Formulation of Self Emulsifying Drug Delivery System of Dolutegravir sodium.

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ABSTRACT

The current research work was focused on the solubility enhancement of Dolutegravir sodium by Self emulsifying drug delivery system. Dolutegravir sodium is an antiretroviral drug which falls under BCS class II drug having low aqueous solubility and high permeability. The saturation solubility was examined in different excipients utilized in SEDDS such as oils, surfactants and co-surfactants (4:1). Excipients were selected based on the maximum solubility of drug in the excipients and compatible studies. Pseudo ternary plots were constructed to determine the region of self nano emulsification utilizing water titration method. Dolutegravir liquid SEDDS formulations were prepared based on pseudo ternary plot utilizing different proportions of oil (Capryol 90), surfactant (Kolliphor EL), co-surfactant (Lauroglycol FCC). Prepared two Dolutegravir sodium liquid SEDDS formulations were chosen for further evaluation tests like Dispersibility test was observed as Grade A, Robustness to dilution test was passed, time taken for self-emulsification(30 seconds), percentage transmittance was showed as clear emulsions, thermo dynamic stability studies showed that the optimized formulation was thermodynamically stable

, Drug loading efficiency was found to be 98.2 , Droplet size analysis was found to be 32.75(d.nm) , PDI (0.296),zeta potential distribution was found to be -11.9mV ,In-vitro dissolution studies. Among two prepared formulations of Dolutegravir liquid SEDDS CK4L1 (4:6) was considered as optimized formulation as it was shown increased dissolution profile i.e., % drug release (87.53%) compared with that of pure drug Dolutegravir sodium (31.26%). The results demonstrated that the solubility of Dolutegravir sodium liquid SEDDS was enhanced significantly by 2.8 times compared with that of pure drug.The current examinations show that Dolutegravir liquid SEDDS can be utilized as expected methods for increasing solubility and bioavailability.

KEYWORDS

Dolutegravir sodium, Solubility, Bioavailability, Water titration method, Self Emulsification.

INTRODUCTION

Self-emulsifying drug delivery system is a novel drug delivery system which mainly aids in improving the solubility, dissolution and bioavailability of drugs. We have several methods for improving dissolution like micronization, increasing solubility using surfactants, complexing agents etc. but, these methods sometimes limit the stability and drug loading efficiency of formulation [1].

About 70% of recent formulation under BCS class 2 or 4 medications shows poor water solubility results in lowering oral bioavailability of drug due to its lipophilicity [2]. In order to overcome such issues an advancement in the Nanotechnology i.e., Nano based drug delivery systems are made such as nanomeric polymers for the non-aqueous i.e., lipid soluble drugs, these are Nano emulsions, nano suspensions and solid lipid nano particles etc. SNEDDS (self nano emulsifying drug delivery system) is a prominent tool for improving drug solvency, dissolution and oral bioavailability [3] .It prevents the pre-systemic metabolism as the medication debasing catalysts are excessively hydrophilic they cannot enter these lipophilic beads. So, the medication which is loaded in the oil beads can be protected from the catalysts which cause degradation thereby improving oral bioavailability [2].

SNEDDS is one of the most encouragement strategy notable for their capability to improve solvency and retention of lipophilic medication by diminishing the size of oil beads such that they are promptly edible and fused in to blended micelles that can pass lumen of intestine, increment in trans-cellular penetrability which can expand the lipid

smoothness of enterocytes and hinder efflux siphons bringing about improved bioavailability [2].

SNEDDS has a remarkable favorable position than polymeric nano particles because their grid is made of physiologically endured lipophilic parts that decline the potential for intense persistent toxicity [4].

Dolutegravir sodium, an anti-Retro-viral drug inhibits HIV integrase by binding to the active site and blocking the strand transfer step of retroviral DNA integration in the host cell. The strand transfer step is essential in the HIV replication cycle and results in the inhibition of viral activity [5].

