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SELF-MICRO EMULSIFYING DRUG DELIVERY SYSTEMS FOR IMPROVED SOLUBILITY & BIOAVAILABILITY OF NEBIVOLOL

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Abstract:

The application of solid self-micro emulsifying drug delivery systems (S-SMEDDS) is one potential formulation approach for Nevibolol. In this study, self-micro emulsifying (SME) combinations of oil, surfactant, and cosurfactant were developed and their emulsifying efficacy was evaluated. Formulation (F4) was shown to be the most effective based on the ternary phase diagram, droplet size, zeta potential, and in vitro drug release data. Self-emulsification in water was quick because of the improved formulation. These results suggest that SMEDDS can be utilized to improve the solubility and dissolution of previously poorly soluble chemicals, such as Nevibolol. In vitro drug release tests revealed that the F4 formulation exhibited a 78.86% and 99.05% drug release at 45 and 120 minutes, respectively.

Keywords: *Nevibolol, Self-emulsification, S-SMEDDS, Oil, Surfactant and Co-surfactant.*

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INTRODUCTION:

Out of the many routes of administration available, the oral route remains the most popular dosage form among patients as it is easy to administer, carry around, has formulation design flexibility, is cost-effectiveness, causes minimal discomfort for many patients, and least sterility restrictions during manufacturing. Most of the newly discovered drugs are lipophilic and have poor aqueous solubility, thereby posing problems in their formulation into delivery systems [1]. The major challenge is the lipophilic drugs oral delivery owing to low aqueous solubility. Water insolubility is the major drawback for BCS class II drugs which leads to poor dissolution, and ultimately, low bioavailability of drugs is a challenge faced by the pharmaceutical industries [2,3]. Different approaches have been attempted to increase the aqueous solubility of poorly soluble drugs. The most promising and new techniques to enhance dissolution and improve the bioavailability of poorly water-soluble drugs are Lipid microemulsion formulations, which particularly emphasize self-nano emulsifying (SNEDDS), self-micro emulsifying drug delivery systems (SMEDDS), and self-emulsifying drug delivery systems (SEDDS) [4-6].

Self-microemulsifying oral drug delivery systems are growing popular in the delivery of poorly water-soluble BCS class II drugs [7,8]. Self-micro emulsifying drug delivery systems (SMEDDS) as lipid-and surfactant-established formulations encompass a practical achievement in improving the oral bioavailability of poorly water-soluble drug compounds by maintaining the drug in a dissolved state, at the molecular level in small droplets of oil, throughout its transit through the GI tract9. SMEDDS are mixtures of oils, surfactants, and co-surfactants, and they are capable of forming thermodynamically stable oil-in-water (O/W) microemulsions upon moderate stirring provided by the stomach and the upper small intestine [9]. Lipids have an immense role in absorption and transportation via intestinal lymphatics. The lipids are likely to augment the lymphatic transport of a lipophilic drug substance leading to enhanced oral bioavailability [10]. The drug, i.e., nebivolol, chosen in the present study is a BCS class II highly selective third generation β1-receptor antagonist, an antihypertensive drug with poor water-solubility and high permeability (log P of 4.03) undergoes rapid first-pass metabolism caused by cytochrome P450 2D6 (CYP2D6) enzymes resulted in poor bioavailability (12%). All these considerations have led to the development of solid oral SMEDDS. Several methods have been suggested to improve the solubility of nebivolol, Microemulsion technique, Solid Dispersion, cocrystals, nanofibrous sheets, solid lipid nanoparticles. To the above, numerous pharmaceutical approaches, including lipid-based formulations, have been developed to improve the dissolution rate and the absorption of poorly water-soluble drugs in the gastrointestinal (GI) tract by enhancing their solubility in vehicles. In the present investigation, SMEDDS were formulated, and their application in improving the oral bioavailability of a lipophilic antihypertensive drug, nebivolol, was also evaluated [11]. The solubility behavior of nebivolol was tested in different vehicles, and an optimized SMEDDS containing nebivolol was formulated. A dissolution study was performed to evaluate the improved solubility and dissolution properties of nebivol-loaded SMEDDS in comparison with pure nebivolol drugs. As a liquid SMEDDS formulation, however, inherent defects, such as migration of the components, potential drug leakage, and low stability during manufacturing, have limited its practical industrial application. To overcome these difficulties, solid SMEDDS (S-SMEDDS) formulations have been investigated as an alternative approach to improve the solubility of nebivolol drugs [12].

