Saudi Journal of Medical and Pharmaceutical Sciences **ISSN 2413-4929 (Print)**
Scholars Middle East Publishers **ISSN 2413-4910 (Online)**
Dubai, United Arab Emirates
Website: https://saudijournals.com/ DOI: 10.36348/sjmps.2016.v02i09.001

Research Article

A Novel Approach in Fabrication and Characterization of Self Micro-Emulsified Tablets (SMET)

Prasanta Kumar Biswal[1], Bibaswan Mishra[1]*, NiharRanjanPani[1], Prasanna Kumar Dixit[2]
[1]Gayatri College of pharmacy, Department of Pharmaceutics, Sambalpur, Odisha, India
[2]Department of Zoology, Berhampur University, Bhanja Bihar, Odisha, India

***Corresponding Author:**
Dr. Prasanta Kumar Biswal
Email: drprasantabiswal74@gmail.com

Abstract: In this study, concentration of cross carmelose sodium (CCS), microcrystalline cellulose (MCC) and maltose have optimized in self-micro emulsified tablet (SMET) of cinnarizine (CNZN), a piperazine derivative antihistaminic drug. The self-micro emulsified liquids (SELS) of CNZN were prepared with Linoleic acid, PEG 400 and Tween 80. The SMET of SELS were prepared by adsorption followed by compression phenomenon using CCS (A), maltose (B) and MCC (C) which were optimized through 2^3 factorial design considering responses like disintegration time (DT), time for 50 % (t50) and time for 80% (t80) of drug release. Droplet size and turbidity of disintegrated SMET emulsion sample was within 2.58 ± 7.48 to 4.84 ± 5.83 µm and 16.47 ± 6.35 to 27.10 ± 6.12 nephlometric turbidity units (NTU) respectively. The factors A and B were directly and C was inversely related with responses. Response surface methodology was used to predict the levels of the factors A, B and C required for obtaining an optimum formulation with minimum dissolution time. Observed responses were in close agreement with the predicted values of the optimized formulation, thereby demonstrating the feasibility of the optimization procedure in developing self-micro-emulsified tablet dosage forms.
Keywords: Cinnarizine, Self-micro emulsified tablet, factorial design, Response surface methodology

INTRODUCTION

Self-emulsifying drug delivery system (SEDDS) is one of the best technique to improve the solubility and bioavailability of poorly soluble drugs [1, 2]. When SEDDS comes in contact with aqueous medium, it emulsifies spontaneously to produce fine oil in-water emulsions having drug in oil part under little agitation. The basic mechanisms to improve the oral bioavailability of this system are (i) drug in dissolved form; (ii) the small droplet size provides a large interfacial area for the drug absorption. SEDDS are normally prepared as liquids formulation having certain disadvantages like low stability and portability, low drug loading, few choices of dosage forms, irreversible drugs/excipients precipitation and use of large quantity (30–60%) of surfactants in the formulations leads to gastrointestinal irritation. An alternative approaches i.e. the Solid-SEDDS has been investigated to overcome such disadvantages of liquid SEDDS.

In the development of Solid-SEDDS, the liquid self-emulsifying ingredients are solidified into powders/nanoparticles to form solid dosage forms (SE tablets and SE pellet) [3, 4]. Thus, Solid-SEDDS combine the advantages of SEDDS (i.e. enhanced solubility and bioavailability) with those of solid dosage forms (e.g. low production cost, convenience of process control, high stability and reproducibility, better patient compliance). Adsorption of liquid self micro-emulsified formulations to solid carrier is one of the best techniques to obtain free flowing powders for compression into tablet dosage form which can be called as self micro-emulsified tablets (SMET). The release rate of microemulsion from SMET is profoundly influenced by the physical and chemical attraction between the liquid self micro emulsified formulation and its adsorbing material. Hence, the concentration of adsorbing materials in SMET has been optimized in present investigation using 2^3 factorial designs. Response surface methodology has used to access the interactions between the factors to obtain optimum SMET. The statistical optimization designs have been documented for the formulation of many pharmaceutical solid dosage forms [5-8]. As part of the optimization process, the main effects, interaction effects and quadratic effects of the formulation ingredients were investigated. The objectives of the present work were to design, develop, optimize and evaluate self micro-emulsified tablet of cinnarizine (CNZN) applying response surface methodology. Cinnarizine is a piperazine derivative antihistaminic drug. It belongs to Calcium L-channel antagonist pharmacological group on the basis of mechanism of

action. It is also used for the control of vomiting due to motion sickness and vertigo [9-12].

MATERIALS AND METHODS

Materials

Cinnarizine was obtained as a gift sample from Macleod's Pharmaceuticals Ltd, Mumbai, India. Microcrystalline Cellulose, Cross carmelose sodium, Maltose and PVP K-30F were procured from Qualigens, Mumbai India. Lineloic acid, Polyethylene glycol (PEG) 400, Tween 80, Sodium Hydroxide, Methanol, Ethanol and Potassium di hydrogen phosphate were purchased from S.D Fine chemical Ltd, Mumbai, India. All other chemicals used were of analytical grade.

Drug-Excipient compatibility testing

The drug excipient compatibility testing was carried out by differential scanning calorimeter and isothermal stress testing[6,7].

Differential scanning calorimeter study

Excipients (Table 1) used in formulation were subjected for drug-excipient compatibility study using differential scanning calorimeter (JADE DSC, PerkinElmer, Waltham, MA, USA). The sifted (80-mesh sieve) drug and its physical mixture with excipients were weighed directly in the DSC aluminum pan and scanned in the temperature range of 50-300 °C under nitrogen atmosphere at heating rate of 20°C/min.

Table 1: Results of IST study of Cinnarizine after 3 weeks of storage at stressed conditions

Samples	Ratios (drug-excipients)	% Drug remaining	
		Control samples	Stressed samples
CNZN	_	101± 0.58	99±0.38
CNZN + Linoleic acid	1:1	104±0.83	100±1.31
CNZN + PEG 400	1:1	102±0.43	100±0.84
CNZN + Tween80	1:1	99±0.93	97±1.02
CNZN + Cross carmelose sodium	1:1	102±1.21	98±1.11
CNZN + Maltose	1:1	99±0.68	97±1.05
CNZN + MCC	1:1	101±1.39	99±1.68

*Values expressed as average ± standard deviation; CNZN, Cinnarizine; MCC, Microcrystalline cellulose.