The physico chemical properties of Dolutegravir sodium (anti Retro-viral drug) was shown that it is BCS class-II drug which is having low solubility and high permeation. It has low bioavailability due to poor dissolution. This problem related to poorly aqueous soluble medications can be overcome by formulating in to SEDDS utilizing various physicochemical methods to produce better dissolution profiles and bioavailability of Dolutegravir sodium [1].

MATERIALS AND METHODS

Materials: Dolutegravir sodium was obtained as a gift sample from Hetero Drugs Limited. Capryol 90, Lauroglycol FCC, Labrafac CC, Plurololeique, Transcutol P were a kind gift samples from GATTEFOSE. Kolliphor EL, Kolliphor HS15 were a kind gift sample obtained from BASF, Capmul PG8NF, Captex 355 EP/NF were gift samples obtained from Abitec corporation. Tween 80 was purchased from Sigma life sciences. HPMC Capsules were purchased from Natural capsules Ltd. Methanol and Hydrochloric acid were purchased from Research-Lab Fine Chem. industries.

Equipments: Analytical balance (Sartorius, India), Cyclomixer (Remi equipment pvt ltd), Rotary shaker (Remi equipment pvt ltd), Micropipette (Pfact), Centrifuge (Remi equipment pvt ltd), UV spectrophotometer (Shimadzu), FTIR (Alpha Bruker), Water bath(Bio technics), Dissolution apparatus(DS8000 Lab India), Magnetic stirrer(PCI Mumbai), Zeta sizer (Nano ZS 90 Malvern zetasizer), MilliQ water purifier (Millipore pvt ltd, India).

Determination of analytical methods:

The different analytical techniques utilized in present study are spectroscopic techniques which include UV-Visible spectroscopy and IR spectroscopy. Dolutegravir sodium was analyzed by Schimadzu UV-VISIBLE 1800 double beam spectrophotometer with data acquisition system UV Probe. The absorbance values of the samples were checked from the wave length range of 400-200nm. Two different stock solutions of Dolutegravir sodium were prepared utilizing methanol and 0.1N HCl. The absorption maximum values were found at 257nm and 257nm respectively. The absorption maximum values which are obtained were utilized for further analysis in the current research study.

Solubility analysis:

The solubility of Dolutegravir sodium was resolved in different oils, surfactants and co-surfactants. Excess amount of formulation was added to 1 gram of each excipient in various cap vials. The mixture was made to cyclo mix immediately using cyclo-mixer for 2 min which facilitates drug solubilisation. Cap vials were stirred in a water bath at 40-50°c for 5 min. then it is allowed to reach equilibrium at room temperature in an isothermal rotary shaker at 100rpm speed for 72hours. Each vial was centrifuged at speed of 3,000 rpm for 15 min using a centrifuge (Remi Equipment) followed by removal of the undissolved drug by separating the supernatant liquid and aliquots of supernatant fluid was drawn utilizing micropipette which are suitably diluted with methanol. The drug (Dolutegravir sodium) concentration in various excipients was obtained spectrophotometrically via a validated UV method at λmax257 nm [6-8].

Drug-excipient compatability studies: (FTIR- spectroscopy)

Study of drug-excipient compatibility is an important phase in the early stage of drug development.it defines the potential interactions between API and the excipients in the formulation. These studies are helpful in the selection of excipients, outline the stability of drug and distinguish the degraded excipients. FTIR studies were performed by screening the samples in the scope of 400-4000 cm-1. The absorption peaks which were observed for the pure drug was compared with the optimized formulation and excipients. The characteristic absorption peaks of Dolutegravir sodium were observed in the combination spectrum which shows that the Drug and excipients are compatible with each other.

