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FORMULATION AND EVALUATION OF NOVEL SELF NANOEMULSIFYING DRUG DELIVERY SYSTEM OF SUMATRIPTAN SUCCINATE

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Keywords:

Sumatriptan succinate, Self-nanoemulsifying pellets, Extrusion-spheronization

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ABSTRACT: In migraine disease which is an autoimmune disorder, 5-HT1 receptor agonist like Sumatriptan succinate (STS) is widely used. Its bioavailability is 15-17% due to extensive presystemic metabolism. The objective of this work was to prepare Sumatriptan succinate (STS) in a self nanoemulsifying drug delivery system (SNEDDS) and then convert it into solid-SNEDDS (S-SNEDDS) *via* extrusion/spheronization technique using Avicel pH 101, lactose monohydrate and Croscarmellose sodium. The component of SNEDDS was based on the solubility of STS in oily phases and surfactants. The screening of surfactants and cosurfactants were carried out in order to check its ability to emulsify the oily phase. Nanoemulsification area for the selected systems was identified by constructing the ternary phase diagrams. SNEP were characterized by scanning electron microscopy. SNEDDS composed of 30% Acrysol EL 135, 47% Tween 80 and 23% Capmul MCM C8. Its globule size was 98.4 nm, and zeta potential was -10.4 mV. S-SNEDDS possessed good mechanical strength and flow properties; angle of repose (25.79 ± 0.167), Hausner's ratio (1.058 ± 0.03) and Carr's index (5.55 ± 1.23). SNE pellets of uniform size and shape were manufactured. The total friability of pellets and disintegration time showed promising results. The time required for 80% drug release of SNE pellets was found to be 18 min, which was significantly higher than SNEDDS, STS containing reference pellets and marketed preparation of STS (SUMINAT® 25). Therefore, STS loaded S-SNEDDS was successfully prepared with improved bioavailability and then formulated into self nanoemulsifying pellets to immediate drug release.

INTRODUCTION: Sumatriptan succinate (STS) is 1-[3-(2-dimethylaminoethyl)-1 H-indol-5-yl]-N-methyl-methane sulfonamide succinate. It is a 5-HT1 receptor agonist used in the treatment of migraine [1]. STS is a BCS class III drug that having oral bioavailability of 15-17% because of extensive presystemic metabolism [2, 3].

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Solid dispersion, use of complexing agents, micronization, lyophilization, solubilization by surfactants, is some of the methods used to enhance dissolution characteristics and bioavailability of the drug. All these techniques might be associated with some problems like instability and poor drug loading efficiency.

To overcome these problems, self nanoemulsifying drug delivery system is a suitable method to improve the solubility, dissolution profile as well as the oral bioavailability of drugs [5]. It also improves thermodynamic stability and drug loading efficiency [6, 7]. Self-nanoemulsifying drug delivery systems (SNEDDS) is one of the most promising

techniques that could prevent the presystemic metabolism of drugs as drug degrading enzymes are generally too hydrophilic; they cannot enter these lipophilic droplets. Drugs being incorporated in these oil droplets are therefore protected towards an enzymatic attack and improve the drug bioavailability [8]. Also, they have a unique advantage over polymeric nanoparticles because their matrix is made from physiologically tolerated lipid components that decrease the potential for acute and chronic toxicity [9]. There is a concern encapsulating these liquid systems in capsules as some possibility of interaction with the capsule shell may lead to brittleness or softness and drug leakage. Adsorbing liquid SNEDDS onto powder would overcome these limitations. Many approaches were cited in literature about the solidification of liquid self-emulsifying (SE) ingredients into powders to create various solid dosage, examples of these techniques include adsorption to solid carriers, spray drying, melt granulation, melt extrusion/extrusion spheron-ization, where the final dosage form might be a SE; dry emulsions, capsules, sustained/controlled-release tablets, beads, microspheres, nanoparticles, suppositories, implants and pellets, which can finally be incorporated into hard gelatin capsules are very well documented in literature.

Pellets being a multiple unit dosage forms possess advantages, such as flexibility of manufacture and reduction of intra- and inter-subject variability of plasma profiles thus improving drug safety and efficacy. It was reported that the bioavailability of the self-nanoemulsifying mixture in a solid dosage form was equivalent to that of a liquid form and it also increases stability, reduces gastrointestinal irritation, reduces the blood concentration variability, extends the storage time of drug and improves patient compliance [12]. Self-emulsifying pellets disperse freely in the gastrointestinal tract and provide maximum drug absorption with a reduce peak plasma fluctuation; as a result, they minimize potential side effects without lowering drug bioavailability [13].

MATERIALS AND METHODS:

Materials: Sumatriptan succinate was kindly supplied by the sun pharmaceutical industry, Vadodara with a purity of 99.9%. Acrysol EL 135 and acrysol K- 140 were kind gifts from Corel Pharma Chem, Ahmedabad. Capmul MCM C8, Capmul MCM, Capmul GMO-50 and Captex-355 were kind gifts from IMCD, Mumbai. Cremophore EL, cremophore RH, Carbitol, Tween 80, Tween 20, span 80, span 20, Microcrystalline cellulose (Avicel® PH101) and Triacetin were supplied by Chemdyes Corporation, Rajkot, Gujarat. Olive oil, basil oil, jojoba oil, Linseed oil and Mustard oil were supplied from the genuine chemical corporation, Surat. Propylene glycol and Glycerol were supplied from Sulab laboratory, Vadodara. Cross-carmellose sodium was supplied from Astron Chemicals. Lactose monohydrate, PEG 400 and Propylene glycol were supplied from Suvidhinath Laboratories, Vadodara. All other chemicals used were of pharmaceutical grade.

Methods:

Selection of Oil Phase: Screening of oil is based on the solubility of the drug in it. Solubility studies of the drug in oil were carried out using different oils like Acrysol K140, Acrysol El, Capmul MCM, Captex, Basil oil, Mentha Oil, Linseed Oil, Jojoba Oil, Olive Oil, Castor Oil and Propylene Glycol. A known excess of the drug was added to 2 mL of oils into 5 mL vials, and mixed thoroughly *via* cyclo mixture. The vials were then stored at 25 °C in a shaker for 24 h. After that, the mixtures were spun by centrifuging for 15 min at 3000 rpm, which separate the supernatants and quantification using a UV-Vis spectrophotometer at 226 nm was done [6].

Selection of Surfactant: Screening of Different surfactants (Cremophor® EL, Cremophor® RH 40, span 20, Span® 80, Tween® 20, and Tween® 80) for the emulsification ability of the selected oil phase were carried out. Surfactant selection was done on the basis of the percentage of transmittance and ease of emulsification. The mixtures were prepared by adding 300 mg of the surfactants with 300 mg of the selected oily phase and gently heated at 50 °C for the homogenization of the components.

Dilution of Each mixture, 50 mg, with distilled water to 50 mL was carried out in a stoppered conical flask. Ease of emulsification was evaluated by the number of flask inversions necessary to yield a homogenous emulsion. The emulsions were kept to stand for 2 h and their % transparency was measured at 650 nm by a double-beam UV spectrophotometer using distilled water as a blank.