Isothermal stress testing study

In isothermal stress testing (IST) studies, drug and different excipients (Table 2) were weighed directly in 15ml glass vials (n = 2) and mixed on a vortex mixer for 2 min. In each of the vials, water (10% v/w) was added and the drug-excipients blend was further mixed with a glass capillary (both the ends of which were heat sealed). To prevent any loss of material, capillary was broken and left inside the vial. Each vial was sealed using a Teflon-lined screw cap and stored at 50°C in a Hot air oven. These samples were periodically examined for any unusual color change. After 3 weeks of storage at the above conditions, samples were quantitatively analyzed using UV-Visible spectrophotometer. Drug-excipients blends without added water stored in refrigerator served as controls. For analytical sample preparation, 10ml of ethanol was added into each vial. The mixture was vortexed for 3 min.The samples were centrifuged and the supernatant (0.2 ml) was withdrawn and subjected for appropriate dilution. Samples were analyzed in UV-Visible spectrophotometer at 253 nm wavelength and drug content was determined from the calibration curve prepared within the expected range.

Table 2: 2^3full factorial design (coded value in bracket) and formulae with observed response value of Cinnarizine self micro-emulsified tablet

Name of ingredients	Quantity (mg/tablet)								
	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	CN-O*
Liquid emulsion Part									
Cinnarizine	10	10	10	10	10	10	10	10	10
Linoleic acid	10	10	10	10	10	10	10	10	10
Tween 80	5	5	5	5	5	5	5	5	5
PEG 400	5	5	5	5	5	5	5	5	5
Tablet part									
Cross carmelose sodium (A)**	40 (-1)	40 (-1)	40 (-1)	40 (-1)	50 (+1)	50 (+1)	50 (+1)	50 (+1)	42.5 (-0.5)
Maltose (B)**	110 (+1)	110 (+1)	90 (-1)	90 (-1)	110 (+1)	110 (+1)	90 (-1)	90 (-1)	100 (0)
Microcrystaline Cellulose (C)**	30 (-1)	40 (+1)	30 (-1)	40 (+1)	30 (-1)	40 (+1)	30 (-1)	40 (+1)	37.5 (+0.5)

*SMET-O, Check point; **Coded Value in bracket

Formulation of self micro-emulsified tablets

Preparation of self-emulsified liquid

The self-emulsified liquid system (SELS) of CNZN was prepared initially by weighing CNZN (23. 1 % w/w) and linoleic acid (23.1 % w/w) as oil base at a ratio of 1:1into glass vial and mixed them at isothermal condition (37°C). PEG 400 (2.69 % w/w) as surfactant and Tween 80 (2.69 % w/w) as co-surfactant [13] were added to oil mixture at a final concentration of 30.04 % w/w each. The resultant emulsion was mixed with magnetic stirrer until a transparent solution was obtained. The SELS were then allowed to cool at ambient temperature for 24 h until a viscous paste was obtained.

Preparation of self micro-emulsified tablets

The self micro-emulsified tablets (SMET) of CNZN were prepared by adsorption followed by compression phenomenon. The formulae of SMET have given in Table 2. SELS paste was initially mixed with Maltose using mortar and pestle to obtain a semisolid waxy paste. The mixture was then grinded with Cross carmelose sodium for 1 min to obtain the dry emulsion based granules. Finally, MCC was added to the granules and blended in polybag for 5 mins. To the adsorbed mass, 12 mg of PVP was mixed and granulated with ethanol. The wet granules were dried in hot air oven at 45^0C and passed through 16 mesh sieve to obtain dried granules. The dried granules were blended with remaining quantity of MCC and Cross carmelose sodium. The final blended mass was subjected to direct compression in eight stations tablet compression machine (Lab press, Modle-1049, Ahmadabad, India) using 8 mm die-punch set.

Characterization of self-emulsified granules

The flow properties of self-emulsified granules can be judged from the angle of repose, compressibility index and Hausner's ratio [14, 15].

Angle of repose of the powder

Angle of repose was determined using the funnel method. The powder was poured through a funnel that was raised vertically on the plane surface until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and the angle of repose (θ) was calculated using the formula.

$$\theta = \tan^{-1}(h/r) \quad (1)$$

Bulk density of the powder

Apparent bulk density (D_b) was determined by pouring the drug powder into a graduated cylinder. The bulk volume (V_b) and weight of the powder (M) was determined. The bulk density was calculated using the formula.

$$D_b = V_b/M \quad (2)$$

Tapped density of the powder

The measuring cylinder containing a known mass of powder was tapped for 100 times. The minimum volume (V_t) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density (D_t) was calculated using the following formula

$$D_t = V_t/M \quad (3)$$

Compressibility Index of the powder

The simplest way for measurement of flowability of powder is compressibility, an indication by which a material can be induced to flow is given by compressibility index (CI) which is calculated as follows,

$$CI = [D_t - D_b/D_t] \times 100 \quad (4)$$

Hausner ratio of the powder

Hausner ratio is an indirect indexof powder flowability. It is calculated by the following formula,

$$\text{Hausner ratio} = D_t / D_b \quad (5)$$

Where D_t is tapped density and D_b is bulk density.

The flow properties of granular powder emulsion were determined by the Carr's method (compressibility, angle of repose and Hausner ratio) [14, 15]

Characterization of self micro-emulsified tablets

The physical characteristics like weight variation, drug content, thickness, hardness and friability and disintegration tests were evaluated for SMET according to methods describe in Acharya, *et al* [7, 8].

Weight Variation

Five tablets were selected randomly from the lot and weighed individually by using digital balance and the weight variation of individual tablet from its mean value was calculated.

Hardness Test

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness Tester. The tablets were placed between two plunges of the tester and the reader knob was set at zero of the scale. The force was exerted on the tablets by rotating the screw of the tester. The force required to crack the tablet was end point of rotation of screw and the distance travel by the knob in the scale was the hardness (kg/cm^2) of the tablets. The experiment was conducted in triplicate.

Friability Test

It is the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition. The friability of tablets was determined using Roche Friabilator. It is expressed in percentage (%). Five tablets were initially weighed ($W_{initial}$) and

transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The final weight of the tablet (W_{final}) was measured. The % friability was calculated by,

$$\text{Friability} = [(W_{initial} - W_{final}) / W_{initial}] \times 100 \quad (6)$$

Disintegration Time

The Disintegration time is calculated using the USP Disintegration test (Veego, Mumbai) apparatus. Three tablets were placed in each tube of the apparatus containing 900 ml of distilled water and the apparatus was started. The time required to complete removal of any particle over the mesh of the tube was considered as disintegration time.

Droplet size and turbidity measurements

The droplet size and turbidity of emulsion obtained from SMET were carried out after the disintegration study of tablets. The medium containing disintegrated tablets were centrifuged at 1000 rpm for 3 min to separate the emulsion layer at supernatant from adsorbed solid materials present in tablets. The resultant emulsions were then subjected for droplet size and turbidity measurement as follows.

Droplet size analysis

The droplet size distribution of emulsion was determined by laser diffraction analysis using Coulter particle size analyzer (Beckman Coulter India, Private Limited, Mumbai) with a particle size measurement range of 0.04–2000 µm. Samples were placed into small volume module and the data were collected for 60 sec. Particle size was calculated from the volume size distribution. All studies were repeated, with good agreement being found between measurements.

