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Formulation Development And Evaluation Of Solid Self-Nano Emulsifying Drug Delivery System Of Rosuvastatin Calcium

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ABSTRACT

The primary aim of this current study is to establish an innovative Self Nano-Emulsifying Drug Delivery System (SNEDDS) to enhance the desired bioavailability and in vitro drug release, thereby amplifying the clinical effectiveness of orally administered drugs.SNEDDS is designed with the purpose of elevating the solubility of lipophilic or inadequately water-soluble drugs. It constitutes a blend of oil, surfactant, co-surfactant, and co-solvent, which amalgamate into an isotropic solution. This amalgam transforms into micro or nano-scale emulsions upon introduction into an aqueous environment with mild agitation. SNEDDS finds substantial utility in augmenting the solubility of drugs classified within the Bio-pharmaceutics classification system (BCS) class II and IV. It is particularly directed towards enhancing the solubility and bioavailability of poorly water-soluble drugs, with a focus on the Continuous-emulsification technique. SNEDDS emerges as a pioneering method in drug delivery, adaptable across diverse administration routes encompassing intravenous, ocular, intra-nasal, suppository, sustained-release oral formulations, pellets, and even cosmetic applications.

The implementation of SNEDDS remarkably accelerates the dissolution rate and diminishes interfacial tension. Upon dilution in aqueous media, such as gastrointestinal fluid, SNEDDS engenders a stable emulsion characterized by an oil-in-water (o/w) arrangement, featuring globule sizes measuring under 150 nanometers.

Keywords: *SNEDDS, Lipophillic, Emulsion, Isotropic, Dissolution rate.*

1. INTRODUCTION

The notion of drug delivery systems has arisen with the aim of mitigating the adverse and toxic effects of medications, expanding their range of applications, diversifying modes of delivery, and surmounting challenges in absorption. The utilization of lipid-based and biocompatible platforms for the solubilization, encapsulation, and conveyance of pharmaceutical agents is anticipated to augment absorption rates, curtail dosage requirements, reduce dosing frequency, and amplify the therapeutic window. The focal point of endeavors has been to ameliorate the oral bioavailability of lipophilic drugs to bolster their clinical efficacy. One prevalent strategy involves the integration of lipophilic components into inert lipid carriers, encompassing oils, surfactant dispersions, self-emulsifying formulations, emulsions, and liposomes—each possessing distinct merits and limitations. The suboptimal aqueous solubility inherent in such drugs frequently results in inadequate absorption following in vivo administration, leading to a portion of the dose inducing toxicity and undesired side effects due to unsought biodistribution patterns. The encapsulation and transportation of pharmaceutical agents via lipid-based mediums, including liposomes, niosomes, microemulsions, organogels, and nanocapsules, have demonstrated potential in augmenting drug effectiveness while mitigating adverse reactions.

These approaches offer several advantages [3]:

1. Improved oral bioavailability, allowing for dose reduction.
2. Consistent drug absorption profiles over time.
3. Targeting specific absorption windows in the gastrointestinal tract.
4. Shielding the drug from the harsh gut environment.
5. Controlling drug delivery profiles.
6. Decreased variability, including effects related to food.
7. Protection of delicate drug substances.
8. Accommodating high drug quantities.
9. Offering both liquid and solid dosage options.

2. DISADVANTAGES OF SNEDDS [11,12]

1. Traditional dissolution methods are not suitable for evaluating these formulations since drug release may depend on the process of digestion. As a result, there are no reliable in vitro models available for prediction.
2. To address this, researchers have developed an in vitro model that simulates the digestive functions of the duodenum.
3. Various lipid-based prototype formulations need to be produced and tested in live animals using a suitable animal model.