MATERIALS AND METHODS:

Nebivolol hydrochloride was a gift sample from MSN lab. PEG – 200, 400, 600; Span – 20, 60 80; Tween – 20, 60, 80; were purchased from SD. Fine-Chem., Mumbai. Pure Cotton Seed Oil, Pumpkin Seed Oil, Corn Oil, Almond Oil, Walnut Oil were purchased from Shree Overseas exports, Begumpur, New-Delhi, India.

Preformulation Studies:

Selection of oil:

The oil was chosen because Nebivolol dissolves in it. The main active ingredient in SMEDDS is oil. The solubilization and absorption of lipophilic drugs are greatly improved. The self-emulsification period of oil is shorter, and the intestinal lymphatic transportation of lipophilic medicines is increased [13]. The effectiveness of SMEDDS preparation relies on the usage of modified or hydrolyzed vegetable oils.

Selection of Surfactant:

Surfactants may be used to expand the drug's surface area. A surfactant's HLB score higher than 12 is the quality scientists look for most. Since nonionic surfactant is non-toxic, it is the preferred choice. To produce stable SMEDDS, a 30-60%w/w non-ionic surfactant is utilized in the formulation. Increasing the surfactant concentration causes the droplets to shrink [14].

Selection of Co-Surfactants:
Using the chosen oily phase and surfactant, a variety of co-surfactants were tested for their emulsification capabilities. Two milliliter (ml) mixes of the co-surfactant and medication were made and tested in the same way as the pure components.

Pseudo Ternary diagram:
Oil-phase grape seed oil, surfactant tween-20, and co-surfactant propylene glycol were chosen. Following the screening, 119 samples were generated, each with a slightly different concentration of excipients. To get the desired results, surfactant and co-surfactant were combined in varying concentrations (1:1,1:2,1:3,1:4,2:1,3:1,4:1). In addition, 17 different combinations of oil and particular surfactant's surfactant were tested, with surfactant: co-surfactant ratios ranging from 1:9 to 9:1. 100 l of the formulations were placed in a beaker with 100 ml of water, and the contents were gently stirred with a magnetic stirrer. The clarity, phase separation, and oil droplet coalescence of the resulting emulsion were evaluated [15]. Unstable emulsions were determined to be those that showed phase separation and coalescence. Oil, surfactant, and co-surfactant were used to determine the excellent self-micro emulsifying zone, and from there ternary phase diagrams were constructed.

Table 1: Construction of Ternary Phase Diagram

S.NO	Oil: Smix	Smix	%Oil	%Surfactant	%Co-Surfactant	% Transmittance
1	1:1	1:1	50	25	25	100.12
2	1:2	1:1	33.33	33.33	33.33	100.41
3	1:4	1:1	20	40	40	100.76
4	1:5	1:1	16.66	41.65	41.65	100.53
5	1:6	1:1	14.28	42.9	42.9	100.42
6	1:8	1:1	11.11	44.44	44.44	100.39
7	1:9	1:1	10	45	45	100.68
8	1:1	1:2	50	16.66	33.32	100.63
9	1:2	1:2	33033	22.22	44.44	100.47
10	1:3	1:2	25	25	50	100.59
11	1:4	1:2	20	26.66	53.32	100.49
12	1:5	1:2	16.66	27.76	55.52	100.21
13	1:6	1:2	14.28	28.5	57	100.28
14	1:7	1:2	12.5	29.16	58.32	100.49
15	1:8	1:2	11.11	29.62	59.24	100.36
16	1:9	1:2	10	30	60	100.67
17	1:1	1:3	50	12.5	37.5	100.08
18	1:3	1:3	25	18.75	56.25	100.53
19	1:4	1:3	20	20	60	100.49
20	1:5	1:3	16.66	20.8	62.4	100.64
21	1:6	1:3	14.28	21.42	64.26	100.69
22	1:8	1:3	11.11	22.22	66.66	100.69
23	1:9	1:3	10	22.5	67.3	100.78
24	1:2	1:4	33.33	13.33	53.32	100.23
25	1:3	1:4	25	15	60	100.29
26	1:4	1:4	20	16	64	100.59
27	1:5	1:4	16.66	16.66	66.64	100.38
28	1:6	1:4	14.28	17.14	68.55	100.50
29	1:7	1:4	12.5	17.5	70	101.63
30	1:8	1:4	11.11	17.78	71.10	100.06
31	1:2	2:1	33.33	44.44	22.22	100.02
32	1:3	2:1	25	50	25	100.03
33	1:5	2:1	16.66	55.52	27.76	100.15
34	16	2:1	14.28	57.1	28.5	100.26
35	1:8	2:1	11.11	59.24	29.62	100.15
36	1:2	3:1	33.33	49.98	16.66	100.19
37	1:3	3:1	25	56.25	18.75	100.15