Turbidity measurement

Turbidity of the resultant emulsions given in nephlometric turbidity units (NTU) was measured using Digital Nephelo-Turbidity (Model 132, Systronics, Ahmedabad) with accuracy of ± 0.01 NTU with stray light less than or equal to 0.01 NTU. Turbidity measurement was carried out in 30 ml of emulsion.

Dissolution study

The *in vitro* dissolution study of Cinnarizine SMET was carried out using USP Dissolution apparatus, type-I at a rotating speed of 75 rpm in 900ml of 0.1 N HCl buffer pH 1.2, maintained at 37 ± 0.5^0C to estimate the drug release. Aliquot of 5ml of sample was drawn at each 5 min interval for analysis of amount of drug released and same amount of fresh buffer was replaced. The drug release was estimated by UV spectroscopy (Shimadzu UV-1700UV/Visible double beam spectrophotometer, Kyoto, Japan) at a wavelength of 253 nm.

Experimental design, statistical analysis and optimization

The independent factors like the percentage of cross povidone (A; 40 and 50%), maltose (B; 90 and 110%) and microcrystalline cellulose of tablets (C; 30 and 40%) were optimized through 2^3 factorial design with eight experimental trials [5-8]. The disintegration time (DT), % drug release at 5min (DR_5), drug release at 30min (DR_{30}), and drug release at 60min (DR_{60}) were selected as dependent responses. Design Expert software was used to generate study design and response surface plots by the analysis of results of SMET formulations (Table 4). The statistical parameters like coefficient of variation (CV), regression coefficient (R^2), adjusted regression coefficient (adjusted R^2), F test and P values were calculated for the selection of best fitting polynomial model. Analysis of variance (ANOVA) was used to identify significant effects of independent factors on dependent responses. The influences of various independent variables on dependent responses were accessed by using following mathematical equation involving independent variables and their interactions for various measured responses generated by 2^3 factorial design is following:

$$Y = b_0 + b_1A + b_2B + b_3C + b_{12}AB + b_{23}BC + b_{31}CA + b_{11}A^2 + b_{22}B^2 + b_{33}C^2 + b_{123}ABC \quad (7)$$

Where Y is the dependent variable, b_0 is the arithmetic mean response of 8 runs, and bi is the estimated coefficient for factors A, B and C. The main effects (A, B and C) represent the average result of changing one factor at a time from its low to high value. The interaction terms (AB, BC, CA and ABC) showed how the response changes when three factors are simultaneously changed. The polynomial terms (AB, BC, CA, A^2, B^2 and C^2) are included to investigate non-linearity. The relationship between the dependent and independent variables was further elucidated using response surface plots. These plots are useful to study the effects of various factors on the response at a given time and to predict the responses of dependent variables at intermediate levels of independent variables. Subsequently, a numerical optimization technique using the desirability approach was used to generate new formulations with the desired responses.

Table 4: *In vitro* drug release profile of factorial batch tablets

Time (min)	Mean percentage of drug release (DR)							
	F-1	**F-2**	**F-3**	**F-4**	**F-5**	**F-6**	**F-7**	**F-8**
5	39.24 ± 2.47	49.05 ± 2.58	43.82 ± 3.19	53.86 ± 1.83	82.65 ± 4.69	80.73 ± 3.28	93.88 ± 2.87	96.19 ± 2.63
15	60.23 ± 3.18	75.28 ± 3.01	85.49 ± 2.93	84.65 ± 2.77	91.01 ± 2.18	101.45 ± 1.88	101.47 ± 2.78	93.79 ± 3.77
30	65.71 ± 3.05	82.13 ± 3.84	85.49 ± 2.84	92.11 ± 4.02	92.15 ± 1.86	102.76 ± 3.66	102.56 ± 4.02	100.66 ± 2.43
45	68.49 ± 2.64	85.62 ± 3.52	101.65 ± 3.62	98.24 ± 3.03	91.10 ± 2.61	103.14 ± 2.84	102.84 ± 1.63	101.65 ± 3.81
60	69.83 ± 2.88	75.29 ± 3.56	87.56 ± 2.42	103.88 ± 2.68	91.19 ± 3.72	103.68 ± 3.54	103.44 ± 2.46	101.99 ± 3.27
90	69.18 ± 3.57	86.47 ± 4..02	102.87 ± 3.29	104.58 ± 2.49	89.96 ± 1.39	104.39 ± 1.74	104.68 ± 2.42	101.95 ± 1.43
120	71.15 ± 3.20	88.94 ± 2.48	103.74 ± 2.11	105.26 ± 2.52	90.22 ± 1.83	105.02 ± 2.59	105.43 ± 2.52	101.55 ± 3.13

Experimental design validation

To validate the chosen experimental design, the experimental values of the responses were quantitatively compared with predicted values and, the relative error (%) was calculated using the following equation (Eq.1). A checkpoint batch (CN-O) was prepared by selecting level of factors arbitrarily (A = –0.5 level, B= 0 level and C = +0.5) (Table 2) and all physical characteristics of tablets were evaluated.

Relative error (%) = [(Predicted value − Experiment value)/ Predicted value] × 100 (8)

Stability testing

Stability studies of optimized SMET formulations were conducted according to International Conference on Harmonization (ICH) guidelines [8, 16]. The formulations covered with polyethylene bottles was kept in a desiccator containing saturated solution of sodium chloride (75% RH) [16]. The desiccator was kept in an oven at 40 ^{0}C for 3 months. At specified time intervals, the tablets were examined for any statistical difference in their hardness values, disintegration time and dissolution time using a paired Student's t-test. Differences were considered to be significant at $p < 0.05$.

Statistical analysis

Statistical optimization was performed using Design-Expert software (Stat-Ease Inc., USA). All measured data are expressed as mean ± standard deviation (S.D.). Each measurement was done in triplicate (n = 3).

RESULT AND DISCUSSION

Drug-Excipient compatibility testing

Drug–excipients compatibility studies an important exercise at initial stage of formulation development for stable dosage form. A sharp endothermic peak was observed at 121 ^{0}C in DSC thermogram of CNZN which was well preserved at 121 ± 2 ^{0}C in the DSC thermo gram of CNZN-excipients mixtures (Figure 1). It inferred that drug and excipients used in formulations are compatible to each other. Moreover, the results of isothermal stress testing (Table 1) indicated that drug is compatible with used excipients as there are no changes found in colour and appearance as well as drug content after storage of drug–excipient blends under stressed conditions.