Any sign of turbidity or phase separation were furthermore observed for prepared emulsions [10, 14].

Selection of Co-Surfactant: Various Co-surfactants like PEG 400, Propylene glycol, Capmul® MCM C8, transcutol, and glycerol were screened for SNEDDS. % transparency and ease of emulsification were the criteria for the selection of co-surfactant. Mixtures of 100 mg of the co-surfactant, 200 mg of the selected surfactant and 300 mg of the selected oil were prepared and checked in a similar fashion as described in the above section on surfactants [10, 14].

Construction of Pseudo-ternary Phase Diagram: A pseudo-ternary phase diagram was constructed by the water titration method to determine the concentrations of component mixtures of oil, surfactant and co-surfactant. Different combinations of oil, surfactant and co-surfactant were grouped for phase studies. On the basis of solubility and emulsification study Acrysol EL 135, Tween 80 and Capmul MCM C8 were selected as oil, surfactant and co-surfactant, respectively. Surfactant and co-surfactant were blended in fixed weight ratios (1:1, 2:1, 3:1, 1:2).For each phase diagram, the ratio of oil to Smix was varied as 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2 and 9:1 (w/w) in different glass vials. Water was added dropwise to each mixture under vigorous stirring by using a magnetic stirrer. Titration of distilled water was carried out into the Smix-oil mixture slowly and vortexed for 2 min and the observation of the transition from clear to the turbid point and vice versa was noted down. No heating was applied during the preparation. The proper ratio of one excipient to another in the SNEDDS formulation was analyzed and the pseudo ternary plot was constructed using CHEMIX software version 10. All studies were repeated three times, with similar observations being made between repeats. Infinite dilution with purified water technique was employed to assess visually the self-nanoemulsifying performance.

Preparation of STS SNEDDS: Accurately weighed amount of oil was taken into a screw-capped glass vial then STS (25 mg) was added and heating in a water bath was carried out at 37 °C. The surfactant and co-surfactant were added in the above mixtures and stirred with a magnetic bar for ensuring complete mixing. The formulations were further sonicated for 15 min to get the clear solution [10].

Characterization of Liquid SNEDDS:

Dilution Test: The reconstitution of STS SNEDDS with double distilled water was carried and its percent transmittance was measured at 650 nm using a UV-Vis spectrophotometer against double distilled water as the blank. The studies were performed by diluting the STS SNEDDS by 50, 100, 250 and 1000 times.

Measurement of Mean Globule Size, Zeta Potential, and PDI: The malvern zeta sizer was used to measure droplet size, zeta potential and polydispersity index (PDI) of the formulation. The formulation was diluted with distilled water before analysis. Size analysis was monitored at 25 °C [15].

Viscosity: The viscosity of STS SNEDDS was determined with a Brookfield viscometer at 20 RPM at room temperature [15].

Cloud Point Measurement: It was measured by diluting Liquid SNEDDS with 500 times with water and placed into a water bath, and gradual increment in temperature applied. The temperature at which a sudden appearance of turbidity occurs was recorded [15].

The Emulsification Time: The emulsification time (the time for a pre-concentrate to form a homogeneous mixture upon dilution) was monitored by visually observing the disappearance of SNEDDS and the final appearance of the nanoemulsion. A dissolution apparatus was employed with 500 ml water, and with a paddle speed of 50 RPM at 37 °C. The SNEDDS (1 ml) was added dropwise to the medium by a dropping pipette and the time required for the disappearance of the SNEDDS was recorded. The entire study was performed in triplicate [15].

***In-vitro* Drug Release Studies:** Dialysis method was used to perform the *in-vitro* release of STS SNEDDS. After STS SNEDDS was installed into the dialysis bag, the dialysis bag was firmly sealed and was placed in 250 ml, 0.1 N HCl and water as the dissolution medium at 37 °C. The RPM was set at 100. Aliquots were withdrawn from the flask at regular time intervals and replacement with an

equivalent amount of fresh medium was done and analyzed spectrophotometrically at λ_{max} 226 nm [6].

Stability Testing: Thermodynamic stability test was carried out by exposing the formulations to heating-cooling, centrifugation and freeze-thawing, where the physical appearances of the formulations were observed at the end of each testing. In heating cooling, all formulations were heated at 45 °C and then cooled at 4 °C, with a duration of 24 h at each temperature, for 2 cycles.

Then, formulations which passed the heating-cooling cycles were subjected to centrifugation at 3500 rpm for 15 min. Finally, only formulations that passed the previous two steps were stored at an alternating temperature of -4 °C and 25 °C, with a duration of 24 hours at each temperature, for 2 cycles [6]. After that SNEDDS were subjected for stability studies at accelerated condition (25 °C ± 2 °C and 60% ± 5% RH) and at 5 °C ± 3 °C for period of 30 days. Viscosity, cloud point, dilution test were determined.

Preparation of Solid-SNEDDS (S-SNEDDS) of STS: Here a fine dried mixture of liquid SNEDDS with avicel and lactose was prepared using kneader until the liquid SNEDDS was completely adsorbed over carriers. Cross carmellose sodium as a super disintegrant was blended with the above adsorbed mixture for around 5 min. A mass with suitable consistency suitable for extrusion was obtained by adding drops of distilled water. Then extrusion of wet mass carried out using screw extruder. The extrudates were spheronized using a merumizer. The produced pellets were then air-dried [12, 13].

Experimental Design: A 3 factors and 2 levels full factorial design was employed for the optimization of S-SNEDDS by varying its components/factors such as Crosscarmelose sodium (X1), lactose monohydrate (X2) and Avicel pH101 (X3). The experimental plan was designed using Design expert version 10. Eight formulations were prepared by mixing various portions of Croscarmellose sodium, lactose monohydrate and Avicel pH 101 as recommended by the experimental plan **Table 2**.

Each formulation was evaluated for disintegration time (Y1) and time required for 80% drug release (Y2). The optimization's goal was kept to minimize Y1 and Y2. A best fitted quadratic equation was built for each response Eq. (1) and (2)

$$Y1 = + 13.34 - 5.40^* X1 - 2.02^* X2 - 1.65^* X3 \ldots\ldots\ldots (1)$$

$$Y2 = +44.12 - 18.88^* X1 - 4.12^* X2 - 4.37^* X3 \ldots\ldots\ldots (2)$$

A positive coefficient indicates a synergistic effect, while a negative one represents an antagonistic effect. ANOVA was employed to validate these models. Model adequacy tested by inspection of residual plots. The optimum S-SNEDDS pre-concentrate composition was determined using the desirability function.

