100 mg of powder was taken into a 50 ml volumetric flask, dissolved in methanol, and the solution was filtered through Whatman Filter Paper No. 41. The filtrate was collected and suitably diluted with phosphate buffer at pH 6.8. The drug content was determined at 260 nm by a UV spectrophotometer.

In-vitro Drug Release Study:

The dissolution studies of tablets were performed using USP the dissolution apparatus type I. A dissolution study was performed in 900 mL of pH6.8. The stirring speed was 50 rpm, and the temperature was maintained at 37±0.5°C. The samples were withdrawn periodically and replenished with fresh dissolution medium. The samples were filtered, diluted, and analysed by a UV spectrophotometer at 260 nm.

3. RESULTS AND DISCUSSION

3.1 PREFORMULATION STUDIES

Solubility study:

Solubility of the drug Sample in Water, Chloroform and Methanol was examined.

Table No. 01 - Solubility profile of the drug

Drug	Water	Methanol	DMSO
Dolutegravir	Slightly soluble in water	Very slightly soluble	Sparingly soluble

Melting point:

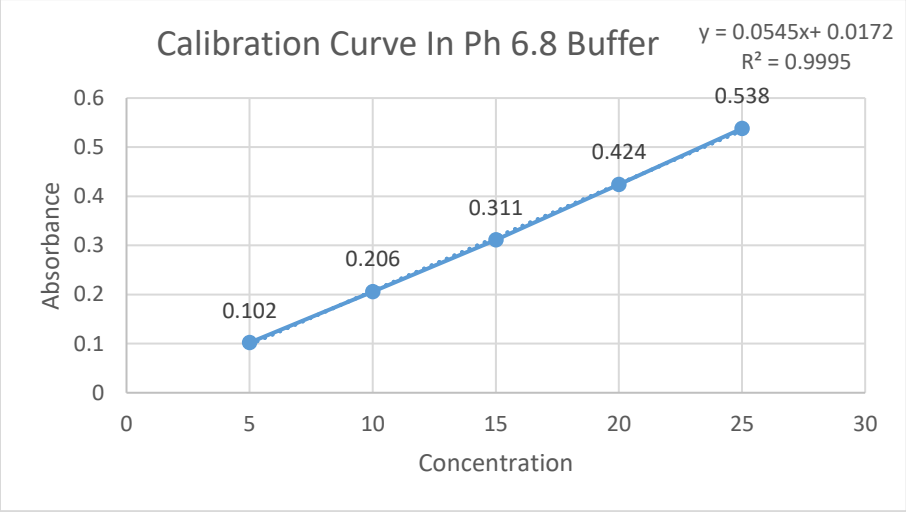
The melting point of the drug matches with the values found in literature.

Table No. 02 – Melting Point

Drug	Practical observed	Theoretical range
Dolutegravir	192°C -193°C	190°C-193°C

Standard calibration curve of Dolutegravir

Calibration curve of the pure drug Dolutegravir was prepared in the concentration range of 5-25mcg/ml at 260nm by using 6.8 phosphate buffer solutions. The calibration curve showed good linearity, with a regression coefficient (r2) value of 0.995 and an intercept of 0.0545.



FTIR Spectroscopy:

FTIR study of Dolutegravir was carried out to check out the purity of the drug. For this the powdered mixture of Dolutegravir and KBr was taken in a sampler and spectrum was recorded by scanning in wavelength region of 4000-400 cm-1using FTIR spectrophotometer. FTIR spectrum of Dolutegravir is shown in the Figure No. 2.

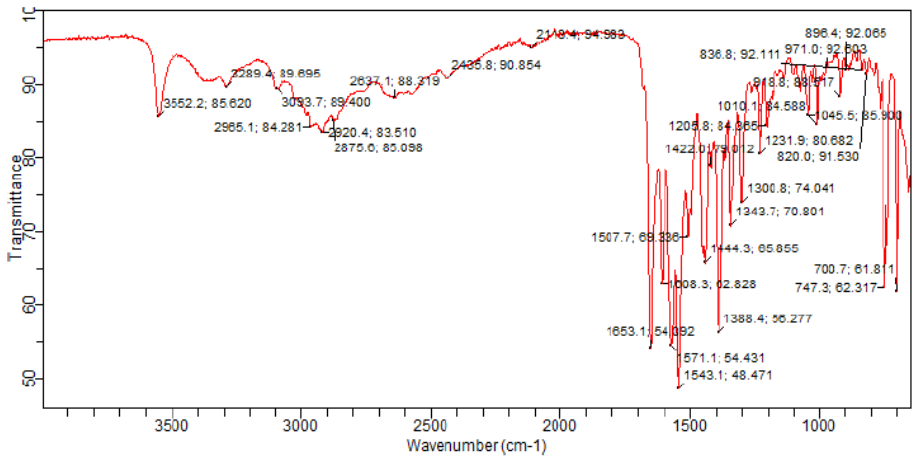


Figure: FTIR spectrum of Dolutegravir

3.2 Preparation of Inclusion Complex Method

Inclusion complex of Dolutegravir and Betacyclodextrin was prepared by using kneading the method. The composition of the dolutegravir inclusion complex is given below