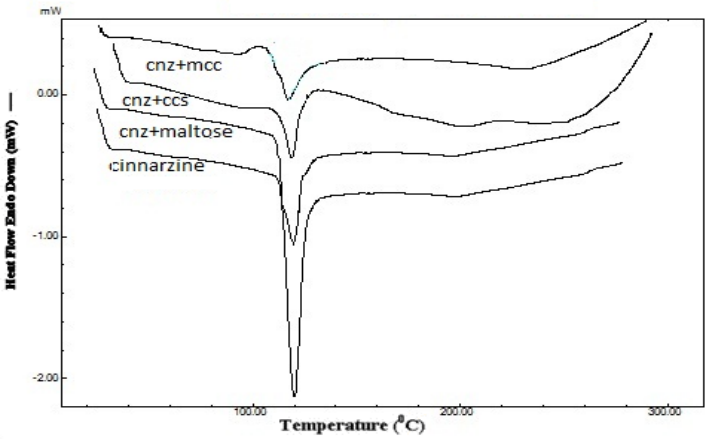

Fig-1: Differential scanning calorimetry of drug and drug-excipient mixture

*CNZ, Cinnarizine; MCC, Microcrystalline Cellulose; CCS, Croscarmelose sodium

Design of Formulation

Self emulsified tablets of Cinnarizine were prepared by adsorption of emulsion followed by wet granulation technique. Development of formulation in the present study based on preparation of non aqueous emulsion with adsorbent (maltose) along with super disintigrant (CCS) and diluent (MCC). The granules of powder mass were formulated by using ethanolic PVP solution. The tablets were compressed by direct compression technique. In preliminary test, Crosspovidone was considered as superdisintigrant in the formulation but tablets were not compressed, but desired strength tablet were obtained by CCS. The formulation having less DT and fast release of drug were considered as the basic parameter for development of entire formulation.

Evaluation of self emulsified granules

The flow properties of granules can be judged from the angle of repose, compressibility index and Hausner ratio. The Hausner ratio 1.03-1.08 indicates free flowing and >1.60 with poor flow properties [18]. Values for angle of repose (θ), compressibility index (%), and Hausner ratio for all prepared granules were found to be in the range of 21.3 to 25.30C, 6.21 to8.21%, and 1.03 to 1.08, respectively, which showed that the granules were free flowing and can be used for tablet compression

Evaluation of self emulsified tablet

Weight variation

The percentage of weight variations for all formulations is shown in Table 2. All the tablets passed weight variation test as the percentage of weight variation was within the Pharmacopoeia limits of ± 7.5% of the total tablet weight. The weights of all the tablets were found to be uniform with low standard deviation values.

Disintegration Time

Disintegration for the tablets was studied by placing six tablets in disintegration apparatus in 900ml water and the mean with S.D. results are shown in Table 2. It is observed that the concentration of CCS is inversely proportional to the DT of the tablet as DT of F-1 to F-4 (CCS, 40 mg/ tab) was less than the DT of F-5 to F-8 (CCS, 50 mg/ tab). The DT of F-2, F-4, F-6 and F-8 (MCC, 40 mg/tab) were less than the DT of F-1, F-3, F-5 and F-7 (MCC, 30 mg/tab) which signifies inverse relationship between MCC and DT. The DT was not significantly change on variation of maltose concentration in F-1 to F-8.

Hardness

The measured mean hardness of six tablets of each batch has shown in Table 2. It was observed that the tablets had sufficient strength and integrity.

Thickness and Diameter

The dimensions determined for factorial batches tablets were tabulated in Table 2. Tablets mean thickness (n =3) were almost uniform in all the eight formulations and were found to be in the range of 3 ± 0.05 mm. The diameter of the tablets of eight formulations was same (8.00 mm).

Friability

The result of friability testing of both factorial batches was tabulated in Table 2. The percentage of weight loss of ten tablets from their initial weight after 100 revolutions in Roche friabilator apparatus was less than 1%. It signifies that tablet having sufficient strength to ensure the mechanical hazards during shipping, transporting and coating.

Disintegration time

The DT of all formulations was very short i.e. within 6.77±2.57 to 10.82 ± 2.61sec (Table 2) which infers the rapid bursting of tablet in to tiny globules.

Particle size and turbidity of oil globules

Droplet size distribution of disintegrated SMET emulsion sample was within 2.58 ± 7.48 to 4.84 ± 5.83 µm (Table 3). Comparison of droplet size data with the visual observations shows that good emulsification properties are reflected by the low globule size. This reflects the fact that the visual test is a measure of the spontaneity of emulsification rather than a measure of the quality of the formed emulsion [19]. Turbidity (in NTU) was measured for the same samples utilized for particle size analysis. Turbidity readings ($NTU_{observed}$) are given in Table 3.

***In vitro* Drug Release Study**

The *in vitro* drug release profile of factorial batch shown in Table 4. It is observed from the data of table at the % of drug release at 5min (DR_5) was maximum in case of F-5 (82.652), F-6 (80.729), F-7 (93.879), F-8(96.197), (containing 36.66mg of C.C.S pre tablet) then F-1(39.242), F-2(49.052), F-3(43.825), F-4(53.858) (containing 26.66mg of C.C.S per tablet). It indicates that as the concentration of super disintegrant (C.C.S) in the tablet increases the amount of drug release increases. DR_5 value was observed maximum in F-8 (96.197) in compared with entire formulation.

It is observed from the data of table at the % of drug release at 30min (DR_{30}) was maximum in case of F-5(92.149), F-6(102.761),F-7(102.561) F-8(102.657), (containing 36.66mg of C.CS pre tablet) then F-1(65.707),F-2(82.133) F-3(85.487), F-4(92.114) (containing 26.66mg of C.C.S per tablet). It indicates that as the concentration of super disintegrant (C.C.S) in the tablet increases the amount of % of drug release increases. DR_{30} value was observed maximum in F-6 (102.761) in compared with entire formulation.

It is observed from the data of table that % of drug release at 60 min (DR_{60}) was maximum in case of F-5(91.197), F-6(103.682), F-7(103.436), F-8(101.187), (containing 36.66mg of C.C.S pre tablet) then F-1(69.829), F-2(75.287), F-3 (87.560), F-4(103.877) (containing 26.66mg of C.C.S per tablet) .It indicates that as the concentration of super disintegrant (C.C.S) in the tablet increases the amount of drug release increases. DR_{60} value was observed maximum in F-6 (103) in compared with entire formulation.

It is observed from the Table 4 and Figure 2 that the dissolution profile of tablet F-6 and F-8 met the official limit for conventional tablet (> 85% of drug released within 30min). Though the maximum amount of C.C.S present in the tablet of F-5 to F-8, the tablets of F-5 and F-7 contain more amount of MCC (30mg/ tablet) than F-6 and F-8 (40mg/tablet). It reveals that the presence of hydrophobic diluents MCC has a significant role on the amount of drug release. Hence, it inferred that formulation F-6 and F-8 are suitable formulation according to *in vitro* dissolution data. As amount of Maltose present in F-6 less than F-8 by keeping quantity of other ingredient constant, the cost of the F-6 will be minimum. Hence F-6 formulation was selected for further evaluation.