3. SELF NANO-EMULSIFYING DRUG DELIVERY SYSTEM [2,3,4,6]

Nanotechnology is widely acknowledged as a pivotal strategy in drug delivery, especially when enhancing the efficacy of hydrophobic medications. This is particularly significant in optimizing the performance of hydrophobic drugs. The utilization of self-nano-emulsifying drug delivery systems (SNEDDS) is a well-established approach for improving the solubility and bioavailability of poorly water-soluble drugs. SNEDDS, whether in the form of nanoemulsion preconcentrates or anhydrous nanoemulsions, facilitates swift digestion and absorption in the gastrointestinal tract due to their nanoscale dimensions. Through the pre-dissolution of the therapeutic compound, SNEDDS effectively eliminate the rate-limiting dissolution stage, resulting in a rapid onset of the drug's action. Self-nanoemulsifying drug delivery systems (SNEDDS) encompass formulations containing a combination of oil, surfactant, co-surfactant, and the drug itself.

4. MATERIALS AND METHODS:

Rosuvastatin calcium was gifted by EnaltecPharma, Ambernath, Mumbai. Olive oil, Polyethylene glycol 4000, Sodium lauryl sulphate,Talcum powder by Research -lab fine Chem industry Mumbai. All other chemicals used were of analytical grade.

5. FORMULATION AND DEVELOPMNT OF S-SNEDDS:

Table 01:Composition of SNEDDS dosage form

Batch	Drug((mg)	Oil(ml)	Emulsifying wax(gm)	Talc(gm)	Sieve size
F1	5	0.5	6	0.25	22
F2	5	1	6	0.25	22
F3	5	1.5	6	0.25	22
F4	5	0.5	7	0.25	22
F5	5	1	7	0.25	22
F6	5	1.5	7	0.25	22
F7	5	0.5	8	0.25	22
F8	5	1	8	0.25	22
F9	5	1.5	8	0.25	22

6. METHOD OF PREPARATION:

PROCEDURES FOR LIQUID SNEDDS FORMULATION:

An accurately measured quantity of Rosuvastatin calcium was introduced to olive oil. The blend underwent mild heating via a water bath within a glass vial. Following this, the components were amalgamated through stirring and underwent sorting and mixing at a velocity of 40 revolutions per minute. To optimize the formulation, the amalgamation was subsequently exposed to ultrasonic waves using an ultrasonicator for a span of 15 minutes. The resultant amalgam was stored at room temperature for later application.

7. PROCEDURES FORSOLID-SNEDDS FORMULATION:

A solid formulation of self-nanoemulsifying drug delivery system (SNEDDS) was developed based on a pre-existing liquid SNEDDS. The procedure encompassed the utilization of hot melt extrusion, during which Polyethylene glycol 4000 was melted. Sodium lauryl sulfate was introduced with continuous agitation, accompanied by the addition of the required volume of water. This mixture could be denoted as an emulsifying wax containing PEG4000.

Subsequently, the liquid SNEDDS, comprising a blend of the drug and oil, was combined with the solid SNEDDS composed of PEG4000 and SLS. This amalgamation continued with consistent stirring until a homogeneous phase was achieved, ensuring the creation of a well-structured emulsion. The resultant fusion of the wax and the drug underwent cooling and was then sifted through a sieve, ultimately producing a granulated powder.

8. CHARACTERIZATION OF S-SNEDDS:

DRUG CONTENT:

Rosuvastatin powder equivalent to 5 mg of Rosuvastatin was taken in a 50ml volumetric flask containing 5ml methanol and the volume was made up to mark with methanol to get a concentration of 100 µg/ml. An aliquot of 1 ml was transferred to a 10ml volumetric flask and volume was made up with methanol to get a concentration of 10 µg/ml. The absorbance of prepared solution was measured at λ max 240 nm by using UV visible spectrophotometer.

9. IN VITRO DISSOLUTION STUDY (% CUMULATIVE DRUG RELEASE):

In-vitro dissolution studies for the prepared powder of Rosuvastatin were carried out using USP apparatus type II at 50 rpm. The dissolution medium used was 0.1 N hydrochloric acid (900ml) maintained at 37 ± 0.5^0C. Aliquots of dissolution media were withdrawn (10 ml) at different intervals and content of Rosuvastatin was measured by determining absorbance at 240 nm. 10 ml aliquot was withdrawn at the 3min, 6min, 9min, 12min and 15min at 3min intervals and filter by Whatman filter paper and analyzed at 240 nm using- visible spectrophotometer.

