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Research Article

FORMULATION DESIGN AND EVALUTION OF RUTIN LOADED SELFEMULSIFYING DRUG DELIVARY SYSTEM (SEDDs) USING EDIBLE OIL

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ABSTRACT

Self-emulsifying drug delivery systems (SEDDS) were prepared in an attempt to improve their release profile. SEDDS were prepared using co-precipitation and melting methods at various drug-polymer ratios. Polyethylene glycol (PEG 6000), polyvinyl pyrrolidone (PVP K30 and PVP K17) or sodium desoxycholate were used to prepare SEDDS by co-precipitation method. PEG 4000, Oral delivery is not possible for 50% of currently marketed drug compounds due to low oral bioavailability. One of the most popular approaches to enhance the oral bioavailability of these molecules is the utilization of a lipid based drug delivery systems .It is estimated that 40% of active substances are poorly soluble in water. The improvement of bio-availability of drugs with such properties presents one of the greatest challenges in drug formulations.

Keywords: Self emulsifying drug delivery system Rutin loaded drug in vitro hepatotoxicity

INTRODUCTION

Emulsions are used as a vehicle for the administration of drug. it is this consideration that has received particular attention, especially due to the possibility of enhancing the oral bioavailability of poorly absorbed drug (Attenwood Det al.,1983).the concept of using SEDDs for pharmaceutical purpose was initially developed by the group of groves (Dunkan QM et al.,2000). After their work on these lines the issue relating to this technology has gained prominence. In these formulation, emulsification takes place in the gut and by this mechanism bioavailability enhancement takes place .the use of SEDDs may reduce required oral dose if there is an extensive improvement in oral bioavailability .the rate of gastric emptying of SEDDS is similar to solution so that they are particularly useful when repeat onset of action is necessary (Greenberger N. J. et al., 1966) In recent years, studies of self-emulsifying drug delivery systems (SEDDS) and self-micro emulsifying drug delivery systems (SMEDDS) have become more and more popular, due to the successful development of several oral pharmaceutical products, such as cyclosporine A (originally marketed as 'Sand immune' and now as the improved product 'Neural') and the two HIV protease inhibitors, ritonavir and saquinavir .Rutin is a yellow crystalline flavonol glycoside ($C_{27}H_{30}O_{16}$) that occurs in various plants (rue, tobacco, buckwheat, etc.). Upon hydrolysis (a chemical reaction that uses water to break down a compound), rutin yields quercetin and rutinose. Rutin is used in many countries as a vasoprotectant and is an ingredient in numerous multivitamin preparations and herbal remedies. The rutosides are naturally occurring flavonoids that have documented effects on capillary permeability and edema (swelling) and have been used for the treatment of disorders of the venous and microcirculatory systems. There is some evidence for the use of rutin for chronic venous insufficiency, edema, and hemorrhoids.

MATERIAL AND METHOD

Rutin was gifted by Torrent Pharmaceutical Ltd. Acrysol K140 was gifted by Corel Chemical Ltd, Ahmadabad. Edible oil was gifted from Abitec Corporation, USA. Sunflower oil and olive oil was purchased from market. Polyethylene glycol 400, ethanol AR grade, Tween 80 and Tween 20 grade were purchased from S.D. Fine Chemical Ltd, Mumbai.

Drug used	Rutin
Surfactant	tween 80
Cross link	edible oil
Co solvent	ethanol
I.R spectroscopy	for preformulation study
S.E.M spectroscopy	for structured characteristic study
T.L.C	For drug assay
Powder microscopy	for particle size
Q.C instrument	B.D & T.D Dissolution, disintegration

Formulation of self emulsifying drug delivery system (SEDDS

The formulations were prepared by initially dissolving the formulation amount of a Rutin in co-solvent at 60˚C in an isothermal water bath. Edible oil was then added and mixture was cooled to ambient temperature. Then surfactant and co-surfactant mixer were added and the final mixture was mixed by vortexing until a clear solution was obtained. The formulation was equilibrated at ambient temperature for at least 48 h, and examined for signs of turbidity or phase separation prior to self-emulsification and particle size studies. Final formulation was filled in suitable container

MECHANISM OF SELF-EMULSIFICATION

The process by which self-emulsification takes place is not yet well understood. However, according to Reiss 48, self-emulsification occurs when the entropy change that favors dispersion is greater than the energy required to increase the surface area of the dispersion. In addition, the free energy of a conventional emulsion formation is a direct function of the energy required to create a new surface between the two phases and can be described by equation.

$$\Delta G = \sum_{i} N_i \pi r_i^2 \sigma$$

Where, G is the free energy associated with the process (ignoring the free energy of mixing), N is the number of droplets of radius, r, and s represents the interfacial energy. With time, the two phases of the emulsion will tend to separate, in order to reduce the interfacial area, and subsequently, the free energy of the systems. Therefore, the emulsions resulting from aqueous dilution are stabilized by conventional emulsifying agents, which form a monolayer around the emulsion droplets, and hence, reduce the interfacial energy, as well as providing a barrier to coalescence. In the case of self-emulsifying systems, the free energy required to form the emulsion is either very low and positive, or negative (then, the emulsification process occurs spontaneously). Emulsification requiring very little input energy involves destabilization through contraction of local interfacial regions.