38	1:4	3:1	20	60	20	100.27
39	1:5	3:1	16.66	62.4	20.8	10013
40	1:6	3:1	14.28	64.26	21.42	100.16
41	1:8	3:1	11.11	66.66	22.22	100.45
42	1:9	3:1	10	67.3	22.5	100.40
43	1:2	4:1	33.33	53.32	13.33	100.79
44	1:3	4:1	25	60	15	100.40
45	1:4	4:1	20	64	16	100.48
46	1:5	4:1	16.66	66.64	16.66	100.69
47	1:6	4:1	14.28	68.55	17.14	100.62
48	1:8	4:1	11.11	71.10	17.78	100.12
49	1:9	4:1	10	72	18	100.26

Preparation of Liquid SMEDDS:
To create drug-loaded liquid SMEDDS, we will use the micro emulsifying zone discovered in the ternary phase diagram's construction. Oil and Smix were used in the development of many different formulations, with surfactant and co-surfactant ratios also playing a role. To make them, we mixed drug-loaded Smix at 37 degrees Celsius. After letting the combination equilibrate for a full day, we checked for turbidity and phase separation to ensure that our new formulations were of the highest quality [16].

Preparation of Solid SMEDDS:
Adsorption of the SMEDDS formulations onto the surface of the inert solid carriers is the simplest way to convert the L-SMEDD formulation into the S-SMEDD formulation. Following the preparation of the dosage equivalent of L-SMEDD, the formulation was moved to a China dish and Aerosil was added gradually while being aggressively agitated. Finally, a free-flowing powder dose equivalent was developed [17].

CHARACTERIZATION OF SMEDDS:
Particle size: Droplet size is a critical aspect of emulsions since it affects how quickly and how much of the medicine is absorbed. As this method requires that the emulsion's properties remain unchanged after infinite aqueous dilution, photon correlation spectroscopy (PCS) is a useful technique for figuring out the emulsion's droplet size.

Polarity: The polarity of the droplets in an emulsion is a key indicator of the success of the emulsification process. The drug's polarity indicates the nature of the forces created and its affinity for oil and/or water [18]. Polarity facilitates the speedy dissolution of the medication into the solvent.

Zeta potential: Regular SMEDDS have a negative charge as of the free fatty acids they contain, but cationic SMEDDS may be made by adding a cationic lipid such oleyl amine at a concentration of 1-3%. As a result, the n-potential of these systems is typically between +35 and +45 mV15. Upon addition of the active pharmaceutical ingredients, the n-potential value remains positive [19].

Drug precipitation /stability on dilution: A medication's solubility in oil phase has a significant impact on SMEDDS's capacity to keep the molecule solubilized. Since dilution of SMEDDS would result in a decrease in the solvent capacity of the surfactant or co-surfactant, it is crucial to ascertain the stability of the system after dilution if the surfactant or co-surfactant is contributing to the drug's solubilization to a significant level. Typically, this is accomplished by diluting a single dosage of SMEDDS with 250ml of 0.1N HCl solution. Potential drug precipitation from this solution is monitored. Assuming a stomach retention duration of two hours, SMEDDS should maintain drug solubility for four to six hours.

Thermodynamic stability studies: Precipitation of the medication in the excipient matrix might reduce the performance of a lipid-based formulation, hence its physical stability is particularly critical. Additionally, formulation performance and aesthetic appeal might be negatively impacted by phase separation of the excipient due to insufficient physical stability of the formulation. Furthermore, incompatibility between the formulation and the gelatin capsules shell might cause brittleness or deformation, delayed disintegration, or inadequate drug release.

Viscosity Determination: Soft gelatin or firm gelatin capsules are used for most SMEDDS administrations. To avoid complications, the system shouldn't be too thick and should be readily pourable into capsules. Micro emulsion rheological characteristics are determined using a Brookfield viscometer.

Droplet Size Analysis: A Zetasizer capable of measuring sizes between 10 and 5000 nm is used to quantify the droplet size of the emulsions by photon correlation spectroscopy (which analyzes the variations in light scattering due to Brownian motion of the particles). External standardization using spherical polystyrene beads allows for the measurement of light scattering at 25°C and a 90° angle.

Refractive Index and % Transmittance: By putting a drop of solution on a slide and comparing it to water, the refractometer can determine the system's refractive index (Refractive index of water1.333). By UV-spectrophotometer and a blank of distilled water, we may determine the system's % transmittance at a given wavelength. If the system's refractive index is close to that of water, and the formulation has a transmittance of more than 99 percent, we say that the formulation is transparent.