TABLE 1: INDEPENDENT VARIABLES FOR FACTORIAL DESIGN

Factors	Levels	
	-1	+1
Crosscamelose sodium %	5	10
Lactose monohydrate %	15	30
Avicel pH 101%	20	40

TABLE 2: COMPOSITIONS OF THE SNE PELLETS

Batches	Crosscarmelose sodium (%)	Lactose monohydrate (%)	Avicel PH101 (%)	SNEDDS (%)
F1	10	30	40	20
F2	10	30	20	20
F3	5	15	40	20
F4	5	15	20	20
F5	10	15	40	20
F6	5	30	20	20
F7	10	15	20	20
F8	5	30	40	20

Characterization of S-SNEDDS of STS: Scanning Electron Microscopy (SEM): The outer macroscopic structure of the pellets was examined by scanning electron microscopy (SEM). Prior to microscopy, samples were coated with carbon by sputtering for 2 min by auto fine coater and scanned at a voltage of 10 kV [16].

Size Distribution of SNE Pellets: 25 g of SNE pellet formulations were vibrated by a set of

standard sieves (0.35, 0.5, 0.71, 1.18, 1.4, and 1.7 mm) for determination of size distribution. The subsequent tests were carried out on the modal size fraction (1180-1400 μm) [13].

Measurement of Flow Property and Friability: The flow characteristics of SNEP (Self-nanoemulsified pellets) were evaluated by determining the angle of repose. The values for Hausner's ratio and Carr's index were also calculated.

The friability of SNEP was assessed using friabilator. 5 mg SNE pellets were placed in the friabilator and rotated for 15 min. Then the rotated SE pellets were sieved by mesh 60 sieve and weighed in order to determine friability [12].

$$\% F = Mb\text{-}Ma/Mb \times 100$$

Where Mb is the weight of pellets before the friability test, and Ma is the weight of pellets after the friability test.

Drug Content: Accurately weighed quantity of 25 mg of STS equivalent pellets were taken into 100 ml volumetric flask, 50 ml of methanol was added and sonicated for 10 min. The solution was cool and diluted with methanol. Filter the solution through what man filter paper.

2 ml of filtrate was taken into a 100 ml volumetric flask and diluted to volume with distilled water. Scanning of the solution against Blank preparation between 200 nm and 400 nm was done the absorbance at 226 nm noted down [18].

Disintegration Time: The mean disintegration time of pellets was determined in deionized water at 37 ºC using a disintegration test apparatus modified including a 30 m sieve at the bottom of the disintegration tube. Pellets of each formulation were evaluated and the endpoint was taken as the time for the disintegration of the pellets [17].

***In-vitro* Dissolution Test:** The *in-vitro* release test was performed using SNEP in 500 ml of 0.1 N HCl using USP dissolution apparatus I. The basket was rotated at 50 RPM. Results were compared with pellets containing plain drug and marketed formulation (SUMINAT® 25). During the release studies, 5 ml sample of the medium was withdrawn and subjected to drug analysis using UV spectrophotometrically at 226 nm. The removed volume was replaced each time with 5 ml of fresh medium [12, 13].

Stability Study of Finished Formulation: Stability study was carried out as per ICH guidelines. The prepared pellets were stored in a humidity chamber with a relative humidity of 75 ± 5% and a temperature of 40 ± 2 °C or at room temperature for 1 month.

Samples were evaluated for their physical characteristics and drug content. The similarity factor (f2) was used for the evaluation of the drug release [19].

$$f_2 = 50 * \log\left\{\left[1 + (1/n)\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} * 100\right\}$$

Where n is the number of time points, R_t and T_t are the cumulative percentages dissolved at each of the selected n time points of the before and after 30 days of the stability study.

Drug-excipients Compatibility Tests: Fourier Transform Infrared (FT-IR) spectra was obtained for the pure STS, excipients (Acrysol EL, Capmul MCM C8 and Tween 80), which were used to formulate the SNEDDS, blank SNEDDS, and drug-loaded SNEDDS in the range of 400-500 cm^{-1}. Potassium bromide was used and each sample was placed in the light path of the sample cell and the spectrum was recorded.

The physical state of sumatriptan succinate in solid SEDDS was characterized by the differential scanning calorimetry analysis. The sample was placed in standard aluminum pans, and dry nitrogen was used as effluent gas. The sample was scanned at a scanning rate of 10 °C/ min between 40-260 °C and 40 ml/min nitrogen flow.

RESULTS AND DISCUSSION:

Screening of Oils, Surfactants and Co-Surfactant: The results of solubility of sumatriptan succinate in various vehicles were shown in **Fig. 1**. The drug loading capability was the main factor when screening the SNEDDS components. The highest solubility of Sumatriptan succinate was found in Acrysol EL 135 then Tween 80 followed

by Capmul MCM C8, which were used as oil phase, surfactant and co-surfactant respectively. A large, efficient self-nanoemulsification region which should be found in the pseudo-ternary phase diagram and should have efficient droplet size after forming a nanoemulsion.