Construction of Pseudo-Ternary Phase Diagram:

Pseudo ternary phase diagrams were plotted among oil, s.mix (surfactant and co-surfactant), and water utilizing aqueous titration method. It helps in determining the self

nano emulsifying region and to determine the ratios of oil, s.mix to be used in the development of formulation. Surfactant and co-surfactant (S.mix) in each group were blended in weight proportions (4:1, 3:1). For each phase plot, oil and Particular S.mix proportions are blended completely in various weight proportions, for example, 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, 1:9 in various glass vials. Every blend was titrated with water and is vortexed for 2mins and permitted to equilibrate. The change in actual state from transparency to turbid were outwardly noticed and set apart on three component pseudo ternary phase diagram where each axis denotes oil, s.mix and water separately. The distinctive phase diagrams were plotted utilizing Sigma plot 14.5 software.Components utilized for development of pseudo ternary stage chart are Capryol 90 (oil), KolliphorEL (surfactant), Lauro glycol FCC (co-surfactant) and Millipore water (watery stage). The phase diagrams were plotted at surfactant to co-surfactant proportions (4:1, 3:1) [8,9].

Formulation of Dolutegravir sodium SEDDS:

After the recognition of self nano emulsifying region through pseudo ternary plot, SEDDS formulation with suitable ratio of component proportions were selected for the incorporation of Dolutegravir sodium. The formulations of SEDDS were prepared by taking the varied proportions of oil (400-500%w/w), surfactant (400-500%w/w), co-surfactant (100-150%w/w) the amount of drug in both formulations was kept constant. Accurately weighed amount of Dolutegravir sodium was added in to the glass vials and oil is added to dissolve the drug then it is cyclomixed to solubilise the lipophilic drug then measured quantity of surfactant and co-surfactant is added and is vortexed till the drug gets dissolve completely. The mixture was placed on a water bath at 40°C for 30mins until the clear solution was obtained the formulation was stored at room temperature for further use.

Evaluation of SEDDS:

Dispersibility test:

The efficiency and dispersibility of Dolutegravir sodium SEDDS was evaluated utilizing the USP type II dissolution apparatus 0.1ml of each formulation was added in to 250ml of distilled water, kept up at 37 °C with gentle blending utilizing magnetic stirrer. Each formulation was assessed visually and categorized depending upon self-emulsification time, clarity and stability. The precipitation of the drug and the phase separation were assessed visually. The formulations were evaluated and categorized by the grading system i.e., Grade A (Rapidly forming emulsion(within 1min) having a clear or bluish appearance), Grade B(Rapidly forming emulsion which is slightly less clear emulsion,

having a bluish white appearance), Grade C(Fine milky emulsion that formed within 2mins), Grade D(Dull, grayish white emulsion having slightly oily appearance that is delayed to emulsify (longer than 2mins)), Grade E(Formulation showing either poor or negligible emulsification with enormous oil globules present on the surface) [10].

Self-emulsification time:

The self-emulsification time (time needed for a pre-concentrate to form a homogenous combination upon dilution) was assessed by noticing vanishing of Dolutegravir sodium SEDDS and last final appearance of nano-emulsion. It was determined by adding 0.1ml of the formulation in 200ml of distilled water and it is gently stirred utilizing magnetic stirrer. Temperature was maintained at 37 ± 0.5°C [10].

Robustness to dilution:

Effect on dilution can be checked by diluting the formulation about 0.1ml to 10, 100, 1000 times with diluents such as water, 0.1N HCl and phosphate buffer of p H 6.8. This study was to done to determine the effect of dilution on the Dolutegravir sodium SEDDS preconcentrate. The diluted formulations were vortexed utilizing magnetic stirrer and temperature was maintained at t 37 ± 0.5°C. The diluted formulations were stored at room temperature and were visually observed for any phase separation [11].

Percentage transmittance:

Each formulation of about 0.1ml was taken in a volumetric flask (10ml) containing distilled water, 0.1N HCL, p H 6.8 phosphate buffer. It is agitated for 1 min and the temperature was maintained at 37 ± 0.5°C. Each mixture was assessed for percentage transmittance at 257nm (λ max) utilizing UV-spectrophotometer. Percentage transmittance mainly gives the idea regarding uniformity and size of the bead [8].