10. RESULTS AND DISCUSSION:

PREFORMULATION STUDY:

1. Organoleptic characterization of drug

Table 02: Organoleptic propeties

Sr.No	Parameter	Observation
1	Colour	An off white to creamish white crystalline powder
2	Odour	Odourless
3	Appearance	Solid powder

a. Melting Point

Melting point of Rosuvastatin calcium was found to be 155°C.

b. UV Spectroscopy: In methanol, Rosuvastatin calcium exhibited a maximum absorbance at 243 nm, representing a distinctive attribute of its pure state.

c. Calibration curve of Rosuvastatin calcium in 0.1N HCL

The calibration curve of Rosuvastatin in 0.1 N HCL was shown in fig no 01. The absorbance at 243 nm for various conc of Rosuvastatin calcium.

Table 03: Calibration curve for Rosuvastatin in 0.1N Hydrochloric acid

Sr.no.	Concentration (ppm)	Absorbance
1.	5	0.2645
2.	10	0.5225
3.	15	0.7511
4.	20	0.9277
5.	25	1.2451

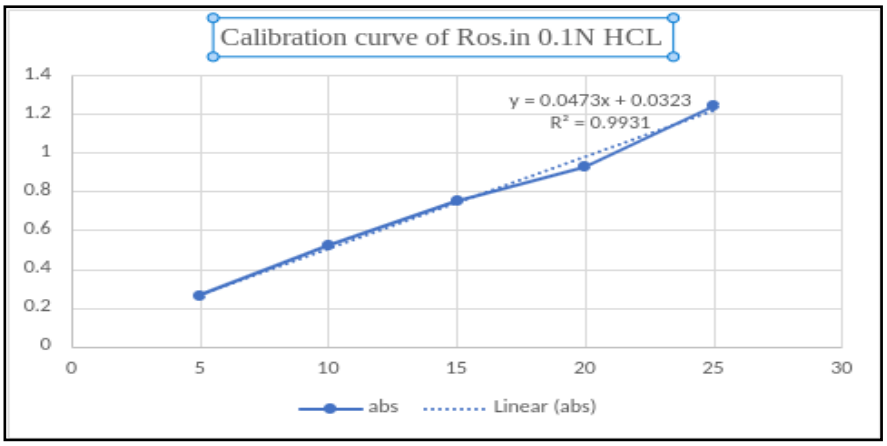

Fig 01: Calibration curve of Rosuvastatin calcium in0.1N HCL

d. Solubility Study

Table 04: Solubility of Rosuvastatin calcium in various oils

Vehicle (oil)	**Solubility of Rosuvastatin calcium(mg/ml)**
Arachis oil	9.6
Olive oil	95.3
Oleic acid	18.1
Coconut oil	12.9
Castor oil	23.05
Almond oil	18.75
Sesame oil	14.25
Cotton seed oil	6.2
Ethyl oleate	19.45

