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Formulation Development and Evaluation of Self Nano Emulsifying Drug Delivery System of Dolutegravir

Suresh Mularam Choudhary[1], Prof S. A Waghmare[2], Hemant V. Kamble[3]

[1]M.Pharm, [3]Principal,

[1,2,3]Loknete Shri Dadapatil Pharate College of Pharmacy, Maharashtra, India

ABSTRACT

The primary objective of the work was to develop a self nano emulsifying drug delivery system of dolutegravir HCL. Self-nanoemulsifying drug delivery system is a lipid based formulation which consists of isotropic mixtures of oils, surfactants and co-surfactants. It can conveniently develop the emulsion on gentle agitation and offers a considerable surface area for interaction between the SNEDDS formulation and the aqueous gastrointestinal fluid. This may lead to enhanced bioavailability of hydrophobic agents. The Liquid SNEDDS was prepared and after that solidified by aerosil 200. For 10 gm of liquid SNEDDS; 5 gm of Aerosil 200 was used and after that product is dried by spray drying method. And 12 gm of product is remaining after the process. The drug-excipients interaction studies were carried out using FTIR and DSC. The interaction studies were carried out to check physical and chemical stability of Dolutegravir with other excipients. FTIR spectra showed the characteristic peaks of drug (i.e. for C-H stretch, N-C stretch) appear in the spectra of physical mixtures at the same wave number indicating no modification or interaction between drug and the polymers. The liquid SNEDDS formulation C1 showed good thermodynamic stability without any precipitation and having globule size 536.6 nm and zeta potential -29.9. Based on thermodynamic stability, precipitation studies, self-emulsification studies, globule size and zeta potential liquid SNEDDS of formulation batch C1 was selected as optimized formulation. Liquid SNEDDS and solid SNEDDS was prepared for Dolutegravir. SEM, IR, and DSC results confirmed that drug was present in an amorphous state in solid SNEDDS. In-vitro drug release and drug content of optimized formulation was found to be 98.64 and 99.35% respectively. F3 batch of capsule formulation shows better drug release than marketed formulation.

KEYWORDS: *Dolutegravir HCL, Self nano emulsifying drug delivery system, Solubility, Lipid*

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INTRODUCTION

Solubility is the property of a solid, liquid, or gaseous chemical substance called *solute* to dissolve in a solid, liquid, or gaseous solvent to form a homogeneous solution of the solute in the solvent. The extent of solubility of a substance in a specific solvent is measured as the saturation concentration where adding more solute does not increase its concentration in the solution. Solubility is based on the highest-dose strength of an immediate release product. A drug is considered highly soluble when the highest dose strength is soluble in 250mL or less of aqueous media over the pH range about 1 to 7

Oral ingestion is the most convenient and commonly employed route of drug delivery due to its ease of administration, high patient compliance, cost effectiveness, least sterility constraints, and flexibility in the design of dosage form. Orally administered drug completely absorb only when they show good solubility in GI fluids and such drugs shows good bioavailability. Bioavailability depends on several

factors, drug solubility in an aqueous environment and drug permeability through lipophilic membranes.

SELF NANO EMULSIFIED DELIVERY SYSTEMS

Lipid based formulations such as self nano emulsified delivery systems (SNEDDS) are said to increase the absorption of the lipophilic drugs. SNEDDS are isotropic mixtures of oil, surfactant, co-surfactant and drug that form oil in water emulsion in aqueous environment under gentle agitation. This forms a good mode for delivering poorly soluble drugs orally by increasing their bioavailability and stability. They offer large interfacial area between the oil and GIT fluids and enhance the rate of absorption of the drugs.

Self-nanoemulsifying Drug Delivery system (SNEDDS) is isotropic mixture of natural or synthetic oil, surfactants and co-surfactants that have unique ability of forming fine oil-in water (O/W) nano-emulsions under mild Agitation follow aqueous media. Self-Nano emulsifying Drug Delivery System having size range of globules is less than 100nm under dispersion of water.

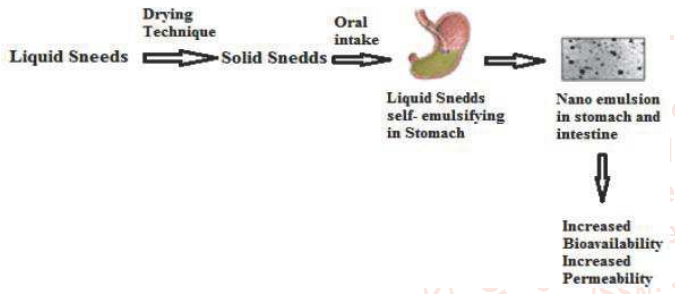


Figure 1: Self Emulsifying drug delivery system

SNEDDS spread readily in the gastrointestinal tract, and the digestive motility of the stomach and the intestine provide the agitation necessary for self-emulsification. Spontaneous emulsification to produce fine oil-in-water emulsion under gentle agitation followed by dilution in aqueous media can occur in oil and surfactants mixture. The production of selfemulsifying formulation involves several combinations of oil and surfactants, also the efficiency of self-emulsifying formulation can be influenced by several factors such as HLB value of the surfactant and surfactant concentration. The components used must be suitable for oral ingestion, such as medium chain triglyceride oils and nonionic surfactants.

1. EXPERIMENTAL WORK

1.1. PREFORMULATION STUDIES

Pre-formulations can be described as the development phase that characterizes the physicochemical and biopharmaceutical properties of drugs. It is an important part of the drug development process. The information related to drug development obtained at this stage is used to make key decisions in the later stages of development. A variety of information must be generated to develop formulas reasonably. In the pre-formulation stage of product development, drug characterization is a very important step, followed by the study of the compatibility characteristics of excipients.