EVALUATION STUDY

In vitro drug release study

In vitro release test was performed using Dialysis bag method and release study was carried out in 250 ml of distilled water, 1 ml of emulsion formulation (Single dose containing 10 mg of AT Calcium) was placed in treated dialysis bag (MWCO 12,000 g/mole; Sigma, USA) and 1 mL samples was withdrawn at regular time intervals (0, 0.5, 1, 1.5, 2,2.5,3,3.5, 4,4.5,5.5, 6,6.5,7, 8,9, 10, 12, 22 and 24 h) and same amount of distilled water was replaced.[21-22]. The withdrawn 1 ml samples were diluted with 3 ml methanol and analyzed for the drug content by using developed UV-spectroscopy

at 247 nm. The same method was used for the suspension containing 10 mg of AT Calcium in 1 ml distilled water. The release of drug from different selected nano emulsion formulations was compared with drug suspension and finally selected formulation was used for the further study i.e. for preparation of solid self-nano emulsifying drug delivery system (SSNEDDS).

In vitro release of Rutin from SMEDDS was performed using a bulk-equilibrium reverse dialysis bag technique (BERDBT) in 900 ml distilled water, 0.1 mol/l hydrochloric acid with/without sodium dicyclosulfate (SDS) and pH 6.8 phosphate buffer at 37 ± 0.5°C, based on the ChP (2005) release test method II. The paddle speed was adjusted to 100 r/min. The SMEDDS placed in the medium in which several dialysis bags containing 3 ml of the same solution had previously been immersed. These dialysis bags were equilibrated with the medium for about 30 min prior to the experiment. At predetermined times, each dialysis bag was removed and the same volume of temperature equilibrated buffer or surfactant solution as that withdrawn was added to the system to maintain volume and sink conditions. The contents of the dialysis bags were analyzed by HPLC to determine the drug released. Triplicate measurements were made on each sample and mean values were calculated.

In Vitro Diffusion Study

An in vitro diffusion study is performed to study the release behavior of formulation from liquid crystalline phase around the droplet using dialysis technique. The drug stock solutions in oil mixture were prepared in such a way that 10 mg dose is present in each formulation complying the oil percentage for each formulae selected from the phase diagram. This was prepared by dissolving the 1000 mg of drug individually in the 10, 15, 20 and 25 mL of oily mixture, which compiles the 10%, 15%, 20% and 25% oil compositions respectively in the formulae. The drug stock is shown in Table Preparation of drug stock for each formula selected in phase diagram

S.NO Oil percentage in formulations Amount of drug (mg) Volume of oil (mL) Final concentration (mg/µL)

1 10% 1000 10 10 mg/100 µL
2 15% 1000 15 10 mg/150 µL
3 20% 1000 20 10 mg/200 µL
4 25% 1000 25 10 mg/250 µL

Surfactant and co-surfactant (mix) in each group were mixed in different volume ratios (1:0, 1:1, 1:2, 1:3, 2:1, 3:1, 4:1) and the stock of 100 mL of each group was prepared. These mix ratios were chosen in increasing concentration of co surfactant with respect to surfactant and increasing concentration of surfactant with respect to co surfactant.

Preparation of Rutin &Edible oil Solid Dispersions: Both solvent evaporation method (co precipitation method) and fusion method (melting method) were used to prepare and Rutin solid dispersions. Rutin &Edible oil Solid Dispersions prepared by Co-precipitation method: Different polymeric carriers were used to prepare Rutin &Edible oil co-precipitation solid dispersion namely: polyethylene glycols exemplified by PEG 6000 in weight ratios of 1:1, 1:2 and 1:3 drug to carrier, polyvinyl pyrrolidone namely PVP K30 and PVP K17 in weight ratios of 1:1, 1:2, 1:3, 1:4 and 1:5 drug to carrier and bile salts represented by sodium desoxycholate in weight ratio of 1:2 and 1:3 drug to carrier. Each of the aforementioned carriers was dissolved in the least volume of methanol then added to drug ethanol solution. The resultant solution was evaporated until dryness using thermostatically controlled magnetic stirrer. The obtained solid masses were kept in desiccators over anhydrous calcium chloride until complete dryness. Finally, the dried masses were pulverized and granules that passed throughout the sieve (USA standard testing