Thermodynamic Stability studies:

Thermodynamic stability studies were performed for the selected formulations to determine the effect on temperature and centrifugation. Nano emulsions were added to Millipore water (1:20) and was made to centrifugation at 3500rpm for 30min and is visually assessed for any changes in the system like phase separation or precipitation. The formulations which are stable are subjected to two freeze thaw cycles between -20°C to +25°C with storage about not less than 48 hours at each temperature and monitored for any change in the formulation includes phase separation or precipitation.[12]

Drug loading efficiency:

Selected formulations were evaluated for the determination of drug content. In this method 0.1ml of the formulation was diluted with methanol (100ml)[11]. The drug loading efficiency was calculated by the formula given below:

Drug loading efficiency= amount of drug (API) present in the formulation ÷ Initial drug load× 100

Determination of globule size and zeta potential analysis:

Dolutegravir sodium SEDDS formulation sample was diluted to 100ml of water and was blended utilizing magnetic stirrer. The globule size and zeta potential analysis were measured after an hour by Dynamic Light Scattering (DLS) spectroscopy utilizing an instrument named Zetasizer Nano ZS 90 Version 7.10 (Malvern Instruments). The sizing of the emulsion was performed by placing a disposable sizing cuvette and zeta potential analysis was done by utilizing an electrophoretic cell with a point of recognition of 90° measurement [14].

In-vitro drug dissolution studies:

In-vitro dissolution studies of Dolutegravir liquid SEDDS were performed utilizing USP Type I dissolution test apparatus (Basket type). A capsule of size 0 which was filled with Dolutegravir liquid SEDDS formulation was placed in a buffer medium consists of 0.1N HCL (900ml). The process was setup at 37 ± 0.5°C and rotated at a speed of 50 rpm. Samples were withdrawn at regular intervals at 5, 10, 15, 20, 30, 45,60min respectively. 5ml sample was withdrawn at each interval of time and it was simultaneously replaced by 5ml buffer solution (0.1N HCL) in order to maintain sink condition. The withdrawn samples were checked for the amount of drug release from standard plot at absorbance 257 nm [14, 15].

Drug release kinetic analysis of Dolutegravir sodium:

To determine the drug release from the optimized formulation of Dolutegravir liquid SNEDDS various mathematical models were utilized such as zero order, first order, korsemeyer-peppas model and Higuchi model. In zero order kinetic pattern the rate of drug release is independent of its concentration whereas in first order kinetic model the rate of drug release depends on the concentration. Higuchi model explain the release of drug in matrix systems and it depicts that the drug release depends on fickian law of diffusion.Korsemeyer-peppas model his model represents the release of drug from

polymeric system. An extended release medication utilizes this model. The equation was given by Korsemeyer in the year 1983

$$M_t/M_\infty = Kt^n$$

The n value determines different release mechanisms like fickian release, non fickian release, case transport and super case II transport.

RESULTS AND DISCUSSION

Characterization of Dolutegravir sodium liquid SEDDS using UV-Visible spectrophotometer:

The UV-Visible spectrum of Dolutegravir sodium was shown in Fig. 1.

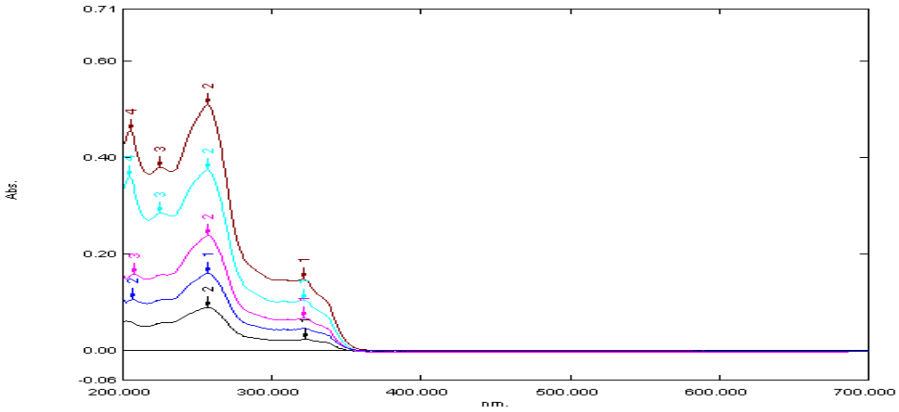

Figure 1: UV-Visible spectrum of Dolutegravir sodium

Solubility studies:

Solubility values of Dolutegravir sodium in various oils were determined utilizing Double beam UV-Visible spectrophotometer at 257 nm by taking methanol as blank. Among all the excipients Capryol 90 was selected as oil phase, Kolliphor EL as surfactant and Lauroglycol FCC as co-surfactant. The solubility values of different oils (Capmul, Peceol, Captex 355, Labrafac CC, Capryol 90), surfactants (PEG 400, KolliphorEL, Tween 85, Labrasol) and co-surfactants(Transcutol P, Lauroglycol FCC, Plurololeique) were given in Fig. 2.

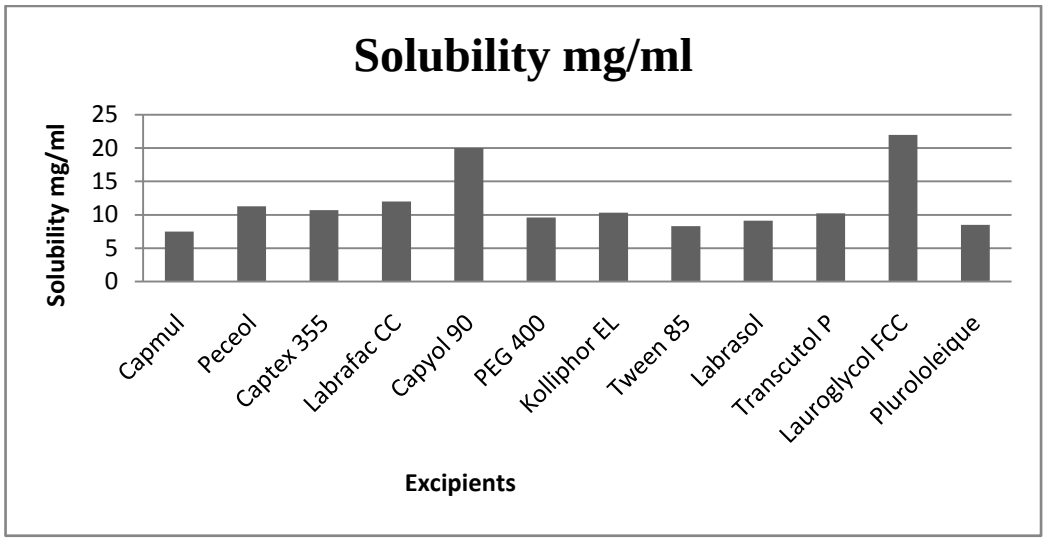

Figure 2: Solubility values of various excipients

Drug Excipient compatibility studies: (FTIR spectroscopy)

The standard absorption peaks obtained for the pure drug are compared with the formulation, if they are within the standard range it shows that both drug and excipients are compatible with each other. The FTIR spectra of Dolutegravir sodium and formulation are shown in Fig. 3.

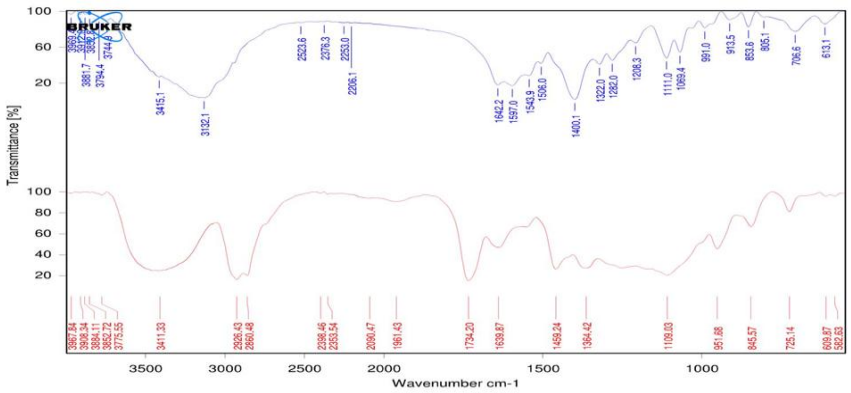

Figure 3: FT-IR spectrum of pure drug(Dolutegravir sodium) and optimized formulation