1.1.1. Organoleptic characterization of Drug:

Organoleptic properties of Dolutegravir Sodium were studied by color, odor and appearance

1.1.2. MeltingPoint:

The capillary method was used for the determination of the melting of Dolutegravir Sodium. The thiels apparatus where in the liquid medicinal paraffin is contained in tube with a closed bent a side-arm. The thermometer is being inserted via a cork A fine powder of Dolutegravir Sodium was filled in a capillary tube, previously sealed at one end and the capillary tube was tied to the bottom of the thermometer. The thermometer and capillary tube were immersed in to the liquid paraffin taken in the tube. Bottom of the tube was heated gently by means of burner. When the sample starts to melt the reading was recorded.

1.1.3. Solubility:

The solubility of Dolutegravir Sodium in different vehicles like oil, surfactant, and cosurfactant changed into decided by way of shaking flask technique. It changed into done through dissolving an extra quantity of drug in 2 ml of the vehicle. Then the combination changed into vortexed. Vials have been then shaken for 48 hrs in a thermodynamically managed shaking water tub at 37 ±1 ℃ observed with the aid of equilibrium for 24 hr. Than the trial have been done by centrifugation at 3000 rpm for 10 min, supernatant layer changed into filtered through membrane of 0.45 µm clear out paper. The answer was filtered and diluted with methanol and UV absorbance changed into measured at 260 nm via UV-spectrophotometer. The drug attention in every vehicle become quantified by way of UV- seen spectrophotometer.

1.1.4. FT-IR Spectroscopy:

The FT-IR is an analytical technique used for identify organic, polymeric, and in some cases inorganic materials. The FT-IR anaylasis method uses infrared light to scan test samples and observe chemical properties. The KBr Pellet Preparation or sample preparation the most important part for IR spectroscopy. Sample should be transparent to IR radiations so it allows the radiations to pass through them. So salts like KBr, NaCl, AgCl are used for mixing of sample in order to obtain the accurate IR spectrum of a sample with sharp peaks, good intensity with high resolution.

1.1.5. UV- Spectroscopy:

Standard curve in methanol:

A standard stock solution of 100 ppm (10mg/ 100 ml) of NTG was prepared in methanol. This stock solution was used to prepare further standard solutions of the drug. Further stock solution was diluted to yield different concentrations of 5-25µg/ml.

The absorbance was measured between 400-200 nm on UV-spectroscopy.

Table no.1 The wavelength of maximum absorbance (ƛmax) was determined.

The absorbance of solutions were determined at 260 nm by using UV-spectrometer as shown in Table no.1

Calibration curve of Dolutegravir Sodium in methanol:

Table No. 1. Parameters for calibration curve of Dolutegravir Sodium in methanol

Sr.no	Parameter	Inference
1	Drug	Dolutegravir Sodium
2	Conc.of stock solution	100 µg/ml
3	Absorption maximum	260 nm
4	Solvent	Methanol
5	Scanning range	400-200 nm
6	Instrument	UV-spectrophotometer (Thermoscientific)
7	Sample holder	Quartz

Calibration curve of Dolutegravir Sodium in 0.1 N HCl

Table No.2 Parameters for calibration curve of Dolutegravir Sodium in 0.1 N HCl

Sr.no	Parameter	Inference
1	Drug	Dolutegravir Sodium
2	Conc.of stock solution	100 µg/ml
3	Absorption maximum	260 nm
4	Solvent	0.1 N HCL
5	Scanning range	400-200 nm
6	Instrument	UV-spectrophotometer (Thermoscientific)
7	Sample holder	Quartz

1.2. DRUG -EXCIPIENT COMPATIBILITY STUDY

The compatibility of Dolutegravir Sodium with selected excipients was done by thermal and isothermal stress testing (IST) techniques. To evaluate the drug-excipient compatibility, different techniques such as differential scanning calorimetric (DSC) study, infra-red (IR) spectrophotometric study were adopted. After selection and screening of the oil, surfactant and co- surfactant for the formation of the SNEDDS formulation next step was the physicochemical compatibility study of Dolutegravir Sodium with excipient. The drug and excipient were equally distributed in glass ampoules. They were kept at room temperature 25℃ and at 40℃/ 75% RH. The samples were drawn at intervals of 0, 2 and 4 weeks and analyzed for its physical appearance and drug stability by FT-IR.

1.3. PREPARATION OF LIQUID SELF NANO-EMULSIFYING DRUG DELIVERY SYSTEM (LIQUID SNEDDS)

1.3.1. Drug Loading

The drug loading capacity of every mixture was determined by adding the excess drug to every prototype mixture till the clear solution was obtained. The solution was filtered, diluted and measured the absorbance at 260 nm using UV-Visible Spectroscopy The liquid formulations containing oleic acid (Oil), Tween 80 (Surfactant) Diethyl glycol (co surfactant) was prepared with the increasing amount of Drug to achieve the highest drug loading in to liquid SNEDDS as shown in Table no.3

Table No. 3 Drug loading in liquid SNEDDS Formulation (B)

Sr. No	Ingedients	Quantity in % w/w						
		A1	A2	A3	A4	A5	A6	A7
1	Dolutegravir Sodium (Drug)	11%	12%	13%	14%	15%	16 %	17%
2	Oleic acid	20	21	22	23	24	25	27
3	Tween 80	51.75	50.25	48.75	47.25	45.75	44.25	42.75
4	Transcutol HP	17.25	16.75	16.25	15.75	15.25	14.75	14.25
5	% W/W	100	100	100	100	100	100	100

Procedures for Liquid SNEDDS Formulation

- A series of SNEDDS formulations were prepared using Oleic acid (oil), Tween 80 (surfactant) and Transcutol HP (co-surfactant).
- Accurately weighed quantity of Dolutegravir Sodium and was placed in a glass vial.
- To this oleic acid added and warmed on water bath.
- Then the components were mixed by stirring and vortex mixing at 40°C.
- Then formulation further sonicated (Ultrasonicator, Electroquip) for 15 min.
- The mixture was stored at room temperature for further use.
- These liquid formulation were then observed visually for 5 day at the interval of 24 hrs for any phase separation.

