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# Formulation & Development of Varenicline Tablets for Smoking Cessation

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**Abstract** In the present investigation, self emulsifying ER tablets containing Varenicline were developed. The objective of the work was to enhance the solubility, dissolution properties and bioavailability of Varenicline. The available conventional dosage forms showing few problems related to dissolution and bioavailability because of low solubility and high presystemic metabolism and also frequency of dosing is another problem which results incompliance to patient. In order to overcome these drawbacks drugs can be developed in the form of self emulsifying extended release drug delivery system. Self emulsifying system was developed by using Oleic acid, Labrafil M 2125CS, Cremophor RH40 and PEG 400 showed acceptable physical characters like size and zeta potential which less than 250 nm size and -20 mv potential respectively. Drug release studies also defined the role of precipitation inhibitor in self emulsifying system and almost 100 % of drug release was showed in dissolution studies. Bioavailability study was conducted for liquid self emulsifying system with and without super saturation promoter. Results showed a significant role of super saturation promoter in different pH conditions. Bioavailability of Varenicline was increased by 3.4 folds with self emulsifying system with 5%w/w of HPMC E5.

**Keywords** HPMC, Varenicline, pH, Solubility, Dissolution

## Introduction

Smoking is a practice in which a substance is burned and the resulting smoke is typically breathed in to be tasted and absorbed into the bloodstream. Most commonly, the substance used is the dried leaves of the tobacco plant, which have been rolled into a small rectangle of rolling paper to create a small, round cylinder called a "cigarette". Smoking is primarily practiced as a route of Administration for recreational drug use because the combustion of the dried plant Leaves vaporizes and delivers active substances into the lungs where they are rapidly absorbed into the bloodstream and reach bodily tissue. In the case of cigarette smoking these substances are contained in a mixture of aerosol particles and gases and include the pharmacologically active alkaloid nicotine; the vaporization creates heated aerosol and gas into a form that allows inhalation and deep penetration into the lungs where absorption into the bloodstream of the active substances occurs. In some cultures, smoking is also carried out as a part of various rituals, where participants use it to help induce trance-like states that, they believe, can lead them to spiritual enlightenment.

Smoking is one of the most common forms of recreational drug use. Tobacco smoking is the most popular form, being practiced by over one billion people globally, of whom the majority are in the developing countries. Less common drugs for smoking include cannabis and opium. Some of the substances are classified as hard narcotics, like heroin, but the use of these is very limited as they are usually not commercially available. Cigarettes are primarily industrially manufactured but also can be hand-rolled from loose tobacco and rolling paper. Other smoking implements include pipes, cigars, bidis, hookahs, and bongs. Smoking can be dated to as early as 5000 BCE, and has been recorded in many different cultures across the world. Early smoking evolved in association with religious ceremonies; as offerings to deities, in cleansing rituals or to allow shamans and priests to alter their minds for purposes of divination or spiritual enlightenment. After the European exploration and conquest of the Americas, the practice of smoking tobacco quickly spread to the rest of the world. In regions like India and Sub-Saharan Africa, it merged with existing practices of smoking (mostly of cannabis). In Europe, it introduced a new type of social activity and a form of drug intake which previously had been unknown. Perception surrounding smoking has varied over time and from one place to another: holy and sinful, sophisticated and vulgar, a panacea and deadly health hazard.

In the last decade of the 20$^{th}$ century, smoking came to be viewed in a decidedly negative light, especially in Western countries. Smoking generally has negative health effects, because smoke inhalation inherently poses challenges to various physiologic processes such as respiration. Smoking tobacco is among the leading causes of many diseases such as lung cancer, heart attack, COPD, erectile dysfunction, and birth defects [1]. Diseases related to tobacco smoking have been shown to kill approximately half of long-term smokers when compared to average mortality rates faced by non-smokers. Smoking caused over five million deaths a year from 1990 to 2015 [2]. The health hazards of smoking have caused many countries to institute high taxes on tobacco products, publish advertisements to discourage use, limit advertisements that promote use, and provide help with quitting for those who do smoke.

Tobacco use results in one premature death every six seconds globally [1]. Every year 7 million people die worldwide from tobacco-related health problems, including cardiovascular and respiratory disease. Of these, 6 million deaths are estimated to result directly from tobacco use, while the remaining represent non-smokers exposed to second-hand smoke [2]. In the United States alone, 16 million individuals are living with a disease caused by smoking [3], and 35.6 million people are current smokers aged 18 or older (15.1% of the U.S. population [3]. With an estimated economic cost of 300 billion U.S. dollars per year, smoking is the second most expensive chronic health condition next to cardiovascular disease in the U.S. [3,4]. Despite the massive individual and public costs of smoking, more than one billion people worldwide continue to use tobacco and nicotine-related products regularly [2].

## Material & Method

### Formulation Development and Optimization of Varenicline Tablets

### Preformulation Studies

#### *Development of Analytical method and validation for quantification of drug content using RP-HPLC method*

#### *Mobile phase preparation*

Methanol and acetonitrile were measured in required quantities with the ratio of 95:5% v/v and mixed. The pH was adjusted to 3 ± 0.05 with OPA and filtered using 0.45µm filter paper made up nylon and degassed.

#### *Stock solutions of Varenicline*

Standard Stock – 1mg/ml in methanol

Working Stock – 100 µg/ml in methanol

#### *$\lambda_{max}$ Determination*

The working stock was scanned in UV-spectrophotometer from 200- 400 nm against the reagent blank. The $\lambda_{max}$ was found to be 241 nm and further analysis was carried at same wavelength.

**Stock solution preparation**

The primary stock solution (1mg/ ml) of Varenicline in various vehicles like water, mobile phase, labrafil M2125, oleic acid and capryol PGMC water were prepared. The working standard solutions were prepared in the range of 5 to 90 µg/mL for construction of calibration curve as well as other validation parameters.

**System suitability test**

The test for System suitability was done by injecting a blank solution and working standard solutions from which a solution was considered as 100% concentration and I is injected six times into the stabilized RP-HPLC system. The establishment of system suitability was done by testing the parameters which were considered from the last peak obtained. In most of the times, System suitability is evaluated by retention factor, resolution, tailing factor, repeatability and number of theoretical plates.

**Method Validation**

***Specificity and selectivity***

The method specificity was determined for the purpose of estimation or quantification of Varenicline in different vehicles by routine HPLC analysis. One more aspect behind the test was to estimate the solubility of Varenicline in various oils to develop a stable lipid-based drug delivery system. The basic need of method of Specificity and selectivity to develop a method in which interference should not takes place in between used vehicles and Varenicline.

