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DEVELOPMENT AND CHARACTERIZATION OF SELF EMULSIFYING DRUG DELIVERY SYSTEMS OF NEXT GENERATION INTEGRASE INHIBITOR: DOLUTEGRAVIR

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Abstract

Self-Emulsifying Drug Delivery System (SEDDS) was prepared to improve the oral bioavailability of antiretroviral drug Dolutegravir, a BCS Class II molecule. Dolutegravir is also a substrate for p-glycoprotein (p-GP), which efflux the molecule into intestinal lumen & hence decrease the oral bioavailability. The SEDDS formulation consisted of Dolutegravir, Capmul MCM, Labrasol, Tween 20, Propylene glycol & Transcutol HP. The saturation solubility study of Dolutegravir was conducted in different oils, surfactants and co-solvents. The pseudo-ternary phase diagrams were constructed to identify the self emulsifying regions. The formulation was characterized for droplet size analysis, zeta potential, poly-dispersibility index, assay, impurities and *in-vitro* dissolution behaviour.

INTRODUCTION& OBJECTIVES:

Self-emulsifying drug delivery system (SEDDS) is an isotropic mixture of oil, surfactant, co-surfactant and drug substance, which rapidly form oil in water emulsion in gastric environment after oral administration. SEDDS can enhance drug absorption by following mechanisms-

- ✓ Drug solubilisation
- ✓ Inhibition of P-glycoprotein mediated drug efflux and pre-absorptive metabolism by gut membrane –bound cytochrome enzymes.
- ✓ Promote lymphatic transport that delivers drug directly to the systemic circulation while avoiding hepatic first pass metabolism.
- ✓ Increasing gastrointestinal membrane permeability.

Dolutegravir is a new generation integrase strand transfer inhibitor for the treatment of HIV infected patients. It is a BCS Class II molecule having poor aqueous solubility and p-GP substrate hence poor bioavailability.

In the present study, SEDDS formulation was designed to improve the oral bioavailability of Dolutegravir by solubilising of BCS class II drug & also inhibiting the efflux mechanism to enhance the absorption since it is a substrate for transporters P-glycoprotein (P-GP).

MATERIAL & METHODS:

Dolutegravir was procured from Cipla Ltd., India. Capmul MCM (Medium chain mono- and diglycerides) was obtained from Abitec Corporation (Columbus). Labrasol (Caprylocaproyl- macrogolglycerides), Transcutol P (Diethylene glycol monoethyl ether) were obtained from Gattefosse (France). Propylene glycol & Tween 80 (Polysorbate 80) was obtained from BASF (Germany). All other chemicals and solvents were used of analytical grade.

Saturation Solubility study:

Solubility of Dolutegravir was evaluated in different oils, surfactants (different HLB value), co-surfactants and co-solvents. The solubility studies were carried out at room temperature using auto shaker for 24 hours.

Construction of pseudo-ternary phase diagram:

Based on the solubility study of Dolutegravir in different vehicles, Capmul MCM, Labrasol, Tween 20, propylene glycol & Transcutol HP were selected as a components of homogenous liquid mixture. The pseudo-ternary phase diagrams were constructed for different Km value.

Preparation of SEDDS formulation:

SEDDS formulation was prepared by solubilising the drug into the homogenous mixture of surfactant, oil and co-surfactant with stirring and heating at magnetic stirrer at 40-45˚C.

In-vitro dissolution test:

The drug release study was performed on preconcentrate of Dolutegravir using USP type II apparatus in 900ml of intestinal buffer pH 6.8 containing 2.5 % SLS at 50 rpm for 60 mins. The samples were withdrawn at different time points.

RESULTS & DISCUSSION:

Solubility study:

The mean solubility of Dolutegravir in various oils, surfactants & co-surfactants is shown in figure 1& 2. Among the oils tested, Capmul MCM showed the highest solubility and was selected as an oil phase for the preparation of SEDDS. Labrasol ALF was chosen due to drug high solubility & p-glycoprotein inhibitor property. Tween 80 was chosen as a surfactant phase due to their self-emulsification capacity. The Transcutol HP & propylene glycol was taken as a co-solvent.