1.3.2. Development of Liquid SNEDDS

The observation from liquid SNEDDS prepared with different drug loading shows that above the 16 % w/w drug loading tends to crystal out upon standing when liquid SNEDDS was diluted to 100 times with water. Hence for further study altogether Formulations, the extent of Dolutegravir Sodium was kept constant (i.e. 16 % w/w). The various liquid formulations that were developments are shown below.

Table No.4: Liquid SNEDDS Formulation

Sr. No	Ingredients	Quantity in % w/w		
		C1	C2	C3
1	Dolutegravir Sodium(Drug)	16 %	16 %	16 %
2	Oleic acid	25	27	29
3	Tween 80	44.25	43.75	41.25
4	Transcutol HP	14.75	14.25	13.75
5	% w/w	100	100	100

1.4. CHARACTERIZATION OF LIQUID SNEDDS

1.4.1. Precipitation assessment

Liquid SNEDDS formulation was diluted up to 100 times with distilled water with continues stirring on magnetic stirrer to make emulsion. Precipitation was evaluated by visual inspection of the resultant emulsion after 24 hours. The formulations were then categorized as clear (transparent or transparent with bluish tinge), non-clear (turbid), stable (no precipitation at the end 24 hours), or unstable (showing precipitation within 24 hours).

1.4.2. Emulsification efficiency

Various compositions were categorized on the basis of clarity and apparent stability of the resultant emulsion. 1 ml of Liquid SNEDDS was added drop wise to 200 ml of distilled water within the breaker during constant stirring on a magnetic stirrer at low speed, at temperature 37° C. SNEDDS assessed visually according to the rate of emulsification and final appearance of the Emulsion.

1.5. Characterization of Liquid SNEDDS

1.5.1. Emulsification Efficacy

Emulsification efficacy and final appearance of the emulsion, result are shown in following table.

Table No.5: Visual Assessment of Liquid SNEDDS Formulation

Sr. No	Formulation Code	Speed of Emulsification		Grade	Observation
1	C1	>	1	A	Formulation spread rapidly, Form clear & transparent slightly bluish emulsion
2	C2	>	1	A	Formulation spread rapidly, Form clear & transparent slightly bluish emulsion.
3	C3	2-3		C	Fine milky emulsion.

Liquid SEMDDS formulation C1 & C2 formulation spread rapidly, Form clear & transparent slightly bluish emulsion when diluted with distilled water. These formulation shows good emulsifying, therefore formulation selected further study. C3 liquid SNEDDS formulation spread rapidly, form dull grayish, milky emulsion, so it's going to be rejected.

1.5.2. Precipitation Assessment:

Formulated SNEDDS diluted with 100 ml of distilled water and diluted SNEDDS observe for precipitation and result form was shown in following table

Sr. No	Formulation Code	Precipitation After	
		24 hrs.	48 hrs.
1	C1	Transparent, Clear emulsion, No Precipitation	Transparent, Clear emulsion, No Precipitation
2	C2	Transparent, Clear emulsion, No Precipitation	Transparent, Clear emulsion, No Precipitation
3	C3	Transparent, Whitish emulsion, No Precipitation	Transparent, Precipitate

From precipitation assessment C1& C2 formulation found to be transparent, clear emulsion with No precipitation and Stable. Therefore C1 & C2 will be selected for the further study. While C3 formulation get whitish emulsion after 24 hrs and obtain Precipitate after 48 hrs.

Hence C3 are going to be rejected.

1.5.3. Drug Contain determination

Amount of drug present in liquid SNEDDS formulation was determined by UV Spectroscopy method.

Table No. 6: Drug Content in different Liquid SNEDDS Formulation

Sr. No	Formulation Code	Drug Contain (% w/w)	Mean Drug Contain (% w/w)
1	C1	98.9± 0.9	99.16 ± 0.5
		99.2± 0.1	
		99.4 ± 0.6	
2	C2	97.5 ± 0.4	97.56 ± 0.3
		96.8 ± 0.2	
		98.4 ± 0.4	

1.5.4. Self – Emulsification Time

The result obtain self – emulsification time given in **Table No.7**

Table No. 7 Self – Emulsification Time of SNEDDS Formulation

Sr. No	Formulation Code	0.1 HCl		Distilled water	
		Time (Sec)	Tendenc y	Time (Sec)	Tenden cy
1	C1	4	Good	7	Good
2	C2	5	Good	9	Good

The C1 formulation requires less time for emulsification than the C2 formulation. Both formulations has good tendency for self- emulsion.

1.5.5. Reflective Index

Reflective index of the liquid SNEDDS formulation was found to be 1.415, these was nearly equal to the reflective index of water 1.321 form these result it'll completed back the liquid SNEDDS formulation most be a transparent in nature.

1.5.6. Zeta potential

Zeta potential was performed for the C1 formulation to determine the potential stability of colloidal systems. Zeta potential was determined by MALVERN zeta sizer instruments and was monitored at 25˚ c at a scattering angle 90˚. The greater the ZP value, more likely the suspension is to be stable because the charged particles repel one another and thus overcome the natural tendency to aggregate. It is currently revealed that higher ZP values, either positively or negatively charged, mean that dispersion will have greater long-term stability.

The zeta potential of liquid SNEDDS was found to be -29.9 Mv

		Mean (mV):	Area (%)	St Dev (mV)
Zeta Potential (mV): -29.9	Peak 1:	-29.9	100	5.59
Zeta Deviation (mV): 116	Peak 2:	0.000	0.000	0.000
Conductivity (mS/cm): 0.246	Peak 3:	0.000	0.000	0.000