***Calibration curve***

Calibration curves for Varenicline in various vehicles were constructed using working standard solutions of 5 to 90 µg/ml of each vehicle. For construction of calibration curve, 3 replicates of working standards were injected. Calibration curves for Varenicline were constructed by taking average peak area (n=3) and conc'n of working standard solution. The unknown or test concentration of the analyte was estimated using linear regression equations obtained from calibration curve data.

***Precision and accuracy***

The method precision was determined by intra-day precision, and it was estimated by analyzing 3 independent replicate quality control samples with 30, 45 and 60 µg/ml of Varenicline in each vehicle on same day by following similar conditions used for previous studies. The reproducibility i.e., inter day precision was determined by, analyzing 3 quality control samples 30, 45 and 60 µg/mL on 2 different days. The Precision was calculated which is the coefficient of variance (CV), and it was expressed as % RSD Accuracy is the nearness of a concord between the values those are acceptable by analyst, either they are predictably true value or a reference one. In this study, accuracy was estimated by analyzing 3 replicates at 3 QC levels like 30, 45 and 60µg/mL on same day and continued for two more days for estimating relative standard deviation.

***Solubility study***

Varenicline solubility in various oils, surfactants and co-surfactants was estimated. The vehicles (10 ml) in which solubility are to be determined were taken separately in a vial with excess of Varenicline and sealed. The mixture was warmed in a water bath at 40ºC and to facilitate solubilization magnetic stirrer was used. These mixtures were agitated for 72h at 37±1ºC. When equilibrium was attained, the vials were taken and centrifuged at 10000 rpm for 5 min (Remi CM12, Remi Elektrotechnik Limited, India). The supernatant was clarified using a 0.45 micrometer using syringe filter. Filtrates were diluted with methanol and analysed using an RP-HPLC method at $\lambda_{max}$ of 241nm. The mobile phase used was methanol and water in 80: 20 ratio, pH adjusted to 3 with OPA, flow rate 1ml/min with an injection volume of 20µl and run time of 8 min. The solubility studies were carried out in triplicate.

**Construction of Pseudo-ternary phase diagram**

Ternary plots were constructed to find out the concentration range of the components which help in self-emulsification under dilution and agitation procedures. It helps to recognize the self- emulsifying region which gave good and stable sub-micron range emulsions. A series of mixtures were prepared using varying conc'n of oleic acid and labrafil M 2125, cremophore RH 40 and PEG 400 in the glass test tube and mixed using magnetic stirrer. A freshly prepared formulation (about 200 mg) was added in to 100 ml distilled water maintained at 37ºC. The contents in the beaker were mixed uniformly using magnetic stirrer. The tendency of self-emulsification and appearance were observed. The formed emulsion was termed as 'good and stable' if the droplets were well in water and gave a milky emulsion, and it was termed 'bad' if coalescence of the oil droplets occurred precipitating out the drug [10]. Prosim software was used to construct the phase diagram. The studies were performed in triplets.

**Formulation of liquid SEDDS**

The self emulsifying formulations were prepared by the Standard Admixture Method. Oil (oleic acid and labrafil M2125 CS in 1:1 w/w), cremophor RH40 (surfactant) and PEG400 (cosurfactant) were mixed in distinct ratios as shown in table 1. Gradually, the drug was solubilized in the mixture using a cyclomixer (Remi CM 101, Remi Elektrotechnik Limited, India). Required quantity of HPMC E5 or PVP K30 was uniformly dispersed in the liquid SEDDS. These mixtures were held to notice any sign of turbidity or phase separation or precipitation for a period of 48 hours. The amount of drug that is to be added to the liquid SEDDS is based on one fact i.e., the solubility of drug in various components of SEDDS.

**Table 1:** Formulation of Self emulsifying formulations containing Varenicline

| Ingredients (mg) | Liquid SEDDS formulations | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **L1** | **L2** | **L3** | **L4** | **L5** | **L6** | **L7** | **L8** | **L9** |
| Varenicline | 48 | 72 | 72 | 72 | 90 | 72 | 72 | 72 | 72 |
| Oleicacid | 100 | 150 | 150 | 150 | 150 | 150 | 150 | 150 | 150 |
| LabrafilM2125CS | 100 | 150 | 150 | 150 | 150 | 150 | 150 | 150 | 150 |
| CremophorRH40 | 400 | 700 | 600 | 500 | 500 | 500 | 500 | 500 | 500 |
| PEG400 | 400 | -- | 100 | 200 | 200 | 200 | 200 | 200 | 200 |
| PVPK30 | -- | -- | -- | -- | -- | 50 | 100 | -- | -- |
| HPMCE5 | -- | -- | -- | -- | -- | -- | -- | 50 | 100 |

**Development of Varenicline self emulsifying extended release tablets**

Polymer(s) and avicel 102 were weighed accurately as per showed in following table, passed through sieve # 40 were added to required quantity of solid SEDDS powder and blended in a poly bag for 15min. To above blend, mg.stearate and talc were added and lubricated for 5min in a polybag. The lubricated blend was made into tablets using 8mm round concave punches in rotary tablet compression machine

**Table 2:** Development of Varenicline self emulsifying extended release tablets

| Name of the ingredient (mg) | Formulation code | | | |
|---|---|---|---|---|
| | **F1** | **F2** | **F3** | **F4** |
| Optimized spraydried solid sedds (Varenicline-10mg) | 283 | 283 | 283 | 283 |
| HPMCK200M | 36 | 45 | 22.5 | .... |
| HPMCK100M | .... | .... | 22.5 | 45 |
| Avicel102 | 33 | 24 | 24 | 24 |
| Mg.Stearate | 4.0 | 4.0 | 4.0 | 4.0 |
| Talc | 4 | 4 | 4 | 4 |

**Evaluation Studies**

*Pre Compression Parameters*

The pre compression or powder blend properties were evaluated and described in following sections.