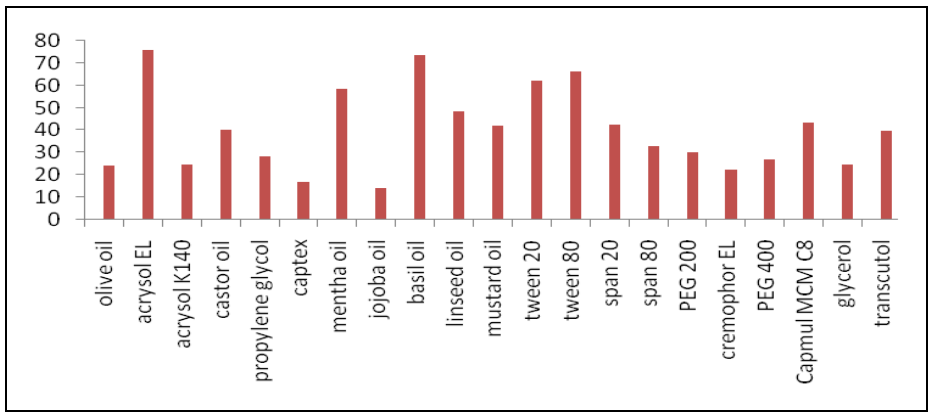

FIG. 1: SOLUBILITY OF STS IN VARIOUS VEHICLES

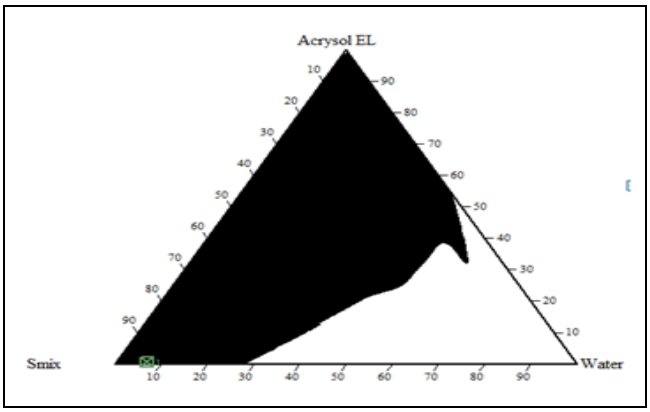

FIG. 2A: PHASE DIAGRAM OF ACRYSOL EL 135, TWEEN 80 + CAPMUL MCM C8 (2:1) AND WATER

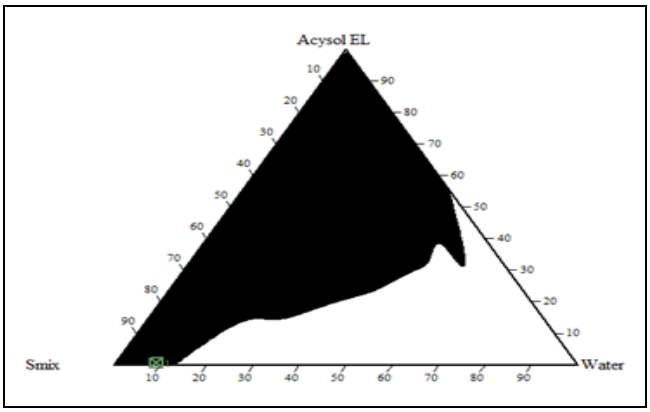

FIG. 2B: PHASE DIAGRAM OF ACRYSOL EL 135, TWEEN 80 + CAPMUL MCM C8 (1:1) AND WATER

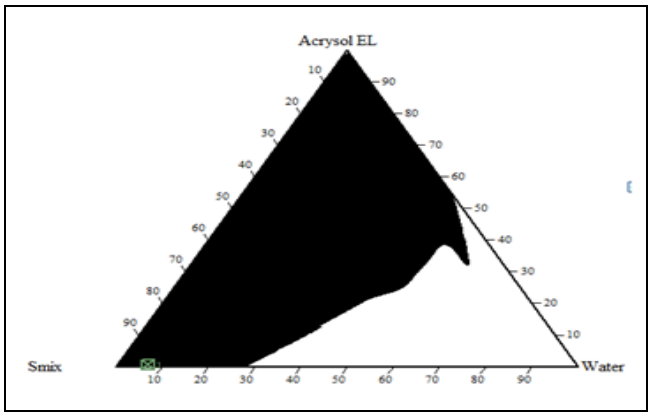

FIG. 2C: PHASE DIAGRAM OF ACRYSOL EL 135, TWEEN 80 + CAPMUL MCM C8 (1:2) AND WATER

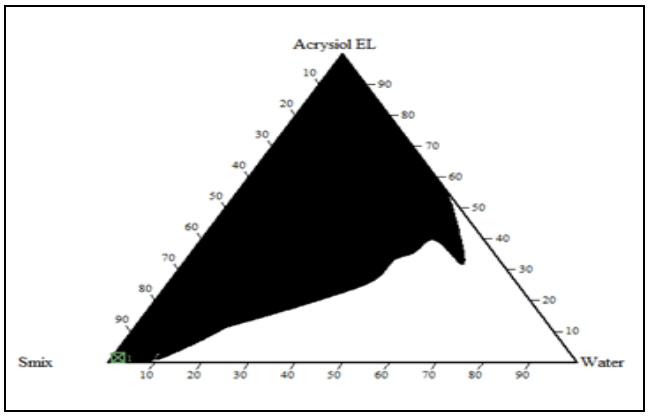

FIG. 2D: PHASE DIAGRAM OF ACRYSOL EL 135, TWEEN 80 + CAPMUL MCM C8 (3:1) AND WATER

The components and their concentration ranges can be obtained by the construction of a pseudo-ternary phase diagram. Their phase behavior was compared by constructing a pseudo-ternary phase diagram. The maximum region of self-nanoemulsion was obtained when the mixture of Tween 80 and Capmul MCM C8 in the ratio of 2:1 was used as a Surfactant co-surfactant ratio (Smix) as shown in **Fig. 2A**. Hence, the mixture of Tween 80 and Capmul MCM C8 in the ratio of 2:1 was selected. Non-ionic surfactants were used in most of SNEDDS because they are less toxic and less affected by pH and ionic strength. It was also noticeable that the 2:1 ratio of Smix, the mixture can take up a greater amount of water and still remain as a clear mixture with bluish tone during

aqueous titration. This could be explained by the fact that a higher amount of surfactants can be adsorbed at the interface and hence, stabilized the formation of nanoemulsions. Shadow area represents the self nanoemulsion region. The influence of the different ratios of surfactant (Tween 80) to co-surfactant (Capmul MCM C8) on the droplet size was also investigated. There were minor differences in mean droplet size when the ratio of surfactant increased from 10 to 30%. Co-surfactant was beneficial to form a nanoemulsion at a proper concentration range. However, an excessive amount of cosurfactant leads the system to become less stable for its intrinsic high aqueous solubility. As the droplet radius approached 100 nm, nanoemulsions seemed hazy and above this, in the submicron range, they appeared white due to significant multiple light scattering.

Drug-excipients Compatibility Study: Analysis by FT-IR spectroscopy was carried out to access any possible interaction between drug and excipients. **Fig. 3** shows FT-IR spectra of the pure drug STS, a mixture of SNEDDS (acysol EL135, Tween 80 and Capmul MCM C8) and STS loaded SNEDDS. They show no substantial shifting of the position of the functional groups of STS indicating no interactions between STS and excipients. Thermograms of pure STS, blank SNEP (without STS) and STS SNEP were obtained using differential scanning calorimeter as shown in **Fig. 4**. The thermogram of pure STS exhibited a sharp endothermic peak at about 166.12 ºC, corresponding to its melting point as shown in **Fig. 4A**. Blank SNEP showed no specific peaks near to STS endothermic peak as presented in **Fig. 4B**.

In the case of STS SNEP formulation, the endothermic peak of STS was absent as shown in **Fig. 4C**. The change in the melting behavior of STS can be attributed to the inhibition of its crystallization and solubilization of STS in SNEP. Therefore, it could be concluded that STS in the solid SNEDDS was in the amorphous form. It is known that transforming the physical state of a drug to the amorphous or partially amorphous state leads to a high-energy state and high disorder, resulting in enhanced solubility. As a result, it was expected that the solid particles would also have enhanced solubility.

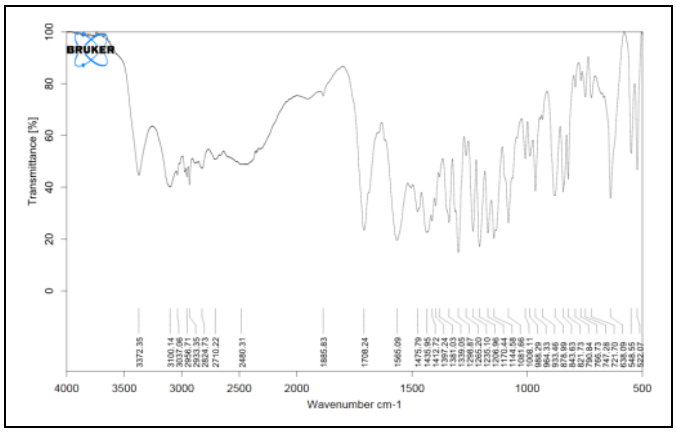

FIG. 3A: FTIR SPECTRA OF SUMATRIPTAN SUCCINATE (STS)