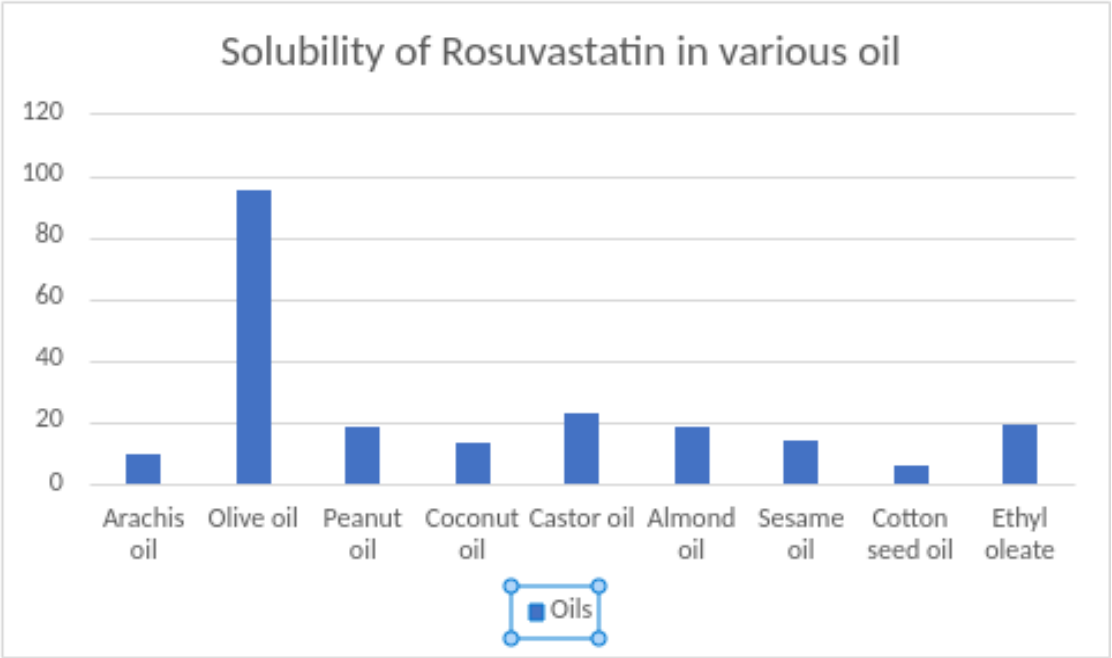

Fig 02: Solubility of Rosuvastatin calcium in various oils

2. Characterization Of Solid Snedds [10-17]

A. POWDER FLOW PROPERTIES:

a. Bulk Density [10]

Table 05 : Bulk Density

Batch	Bulk density(gm/ml) ± SD
F1	0.487 ± 0.003
F2	0.404 ± 0.0015
F3	0.389 ± 0.001
F4	0.501 ± 0.0015
F5	0.414 ± 0.003
F6	0.521 ± 0.001
F7	0.439 ± 0.011
F8	0.475 ± 0.004
F9	0.489 ± 0.003

The prepared SNEDDS exhibited bulk densities ranging from 0.389 ± 0.001 to 0.521 ± 0.001. Powders with elevated bulk densities generally demonstrate improved flow characteristics.

b. Tapped Density [11]

In the F9 batch, the highest tapped density recorded was 0.674 ± 0.004, while the F2 batch demonstrated the lowest tapped density of 0.485 ± 0.003. Tapped density is widely utilized in powder assessment due to its straightforward and swift measurement process. The capacity of a powder sample to compact under tapping conditions provides insight into its cohesiveness, which is interconnected with its flow behavior.

Table 06: Tapped Density

Batch	Tapped density(gm/ml) ± SD
F1	0.616 ± 0.003
F2	0.485 ± 0.003
F3	0.536 ± 0.002
F4	0.576 ± 0.0025
F5	0.552 ± 0.003
F6	0.566 ± 0.003
F7	0.501 ± 0.001
F8	0.545 ± 0.002
F9	0.674 ± 0.004

c. Angle of Repose [14]

Table 07: Angle of Repose

Batch	Height (H)(cm)	Radius(r)(cm)	Angle of repose(θ)	Flow property
F1	2.01	2.75	36.01 ± 0.01	Fair
F2	1.88	3.13	29.89 ±0.02	Excellent
F3	2.31	3.23	36.61 ±0.01	Fair
F4	1.89	2.91	29.12 ±0.03	Excellent
F5	2.72	3.05	41.52 ±0.03	Passable
F6	2.00	3.03	35.54 ±0.02	Good
F7	1.91	3.18	30.85 ±0.015	Excellent
F8	1.72	3.15	28.35 ±0.021	Excellent
F9	1.99	3.27	31.98 ±0.02	Good

The angle of repose for all formulated SNEDDS variations fell within the bracket of 28.35 to 36.61 degrees. A smaller repose angle signifies enhanced powder flow. Hence, the flow characteristics of F8 batch areassessed as highly favorable.