***Micromeritic properties [35]***

**Angle of repose:**

It was measured using fixed funnel method. At a specific height funnel was placed on a graph paper. The blend was filled in to funnel and run on graph paper until the pile of blend reaches tip of funnel. The exact height and radius (r) of the pile was determined. The θ-value was calculated by using following formula:

Tanθ = pile height / radius

**Table 3:** Corresponding flow behavior of powders with angle of repose

| Flow behaviour | Angle of repose (θ) |
|---|---|
| Excellent | 25to30 |
| Good | 31to35 |
| Fair | 36to40 |
| Passable | 41to45 |
| Poor | 46to55 |
| Very poor | 56to65 |
| Very very poor | >66 |

***Bulk density***

Bulk density is an important parameter it indirectly affects appearance and physical properties of tablet. Powder blend was taken in a measuring cylinder (50 ml) and leveled there by bulk volume (Vo) was measured. It was determined by using following formula:

ρb = Bulk density, M = sample weight, Vo = bulk volume

***Tapped density***

It was measured by using tapped density tester (USP type 1) gives fixed drops with 14 ± 2 mm height at 300 drops/minute. Initially, 500 tapings were done and followed by 750 tapings awaiting a difference between succeeding measurements should be <2%, at this point tapped volume was measured. By using following formula, the tapped density was calculated.

$$\rho tap = M / Vf$$

Where ρtap = Tapped Density, M = Sample weight, Vf = Tapped volume

***Powder compressibility***

The Compressibility Index (Carr's Index) is an assess of the susceptibility of microparticles to be compacted and flow ability of particles in various positions of tablet compression machine. It is determined by considering computed values of bulk as well as tapped densities.

***Hausner's ratio***

It was determined by calculating the ratio of powder or granular blend's tapped and bulk densities. Hausner establish concept of flow and compact behavior of powder by considering interparticle friction. Normally, the value should be <1.25 indicates good flow. The relationships between powder flow and compressibility parameters shown in table.

**Table 4:** Various flow behaviors of powder blends and correlated with Carr's index and Hausner's ratio

| Carr's index | Hausner's ratio | Flow behavior |
|---|---|---|
| Less than 10 | 1.0-1.1 | Excellent |
| 11to15 | 1.12-1.18 | Good |
| 16to20 | 1.19-1.25 | Fair |
| 21to25 | 1.26-1.34 | Passable |
| 26to31 | 1.35-1.45 | Poor |
| 32 to 37 | 1.46-1.59 | Very poor |
| More than 38 | More than 1.60 | Very, Very poor |

**Evaluation of Varenicline Self Emulsifying Extended-Release Tablets**

***Thickness***

From each batch, six tablets were randomly taken and thickness was determined using vernier calipers. The variation allowed was ± 5% of the standard value.

***Hardness***

It is an important parameter and difficult to control, depends on many formulation factors. Many hardness esters are available to determine the hardness of a tablet compact among those Monsanto tables hardness tester was used and it consists, a barrel have a spring is compressible and holed between 2 plungers. Zero reading was taken a lower plunger was attached and upper plunger was forced along spring side by rotating bolt until tablet get fractured. Six tablets from each batch were evaluated for hardness and expressed as average with SD-value.

***Weight variation***

From executed batches, 20 tablets were randomly selected and individually weighed using an electronic balance. The AVG±SD (n=3) was determined and test confirms when no more than 2 tablets. Results were correlated with specifications showed in table 5 and 6.

**Table 5:** Weight Variation test specification (IP)

| Tablets Average weight | % deviation allowed |
|---|---|
| <80mg | 10 |
| >80mgand<250mg | 7.5 |
| >250mg | 5 |

**Table 6:** Weight Variation limits (USP)

| Average weight of tablet (mg) | Allowed deviation |
|---|---|
| <130 | 10 |
| >130and<324 | 7.5 |
| >324 | 5 |

***Friability***

The friability is one of the relative measures of tablets physical strength. In most of the times, friability is a prime factor during tablet coating. Friability is tested by using roche friabilator. As per the procedure mentioned in USP, twenty tablets were randomly selected and total weigh was taken and tablets were loaded in friability apparatus and operated at 25rpm for 4min. After friabilation tablets were reweighed and % friability was calculated.

$$\% \ Friability = (w0\text{-}w)/w0 \ X100$$

WO = Initial weight, W = Final weight

***Drug content***

The drug content was estimated for randomly selected 6 tablets of each developed formulation. First, tablets were crushed and made as powder using mortar & pestle. Equivalent weight of powder was added to specific volume of mobile phase and sonicated to dissolve the drug or either components. The resultant solution was filtered using membrane filter (0.45µm nylon filter). The filteraed was preceded with proper dilution and drug concentration was analyzed at a wavelength of 241nm using UV-detector equipped in RP-HPLC. The experiment had triplicate and standard deviation was calculated.

**Stability Studies for Optimized Formulation**

Randomly selected samples were stored at 400C / 75% RH for about 3 months in REMI environmental chamber. At the end of time points, drug content and in-vitro release profile were determined.

## Results and Discussion

### Development of Self Emulsifying Extended-Release Matrix Tablets Containing Varenicline

#### *RP-HPLC Method development and validation*

For quantitative estimation of Varenicline in selected oils by using RP-HPLC the method was optimized by using different types of buffers like $K_2HPO_4$, acetonitrile and methanol, with different mixture compositions were attempted. Different columns were used, including C18, C8 in this study. The HPLC method was optimized with a combination of Aceto nitrile and Methanol in a ratio of 90:10 in %v/v and a flow rate of 1 ml/ min was maintained. The drug peak was appeared at RT 3.96 min with symmetric shape. The run time was set for 7 min and detection wavelength was 242 nm.