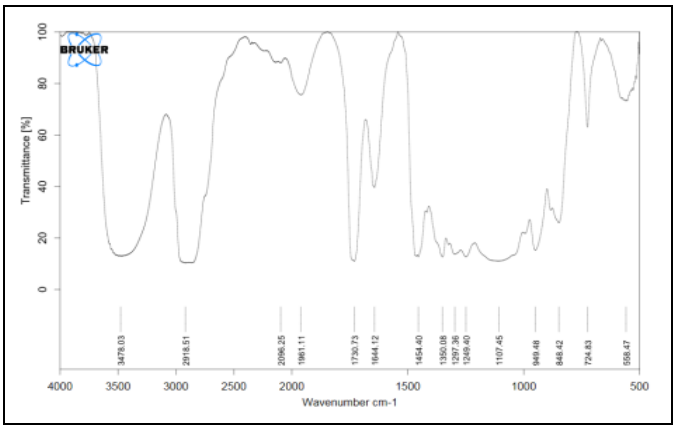

FIG. 3B: FTIR SPECTRA OF SNEDDS

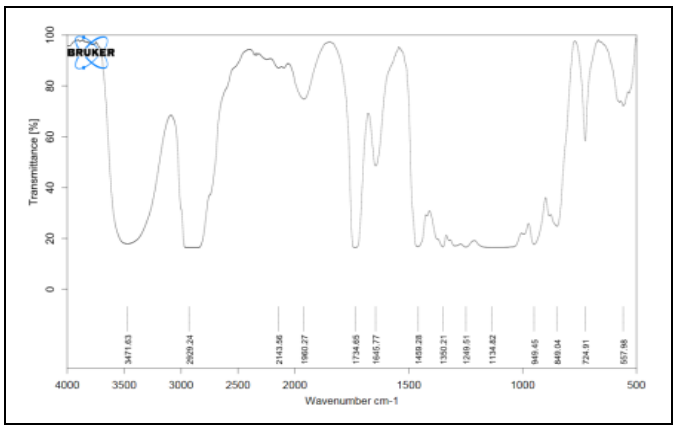

FIG. 3C: FTIR SPECTRA OF STS LOADED SNEDDS

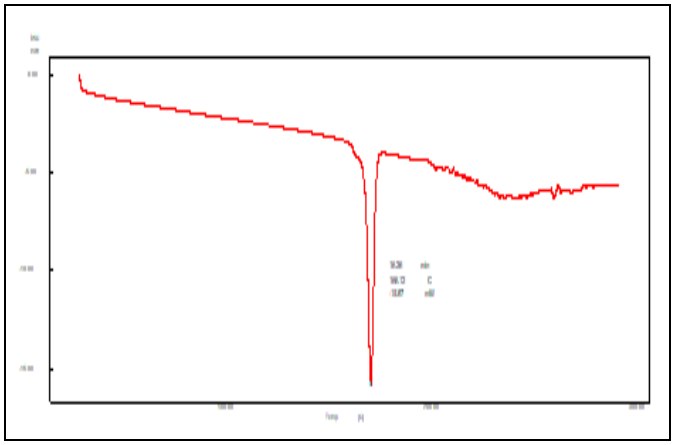

FIG. 4A: DSC SPECTRA OF PURE DRUG

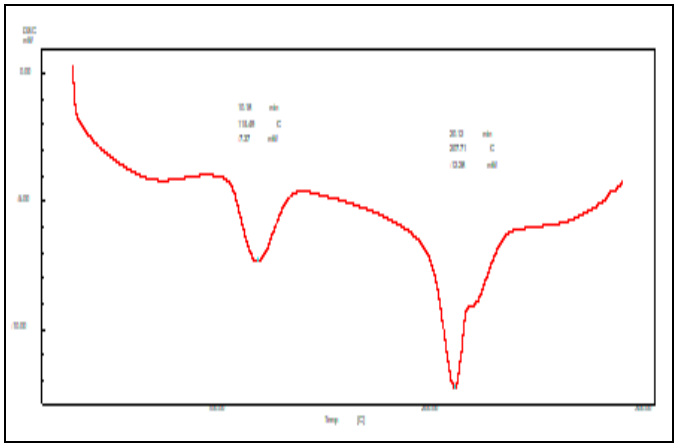

FIG. 4B: DSC SPECTRA OF BLANK SNEP

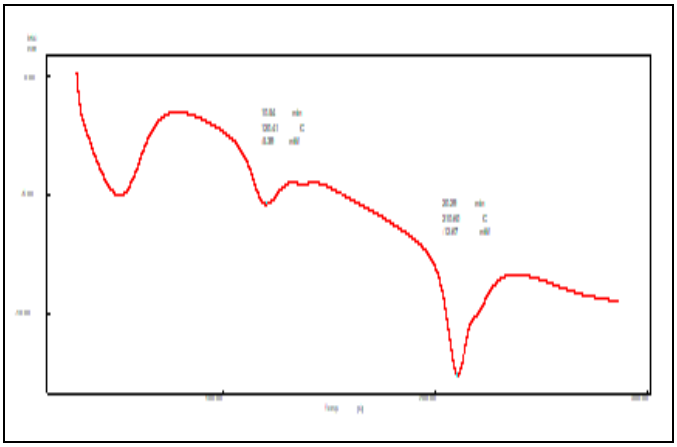

FIG. 4C: DSC SPECTRA OF DRUG LOADED SNEP

Effect of pH on Dilution: SNEDDS formulations were exposed to different folds of dilution in different media in an attempt to mimic the *in-vivo* conditions where the formulation would encounter. It has been observed that the pH of dilution media does not show a major effect on the percent transmittance of formulations.

TABLE 3: EFFECT OF DILUTION ON DIFFERENT SNEDDS FORMULATIONS USING DOUBLE DISTILLED WATER AS A DILUTION MEDIA

Percentage of transmittance (650 nm)	Batch no.									
	B1	B2	B3	B4	B5	B6	B7	B8	B9	B10
50 times	79	89	96.2	96.2	94.9	93.3	92.8	92.1	92.1	93.4
100 times	82	93	98	98	95.2	94.8	93.6	95.4	95.4	95.1
250 times	94	96	99	99	97.5	97.6	96.7	98.7	98.7	97.6
1000 times	98.2	98.7	99.1	99.8	99.7	99.8	99.6	99.4	99.4	98.9

Measurement of Mean Globule Size: The efficiency of self-nanoemulsification can be determined by the droplet size distribution. This is a critical factor in liquid SEDDS as it determines the bioavailability of drugs.

Globule size of the nanoemulsion was measured by diluting Liquid SEDDS with Distilled water. It was found to be 98.4 nm in B4, which contained 30% acrysol EL, 47% Tween 80 and 23% Capmul MCM C8.