d. %Carr'sCompressibility Index [15]

Table 08: %Carr's compressibility Index

Batch	Bulk density(gm/ml)	Tapped density(gm/ml)	%Carr's compressibility Index	Flow property
F1	0.521	0.616	15.42 ± 0.02	Fair
F2	0.404	0.485	16.70 ±0.03	Fair
F3	0.389	0.536	27.42 ±0.027	Poor
F4	0.501	0.576	13..02 ±0.013	Good
F5	0.414	0.552	25.00 ±0.04	Poor
F6	0.487	0.566	13.95 ±0.01	Good

F7	0.439	0.501	12.37 ±0.02	Good
F8	0.489	0.674	27.44 ±0.01	Poor
F9	0.475	0.545	12.84 ±0.03	Good

Flowability is determined using the Carr index, where values above 25 suggest inadequate flow, while those below 15 indicate satisfactory flow. Applying this criterion, batches F6, F7, and F8 exhibit favorable flow characteristics, while batch F9 displays good flow properties.

e. Hausner's Ratio [16]

Table 09: Hausner's Ratio

Batch	Bulk density(gm/ml)	Tapped density(gm/ml)	Hausner's Ratio	Flow property
F1	0.521	0.616	1.18 ±0.015	Good
F2	0.404	0.485	1.20 ±0.021	Fair
F3	0.389	0.536	1.37±0.017	Poor
F4	0.501	0.576	1.14±0.02	Good
F5	0.414	0.552	1.33±0.032	Passable
F6	0.487	0.566	1.16±0.02	Good
F7	0.439	0.501	1.14±0.03	Good
F8	0.489	0.674	1.37±0.01	Poor
F9	0.475	0.545	1.14±0.02	Good

Hausner's ratio is a common parameter used to assess the flow index in pharmacopoeias. It serves as an indicator to distinguish between powders that flow easily and those that exhibit poor flow. In the context of pharmaceuticals, batches labeled as F1, F3, F4, F5, and F6 demonstrate favorable flow characteristics.

f. Drug Content [20]:

Table 10: Drug Content

Batches	Drug Content (%)
F1	98.63 ± 0.020
F2	99.89 ± 0.036
F3	98.31 ± 0.02
F4	100.95 ± 0.01
F5	101.01 ± 0.031
F6	98.86 ± 0.026
F7	99.20 ±0.04
F8	101.04 ± 0.01
F9	101.16 ± 0.02

The percentage drug content of all prepared formulation of S-SNEDDS was found to be in the range of 98.31% ± 0.02 to 101.16 ± 0.02 %.

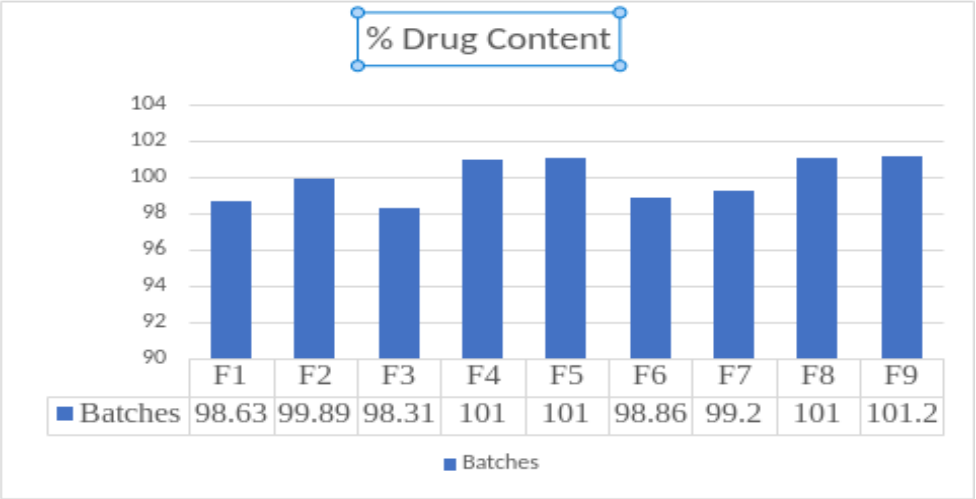

Fig 03:Drug content

g. In Vitro Dissolution Study:

Table 11: % Cumulative Drug Release

Time (min)	Batches	% Cumulative Drug Release (%)								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
3		12.55	18.78	19.66	15.69	17.65	21.36	19.65	18.67	22.45
6		38.56	42.66	40.47	36.36	45.23	49.85	44.36	44.78	49.78
9		63.98	56.82	65.99	61.78	67.75	68.37	63.99	64.85	68.56
12		82.41	78.95	82.98	79.88	85.22	84.21	82.32	79.69	86.89
15		98.15	94.86	96.65	95.66	98.78	97.29	97.75	95.65	99.06

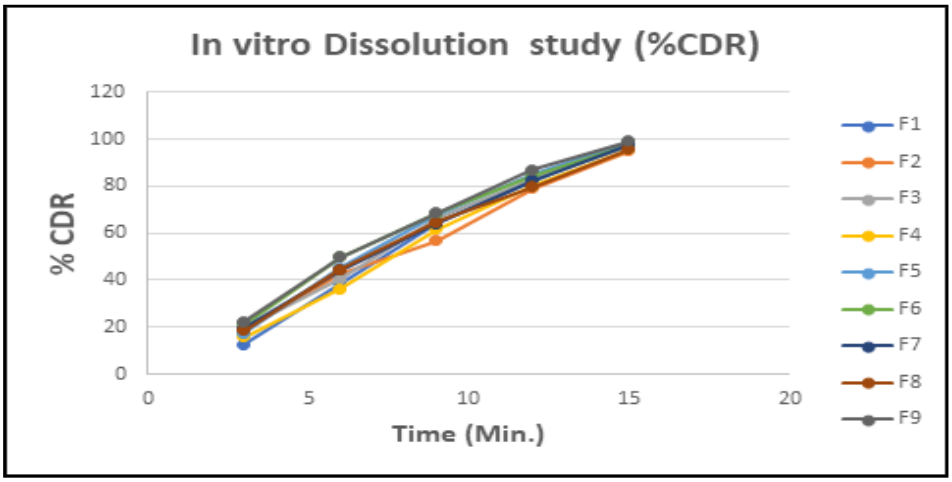

Fig 04: In vitro dissolution study

11. SUMMERY AND CONCLUSION

Rosuvastatin is a selective and competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts -3-hydroxy-3- methylglutaryl coenzyme A to mevalonate, a precursor of cholesterol.

To overcome the problems associated with the development of poorly soluble drug Rosuvastatin calcium, 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 by adding oil in drug. The S-SNEDDS was formulated by adding L-SNEDDS into excipients like PEG4000, SLS and water and pass the prepared formulation through various sieves.

The F9 batch has good flow properties according to characterization of powder S-SNEDDS. The angle of repose of F9 batch was found to be 31.98 ±0.02which indicates it has good flow properties and according to Carr's index and Hausner's ratio i.e. 12.84 ±0.03 and 1.14±0.02 respectively which means it has good flow properties.

Liquid SNEDDS and solid SNEDDS were prepared for Rosuvastatin calcium. In- vitro drug release and drug content of optimized formulation was found to be 99.06% respectively after 15 minutes. F9 batch of powder formulation shows better drug release. 101.16 was the drug content of F9 batch. For F9 batch, 22.45 % was %CDR at 3 minutes, 49.78%, 68.556%, 86.89%, 99.06% at 6,9,12 and 15 minutes respectively which is better in comparison with other batches.

The reported dissolution of marketed formulation has shown 40 % drug release, but F9 formulation in S-SNEDDS has shown 99.06 % drug release within 15 minutes, so the objective of increasing dissolution by formulating S-SNEDDS has been achieved in present study.

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