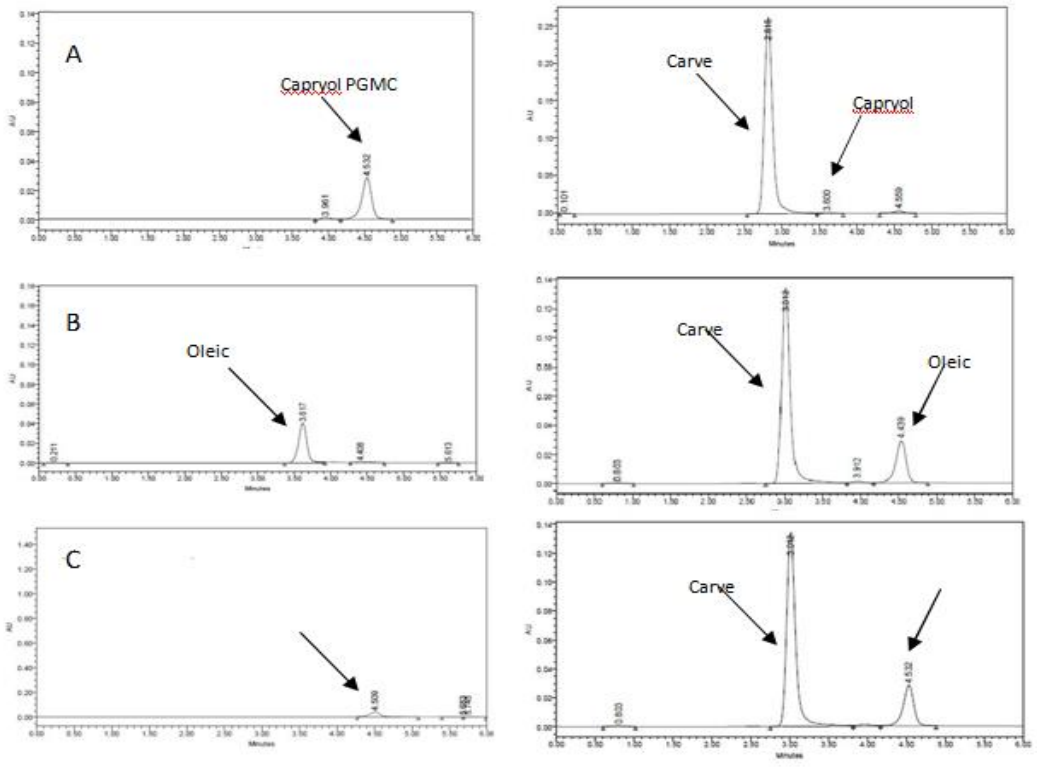


*Figure 1: The chromatograms of oils and spiked oil matrix with Varenicline: (A) Capryol PGMC (B) Oleic acid (C) Labrafil M2125*

#### *System suitability*

The System suitability study was conducted using 100% test concentration under degradation conditions. The test was performed by injecting blank for once and a standard solution of 100% test concentration 6 times in to a stabilized HPLC system. The system suitability was established by evaluation parameters from last peak characteristics. The following parameters includes retention factor, theoretical plates, tailing factor, repeatability and resolution. For calculation part, response of concentration 90µg/ml. The results of suitability data was shown in the table.

#### *Specificity and selectivity*

Chromatograms showed in Figure 1 states that optimized method was specific and responses of different oils not interfere with the peak of Varenicline which was added in oil. Figures illustrate chromatograms for plain oils extracted from mobile phase and oils spiked with the analyte in various oils like capryol PGMC, labrafil M2125 and oleic acid. Drug and oil were successfully resolved and well separated. Results depicted that developed method was specific and selective.

***Linearity***

The calibration curves for selected oils were constructed and evaluated. Resultant curves were linear and calculated correlation co-efficient ($r^2$) were in the range of 0.998, 1.0 and 0.999 over specific concentration from 5 to 90 mg/ml in oleic acid, capryol PGMC and labrafil M2125. Triplicate values were taken by injecting each concentration. The concentrations were determined by back calculation method and expressed as mean±SD by developed HPLC method for Varenicline and three oils.

**Precision and accuracy**

The relative standard deviation of repeatability and an intermediate precision were key parameters to evaluate precision. The intraday precision of Varenicline in labrafil M2125, capryol PGMC and oleic acid ranges from 0.58 – 0.80, 0.91 – 1.25 and 0.92 – 1.82 and the inter day precision ranges from 0.50–1.62, 0.93–1.63 and 1.06–2.22. Results were showed in Table.

**Table 7:** Data of Accuracy and Precision – prediction of intraday and interday

| Spiked concentration (µg/ ml) | Mean + SD (µg/ml) | Accuracy % | % CV |
|---|---|---|---|
| 30 | 29.90 ± 0.102 | 99.59 - 100.99 | 0.98 |
| 45 | 44.94± 0.112 | 99.87 - 100.96 | 0.75 |
| 60 | 59.88 ± 0.099 | 99.82 - 101.09 | 1.05 |
| **Varenicline in Capryol PGMC** | | | |
| 30 | 29.87 ± 0.13 | 99.5 - 101.1 | 0.57 |
| 45 | 44.9± 0.18 | 99.9 - 100.9 | 1.03 |
| 60 | 59.7 ± 0.1 | 99.6 - 101.1 | 0.47 |
| **Varenicline in Oleic acid** | | | |
| 30 | 29.9 ± 0.18 | 99.76 - 100.0 | 1.03 |
| 45 | 44.9± 0.1 | 99.96 - 101.2 | 1.33 |
| 60 | 59.8 ± 0.1 | 99.76 - 101.2 | 1.09 |

**Pre-formulation studies**

**Solubility study**

Formulation of a microemulsion system for lipophilic drugs is very important. The amount of the formulation that is to be administered to a patient needs to be kept at a minimum with exact amount of therapeutic dose to achieve patient compliance. Constituents utilized in formulation should solubilize the active in high amounts so as to prepare a concentrated form of a microemulsion. Preliminary solubility studies was done in various oils in order to show Varenicline solubilization. The estimated solubilities of Varenicline in different oils. Maximum drug solubility was seen with Oleic acid: Labrafil M2125CS at a ratio of 1:1 (296.54 mg/ml). In contrast, Cremophor RH40 and PEG 400 had a maximum solubility of Varenicline of 85.48 and 233.57 mg/ml. `By considering these results, oil phase selected was Oleic acid: Labrafil M 2125CS at a ratio of 1:1, surfacant was Cremophor RH40 and cosurfactant was PEG 400 choosed. Based on HLB value, surfactants were chosen to form o/w type microemulsion which is needed to be greater than 10. In this study, cremophor RH40 is a nonionic emulsifiers, was choose because its HLB ranges 14-16.

**Table 8:** Varenicline solubility in various oils

| Oils | Drug solubility (mg/ml)* |
|---|---|

| | |
|---|---|
| Captex 355 | 13.65±0.8 |
| Capmul GMO 50 | 0.54±0.03 |
| Lauroglycol 90 | 26.13±0.9 |
| Oleic acid | 116.57±9.7 |
| Capryol PGMC | 35.12±1.21 |
| Labrafil M 2125CS | 23.48±0.8 |
| Oleic acid: Captex 355 (1:1) | 182.45±11.4 |
| Oleic acid: CapmulGMO 50 (1:1) | 150.45±8.3 |
| Oleic acid: Lauro glycol 90 (1:1) | 268.56±9.6 |
| Oleic acid: CapryolPGMC (1:1) | 196.24±7.7 |
| Oleic acid: Labrafil M2125CS (1:1) | 296.54±12.5 |

**Table 9:** Varenicline solubility in various surfactants

| Surfactants | Drug solubility (mg/ml)* |
|---|---|
| Tween 20 | 80.94±7.0 |
| Tween 80 | 29.94±2.6 |
| Cremophor RH40 | 85.48±3.3 |
| Span 80 | 49.71±3.8 |

**Table 10:** Varenicline solubility in various co-surfactants

| Co-surfactants | Drug solubility (mg/ml)* |
|---|---|
| PEG 200 | 191.08±10.1 |
| PEG 400 | 233.57±13.8 |
| PEG 600 | 144.32±11.5 |
| Propylene glycol | 9.80±0.1 |

*Values in Table 10 (a, b & c) expressed as Mean±Standard deviation, n=3*

**Solid State Characterization**

**Differential Scanning Calorimetry**

DSC thermograms studies were conducted in Varenicline and solid SEDDS formulation F1, F2, F3, were shown in below figure.