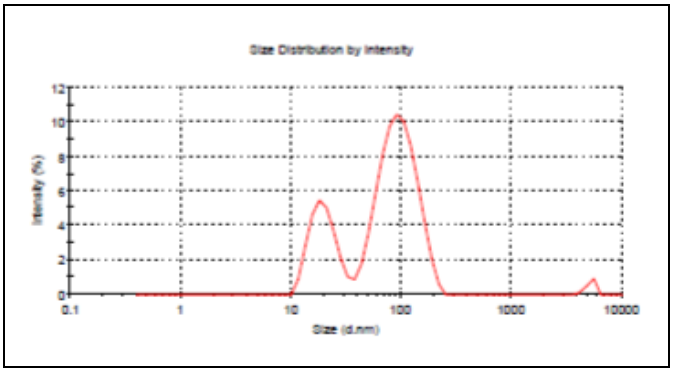

FIG. 5: GLOBULE SIZE OF OPTIMIZED BATCH

Viscosity: Viscosity of prepared STS SNEDDS was found to be 24 cps which is considered as suitable for liquid SNEDDS as it affects the droplet size and rate of drug diffusion. Viscosity B4 formulation was found to be 24 cps, which is desirable for SNEDDS.

Cloud Point Measurement: The cloud point of prepared SNEDDS was found to be 71-73 °C, which is above the body temperature (37 °C) that showed the stability of prepared STS SNEDDS at body temperature.

Emulsification Time: It is an important index for the assessment of the efficiency of emulsification, that is, the SNEDDS should disperse completely and quickly when subjected to aqueous dilution under mild agitation. B4 Liquid SNEDDS was emulsified within 24 s.

TABLE 4: CHARACTERIZATION OF SNEDDS

Test parameter	SNEDDS batches									
	B1	**B2**	**B3**	**B4**	**B5**	**B6**	**B7**	**B8**	**B9**	**B10**
Z-average diameter (nm)	---	51.47	72.78	98.4	137.8	234.5	312.8	487.4	612.2	748
PDI	---	0.52	0.673	0.438	0.458	0.663	0.578	0.5	0.54	0.64
Zeta potential (mV)	---	0.071	0.039	-10.4	-6.63	-15.5	-9.8	-8.6	-8.1	-12.8
Viscosity (cps)	39 ± 2	35 ± 1	29 ± 3.52	24 ± 1.75	27 ± 2	31 ± 2.52	34 ± 2	36 ± 2.57	38 ± 3	41 ± 1.75
Cloud point (°C)	33-35	39-41	42-43	71-73	70-72	69-71	67-70	61-62	58-60	47-48
Emulsification time (sec)	3 3± 3	29 ± 3.154	27 ± 4.027	24 ± 3.75	32 ± 2.15	39 ± 3.15	45 ± 2. 527	50 ± 3.54	54 ± 4	59 ± 3.154

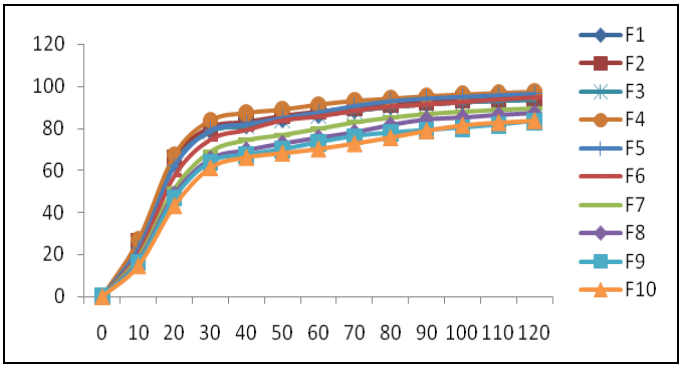

FIG. 6: *IN-VITRO* RELEASE PROFILE OF LIQUID SNEDDS

***In-vitro* Drug Release of SNEDDS:** When SNEDDS encounter aqueous medium, different forms of the solubilised drug are formed, that encompass free molecular state, drug in nano-emulsion and drug in micellar solution. Under these circumstances, it is necessary to separate free drug molecules from those entrapped in the nano-emulsion droplets or micelles to assess the real release pattern. Thereby, conventional release testing is not adequate for this system. For that purpose, the dialysis bag method is reported. It is reported that a dialysis bag with a molecular weight cut-off of 10,000 circumscribes escape of nano-emulsion into the release medium. The initial step shows a burst release, which can be attributed to the surface-associated drug, followed by a slower sustained release phase. The measured release rate from SNEDDS was significantly faster than that from the conventional tablet.

Stability Study: SNEDDS were passed the thermodynamic stability testing as there was no sign of phase separation or drug precipitation at the end of all cycles in B4 to B7 SNEDDS batches as per **Table 5**. SNEDDS was subjected to stability studies at accelerated temperature (25 °C ± 2° C and 60% ± 5% RH) and 5 °C ± 3 °C for period of 30 days.

Results of stability studies showed no significant change in thermodynamic stability, as there was no phase separation in B4 to B7 batch and no significant change in viscosity (*i.e.* 25 ± 2) as well as on dilution test.

Size Distribution: Sumatriptan succinate SNE pellets were successfully prepared by extrusion-spheronization technique, using different factors and levels applied in this study. The calculated pelletization yield for most of the formulation was over 80% **Table 7**. Quality assessment of the produced pellets was made by evaluating their size and shape and percentages of the SE pellets in the sieve fraction are shown in **Table 7**. The size of the modal fraction was 1 - 1.7 mm which more than 60% of the pellets were in this range [12, 13].

TABLE 5: THERMODYNAMIC STABILITY STUDY OF SNEDDS

Formulations	Heating cooling cycle	Centrifugation	Freeze thaw cycle
B1	F	---	---
B2	F	---	---
B3	F	---	---
B4	P	P	P
B5	P	P	P
B6	P	P	P
B7	P	P	P
B8	P	P	F
B9	P	P	F
B10	P	P	F

Scanning Electron Microscopy (SEM): The surface morphology of the SNEP formulation of STS was determined using a scanning electron microscope. A blank adsorbant mixture of Avicel pH 101 and lactose monohydrate was shown in **Fig. 7A** and after adsorbing SNEDDS on adsorbant was shown in **Fig. 7B** and **Fig. 7A** appeared with a rough surface and a porous particle.

However, **Fig. 7B** appeared as smooth surface of avisel pH 101 and lactose monohydrate, indicating that the liquid SNEDDS either adsorbed or coated inside the pores of the adsorbent powder mixture. The image of the self-nanoemulsifying pellets containing STS had the same outer macroscopic morphology consisting of well-separated spherical particles.