***In vitro* Diffusion Study:** To investigate the release behavior of formulation from the liquid crystalline phase surrounding the droplet, in vitro diffusion experiments employ the dialysis method.

Drug content: The drug is extracted from the SMEDDS by dissolving them in the appropriate solvent after they have been preweighed. An appropriate analytical approach was used to compare the drug content of the solvent extract to the drug's standard solvent solution.

Droplet polarity: The polarity of the droplets and the size of the droplets in an emulsion are two very significant properties. When the droplets are tiny enough and have the right polarity (a lower partition coefficient o/w of the medication), the drug may be released at a pace that is tolerable. The oil/water partition coefficient of the lipophilic medication may also be used as a proxy for estimating the polarity of the oil droplets.

Scanning Electron Microscopy (SEM): A scanning electron microscope creates pictures by moving a beam of electrons over a sample's surface. A variety of signals are produced when electrons strike sample atoms; these signals can be decoded to reveal information about the sample's atomic composition and surface topography. It was attached using several improved formulas. This specimen, which had been sputter coated with gold particles, was seen at an acceleration voltage of 10 kV in a SEM (JSM-5610, JEOL, Japan). Surfaces of powder have been photographed.

In Vitro Dissolution : The USP class II dissolution test equipment was used to conduct the study (Lab India). The dissolving media was 900ml of a pH- and pKa-adjusted buffer that was kept at 370.5 C with a paddle speed of 100rpm. The dissolving tester has an outside water bath to keep everything at a consistent temperature. At 0, 5, 10, 15, 30, 45, 60, 90, and 120 minutes, 5 ml samples were taken, filtered, and then replenished with new dissolving media. When required, dissolving fluid was added to the collected samples before UV analysis at 284 nm to detect the presence of the medication. After doing each dissolving experiment three times, we averaged the results [20].

FTIR Studies: For the FT-IR measurements, a Hitachi 295 spectrophotometer was used using the KBR disc technique. Over the range of 4000 to 400cm-1, the samples were scanned. To create discs, a hydraulic press was used to exert a force of 15000 pounds of pressure on the mixture of pure medication, aerosol, and optimum formulation and infrared (IR) grade KBR.

RESULTS AND DISCUSSION:

Selection of Oil:

Using separate Eppendorf tubes, 1 ml of various oils are extracted. The right amount of medication must be added. 15 minutes of mixing in a vortex. Maintain a steady stream of medicine additions until the powdery substance sinks to the bottom, at which point you should start again. The tubes should then be left in an orbital shaker for 72 hours (37.5 degrees Celsius, 100 rpm). The tubes are then centrifuged on a micropipette centrifuge at 8000 rpm for 15 minutes. In a 50-milliliter volumetric flask, 10 milliliters of the supernatant liquid (oil + medicine) was combined with 50 milliliters of distilled water. After setting aside 100 tilts for an hour, the absorbance was measured at 252 nm. Based on the absorbance value and the estimated medication concentration in oil, the optimal oil was chosen.

Selection of Surfactant:

One milliliter of each surfactant is collected in individual Eppendorf tubes (tween 80, tween 20, span 20, span60, span 80). The right amount of medication must be added. For 15 minutes, ingredients were whirled together in a vortex mixer. The medicine should be added steadily until the powder settles to the bottom, at which point the process should be repeated. The tubes should then be left in an orbital shaker for 72 hours (37.5 degrees Celsius, 100 rpm). The tubes are then centrifuged on a micropipette centrifuge at 8000 rpm for 15 minutes. A volumetric flask containing 50 ml of distilled water was used to

dilute the 10 L of supernatant liquid (surfactant + medication). After setting aside 100 tilts for an hour, the absorbance was measured at 252 nm. The absorbance was recorded, the solubilized drug concentration was computed, and the surfactant was chosen per the determined solubilized drug concentration.

Selection of Co-Surfactant:

The absorbance was recorded, the solubilized drug concentration was computed, and the surfactant was chosen by the determined solubilized drug concentration. The right amount of medication must be added. 15 minutes of mixing in a vortex. Repeat the previous steps while constantly adding the medicine until the powder settles to the bottom. The tubes should then be left in an orbital shaker for 72 hours (37.5 degrees Celsius, 100 rpm). The tubes are then centrifuged on a micropipette centrifuge at 8000 rpm for 15 minutes. In a 50 ml volumetric flask, 10 L of the supernatant liquid (Co-Surfactant + medication) was added to a total volume of 50 ml of distilled water. After setting aside 100 tilts for an hour, the absorbance was measured at 252 nm. Drug solubilization concentration was determined by measuring absorbance, and the Co-Surfactant was chosen under this value.