Sieve set) of 0.63 mm size were clarified for further investigation. 2.2.1.2. Preparation of Rutin Solid Dispersions using Melting Method: Different polymeric carriers were used to prepare Rutin solid dispersions using melting method, namely: polyethylene glycols represented by PEG 4000 and PEG 6000 in weight ratio of 1:1, 1:2, and 1:3 drug to carrier and poloxamers exemplified by poloxamer F68 in weight ratio of 1:1, 1:2, 1:3, 1:4 and 1:5 drug to carrier and poloxamer F127 in weight ratio of 1:1, 1:2 and 1:3 drug to carrier. Each of the aforementioned carriers was melted over a heated water bath maintained at 70oC. Then, the drug was added to the melted mass and stirred well till homogenous matrices were formed. The obtained masses were kept in desiccators over anhydrous calcium chloride until complete dryness. Finally, the dried masses were pulverized and the granules that passed through sieve (USA standard testing sieve set) of 0.63 mm in diameter were clarified for further investigation. 2.2.1.3. Preparation of Rutin Physical Mixtures: The physical mixtures of Rutin with aforementioned carriers were prepared in the same molar ratios utilized previously for comparative purpose

Thermodynamic stability studies

Heating cooling cycle

Six cycles between refrigerator temperature (40C) and 450C with storage at each temperature of not less than 48 h is studied. Those formulations, which are stable at these temperatures, are subjected to centrifugation test.

Centrifugation

Passed formulations are centrifuged thaw cycles between 21 0C and +25 0C with storage at each temperature for not less than 48 h is done at 3500 rpm for 30 min. Those formulations that does not show any phase separation are taken for the freeze thaw stress test.

Freeze thaw cycle

Three freeze for the formulations. Those formulations passed this test showed good stability with no phase separation, creaming, or cracking. [8]

Turbidity Measurements

From each formulation, 1025 mg was introduced into 50 ml of water at 25 °C and the contents were gently stirred manually. Turbidity of the resultant emulsions given in nephrometric turbidity unit (NTU) was measured using Orbeco-Hellige model 966, Orbico Analytical System Inc., Farming dale, NY, USA. All measurements were done in triplicate. Dull, grayish white emulsion having slightly oily appearance that is slow to emulsify (longer than 2 min). Formulation, exhibiting either poor or minimal emulsification with large oil globules present on the surface. Grade A and Grade B formulation will remain as nanoemulsion when dispersed in GIT. While formulation falling in Grade C could be recommend for SEDDS formulation. [8]

Turbidimetric Evaluation

Nepheloturbidimetric evaluation is done to monitor the growth of emulsification. Fixed quantity of Self emulsifying system is added to fixed quantity of suitable medium (0.1N hydrochloric acid) under continuous stirring (50 rpm) on magnetic plate at ambient temperature, and the increase in turbidity is measured using a turbidimeter. However, since the time required for complete emulsification is too short, it is not possible to monitor the rate of change of turbidity (rate of emulsification) 8

Viscosity Determination

The SEDDS system is generally administered in soft gelatin emulation. So, it can be easily

Pourable into bottle and such system should not too thick to create a problem. The rheological properties of the micro emulsion are evaluated by Brookfield viscometer. This viscosities determination conform whether the system is w/o or o/w. If system has low viscosity then it is o/w type of the system and if high Viscosities then it is w/o type of the system. 9

Droplet Size Analysis Particle Size Measurements

The droplet size of the emulsions is determined by photon correlation spectroscopy (which analyses the fluctuations in light scattering due to Brownian motion of the particles) using a Zetasizer able to measure sizes between 10 and 5000 nm. Light scattering is

monitored at 25°C at a 90° angle, after external standardization with spherical polystyrene beads. The nanometric size range of the particle is retained even after 100 times dilution with water which proves the system's compatibility with excess water.

Refractive Index and Percent Transmittance

Refractive index and percent transmittance proved the transparency of formulation. The refractive index of the system is measured by refract meter by placing drop of solution on slide and it compare with water (1.333)**.** The percent transmittance of the system is measured at particular wavelength using UV-spectrophotometer keeping distilled water as blank. If refractive index of system is similar to the refractive index of water (1.333) and formulation have percent transmittance > 99 percent, then formulation have transparent nature.

CONCLUSION

The results obtained from this study revealed that by using the proper ratio and kind of oil, surfactant and co-surfactant, Rutin can be easily formulated into a SMEDDF with desired particle size range, turbidity and the amount of drug released. Formulation 8which contains Edible oil, tween 80 and Ca-8 in a ratio of 1:1:8 characterized by having the lowest turbidity and droplets size values (1.2 NTU and 30 nm, respectively) and the highest amount of drug release after 30 minutes (93%).

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