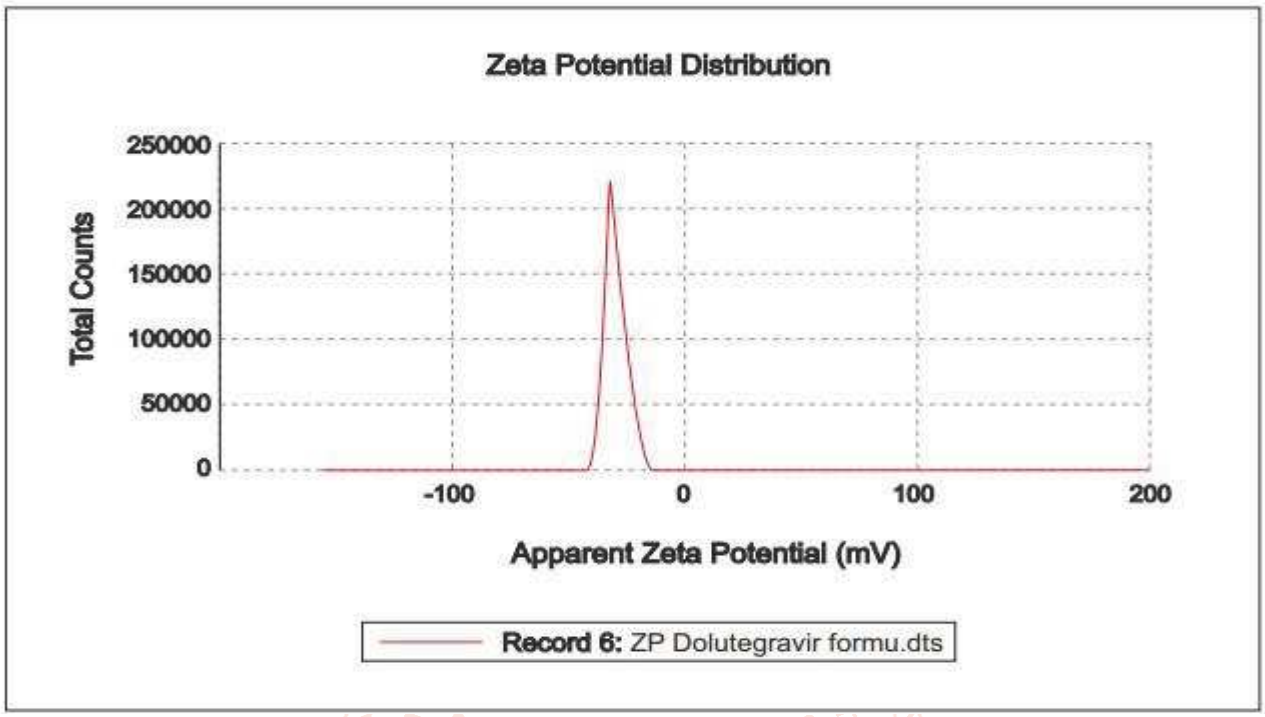


Figure 2: Zeta potential of liquid SNEDDS

1.6. CHARACTERIZATION OF LIQUID SNEDDS

1.6.1. Drug content determination

Amount of drug present within the liquid SNEDDS formulation was determined by UV Spectrometric method. Weighed accurate quantity of liquid SNEDDS formulation equivalent to 10 mg of drug (Dolutegravir Sodium) in 100 ml volumetric flask and diluted with methanol to form up volume upto100 ml. Further 1 ml of the solution was diluted to 10 ml using methanol to make 10 µg/ml solutions. The drug content was analyzed by taking UV absorbance at 260 nm.

1.6.2. Refractive index

Refractive Index proved the transparency of formulation. The refractive index of the system is measured by Abbe's refractometer by placing drop of solution on slide and it compare with water (Refractive Index of water 1.333). If refractive index of system is similar is to the refractive index of water, then formulation has transparent nature.

1.6.3. Self emulsification time

Few ml of prototype formulation (approximately 1 ml) was added to 250 ml of purified water, stirred gently and checked for clarity of solution. Self-emulsification time of formulation was determined using USP II dissolution apparatus. 1 ml of formulation was added drop wise to 250 ml of purified water at 37 ^{o}C, gentle agitation was provided by dissolution paddle rotating at 75 rpm. Time taken for formation of clear solution was noted as self-emulsification time.

1.6.4. Measurement of globule size

It has been reported that the smaller particle size of the nanoemulsion droplet may lead to more rapid absorption and improve the bioavailability. Prepared Dolutegravir Sodium SNEDDS (1 mL) was diluted 100 times with distilled water and 0.1 N HCl in breaker with constant stirring on a magnetic stirrer to make a nanoemulsion.

1.6.5. Zeta potential measurement

SNEDDS formulation containing 10 mg of Dolutegravir Sodium was diluted to 20 mL with distilled water during a flask and was mixed gently by inverting the flask. The particle size so formed was determined by dynamic light scattering (DLS) technique.

1.6.6. Surface Topography

The morphological characteristics of the liquid SNEDDS were observed by using SEM. Before SEM analysis, the samples were coated with gold or palladium under an argon atmosphere using a sputter coater Bal-Tec SCD 005. The photomicrographs were taken at an acceleration voltage of 25 kV at different magnifications.

1.6.7. Drug release study

The in-vitro dissolution study of liquid SNEDDS and plain drug were carried out using dissolution test apparatus no. 1 as per IP. Quantity equivalent to 10 mg of liquid SNEDDS formulation was added to dissolution media. The dissolution media used was 900 ml of 0.1 N HCl. The paddle rotation speed was kept at 75 rpm. Samples of 5 ml at 5 min interval were with – drawn at regular time 5 min to 30 min and filtered using 0.45 µm filter. An equal volume of respective dissolution medium was added to maintain the volume constant. Drug Content from sample was analyzed using UV-spectroscopy at 260 nm. The parameters during study are given table 10.

Table No. 8: Parameters for Drug Release Study Liquid SNEDDS

Sr. No	Parameter	Specification
1	Dissolution Apparatus	No. I
2	Dissolution Medium	900 ml 0.1 N HCl
3	Speed	75 rpm
4	Time	30 minutes

1.7. CHARACTERIZATION OF SOLID SNEDDS

1.7.1. POWDER FLOW PROPERTIES

Bulk Density It is the ratio of total mass of powder to the bulk volume of powder. it had been measured by filling the weighed powder into a measuring cylinder and therefore the volume noted in gm/ml.

Bulk density = Mass of powder / Bulk of powder

Tapped Density 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 and represented with unit gm/ml.