Construction of Pseudo Ternary Phase Diagram:

Pseudo ternary plot shows the region of nano emulsification and the excipients utilized in the formulation shows the properties of Nano emulsification. For S.mix 4:1 formulations CK4L1 of 9:1 to 6:4 was appeared milky white emulsion (MWE), 5:5 was appeared bluish white clear emulsion (BWE),4:6 was appeared transparent clear emulsion with light blue colour appearance(CTE) ,3:7 to 1:9 appeared dull grayish white

emulsion(GWE). The pseudo ternary plot of optimized formulation CK4L1 (4:6) was shown in Fig. 4. The values were listed in Table 1.

Table 1:Percentage composition of Capryol 90, Kolliphor EL (4), Lauroglycol FCC (1) upon water titration method

Formulation	Oil (mg)	Smix (4:1)	Water(mg)	Total (mg)	%Oil	%S.mix	%Water	Comments	Stability
9:1	450	50	2453	2953	15.24	1.69	83.07	MWE	Unstable
8:2	400	100	1993	2493	16.04	4.01	79.95	MWE	Unstable
7:3	350	150	2512	3012	11.62	4.98	83.40	MWE	Unstable
6:4	300	200	2190	2690	11.15	7.43	81.42	MWE	Unstable
5:5	250	250	2182	2682	9.32	9.32	81.36	BWE	Stable
4:6	200	300	2236	2736	7.31	10.97	81.72	TCE	Stable
3:7	150	350	2634	3134	4.79	11.17	84.04	GWE	Unstable
2:8	100	400	1882	2382	4.19	16.79	79.02	GWE	Unstable
1:9	50	450	2152	2652	1.9	16.97	81.13	GWE	Unstable

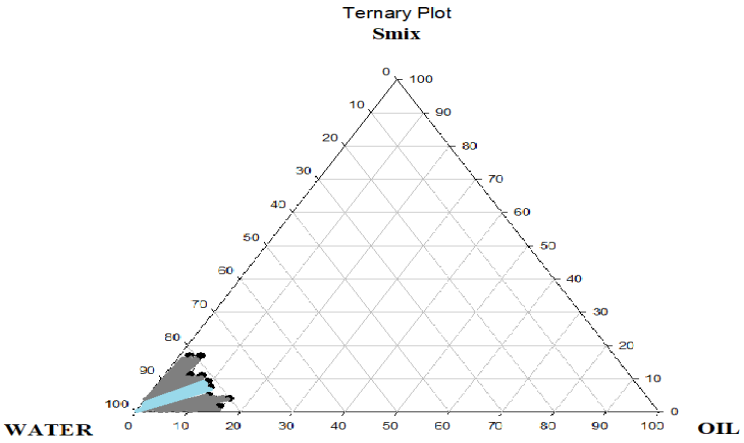

Figure 4: Pseudo Ternary plot of optimized formulation CK4L1 (4:6)

Formulation of SEDDS:

Formulation of Dolutegravir sodium liquid SEDDS formulation. (Table 2).

Table 2: Composition of prepared Dolutegravir sodium liquid SEDDS formulation

S.No	Formulation	Drug(Dolutegravir sodium)	Capryol	Kolliphor EL	Lauroglycol FCC	Total
1	CK4L14:6	30mg	800	960	240	2ml
2	CK4L15:5	30mg	1000	800	200	2ml

Evaluation of SEDDS:

Self-emulsification time: When 0.1ml of formulation was diluted with distilled water under agitation it should get dispersed quickly and completely. The results have shown that the formulations were self-emulsified within 30 to 36 seconds that proves it undergo easy and rapid emulsification.