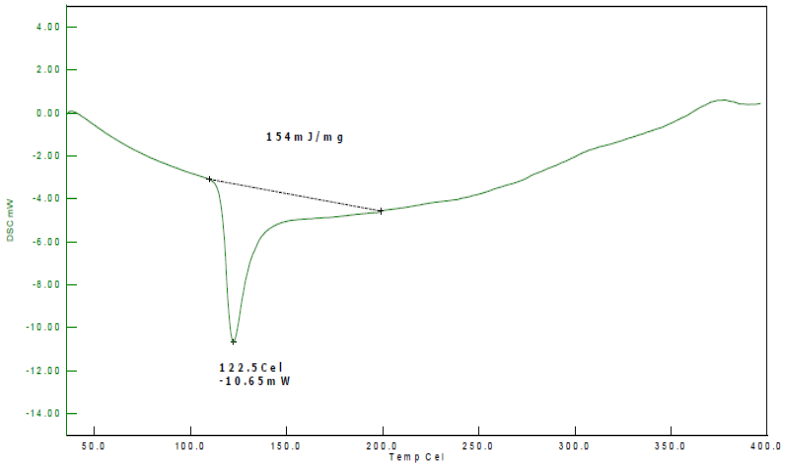


*Figure 2: DSC Thermogram of Varenicline*

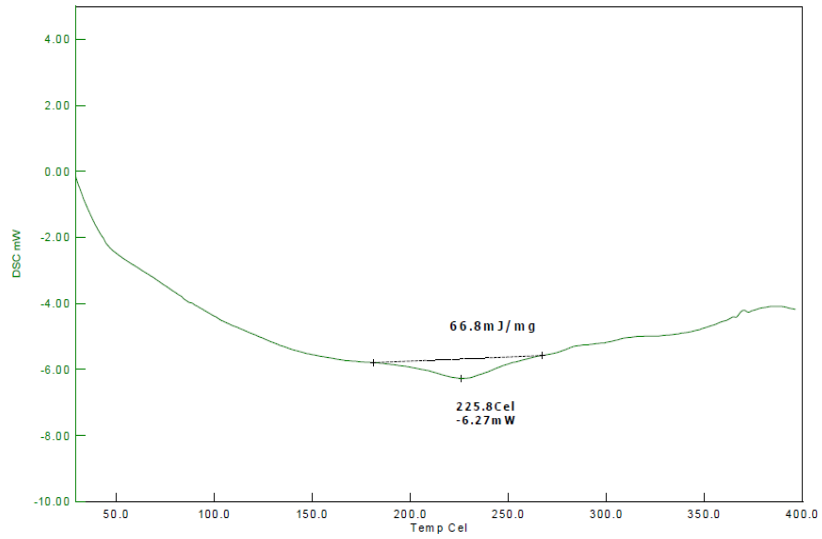


*Figure 3: DSC thermogram of F1 formulation*

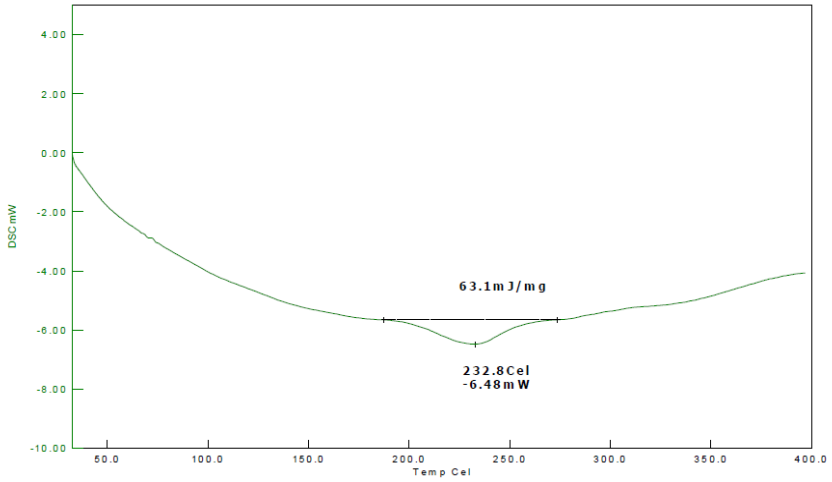


*Figure 4: DSC thermogram of F2 formulation*

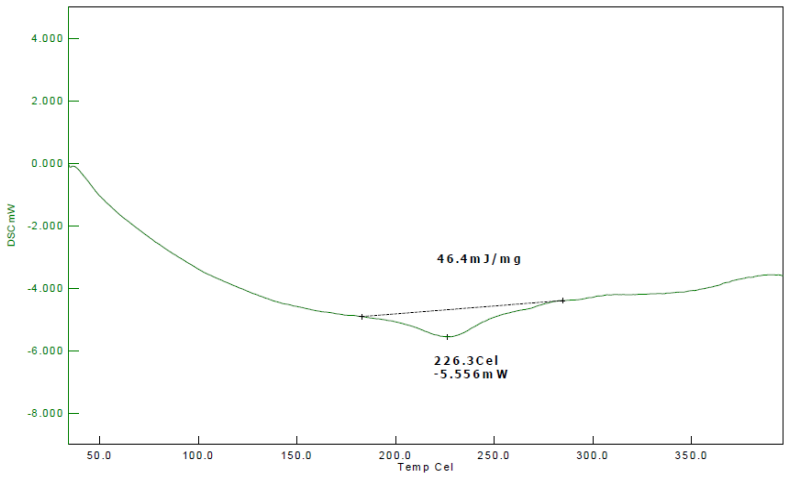


*Figure 5: DSC Thermogram of F3 formulation*

The thermogram Varenicline drug exhibited on endotherm peak at about 122.5ºc, which was corresponding to its melting point. In case of Varenicline loaded solid SEDDS (F1, F2, F3 samples**),** the endothermic peak of the drug was absent. Therefore, it would be concluded that cavedilol in solid SEDDS was dispersed or distributed in molecular form or existed as amorphous form after fabrication. The phase transformation of drug from crystalline to amorphous, a high energy results in faster dissolution of drug or if drug completely dissolved in oil portions, resulting rapid formation of micro or nano range emulsion and further absorption occurs.