Tapped density = Mass /Tapped volume

Angle of Repose The angle of repose of S-SNEDDS was determined by funnel method. Accurately weighed sample were taken during a funnel. Height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of S-SNEDDS powder. The powder samples were allowed to flow through funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose calculated using the following equation:

tan θ = h/r (or) θ = tan-1 h/r Where θ – Angle of repose

h – height r - radius

Carr's Index Carr's Compressibility Index is a measure of powder flow properties and was calculated using the following equation:

$$\textbf{Carr's Index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Bulk density}} \times 100$$

Hausner Ratio A similar index like compressibility index has been defined by Hausner. Hausner's ratio is that the ratio of tapped density to bulk density and can be calculated by using the following equation

Hausner Ratio = Tapped density / Bulk density

2. RESULT AND DISCUSSION

2.1. PREFORMULATION STUDY

2.1.1. Organoleptic Characterization of Drug

Table no.9 Organoleptic Properties of drug

Sr. No.	Parameter	Observation
1	Colour	White powder
2	Odour	Odourless
3	Appearance	Solid powder

2.2. Melting point:

Melting point of Dolutegravir was found to be 192°C by DSC Thermograph that compliance to the reported literature.

2.2.1. FT – IR Spectroscopy:

FTIR Spectrum of the drug sample showed the entire characteristic IR peak reported within the literature indicating the presence of functional groups of Dolutegravir.

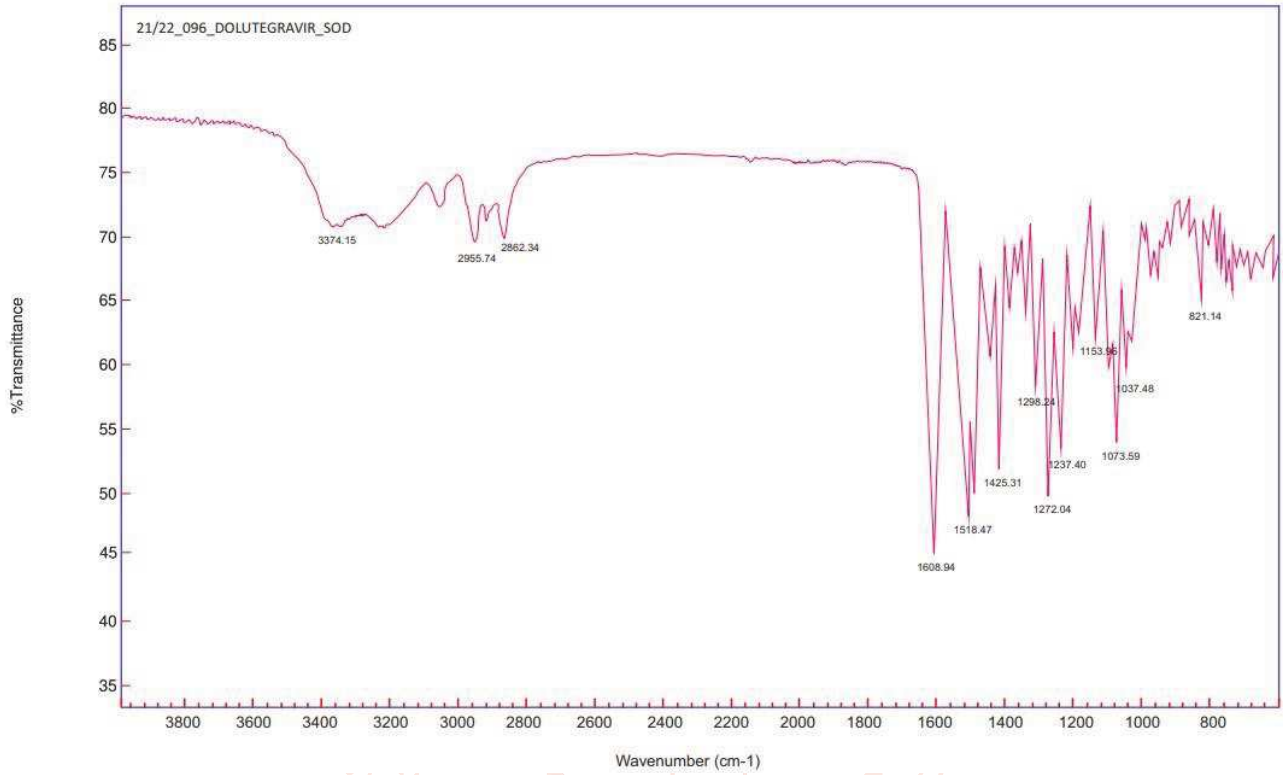
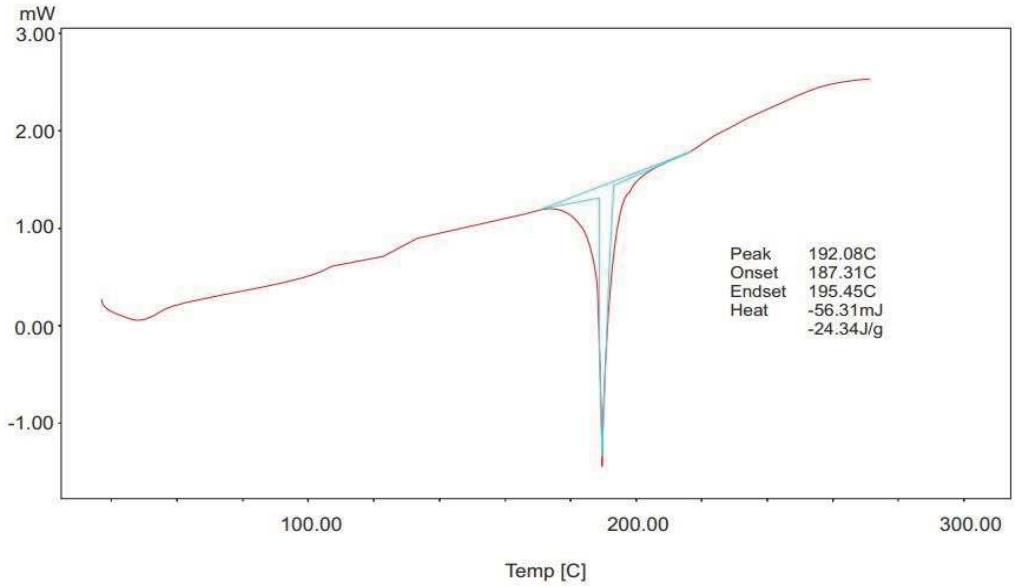