Table 2: Solubility Profile of Nebivolol

S.No	Solvents	Solubility mg/ml
	OILS	
1.	Corn Oil	6.3
2.	Olive Oil	6.3
3.	Walnut Oil	10.58
	SURFACTANTS	
1.	Span – 20	42.67
2.	Span – 80	638.7
3.	Tween – 20	182.8
4.	Tween – 80	180.6
	CO-SURFACTANTS	
1.	Propylene Glycol	153.1
2.	PEG – 200	31.94
3.	PEG – 400	43.45
4.	PEG - 600	147.4

Ternary Phase Diagram:

Based on the different oil, surfactant, and co-surfactant concentrations, seven different solutions (oil + Smix) with different ratios of oil to Smix (1:1, 1:2, 1:3, 1:4, 2:1, 3:1, and 4:1) were made. Formulations were made for 100 l and diluted with 50 ml of distilled water in 50 ml volumetric flasks; the solution was mixed thoroughly by 100 tiltings; the flasks were set aside for 1 hour; and the % Transmittance was measured at 638.2 nm using a UV double beam spectrophotometer. The ternary phase diagram was built in CHEMIX SCHOOL VERSION 7.0 using the fixed ratios determined by the transmittance measurements. Once a darkened area has been identified, it is used as the emulsification zone.

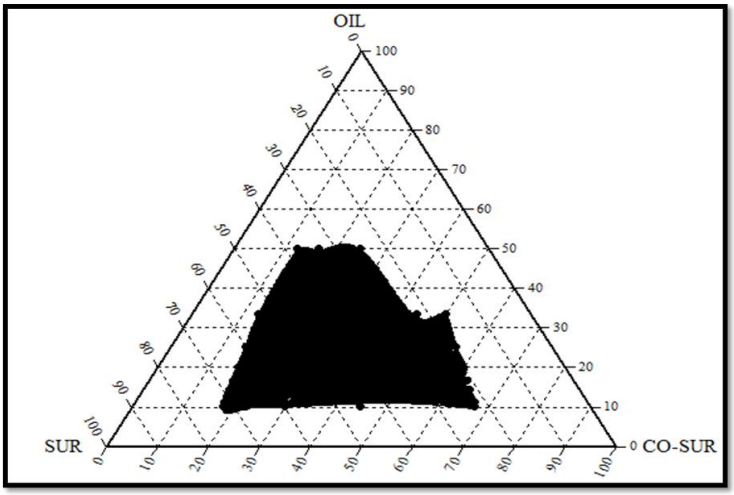


Fig.1: Ternary phase diagram. (Black indicates the self-emulsification zone.)

Preparation of Liquid SMEDDS

Variable quantities of walnut oil, Tween 20, and propylene glycol were used to create a variety of L-SMEDDS containing Nebivolol (2.5mg). The necessary quantity of each component was measured out, and then thoroughly combined in a vortex mixer until a clear solution was achieved. Particle size was measured using a Malvern Zeta sizer after the final solution was diluted with 100 times its original volume of pure water.

Preparation of S-SMEEDS

Adsorption of an improved liquid self-micro emulsifying emulsion drug delivery system (L-SMEEDS) formulation onto Aerosil 200 was used to create a solid self-micro emulsifying drug delivery system (S-SMEDDS) (1:1, 1:2 ,1:3 ,1:4 ,2:1 ,3:1,4:1). After placing Aerosil in the motor, the liquid SMEDDS was added drop by drop while the substance was being stirred. The procedure carried on until a powder that could be easily poured was achieved. The resulting powder was used to stuff the gelatin capsule (size -00).