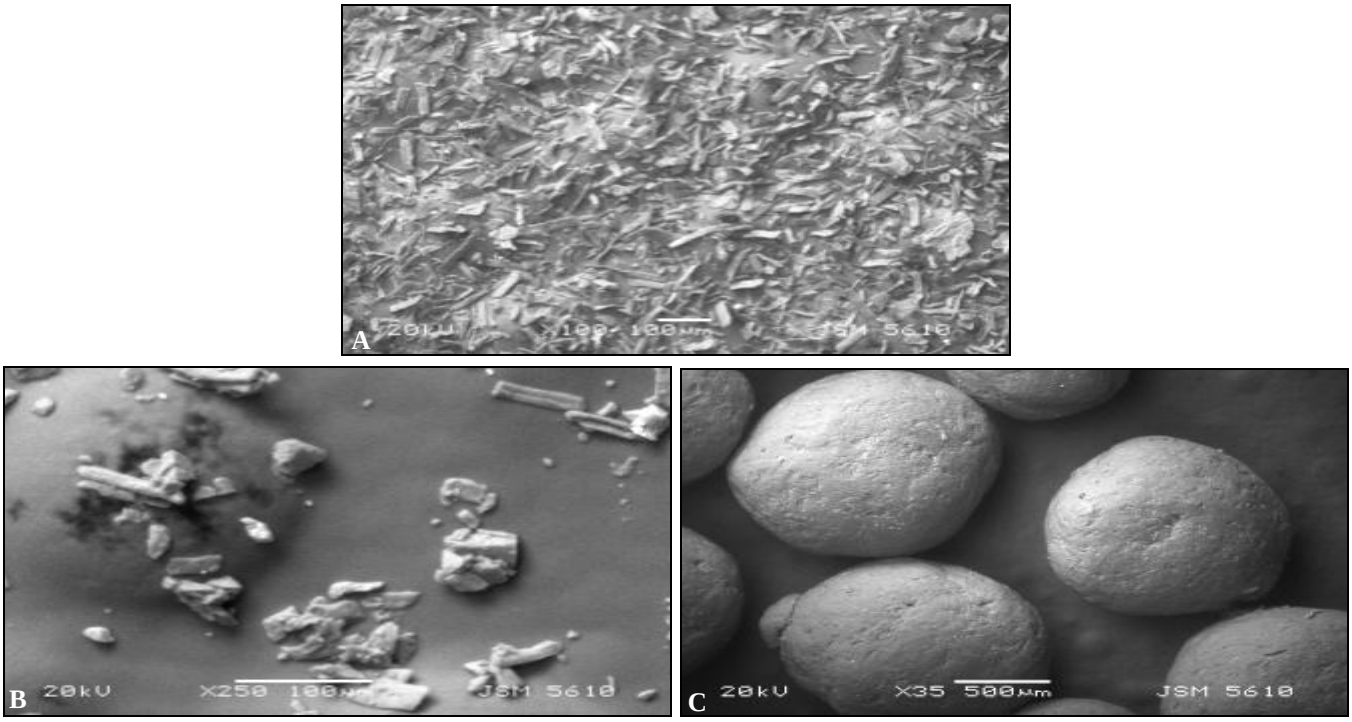

FIG. 7: (A) SEM PHOTOGRAPH OF ADSORBANT MIXTURE (B) SEM PHOTOGRAPH OF ADSORBANT MIXTURE AFTER ADSORBING SNEDDS (C) SEM PHOTOGRAPH OF SNEP

Determination of Flow Property and Friability: The angle repose, which was near to 25° and Hausner's ratio indicates the good flowability of the self-nanoemulsifying pellets. The value for Carr's index was less than 15 thus confirming excellent flow property of SNEP.

All formulations were exhibited friability values less than 1%, indicating good mechanical strength. Pellets prepared with only Avicel pH 101, showed poor hardness, poor flowability and easy agglomeration. Therefore, lactose monohydrate was added to improve the above parameters. It showed that as the amount of lactose monohydrate were increases, the friability of pellets decreases. This could be attributed to the utilization of different amounts of granulating water in different formulations to achieve suitable consistency which can affect the pellet's mechanical strength.

Disintegration of SNEDDS Pellets: The effect of croscarmellose on disintegration time is shown as a 3D surface plot **Fig. 8**. The plot demonstrates that increasing the amount of croscarmellose lead to faster pellet disintegration. It is well known that croscarmellose possesses wicking and swelling abilities and hence favors the water ingress inside the pellets and improves disintegration of pellets.

As we found out in this test and according to a previous study, adding the lactose had less effect on disintegration time but would be useful to improve the appearance of the pellets.

However, the amount of liquid SNEDDS had no significant effect on disintegration time. The disintegration time of various SNEDDS pellets was shown in **Table 7**.

TABLE 6: FLOW PROPERTIES OF STS S-SNEDDS

Formulation batch	Carr's index	Hausner's ratio	Angle of repose
F1	5.55 ± 0.002	1.058 ± 0.003	25.79 ± 0.167
F2	12.5 ± 0.005	1.142 ± 0.005	31.33 ± 0.091
F3	6.25 ± 0.008	1.066 ± 0.001	30. 87 ± 0.138
F4	5 ± 0.002	1.081 ± 0.006	27.83 ± 0.083
F5	10.2 ± 0.007	1.111 ± 0.002	29. 89 ± 0.123
F6	6.1 ± 0.003	1.081 ± 0.006	24.97 ± 0.28
F7	14.28 ± 0.005	1.166 ± 0.004	30.33 ± 0.114
F8	11.76 ± 0.008	1.133 ± 0.002	32.81 ± 0.097

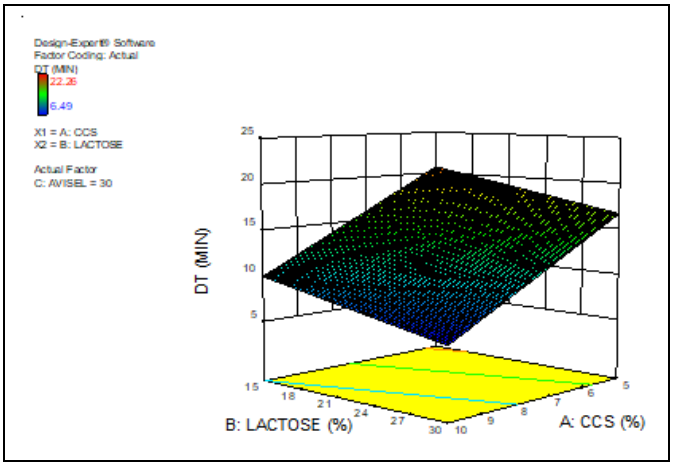

FIG. 8: 3D PLOT FOR DISINTEGRATION TIME OF S-SNEDDS

***In-vitro* Dissolution Test of S-SNEDDS:** *In-vitro* dissolution profile of different pellets formulations are shown in **Fig. 10**. The time required for 80 percent drug release (Q80) was used to compare the release profiles easily, The results are shown in **Fig. 9**, as a 3D surface plot. According to the plot increasing the amount of Crosscarmelose, decreasing the disintegration time, which leads to the fast release of drugs from pellets.