Fig No. 3: FT-IR Spectra of Dolutegravir sodium

Table No.10 IR- Interpretation of Dolutegravir

Functional Group	Observed Peak (cm -1)	Reported Peak(cm -1)
O-H Stretch	3374.15	3550-3200
N-H Stretch	2955.74	3000-2800
C=O (Aromatic)	1608.94	1650-1550
C-F Stretch	1272.04	1400-1000
C-N Stretch	1073.59	1250-1020

2.2.2. Differential scanning calorimetry



DSC thermograph of pure Dolutegravir is shown in figure 4

Dolutegravir was confirmed by DSC thermograph showed sharp endothermic peak at 192ºC.

It was within the standard range of melting point of Dolutegravir (187-195 ºC).

2.2.3. UV Spectroscopy

Maximum absorbance of Dolutegravir in methanol is shown in table no. and figure no. the maximum absorbance of Dolutegravir in methanol was found to be at 260 nm. The characteristic property of Dolutegravir in pure form.so it will be confirmed that obtained sample was genuine

Table No. 11 Maximum wavelength (ƛ max) of Dolutegravir in Methanol

Solvent	Wavelength of maximum absorbance ƛ max(nm)	
	Observed	Reference
Methanol	260	260

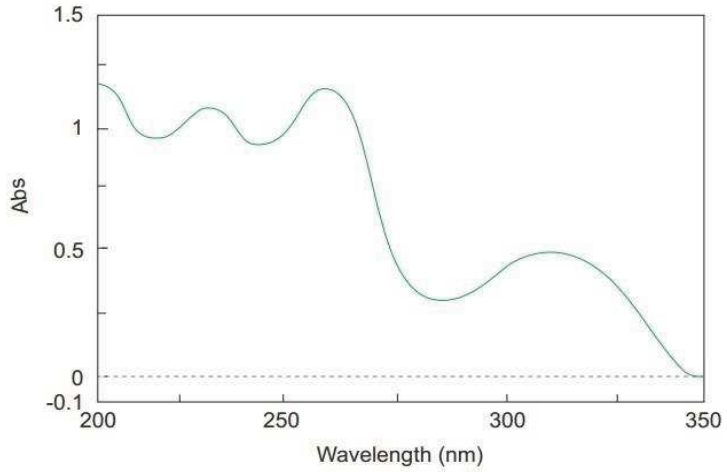


Figure No.5 UV-Spectra of Dolutegravir in Methanol

Calibration Curve of Dolutegravir in methanol

The calibration curve of the Dolutegravir was prepared in methanol Table no. 12 Shows the absorbance at 260 nm for various concentration Dolutegravir and figure no 6 shows calibration curve of Dolutegravir in methanol.

Table No.12: Calibration data of Dolutegravir in Methanol

Sr. No	Concentration (µg/ml)	Absorbance
1	5	0.3565
2	10	0.5767
3	15	0.7735
4	20	0.9858
5	25	1.2136

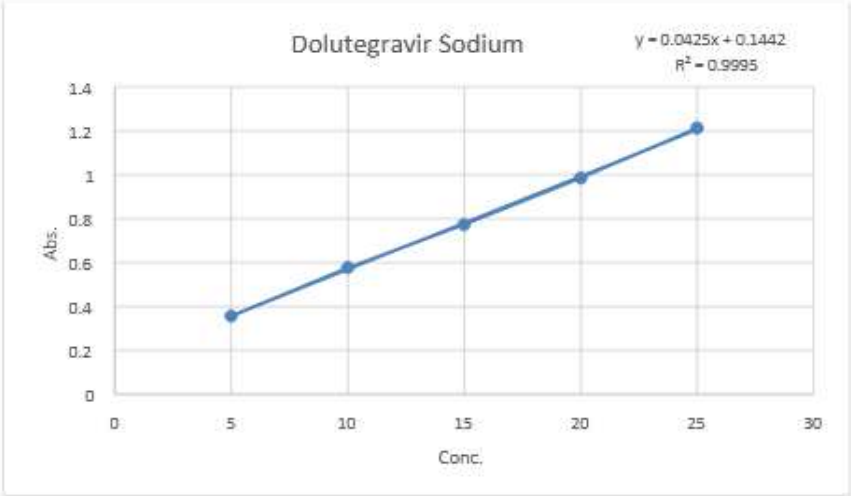


Figure No. 6. Calibration curve of Dolutegravir in Methanol

Calibration Curve of Dolutegravir in 0.1 N HCl

The calibration curve of the Dolutegravir was prepared in 0.1 N HCl .Table no 13 shows the absorbance at 260 nm for various concentration of Dolutegravir and Figure no. 7 shows calibration curve

Table No.13 Calibration Data for Dolutegravir in 0.1 N HCl

Sr. No	Concentration (µg/ml)	Absorbance
1	5	0.3378
2	10	0.5415
3	15	0.7419
4	20	0.9527
5	25	1.1849