Table 3: Characterization of granules and self micro-emulsified tablet

Evaluation of granules								
	F-1	**F-2**	**F-3**	**F-4**	**F-5**	**F-6**	**F-7**	**F-8**
Angle of repose (θ)	23.8	21.4	22.7	24.4	24.7	23.4	24.1	23.7
Compressibility index (%)	5.45	5.77	5.56	6.94	6.76	6.15	4.41	6.56
Hausner ratio	1.06	1.06	1.06	1.07	1.07	1.07	1.05	1.07
Evaluation of tablets								
Weight variation (mg)	227.04 ± 1.71	234.38 ± 2.42	202.17 ± 2.56	216.09 ± 1.86	244.67 ± 1.89	247.54 ± 2.33	222.64 ± 1.44	233.89 ± 2.16
Content Uniformity (%)	99.48 ± 3.72	100.53 ± 2.81	100.92 ± 3.28	101.21 ± 4.17	100.73 ± 1.78	99.68 ± 2.84	100.82 ± 2.66	99.47 ± 3.26
Hardness (Kg/cm^2)	4 ± 1.62	5 ± 2.84	5 ± 2.18	4 ± 3.21	5 ± 3.28	5 ± 2.71	5 ± 3.18	6.03 ± 2.65
Thickness (mm)	3	3	3	3	3	3	3	3
Diameter (mm)	8	8	8	8	8	8	8	8
Friability (%)	0.43	0.61	0.56	0.48	0.71	0.46	0.59	0.41
Disintegration time (Sec)	5.82 ± 2.61	5.49 ± 2.54	6.16 ± 3.01	6.37 ± 3.11	6.42 ± 2.89	5.95 ± 2.66	6.11 ± 2.41	5.77 ± 2.57
Evaluation of oil globules								
Particle size (µm)	4.84 ± 5.83	3.72 ± 4.91	3.89 ± 4.81	4.81 ± 5.29	2.58 ± 7.48	3.71 ± 6.21	4.81 ± 4.44	3.26 ± 4.61
Turbidity (NTU)	16.47 ± 6.35	19.37 ± 5.83	27.10 ± 6.12	17.13 ± 4.24	24.46 ± 5.27	22.39 ± 4.88	19.47± 5.81	26.31 ± 4.68

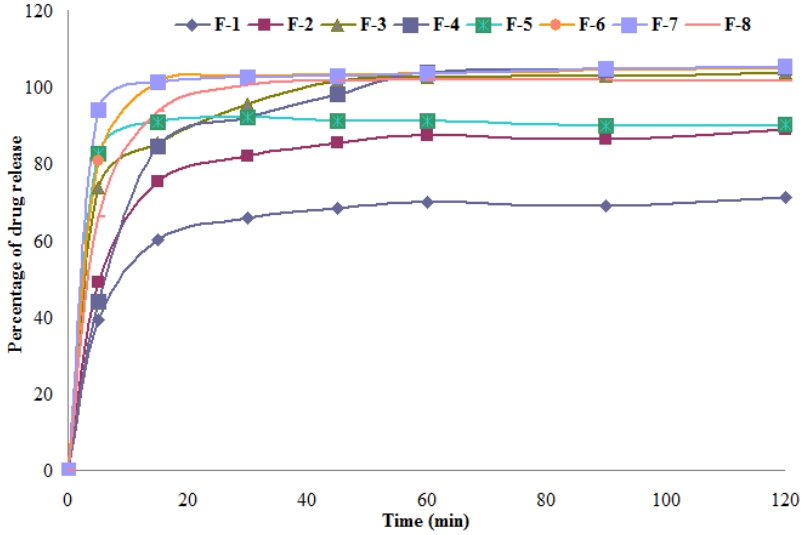

Fig-2: *In vitro* drug release of self microemulsified tablet of Cinnarizine

Optimization

Experimental design

The formulation of SEDDS tablets were design through 2^3 factorial designing where three factors i.e. concentration of C.C.S. (A), Maltose (B) and MCC (C) were treated at 2 levels i.e. +1 and -1. The level of factor A was 40 and 50 mg, factor B was 90 and 110 mg and, factor C was 30 and 40 mg. The layout of the design has been depicted in table 2

Statistical Optimization of Study Design

In order to optimize the self emulsifying tablets of Cinnarizine, the investigator studied the effect of ratio of C.C.S, Maltose, and MCC as three important variables on the performance of solid self emulsifying tablets. The drug release at 5min (DR_5), drug release at 30min (DR_{30}), and drug release at 60min (DR_{60}) were consider as the response of variables. DR_5 was selected to access the burst release of tablets. DR_{30} was selected to access the official limits. DR_{60} was selected to access the complete release of the drug.

Effect of Independent Variables on Dependent Variables (DR_5)

The value of drug release and responses obtained from different experimental conditions for all the final eight formulations are summarized in table 4. The application of response surface methodology (RSM) offers empirical relationship between the model dependent and model independent variables. Quadratic model partial sum square type III was selected for all RSM studies by applying multiple regression analysis. The response variables (DR_5) and test variable A (C.C.S), B (Maltose) & C (MCC) are related to a second order polynomial equation. A summary of analysis of variance (ANOVA) for selective response surface quadratic predictive method of DR_5 is shown in table 5. Statistical testing of model was done in the form of ANOVA which is required to test the significance and adequacy of the model. The model F value implies that the model is significant ($p<0.05$). There was only 0.5% chance that the large model F value occurred due to noise. The values of "Prob" >F less than the value 0.05 indicate that model terms are significant and model "Prob1" indicated that the model test are not significant. In this case A, B, C, AB, AC, BC, ABC are significant in the model at 5 % confidence interval ($P<0.05$). The "Pred R- squared was in reasonable agreement with the "Adj R- Squared" (not defined). The optimized equations of DR_5 in actual factor and coded factor has been given in Eqn. 11 and 12.

$$DR_5 = 1416.83 + 153.30 \times CCS + 123.53 \times MALTOSE - 512.58 \times MCC + 13.85 \times CCS \times MALTOSE + 64.16\ CCS \times MCC + 44.20 \times MALTOSE \times MCC - 5.40 \times CCS \times MALTOSE \times MCC \quad \text{(Eqn. 11)}$$

$$DR_5 = 62.54 + 18.33 \times A + 6.90 \times B - 2.58 \times C + 7.73 \times Ax\ B - 4.82 \times A \times C - 11.83 \times B \times C - 5.39 \times A \times B \times C \quad \text{(Eqn. 12)}$$

It is observed from the equation that coefficient of A, B and C bears a (+), (+) and (-) sign respectively. The + ve sign of A and B signifies that the response is directly proportional with factor A and B where -ve sign indicates the inverse relationship of factor C with response (DR_5).