S-SMEDDS Optimal formulation particle size

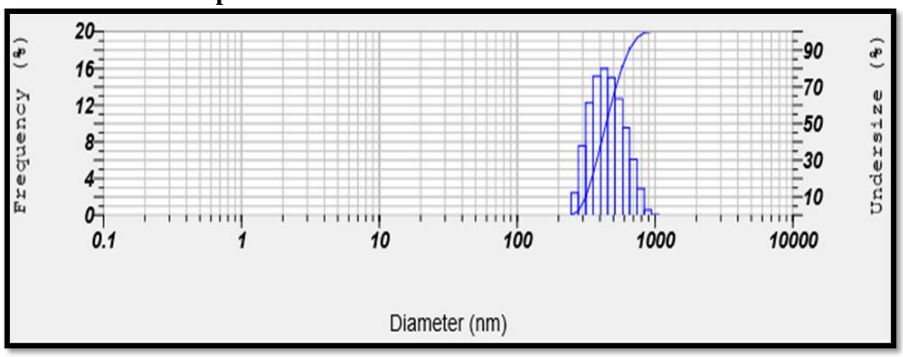


Fig 2: Size distribution of best SMEDDS formulation

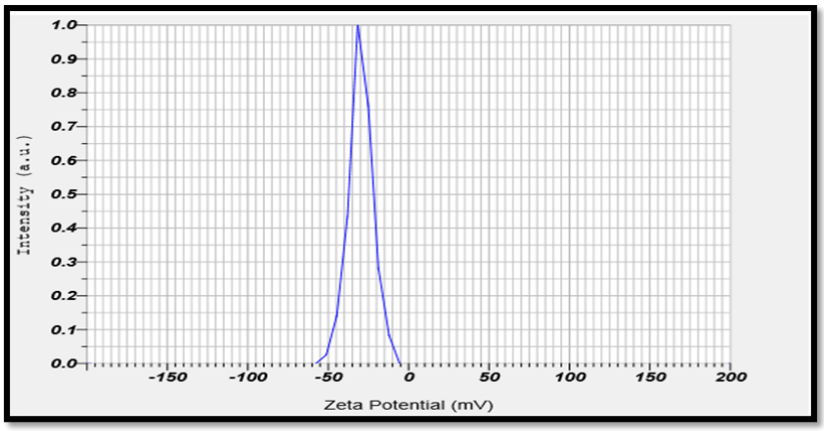


Fig 3: Zeta potential of the best SMEDDS formulation

In Vitro Drug Release Profile:

Various dissolving media were used to investigate the in vitro dissolution profiles, which were chosen to reflect the range of acidity seen in the gastrointestinal system. Raw TMS dissolved poorly and pH-dependently, dissolving very slowly (1% for 2 hours) in water, pH 4, and pH 6.8 media, and quickly (> 90% in 5 minutes) in pH 1.2 medium. These results are consistent with earlier studies that demonstrated TMS's pH-dependent solubility, with high solubility in highly basic and acidic environments (nearly 100% dissolution in gastric fluid in 20 minutes) and low solubility in neutral environments, which led to a low dissolution rate (1% for 90 minutes) in a pH 6.8 medium.

Table 3: Dissolution release profile data of Nebivolol pure, liquid and Solid SMEDDS formulations using 6.8pH Buffer

Time	Pure Drug	Liquid SMEDDS	Solid SMEDDS
0 mins	0	0	0
5 mins	5.68 ± 0.0031	37.46 ± 0.0596	28.35 ± 0.0434
10 mins	9.45 ± 0.0098	49.44 ± 0.0809	38.36 ± 0.0612
15 mins	13.79 ± 0.0193	60.13 ± 0.0999	55.237 ± 0.0912
30 mins	18.28 ± 0.0255	72.78 ± 0.1224	68.96 ± 0.1156
45 mins	22.66 ± 0.0333	80.66 ± 0.1364	78.86 ± 0.1332
60 mins	26.88 ± 0.0408	88.2 ± 0.1498	89.55 ± 0.1522
120 mins	32.27 ± 0.051	100.97 ± 0.1725	99.05 ± 0.1671