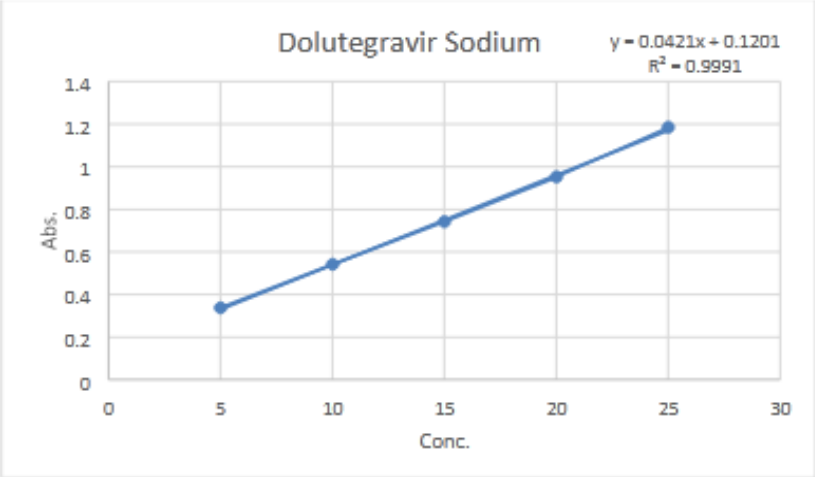


Figure No.7 Calibration curve of Dolutegravir in 0.1 N HCl

2.2.4. Surface topography of liquid SNEDDS

Surface topography of optimized liquid SNEDDS formulation C1 was studied using SEM, and is given in Figure 15.

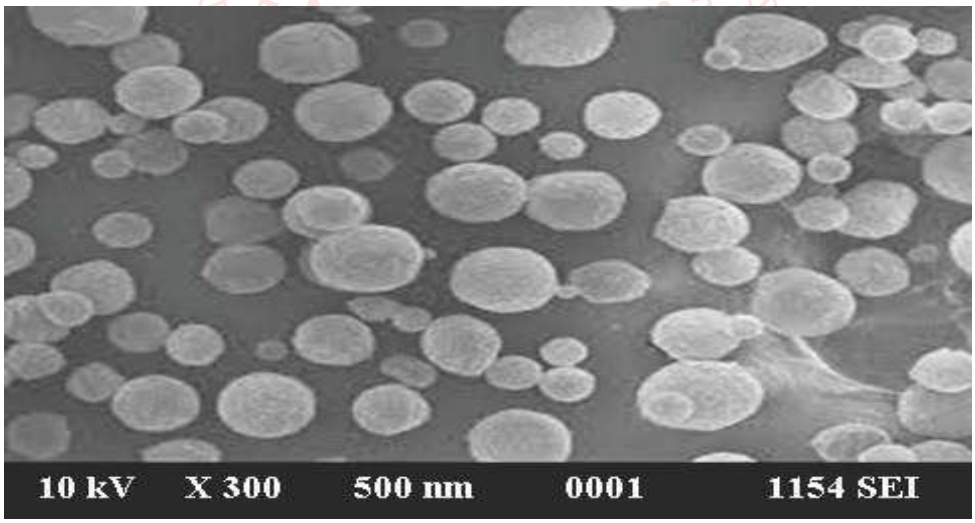


Figure:8 SEM Micrograph of optimized formulation code C1

Photomicrograph of the reconstituted liquid SNEDDS (C1) showed well dispersed spherical globules without any agglomeration of droplets. The image showed the emulsification of the oil phase in the aqueous phase to form fine droplets of emulsion.

2.3. CHARACTERIZATION OF SOLID SNEDDS:

2.3.1. Powder flow properties;

Bulk density, Tapped density, Compressibility index, Hausner ratio, Angle of repose was performed of dried powder result are shown in **Table no 14**

Sr. No.	Parameter	F1	F2	F3	F4
1	Bulk density (g/ml)	0.79	0.78	0.84	0.72
2	Tapped density (g/ml)	0.89	0.96	0.93	0.88
3	Compressibility index	12.66	23.08	10.71	22.22
4	Hausner ratio	1.13	1.23	1.11	1.22
5	Angle of repose	31.42	28.56	27.64	32.15

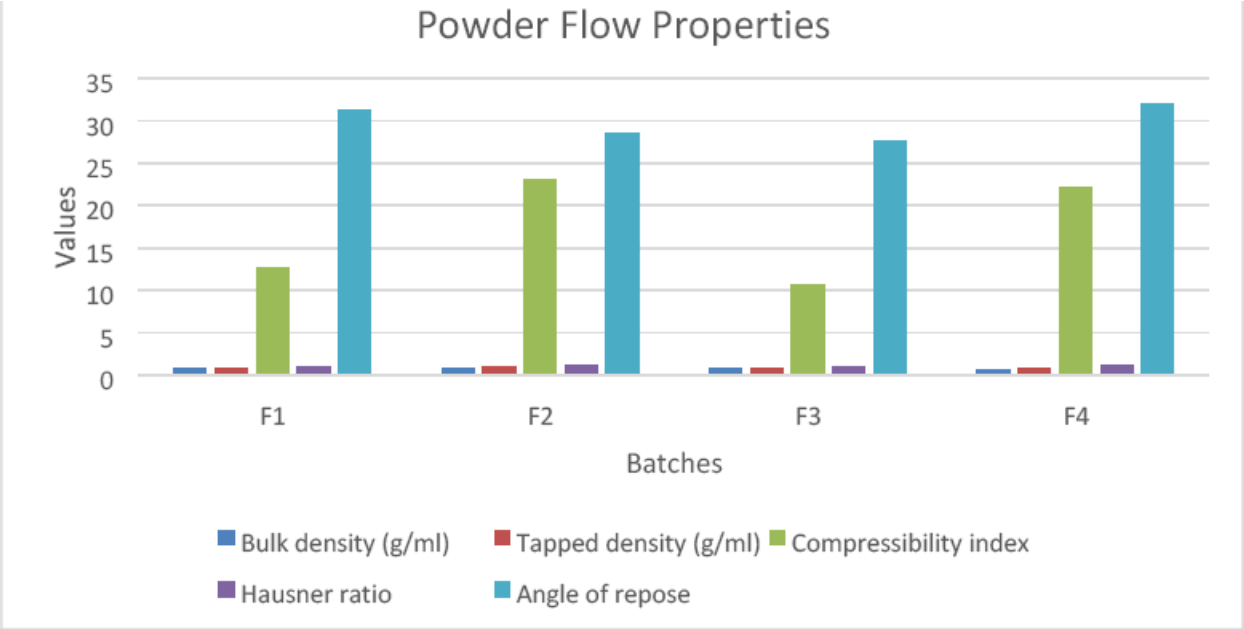


Fig No 9: Nanometric properties of dried powder

2.3.2. In- Vitro Dissolution Study

In-vitro drug release studies were performed for liquid SNEDDS, Solid SNEDDS and plain Drug Dolutegravir sodium. Also the comparison of these with the marketed capsule formulations, during this study the five samples were taken as –

1. – Plain drug
2. – Solid SNEDDS
3. – Instgra – 50 mg (Marketed formulation)

All the three formulation were subjected for in vivo dissolution studies using USP dissolution test apparatus II (basket). The dissolution medium 0.1 N HCl was used to study the drug release.