Table 5: Analysis of variance table for Percentage of drug release at 5 minutes from full factorial design

Source	Sum Square	df	Mean Square	F- Value	Prob> F
Percentage of drug release at 5 minutes (DR_5)					
Model	5138.667	7	734.0953	34.75	0.023
A	2687.105	1	2687.105		0.01
B	381.1837	1	381.1837		0.03
C	53.16867	1	53.16867		0.04
AB	477.8995	1	477.8995		0.02
AC	186.1099	1	186.1099		0.01
BC	1120.396	1	1120.396		0.03
ABC	232.805	1	232.805		0.03

Perturbation, Interaction and 3 D plot of response DR_5

It represent the comparison of the effect of three factor at the midpoint coded (0) in the design space. The response DR_5 is plotted by changing only one factor over its range while holding of other two factors constant. It is seen in Figure 3.a line AA, BB and CC are not straight line. Hence response DR_5 was sensitive to the concentration of CCS, Maltose and MCC. The graphical representation (3 dimension plot) of the regression equation was obtained by using the software Design Expert and present in figure 4.a. The 3D plot showed that a downward trend of the wire mesh was depicted at higher level (+1) and the upward trend was at lower level of (-1) of the concentration of A and B, it is predicted that DR_5 is directly proportion to A (significant) and B.

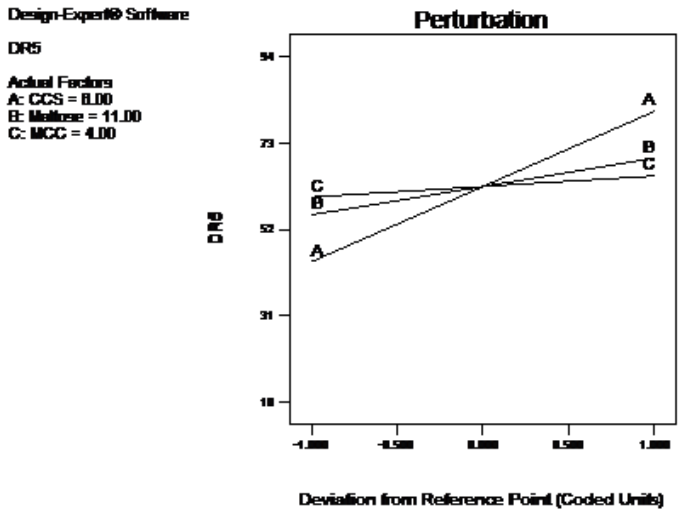

Fig-3a: Perturbation plot of DR_5
* DR_5; Percentage of drug release at 5 min

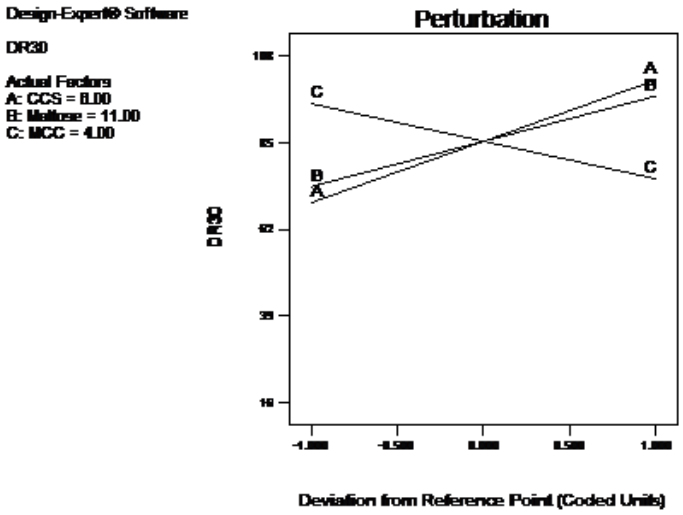

Fig-3b: Perturbation plot of DR_{30}

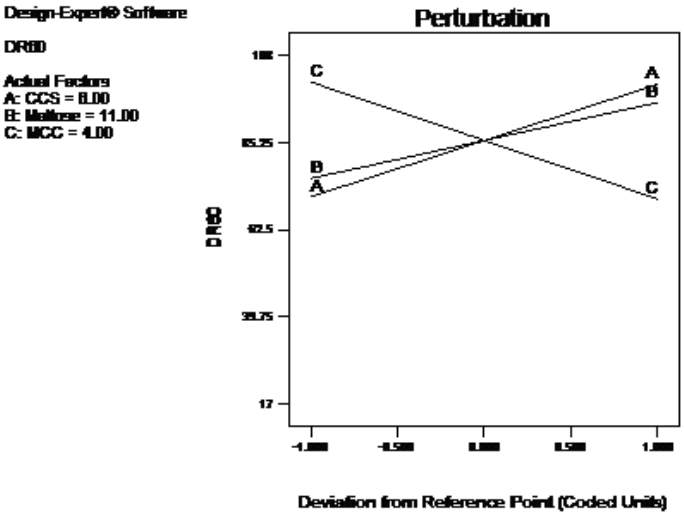

Fig-3c: Perturbation plot of DR_{60}

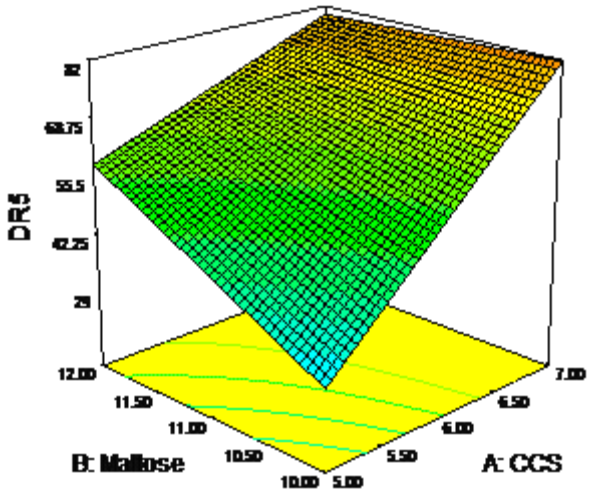

Fig-4a: 3Dimension surface plot of DR_5
* DR_5, Percentage of drug release at 5 min

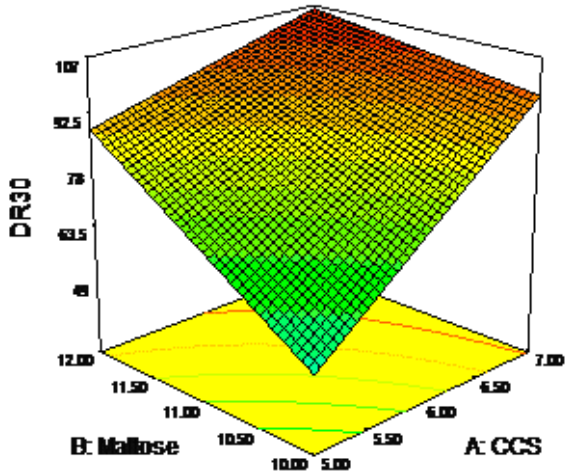

Fig-4b: 3Dimension surface plot of DR_{30}
* DR_{30}, Percentage of drug release at 30 min