Dispersibilitytest: The formulations were visually examined utilizing grading system. Based on the resultant values it was obvious that the formulations of Dolutegravir liquid SEDDS were belongs to Grade A (Clear Emulsion which forms rapidly i.e., in less than 1min and shows transparent or bluish appearance).

Robustness to dilution: The formulations of Dolutegravir sodium liquid SEDDS were subjected to dilutions in various solvents (Distilled water, Phosphate buffer pH6.8, 0.1N HCL) and was examined after 24hours for any kind of phase separation or precipitation. The formulations were appeared clear, bluish, and transparent without any phase separation and precipitation.

Thermodynamic stability studies: Phase separation and any kind of precipitation was not observed for the formulation under the influence of temperature that shows the formulations are stable under the influence of temperature.

Drug loading efficiency: The drug loading efficiency values of both Dolutegravir sodium liquid SEDDS formulations were obtained in the range of 98.2% for F1 and 94.1% for F2 which in turn shows that there is uniformity in the drug dispersion in both the formulations.

Percentage transmittance: Both the formulations have showed the values of percentage transmittance >95% it shows that the formulations were clear emulsions. The values were listed in Table 3.

Table 3: Values of Percentage transmittance for Dolutegravir sodium liquid SEDDS

Formulation	Distilled water	Phosphate bufferpH6.8	0.1N HCL
CK4L1(4:6)	98.52	98.26	98.76
CK4L1(5:5)	97.15	97.23	97.45

Determination of globule size and zeta potential analysis: Values of Globule size and Zeta potential analysis for Dolutegravir sodium liquid SEDDS formulation F1 i.e., CK4L1 (4:6) was found to be 32.75 d.nm and -11.9 MV respectively and for F2 i.e.,

CK4L1 (5:5) it was found to be 34.60 d.nm and -18.4 MV respectively. The globule size of F1 is less than F2. The values of globule size and zeta of formulation F1 are given in Fig. 5 & 6.

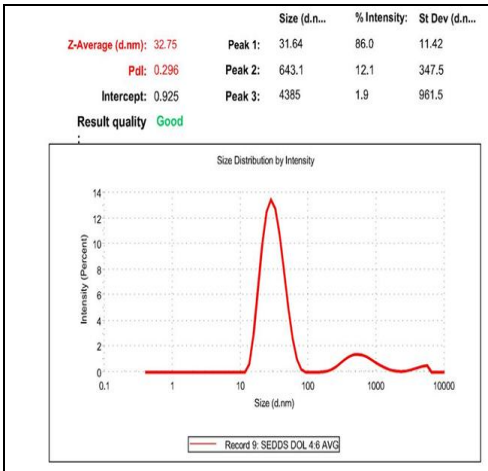

Figure 6: Graph showing globule size of optimized formulation CK4L1 (4:6)

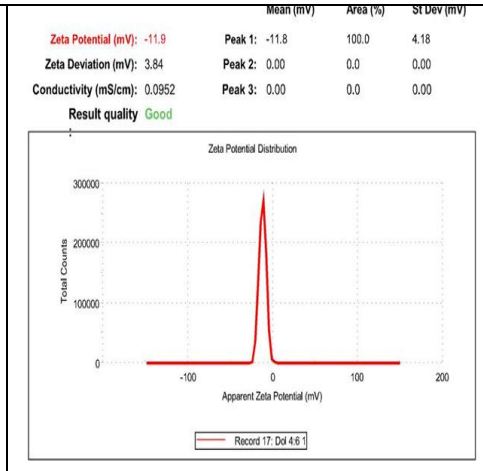

Figure 7: Graph showing zeta potential of optimized formulation CK4L1 (4:6)

Invitro dissolution studies:

The drug release of pure drug (Dolutegravir sodium) was found to be 31.26% at the end of 90min. The drug release of Dolutegravir sodium formulation CK4L1 (4:6) was found to be 87.53% at the end of 90min. The formulation CK4L1 (5:5) has shown 63.21% drug release at the end of 90min. The formulation CK4L1 (4:6) was taken as optimized formulation as the percentage drug release was found higher than pure drug and another formulation (CK4L1 (5:5). The dissolution data was given in Table 4.The percentage drug release values are shown in Fig. 8.