TABLE 7: CHARACTERIZATION OF S-SNEDDS

Batch no.	Sieve analysis (%)				% yield	Friability (%)	Disintegration Time (min)	Drug content (%)
	0.5-0.7 (mm)	0.71-1.18 (mm)	1.18-1.4 (mm)	1.4-1.7 (mm)		0.5-0.7 (mm)	0.71-1.18(mm)	1.18-1.4 (mm)
F1	9.9	11.3	67.7	7.6	96.3	1 ± 0.41101	6:6 ± 2.317	97.12
F2	0.1	0.9	22.4	59.9	83.3	0.9 ± 0.138	11 ± 1.305	98.87
F3	1.9	5.9	56.1	35.8	99.7	0.8 ± 0.62	21:03 ± 2.256	96.91
F4	1	5.4	47.1	46.6	99	0.22 ± 0.15	23:26 ± 1.330	98.39
F5	11.2	18.3	63.9	1.5	94.8	0.2 ± 0.7	7:58 ± 2.212	98.23
F6	0.1	1.2	17.3	72.5	91.1	0.27 ± 0.66	20:01 ± 3.210	97.85
F7	10.2	17.9	59.9	1.6	89.6	0.3 ± 0.45	10:56 ± 2.431	98.39
F8	0.6	2	21.3	73.9	97.8	0.4 ±0.58	20:65 ± 0.310	98.85

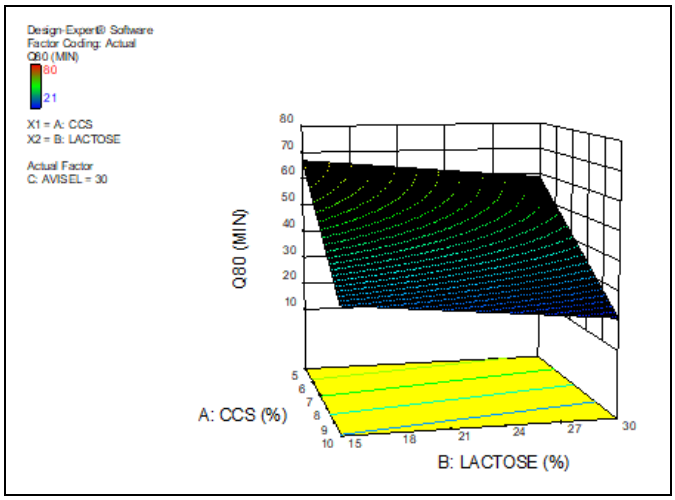

FIG. 9: 3D PLOT FOR Q80 OF S-SNEDDS

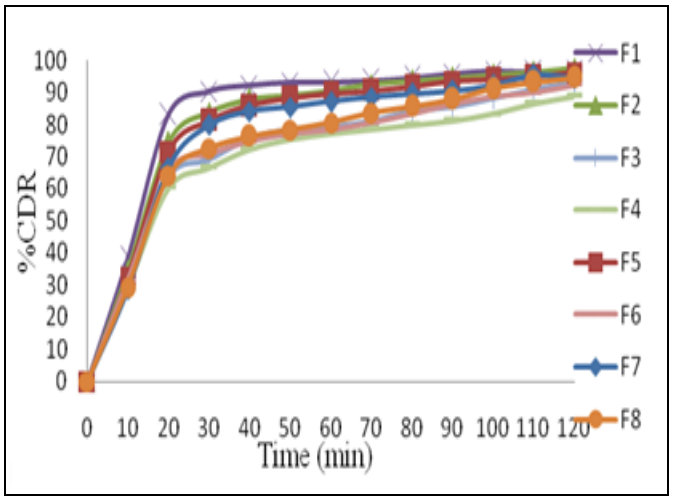

FIG. 10: *IN-VITRO* RELEASE PROFILE OF SOLID SNEDDS

Stability Study of S-SNEDDS: The STS SNEP was kept for one month at 40 °C ± 2 °C 75% ± 5% RH and evaluated for % drug content. The drug content in the SNEP remained at about 97.28–95.83%, which reflected that the optimized formulation was stable under the experimental condition. Furthermore, no significant change was found in STS content and in physical stability with no drug precipitation.

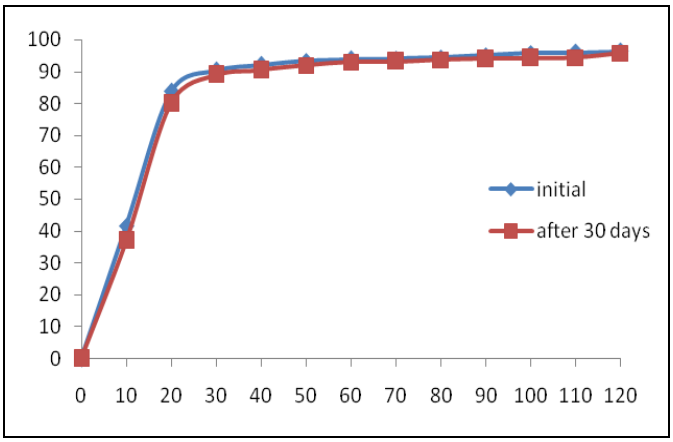

FIG. 11: *IN-VITRO* RELEASE PROFILE OF STS SNEP AT INITIAL AND AFTER 30 DAYS OF STABILITY STUDIES

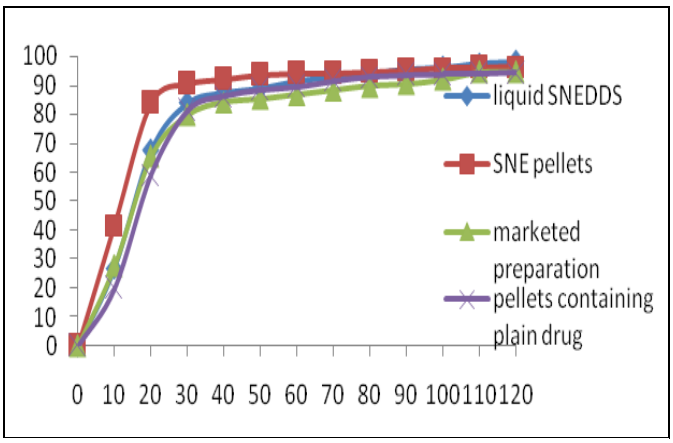

FIG. 12: *IN-VITRO* RELEASE PROFILE OF LIQUID SNEDDS, SOLID SNEDDS, MARKETED PRODUCT (SUMINAT® 25) AND PLAIN DRUG CONTAINING PELLETS

Study: *In-vitro* drug diffusion is shown in **Fig. 12**. The drug diffused at a faster rate from the SNE pellets than from SNEDDS, pellets containing plain drug and marketed preparation of STS (SUMINAT®25). After 120 min, the total percentage diffusion was the highest from the SNE pellets (96.4%) than from the market dosage (94.3%) and pellets contain plain drug (94.7%).

CONCLUSION: A SNEDDS containing Sumatriptan succinate was formulated for oral application. The components and their ratio ranges for the formulation of SNEDDS were obtained by solubility study, pseudo-ternary phase diagram construction, and droplet size analysis. The optimum formulation of the SNEDDS had sufficient drug loading, rapid self-nano emulsification in aqueous media, and forming droplet size in the range of nanoemulsion. Bioavailability of STS was enhanced by formulating a SNEDDS that was further transformed into S-SNEDDS pellets by extrusion/ spheronization technique. Visual observation and scanning electron microscopic analysis demonstrated good surface properties for the solid SNEDDS pellets. It also possessed good mechanical strength with preserved selfnanoemulsifying properties. The results of in vitro dissolution revealed that the pelletization process of STS SNEDDS had an appropriate effect on its self emulsification properties, also improve the drug release rate from resulted nano-emulsions.

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