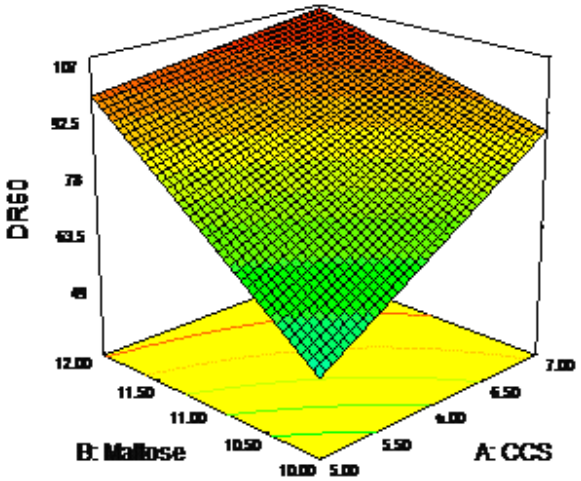

Fig-4c: 3Dimension surface plot of DR_{60}
* DR_{60}, Percentage of drug release at 60 min

Effect of Independent Variables on DR_{30}

The value of drug release and responses obtained from different experimental conditions for all the final eight formulations are summarized in table 4. The application of response surface methodology (RSM) offers empirical relationship between the model dependent and model independent variables. Quadratic model partial sum square type III was selected for all RSM studies by applying multiple regression analysis. The response variables (DR_{30}) and test variable A (CCS), B (Maltose) and C (MCC) are related to a second order polynomial equation. A summary of analysis of variance (ANOVA) for selective response surface quadratic predictive method of DR_{30} is shown in table 6. Statistical testing of model was done in the form of ANOVA which is required to test the significance and adequacy of the model. The model F value implies that the model is significant ($p<0.05$). There was only 0.5% chance that the large model F value occurred due to noise. The values of "Prob" >F less than the value 0.05 indicate that model terms are significant and model "Prob1" indicated that the model test are not significant.In this case A, B, C, AB, AC, BC, ABC are significant in the model. The "Pred R-squared" was not defined. The "Pred R- squared was in reasonable agreement with the "Adj R- Squared". The optimized equations of DR_{30} in actual factor and coded factor has been given in Eqn. 13 and 14.

$$DR_{30} = 1484.34 + 182.97 \times CCS + 115.33 \times MALTOSE - 535.02 \times MCC + 115.22 \times CCS \times MALTOSE - 70.98 \times CCS \times MCC - 43.38 \times MALTOSE \times MCC \quad \text{Eqn. 13}$$

$$DR_{30} = 85.48 + 16.31 \times A + 12.03 \times B - 9.99 \times C - 7.70 \times A \times B + 7.79 \times A \times C + 9.01 \times B \times C - 5.73 \times A \times B \times C \quad \text{Eqn. 14}$$

It is observed from the above equation that coefficient of A, B and C bears a (+), (+) and (-) sign respectively. The +ve sign of A and B signifies that the response is directly proportional with factor A and B where -ve sign indicates the inverse relationship of factor C with response (DR_{30}).

Table 6: Analysis of variance table for Percentage of drug release at 30 minute from full factorial design

Source	Sum Square	df	Mean Square	F- Value	Prob> F
Percentage of drug release at 30 minute (DR_{30})					
Model	5979.483	7	854.2118	64.58	0.023
A	2129.042	1	2129.042		0.01
B	1158.008	1	1158.008		0.03
C	798.8804	1	798.8804		0.04
AB	474.0428	1	474.0428		0.02
AC	507.5298	1	507.5298		0.01
BC	649.4768	1	649.4768		0.03
ABC	262.5028	1	262.5028		0.03

Perturbation, Interaction and 3 D plot of response DR_{30}

It represent the comparison of the effect of three factor at the midpoint coded (0) in the design space. The response DR_{30} was plotted by changing only one factor over its range while holding of other two factors constant. It is seen in Figure 3.b that line AA, BB and CC are not in straight line. Hence response DR_{30} was sensitive to the concentration of CCS, Maltose and MCC.

The graphical representation (3 dimension plot) of the regression equation was obtained by using the software Design Expert and present in figure 4.b. The 3D plot showed that a downward trend of the wire mesh was depicted at higher level (+1) and the upward trend was at lower level of (-1) of the concentration of A and B, it is predicted that DR_{30} is directly proportion to A (significant) and B.

Effect of Independent Variables on DR_{60}

The value of drug release and responses obtained from different experimental conditions for all the final eight formulations are summarized in table 4. The application of response surface methodology (RSM) offers empirical relationship between the model dependent and model independent variables. Quadratic model partial sum square type iii was selected for all RSM studies by applying multiple regression analysis. The response variables (DR_{60}) and test variable A (CCS), B (Maltose) and C (MCC) are related to a second order polynomial equation. A summary of analysis of variance (ANOVA) for selective response surface quadratic predictive method of DR_{60} is shown in table 7. Statistical testing of model was done in the form of ANOVA which is required to test the significance and adequacy of the model. The model F value implies that the model is significant ($p<0.05$). There was only 0.5% chance that the large model F value occurred due to noise. The values of "Prob" >F less than the value 0.05 indicate that model terms are significant and model "Prob1" indicated that the model test are not significant.In this case A, B, C, AB, AC, BC, ABC are significant in the model. The "Pred R-squared" was not defined. The "Pred R- squared was in reasonable agreement with the "Adj R- Squared". The optimized equations of DR_{60} in actual factor and coded factor has been given in Eqn. 15 and 16.

DR_{60} = 959.75 - 108.09 x CCS - 62.01 x MALTOSE - 411.78 x MCC + 7.85 x CCS x MALTOSE + 54.69 x CCS x MALTOSE + 31.670 x MALTOSE x MCC -4.14 x CCS x MALTOSE x MCC Eqn. 15

DR_{60} = 85.90 + 14.72 x A + 9.93 x B - 15.28 x C + 8.72 x A x B - 9.12 x A x C - 6.21 x B x C - 4.14 x A x B x C Eqn. 16

It is observed from the above equation that coefficient of A, B and C bears a (+), (+) and (-) sign respectively. The +ve sign of A and B signifies that the response is directly proportional with factor A and B where -ve sign indicates the inverse relationship of factor C with response (DR_{60}).