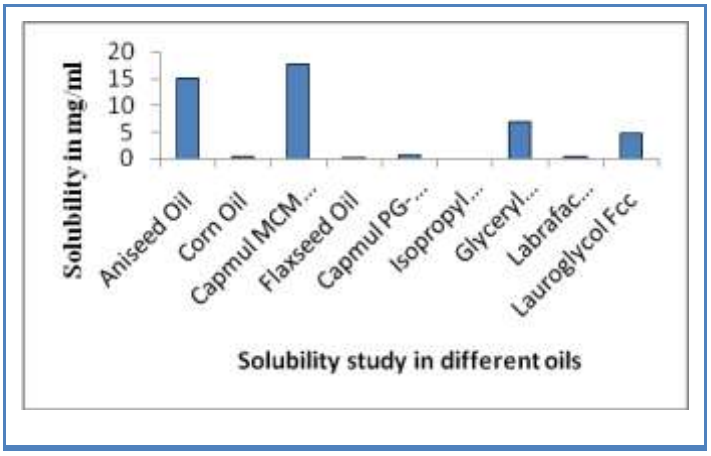

Figure 1: Solubility (mg/ml) in different oils

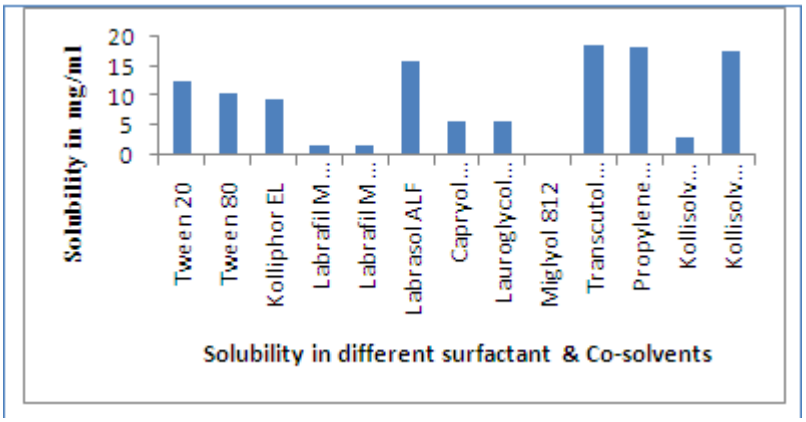

Figure 2: Solubility (mg/ml) in different surfactants & co-solvents

Pseudo-ternary phase diagram:

Pseudo-ternary phase diagram were constructed in the absence of Dolutegravir to identify the self emulsifying regions and to optimize the percentage of oil, surfactant and co-surfactant in the SEDDS formulation.

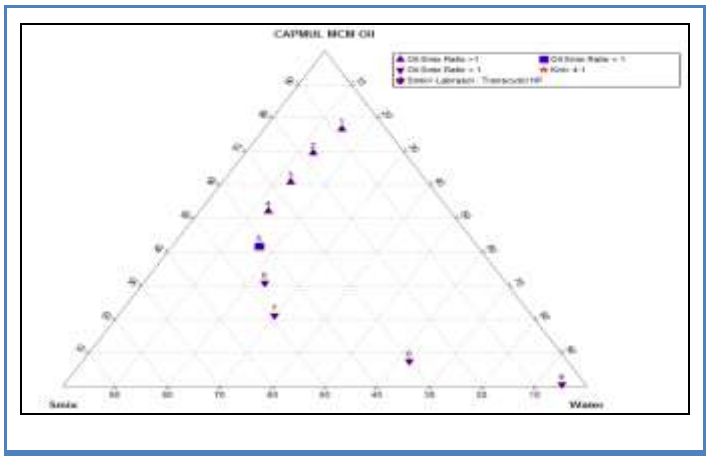

Figure 3: Pseudo-ternary phase diagram (Km=4)

Droplet size & zeta potential:

The droplet size of formed emulsion is an important aspect in self emulsification performance because it evaluates the rate and extent of drug release & absorption of drug. The mean droplet size (z avg.), poly-dispersibility index and zeta potential value of Dolutegravir loaded formulation was 338.1nm 0.284 & -17.6mV respectively.

Assay & impurities:

The assay value of drug loaded SEDDS formulation was found 100.4 % & no major impurity detected.

In-vitro dissolution test:

The SEDDS formulation showed very rapid drug release and showing more than 90% release in 5 minutes.

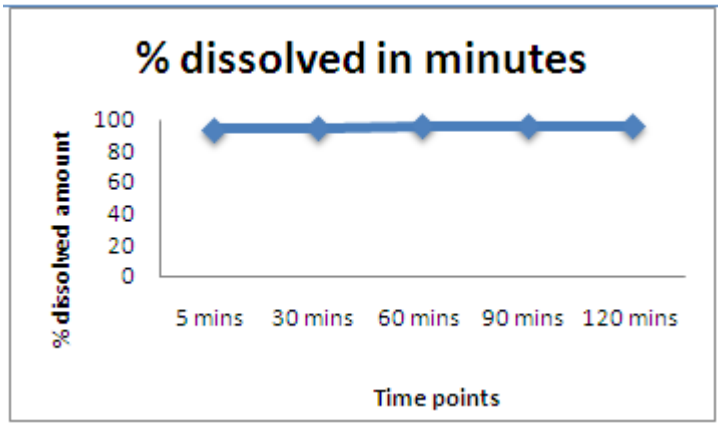

Figure 4: *In vitro* % dissolved amount –time profiles for the SEDDS formulation.

Stability study:

During the 3 months of stability study, the entire stored sample showed no changes in appearance under all different storage conditions. No marked difference was observed between the pH, specific gravity, viscosity, emulsification time, drug contents and % drug released at initial and under all storage conditions (data not shown here). Hence, indicates the stable self emulsifying dosage form of next generation integrase inhibitor drug Dolutegravir.

Conclusions & Perspectives:

In the present study, in order to increase the oral bioavailability of antiretroviral drug, the SEDDS formulation was developed through the construction of Pseudo-ternary phase diagram. Based on the microemulsion range observed, the ratio of surfactants and co-surfactants were selected. The droplet size of formed emulsion was in nano-range which describes the large surface area for drug absorption. The in-vitro dissolution test clearly indicates the rapid release i.e. 94% of drugs in 5 minutes. This

study demonstrates the successful development of SEDDS formulation of next generation antiretroviral drug.

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