**X-Ray diffraction studies:**

XRD studies were carried out for pure drug, solid SEDDS formulation, and Neusilin. The XRD patterns of pure drug, placebo and solid SEDDS formulation were shown in figure 6. The XRD spectra of Solid SEDDS indicate that the characteristic Varenicline peaks were reduced in intensity or absent. The disappearance of peak in solid SEDDS formulation unravels the transformation of the physical state of drug from crystalline to amorphous

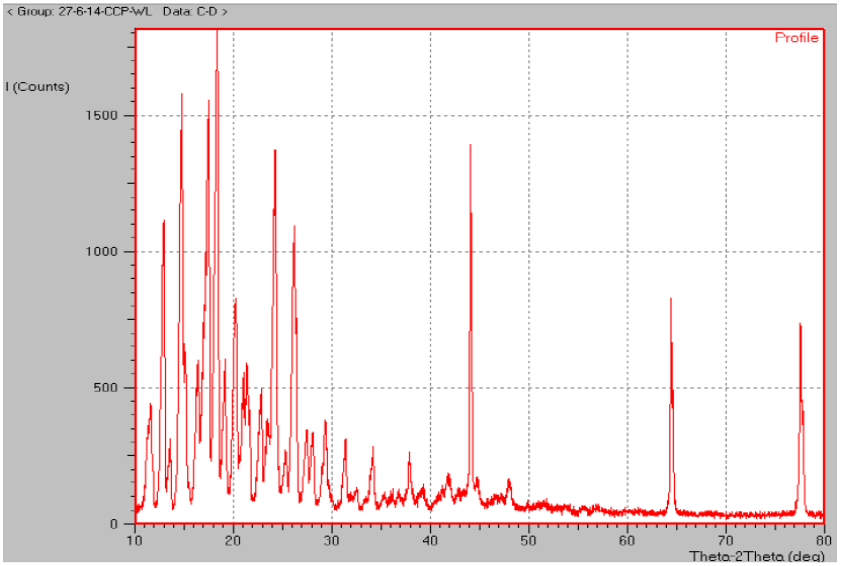


*Figure 6: XRD Spectrum of Varenicline*

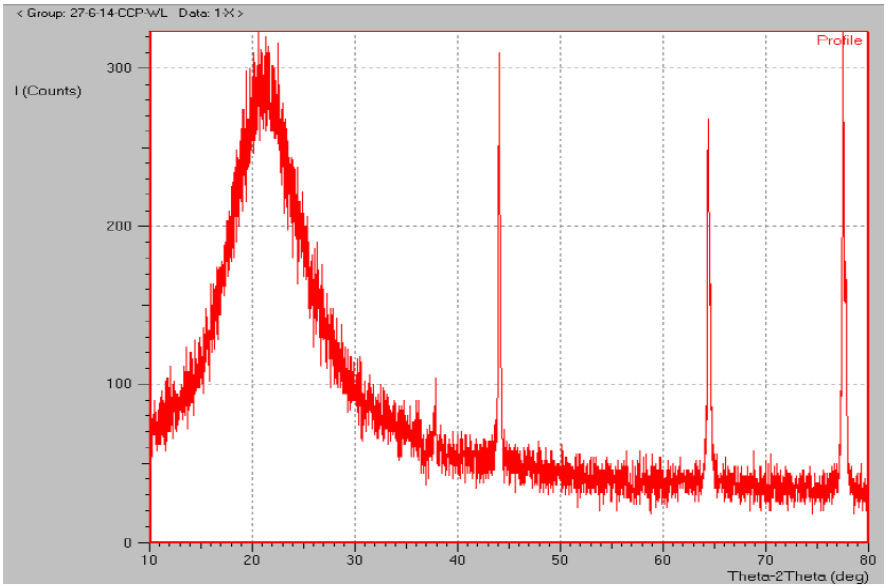


*Figure 7: XRD Spectrum of placebo*

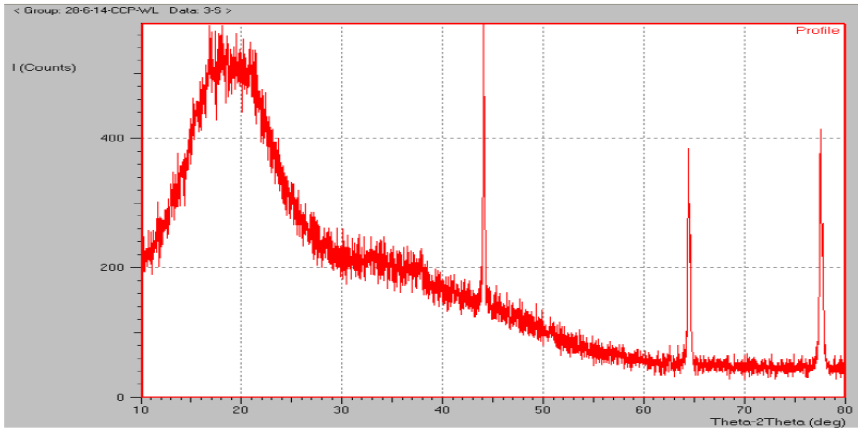


*Figure 8: XRD Spectrum of optimized SEDDS formulation*

**Surface morphology characterization**

**Scanning electron microscopy**

Surface morphology of solid SEDDS (F3) and plain Neusilin and Varenicline powder were examined by SEM analysis. The surface morphology of solid SEDDS powder was different as compared to plain Neusilin and Varenicline powder respectively as shown in SEM. From SEM photographs it was clear that, the Varenicline powder (figure 9(a)) appeared with rectangular, crystalline shape with a smooth surface. The surface of Neusilin (figure 9(b)) appeared as a rough surface with porous particles. The surface morphology of solid SEDDS powder without and with wetting was shown in figure 9 (c and d).