Table 7: Analysis of variance table for Percentage of drug release at 60 minute from full factorial design

Source	Sum Square	df	Mean Square	F- Value	Prob> F
Percentage of drug release at 60 minute(DR_{60})					
Model	6110.498	7	872.9283	32.83	0.023
A	1734.428	1	1734.428		0.01
B	788.2832	1	788.2832		0.03
C	1867.338	1	1867.338		0.04
AB	608.6561	1	608.6561		0.02
AC	665.5411	1	665.5411		0.01
BC	308.8855	1	308.8855		0.03
ABC	137.3653	1	137.3653		0.03

Perturbation, Interaction and 3 D plot of response DR_{60}

It represent the comparison of the effect of three factor at the midpoint coded (0) in the design space. The response DR_{60} was plotted by changing only one factor over its range while holding of other two factors constant. It is seen in figure 3.c that line AA, BB and CC are not straight line. Hence response DR_{60} was sensitive to the concentration of CCS, Maltose and MCC.

The graphical representation (3 dimension plot) of the regression equation was obtained by using the software Design Expert and present in figure 4.c. The 3D plot showed that a downward trend of the wire mesh was depicted at higher level (+1) and the upward trend was at lower level of (-1) of the concentration of A and B, it is predicted that DR_{60} is directly proportion to A (significant) and B.

Validation of experimental model

A checkpoint batch (CN-O) was prepared by selecting level of factors arbitrarily (A = –0.5 level, B= 0 level and C = +0.5) (Table 2) and all physical characteristics of tablets were evaluated. The predicted values of responses, calculated from optimized equation(DR_5, DR_{30} and DR_{60}) were good agreement with actual value of responses obtained from experiments (DR_5, DR_{30} and DR_{60}).Thus, from the results of statistical optimization technique it can be conclude that all models were found to be mathematically significant.

Stability Study

The formulations were evaluated after 3 months of storage at accelerated stability condition (40^0C ± 2^0C and 75% ± 5% RH). Stability studies indicate no significant change in appearance of the tablets, assay (p< 0.05), DT, DR_5, DR_{30} and DR_{60} (p<0.05).

CONCLUSION

The influence of excipients such as cross carmelose sodium (A), maltose (B) and microcrystalline cellulose (C) on tablet performances, especially dissolution time of Cinnarizine SMET was accessed through the optimization of formulation using 2^3 factorial design. The quantitative effect of factors at different levels was predicted by using polynomial equations. All responses were observed inversely proportional with concentration MCC, and were directly proportional to the concentration of CCS and maltose in tablet. Response surface methodology was used to predict the levels of the factors A, B and C required for obtaining an optimum formulation with minimum dissolution time. A new check point formulation was prepared according to these levels. Observed responses were in close agreement with the predicted values of the optimized formulation, thereby demonstrating the feasibility of the optimization procedure in developing self-micro-emulsified tablet dosage forms. The formulations were stable at accelerated condition (40^0C ± 2^0C and 75% ± 5% RH) and droplet size of disintegrated SMET emulsion sample of CNZN was in micron range (2.58 to 4.84 µm). Hence the prepared SMET formulations are proved useful for commercial approach.

REFERENCES

1. Constantinides, P. P. (1995). Lipid microemulsions for improving drug dissolution and oral absorption: physical and biopharmaceutical aspects. *Pharmaceutical research*, *12*(11), 1561-1572.

2. Pouton, C. W. (2000). Lipid formulations for oral administration of drugs: non-emulsifying, self-emulsifying and 'self-microemulsifying'drug delivery systems. *European Journal of Pharmaceutical Sciences*, *11*, S93-S98.
3. Singh, S. K., Reddy, I. K., & Khan, M. A. (1996). Optimization and characterization of controlled release pellets coated with an experimental latex: II. Cationic drug. *International journal of pharmaceutics*, *141*(1), 179-195.
4. Spireas, S., & Sadu, S. (1998). Enhancement of prednisolone dissolution properties using liquisolid compacts. *International Journal of Pharmaceutics*, *166*(2), 177-188.
5. Bolton, S. (1990). Pharmaceutical statistics, (2nd ed.). NY, USA,1990, Marcel Decker Inc.
6. Pani, N. R., Nath, L. K., & Bhunia, B. (2010). Formulation, development, and optimization of immediate release nateglinide tablets by factorial design. *Drug Discov. Ther*, *4*, 453-8.
7. Pani, N., Nath, L., & Acharya, S. (2011). Compatibility studies of nateglinide with excipients in immediate release tablets. *Acta Pharmaceutica*, *61*(2), 237-247.
8. Acharya, S., Patra, S., & Pani, N. R. (2014). Optimization of HPMC and carbopol concentrations in non-effervescent floating tablet through factorial design. *Carbohydrate polymers*, *102*, 360-368.
9. Godfraind, T., Towse, G., & Van Nueten, J. M. (1982). Cinnarizine: a selective calcium entry blocker. *Drugs Today*, *18*(1), 27-42.
10. Singh, B. N. (1986). The mechanism of action of calcium antagonists relative to their clinical applications. *British journal of clinical pharmacology*, *21*(S2), 109S-121S.
11. The Merck Index. (2006). An encyclopedia of Chemicals, Drugs, and Biologicals, (14th ed.) Neil MJO, Editor Merck & Co. Inc. *White house station, NJ, USA*, 924 – 825.
12. Remington. (2006). The science and practice of pharmacy, (21th ed.) *Lippincott Williams and Wilkins*, 1373-1379.
13. Nazzal, S., Nutan, M., Palamakula, A., Shah, R., Zaghloul, A. A., & Khan, M. A. (2002). Optimization of a self-nanoemulsified tablet dosage form of Ubiquinone using response surface methodology: effect of formulation ingredients. *International journal of pharmaceutics*, *240*(1), 103-114.
14. Lachman, L., Lieberman, H., & Kanig, J. (1987). The theory and practice of industrial pharmacy, (3rd ed), *Varghese publication house*.
15. United State Pharmacopoeia. (2004). National Formulary. USP.
16. Stability testing of new drug substances and products, ICH harmonized tripartite guideline.2003.http://www.ich.org/LOB/media/MEDIA419.pdf (accessed Aug 14, 2007).
17. Puttemans, M., Bogaert, M., Hoogewijs, G., Dryon, L., Massart, D. L., & Vanhaelst, L. (1984). Determination of Cinnarizine in Whole Blood and Plasma by Reversed Phase HFLC and its Application to a Pharmacokinetic Study. *Journal of liquid chromatography*, *7*(11), 2237-2251.
18. Lachman, L., Lieberman, H., & Kanig, J. (1987). The theory and practice of industrial pharmacy, (3rd ed), Varghese publication house.
19. Craig, D. Q. M., Lievens, H. S. R., Pitt, K. G., & Storey, D. E. (1993). An investigation into the physico-chemical properties of self-emulsifying systems using low frequency dielectric spectroscopy, surface tension measurements and particle size analysis. *International journal of pharmaceutics*, *96*(1-3), 147-155.