Table No. 15: Dissolution Data of Dolutegravir in different formulation

Sr. No.	Time (min)	% Drug Release (% w/w)	
		F3	Marketed Formulation
1	0	0	0
2	10	59.65	30.23
3	20	74.15	51.32
4	30	84.65	59.32
5	40	93.45	67.23
6	50	95.32	74.31
7	60	98.64	85.31

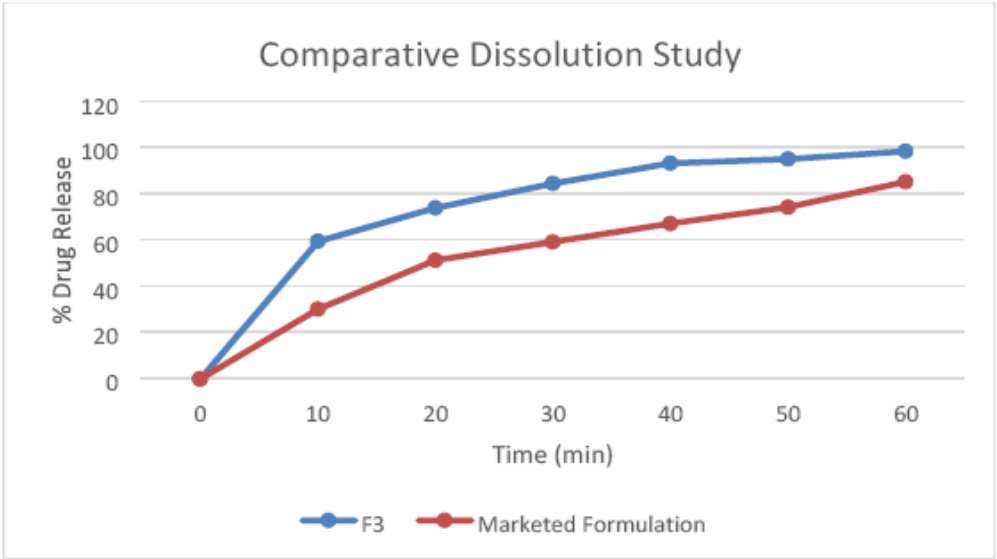


Fig No 10: Dissolution Data of Dolutegravir in Optimised batch (F3) and marketed formulation

3. SUMMARY AND CONCLUSION

3.1. SUMMARY

Solubility plays an important role in drug disposition, since the maximum rate of passive drug transport across a biological membrane, is the product of permeability and solubility. According to the biopharmaceutics classification system, aqueous solubility and permeability are the most important parameters affecting drug bioavailability. Retrospective studies show that greater than 40% of drug failures in development can be traced to poor biopharmaceutical properties, mainly due to poor dissolution or poor permeability. Thus improvement of aqueous solubility in such case is valuable goal to effectively formulate them into bioavailable dosage forms.

Dolutegravir is a HIV-1 intergrase 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 an 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.

To overcome the problems associated with the development of poorly soluble drug Dolutegravir, self-nanoemulsifying drug delivery systems have gained attention of researcher in the last decade. Self-nanoemulsifying drug delivery system is a lipid based formulation which consists of isotropic mixtures of oils, surfactants and co-surfactants. It can conveniently develop the emulsion on gentle agitation and offers a considerable surface area for interaction between the SNEDDS formulation and the aqueous gastrointestinal fluid. This may lead to enhanced bioavailability of hydrophobic agents. The Liquid SNEDDS was prepared and after that solidified by aerosil 200. For 10 gm of liquid SNEDDS; 5 gm of Aerosil 200 was used and after that product is dried by spray drying method. And 12 gm of product is remaining after the process.

The drug-excipients interaction studies were carried out using FTIR and DSC. The interaction studies were carried out to check physical and chemical stability of. Dolutegravir with other excipients. FTIR spectra showed the characteristic peaks of drug (i.e. for C-H stretch, N-C stretch) appear in the spectra of physical mixtures at the same wave number indicating no modification or interaction between drug and the polymers

The endothermic peak of pure drug and different mixtures showed no shift in peak this showed that drug was compatible with other excipients.

The liquid SNEDDS formulation C1 showed good thermodynamic stability without any precipitation and having globule size 536.6 nm and zeta potential -29.9. Based on thermodynamic stability, precipitation studies, self emulsification studies, globule size and zeta potential liquid SNEDDS of formulation batch C1 was selected as optimized formulation.

3.2. CONCLUSION

Liquid SNEDDS and solid SNEDDS was prepared for Dolutegravir. Optimized liquid SNEDDS contains 25% w/w oleic acid as the oil phase, 44.25% w/w tween 80 as the surfactant, and 14.75%, w/w Transcutol HP as the co-surfactant, which showed spontaneous emulsification properties and good thermodynamic stability. Liquid SNEDDS and Solid SNEDDS showed a better in vitro release profile compared to pure API. SEM, IR, and DSC results confirmed that drug was present in an amorphous state in solid SNEDDS. In-vitro drug release and drug content of optimized formulation was found to be 98.64 and 99.35% respectively. F3 batch of capsule formulation shows better drug release than marketed formulation.

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