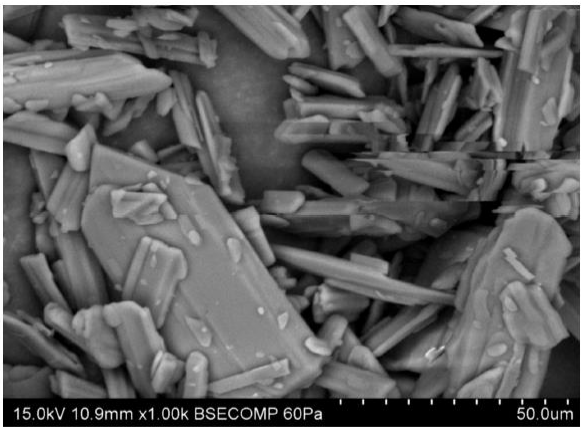


*Figure 9a: SEM picture of pure Varenicline*

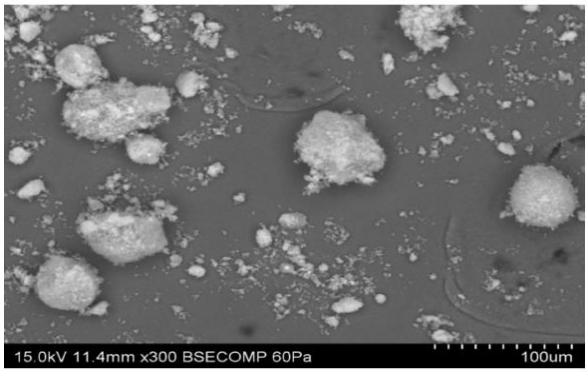


*Figure 9b: SEM Picture of NeusilinUFL2*

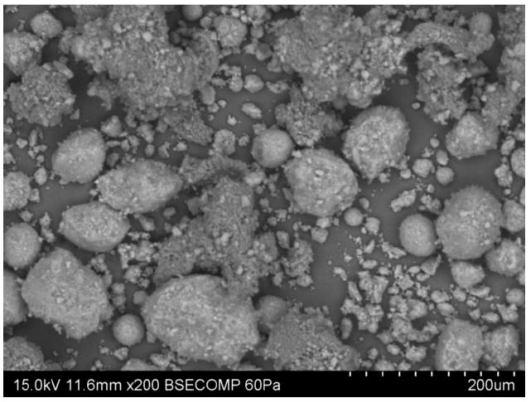


*Figure 9c: SEM Picture of Spray Dried SEDDS formulation*

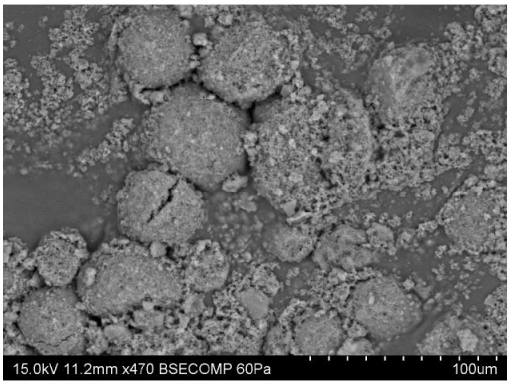


*Figure 9d: Scanning Electron Microscopic Picture of Spray Dried SEDDS formulation wetted with water*

**Evaluation studies for self emulsifying extended release tablets**

After optimization studies of solid self emulsifying powder form prepared by spray drying technology, an attempt was made to develop extended release formulation by using it. The formulations were prepared and evaluated for pre compression as well as post compression parameters. In following sections results were explained extensively.

***Pre-compression parameters:***

The lubricated blend of different formulations were evaluated for angle of repose, bulk density, tapped density and carr's index and Hausner's ratio and their values were shown in table.

**Table 11:** Pre-compression parameters of powder blend

| Formulation code | Angle of repose(θ) | Bulk density ($g/cm^3$) | Tapped density ($g/cm^3$) | Carr's index (%) | Hausnerratio |
|---|---|---|---|---|---|
| F1 | 26.5± 0.47 | 0.426± 0.22 | 0.492± 0.22 | 13.41 ± 0.24 | 1.15 |
| F2 | 25.8± 0.32 | 0.402± 0.25 | 0.455± 0.51 | 13.54 ± 0.16 | 1.13 |
| F3 | 28.4± 0.44 | 0.410± 0.18 | 0.476± 0.24 | 15.46 ± 0.21 | 1.16 |
| F4 | 27.1± 0.12 | 0.415± 0.35 | 0.483± 0.26 | 15.23 ± 0.24 | 1.16 |

Data represents Mean ± SD, n=3

The bulk density values ranged from 0.402 ± 0.25 to 0.426 ± 0.22 respectively. The results of angle of repose and carr's index ranged from 25.8 ± 0.32 to 28.4 ± 0.44 and 13.41 ± 0.24 to 15.46 ± 0.21 respectively. The results of angle of repose for all formulations F1-F4 (< 30) have shown excellent flow properties for powder blend. The compressibility index (<20) and Hausner's ratio results indicate good to fair flow properties of the powder for all formulations.

***Post compression parameters***

All the prepared tablets of Varenicline were evaluated for hardness, friability, weight variation, uniformity of drug content and results were showed in table.

**Table 12:** Post compression parameters of tablets

| Formulation code | Hardness ($kg/cm^2$) | Friability (%) * | Weight variation | Drug content (%) # |
|---|---|---|---|---|
| F1 | 5.4 ± 0.41 | 0.512 | 361.7± 0.34 | 98.43±0.88 |
| F2 | 5.5±0.152 | 0.612 | 362.6± 0.72 | 98.45±0.27 |
| F3 | 5.7 ± 0.47 | 0.613 | 361.5± 1.52 | 99.48±1.18 |
| F4 | 5.6±0.208 | 0.658 | 360.6± 1.32 | 97.05±0.27 |

Data represents mean±SD, #n=6, *n=20

The hardness of prepared tablets was from 3 to 4kg/cm2. All the prepared tablets complies the IP standards for weight variation and friability. The results of friability and weight variation ranged from 0.512 to 0.658 and 336.7 ± 0.34 to 346.6 ± 1.32 respectively.

**Percent drug content**

The percent drug content test was performed to ensure uniform and accurate distribution of drug. All the tablet formulations were analyzed for the drug content and drug content was found to be varying from 97.05 ± 0.27 to 99.48 ± 1.18. The results indicated uniform mixing of drug.

***In vitro* dissolution studies**

The in vitro drug release studies was performed by USP paddle apparatus, using 900 ml of 0.1N HCl as medium at 50 rpm and at a temperature of 37°C ± 0.5 °C. Results were shown in table and figure.