Table 4: Dissolution data for Dolutegravir sodium (Drug) and Dolutegravir sodium liquid SEDDS formulations

Time(min)	% Drug released (Dolutegravir sodium)	% Drug released (CK4L1)4:6
5	9.87	5.73
10	12.16	16.23
15	18.35	28.50
20	22.91	38.29
30	24.12	55.85

45	26.34	69.70
60	28.21	73.23
90	31.26	87.53

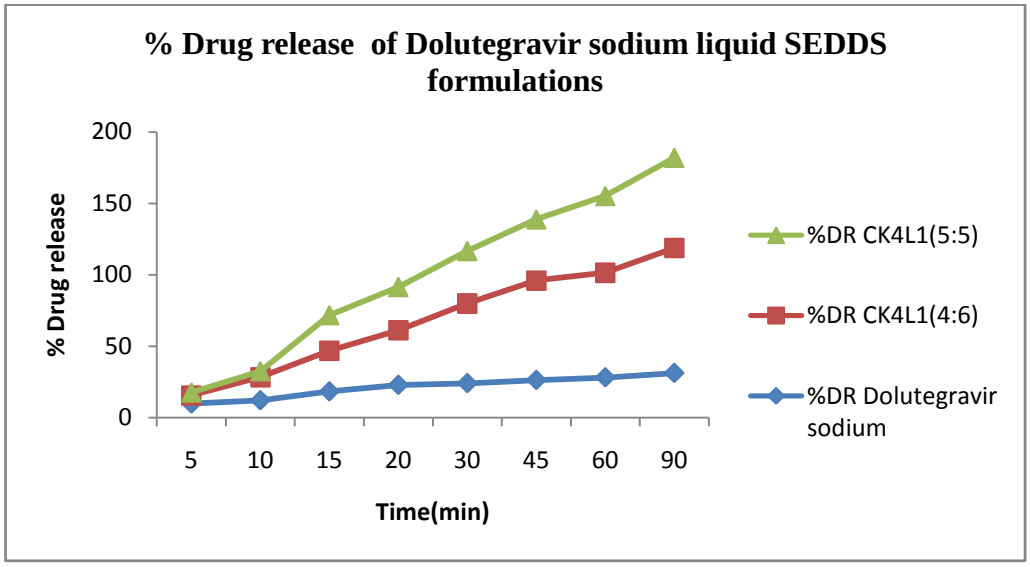

Figure 8: Graph showing % drug release of Dolutegravir sodium and Formulations (F1 and F2)

Drug release kinetic analysis of Dolutegravir sodium:

The results obtained from the mathematical model reveals that the prepared Dolutegravir sodium liquid SEDDS follows First order kinetics and Higuchi model. The regression coefficient values of Zero order kinetics, first order kinetics, Higuchi model, and KorsemeyerPeppas model are found to be 0.875, 0.985, 0.963, and 0.927 respectively.

CONCLUSION

Dolutegravir sodium was picked as model drug candidate in the formulation of SEDDS since it has close ideal qualities that a drug should possess in the formulation of SEDDS. It includes: The drug must belong to BCS Class 2, Log P value <4, less oral bioavailability, low dose and low melting point.

The formulation CK4L1 (4:6) was chosen as optimized formulation as it showed maximum drug release (87.53%) compared to other formulation and pure drug (Dolutegravir sodium) at the end of 90min. The percentage drug release of pure drug was found to be 31.26% at the end of 90min. It shows that Dolutegravir sodium SEDDS formulation has increased solubility about 2.8 times to that of pure drug.

The increased dissolution profile i.e., good drug release showed increase in solubility and dissolution of Dolutegravir sodium. Subsequently, the prepared Formulation of Dolutegravir sodium liquid SEDDS have the capacity to deliver inadequately water soluble drug Dolutegravir sodium in liquid state in to GIT (Gastro intestinal tract).

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