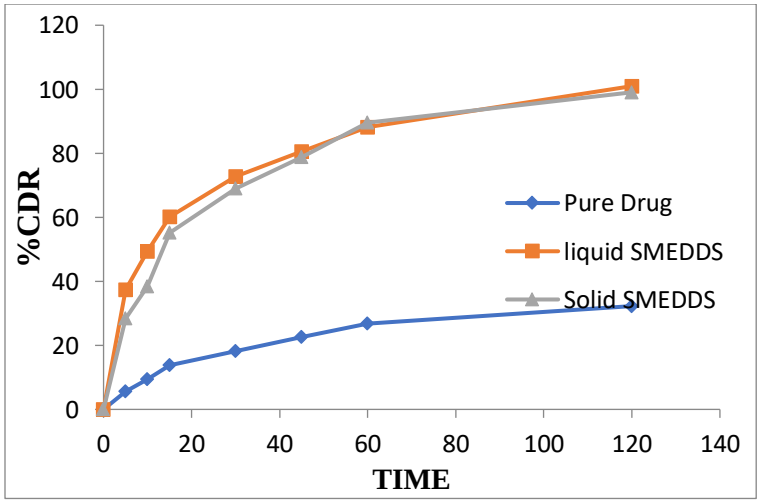
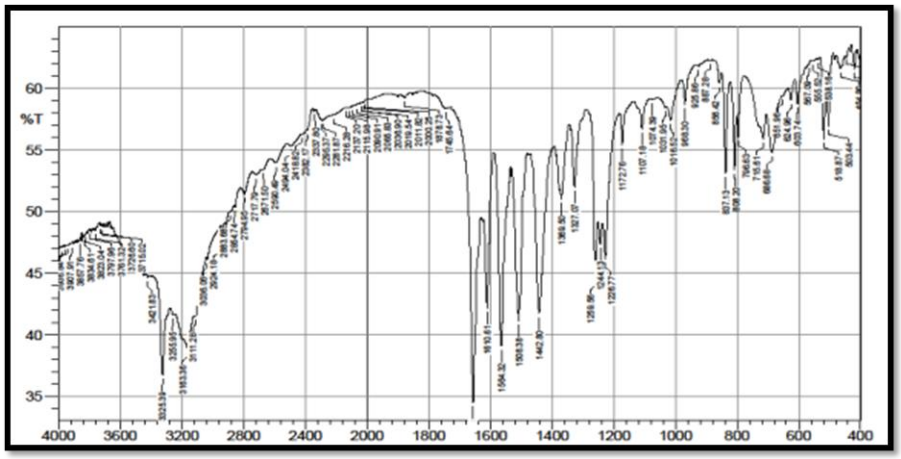


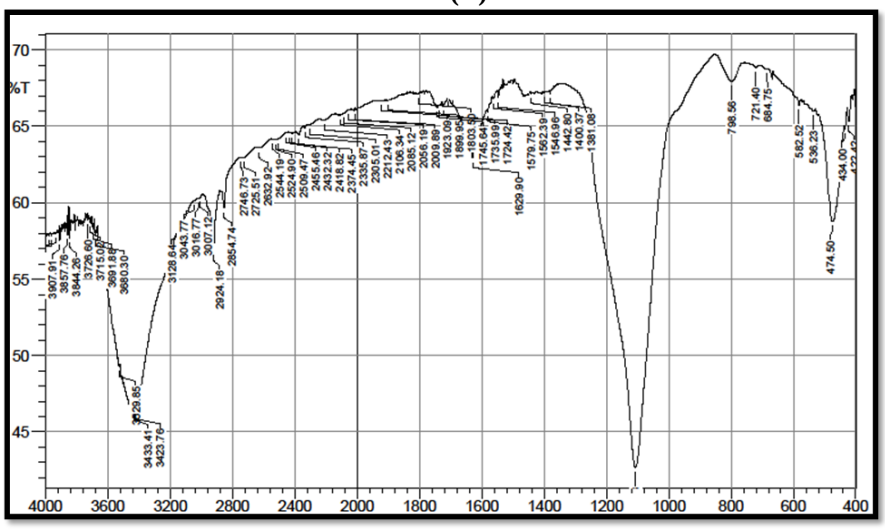
Fig. 4: A plot between time Vs %CDR for dissolution

Fourier –Transform Infrared Spectroscopy:

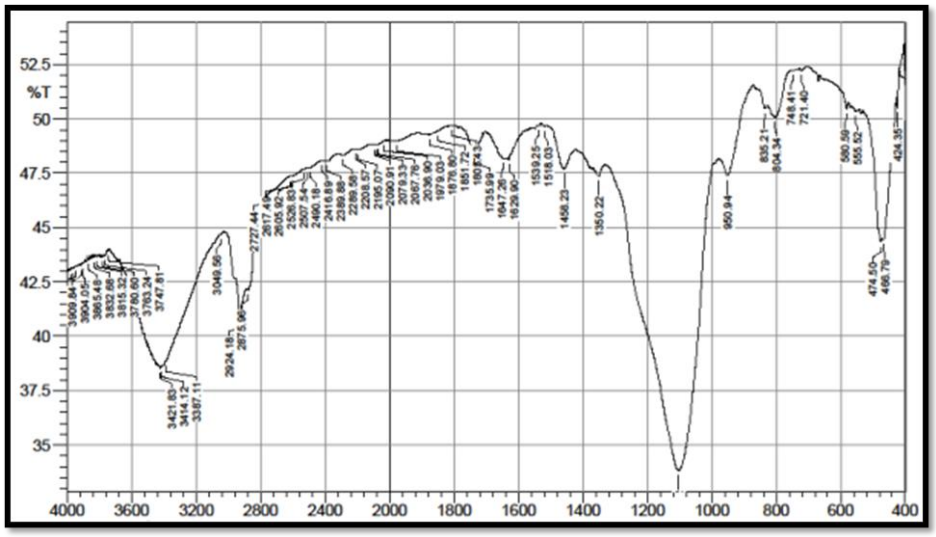
To ascertain whether or not the medicine and the carrier utilized can interact with one another, FT-IR was performed. The table below explains the FT-IR data (5.12). The vibrational frequencies of the bonds in Nebivolol are as follows: -OH: 3352 cm-1, NH2: 3012 cm-1, C=N: 2243 cm-1, C=O: 2905 cm-1, and C=N: 2642 cm-1 (C-H stretching). Spectra with corresponding peaks at 3355 cm-1 (-OH Stretching), 3151 cm-1 (NH2 Stretching), 2131 cm-1 (C=N Stretching), 2875 cm-1 (C=O Stretching), and 2468 cm-1 (C=O Stretching) were generated using the S-SMEDDS formulation (C-H stretching). This indicates that the drug and the carrier did not interact chemically and that the drug's molecular structure was maintained.