Table No. 03 - Preparation of Inclusion Complex Method

CODE	COMPOSITION	RATIO	METHOD
KM1	DOLUTEGRAVIR: β- CD	1:0.5	KNEADINGMETHOD
KM2		1:1	
KM3		1:2	

3.3 EVALUATION OF INCLUSION COMPLEX

Percentage Yield:

The percentage yield of the prepared Inclusion complex of Dolutegravir was in the range of 85.70% to 88.76%, with the highest being for the formulation KM3, which was prepared by using β-CD. The percentage yield data for all formulations is shown in Table no 4.

Drug content:

The percent drug content of the prepared Inclusion complex of dolutegravir was in the range of 85.6% to 98.1%, with the highest being for formulation KM3, which was prepared by using β- CD. The percentage drug content data for all formulations is shown in Table no 4.

Table No. 04 - Percentage yield and drug content of Inclusion Complex

Formulation	Percentage yield (%)	Drug Content (%)
KM1	85.70	84.6
KM2	88.76	93.9
KM3	95.16	98.1

3.4 Evaluation of pre-compression parameters

Formulation	Angle of repose (θ)	Bulk Density (gm/ml)	Tap Density (gm/ml)	% Carr's Index	Hausner's Ratio
F1	28.59	0.58	0.66	11.76	1.13
F2	26.57	0.52	0.58	10.34	1.11
F3	27.26	0.53	0.58	17.18	1.20
F4	26.26	0.63	0.76	17.10	1.20

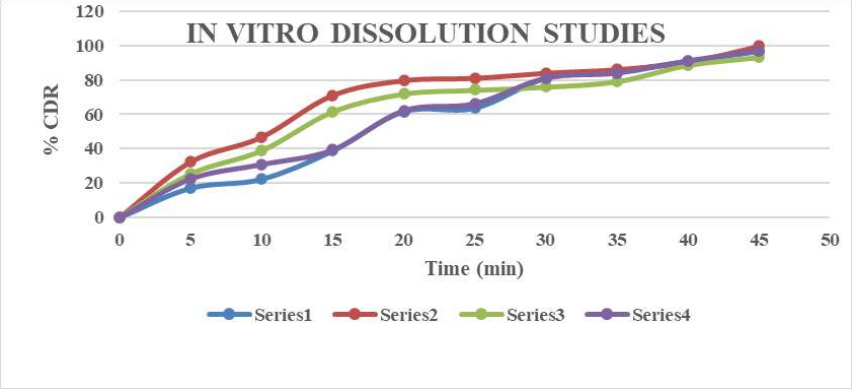
3.5 Evaluation of post compression parameters

Formulation	Weight variation (mg)	Hardness (kg/cm2)	Thickness (mm)	Friability (%)	Disintegration Time	Drug Content(%)
F1	199.4	3.4	2.58	0.9	2 min55 sec	74.4
F2	200.0	3.31	2.63	0.8	3 min 60 sec	89.1
F3	199.4	3.59	2.56	0.5	3 min 55 sec	77.3
F4	199.2	3.85	2.72	0.7	2 min 19 sec	86.7

All formulations were tested for physical parameters like hardness, thickness, weight variation, friability, disintegration, and drug content and found to be within the pharmacopeial limits. The results of the tests were tabulated.

3.6 In vitro Dissolution profile of different formulation (F1 to F4)

Time	F1	F2	F3	F4
5	17.20	32.39	25.49	22.48
10	22.37	46.85	39.01	30.89
15	38.77	71.15	61.57	39.32
20	61.59	79.79	72.02	62.11
25	63.59	81.15	74.20	66.16
30	80.95	84.11	76.05	80.98
35	85.03	86.16	79.21	83.40
40	90.80	90.44	88.73	90.97
45	96.52	99.75	93.34	96.99



Dissolution profile of Dolutegravir

Among all formulations, F2 shows better drug release when compared with all other formulations.

CONCLUSION

In this study, the increase in dissolution rates of the dolutegravir inclusion complex can be observed. Solubility studies showed a solubilizing effect of carriers on Dolutegravir. The preparation method of kneading could increase the solubility and dissolution rate of dolutegravir via the formation of the inclusion complex with β-CD. The most effective method in terms of Dolutegravir solubilization and drug content was the kneading method. From the above experimental results, it can be concluded that an immediate release tablet of Dolutegravir can be prepared by using beta-cyclodextrin and different proportions and combinations of solubility enhancers and superdisintegrants, and F2 was selected as the best formulation based on dissolution profile and physical characteristics. Formulation F2 showed 99.75% drug release in 45 minutes when compared to other formulations and showed good flow properties.

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