**Table 13:** Comparative percent drug release profiles of formulations F1 to F4.

| Time (hours) | Cumulative % Drug Release | | | |
|---|---|---|---|---|
| | F1 | F2 | F3 | F4 |
| 1 | 21.2±0.24 | 12±0.25 | 16.6±0.38 | 18.5±0.25 |
| 2 | 27.75±1.02 | 17.8±0.14 | 22.7±0.12 | 25.2±0.60 |
| 4 | 41.2±0.64 | 26.6±0.54 | 32.2±0.23 | 37.4±1.42 |
| 6 | 53.1±0.19 | 38.9±0.26 | 46.05±0.15 | 49.6±0.58 |
| 8 | 64.2±0.21 | 50.6±0.76 | 57.4±0.13 | 61.3±0.14 |
| 12 | 72.3±0.24 | 69.2±0.65 | 65.7±0.50 | 70.2±0.25 |
| 18 | 87.2±0.34 | 85.2±0.21 | 86.3±0.41 | 86.9±0.16 |
| 24 | 93.6±0.45 | 92.5±0.13 | 92.2±0.11 | 92.4±0.18 |

Data represents mean ± S.D (n=3)

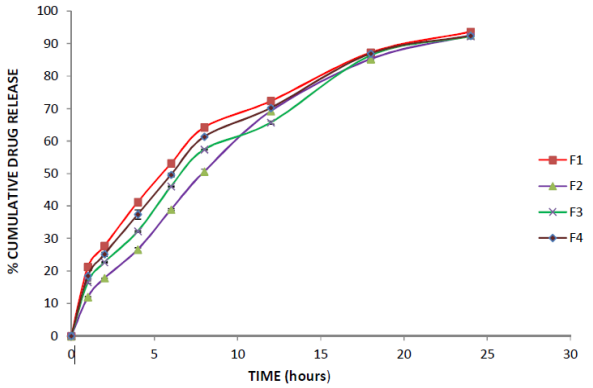


*Figure 10: Dissolution profile of formulations F1 to F4*

F1 and F2 formulations were formulated using HPMC K200M as a polymer at concentrations of 10%w/w, 12.5 % w/w respectively. As the polymer level was increased drug release rate was decreased. It may be due to the delay in the erosion of the polymer. F3 formulation was formulated using HPMC K200M: HPMC K100M at a ratio of 1:1 as a polymer at concentrations of 12.5%w/w. F4 formulation was formulated using HPMC K100M as a polymer at concentrations of 12.5%w/w. Formulations F3 and F4 showed slightly higher initial drug release than F2 formulation due to low viscosity of polymer but the release of the drug was found to be same at the end of 24 hrs for F2, F3 and F4 formulation. F2 formulation was found to exhibit good initial drug release and was extended upto 24 hrs.

**Stability studies**

The samples were stored at 40OC/75%RH for three months. There was no significant change observed in assay and in-vitro release profile when compared with initial samples. The formulation F2 was found to be stable. Stability data was showed in tables.

**Table 14:** Stability data of optimized formulation

| Time | Test % | Temperature |
|---|---|---|
| | | **40$^{O}$C / 75% RH** |
| 1 month | Assay | 98.1±0.76 |
| 2 months | Assay | 98.1±0.67 |
| 3 months | Assay | 98.0±0.79 |

***In-vitro* Drug release:**

0.1N HCl, 900ml, paddle type, 50rpm, 24hours.Sampling points 1, 2, 4, 6, 8, 12, 18 and 24 hours.

**Table 15:** Dissolution Profile for Stability Samples

| Time (Hours) | 40$^{O}$C / 75% RH | | |
|---|---|---|---|
| | 1 month | 2 months | 3 months |
| 1 | 11.6±0.92 | 11.4±0.89 | 11.1±0.45 |
| 2 | 17.5±1.30 | 16.6±0.76 | 16.4±0.87 |
| 4 | 25.9±0.36 | 24.8±0.93 | 24.7±0.56 |
| 6 | 37.4±0.26 | 36.9±0.16 | 36.4±0.32 |
| 8 | 50.4±1.56 | 49.4±1.00 | 48.2±0.95 |
| 12 | 68.5±0.97 | 68.5±0.78 | 68.1±0.76 |
| 18 | 84.1±0.31 | 83.7±0.26 | 83.5±0.30 |
| 24 | 91.4±0.12 | 91.2±0.16 | 90.8±0.25 |

**Summary & Conclusion**

In the present investigation, self emulsifying ER tablets containing Varenicline were developed. The objective of the work was to enhance the solubility, dissolution properties and bioavailability of Varenicline. The available conventional dosage forms showing few problems related to dissolution and bioavailability because of low solubility and high presystemic metabolism and also frequency of dosing is an another problem which results incompliance to patient. In order to overcome these drawbacks drugs can be developed in the form of self emulsifying extended release drug delivery system.

Self emulsifying system was developed by using Oleic acid, Labrafil M 2125CS, Cremophor RH40 and PEG 400 showed acceptable physical characters like size and zeta potential which less than 250nm size and -20mv potential respectively. Drug release studies also defined the role of precipitation inhibitor in self emulsifying system and almost 100% of drug release was showed in dissolution studies. Bioavailability study was conducted for liquid self emulsifying system with and without super saturation promoter. Results showed a significant role of super saturation promoter in different pH conditions. Bioavalability of Varenicline was increased by 3.4folds with self emulsifying system with 5%w/w of HPMC E5.

Development of solid SEDDS was done by using lab spray drier using response surface methodology. Boxbehnken design was employed for trials and resultant sprayed powder was evaluated for micromeritic properties, loading efficiency and dissolution studies.

Results showed that all the tablets met the compendia limits in terms of physical parameters and dissolution efficiency. Among all formulations, F2 which contain the drug Varenicline and HPMCK200M as polymer with other excipients was found to exhibit good initial drug release and was extended up to 24 hours.

Pre compression as well as post compression parameters were evaluated and found that results were satisfactory and also met compendia limits. The dissolution profile met innovator release profile after 4hr time point. The release kinetic studies showed that drug release follows nearly zero order kinetics with diffusion and erosion-based mechanism. Stability studies were conducted and results were showed satisfactory end result. The drug release follows first order kinetics with diffusion and erosion mechanism. The burst release was achieved by addition of super disintegrates in the formulation. Stability studies were conducted for optimized formulation, results showed that there was no significant change in tablet properties.

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