(A)



(B)



(C)

Fig 5: FTIR Spectra of (A) Pure Nebivolol (B) Aerosil 200 (C) Optimised Formulation

Table 4: FTIR data Interpretations

Functional Group (Stretching**)**	**Wave numbers**	
	Pure drug	**optimized formulation**
-OH	3351	3354
-NH2	3012	3151
C = N	2243	2131
C = O	2905	2875
-C-H	2642	2468

Scanning Electron Microscopy (SEM):

The formulation's size distribution ranged from 10 to 100 nm, and its shape was spherical.

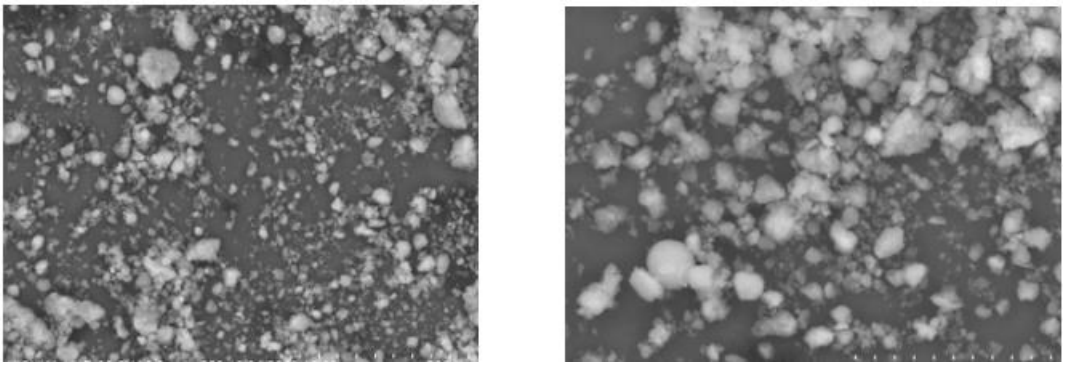


Fig 6: SEM of Optimized formulation of Nebivolol

SUMMARY AND CONCLUSION:

A possible strategy for the formulation of Nevibolol is the use of solid self-micro emulsifying drug delivery systems (S-SMEDDS). S-SMEDDS have exhibited significantly enhanced oral bioavailability, suggesting that they may one day allow for the oral administration of hydrophobic medicines.

The ternary phase diagram, droplet size, zeta potential, and in vitro drug release data were used to determine that formulation 4 (f4) was the most effective. Since the formulation was enhanced, self-emulsification in water was rapid. SMEDDS may be used to increase the solubility and dissolution of compounds like Nevibolol that are already rather poorly soluble, according to these studies. The F4 formulation showed a 78.86% and 99.05% drug release at 45 and 120 minutes, respectively, according to in vitro drug release assays. According to studies conducted in an ex vivo environment, the F4 formulation permitted 71.3% of the medication to

enter after 120 minutes, while the pure drug only permitted 30.75 percent to do so.

Oil, surfactant, and cosurfactant self-micro emulsifying (SME) combinations were created and tested for their emulsifying efficiency in this research. An oil-in-water microemulsion forms spontaneously when such mixes are diluted in water. It was observed that all of the excipients, to varied degrees, attempted to produce a microemulsion. Liquid and solid SMEDDS loaded with Nebivolol were made using the optimum SME combination, and their propensity for self-micro emulsification was assessed and described. A microemulsion with a droplet size of around 330 nm and a zeta potential of zero was produced by the enhanced formulation (F4).

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