Original Article

Development And Characterization Of Aripiprazole Loaded Solid Lipid Microparticles

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DOI: 10.47750/pnr.2023.14.S01.10

Abstract

The major challenge for brain targeting is to cross the blood-brain barrier (BBB) which limits several drugs and molecules to penetrate into the brain. In our research, we developed aripiprazole encapsulated solid lipid microparticles and characterized them according to standard methods. Microparticles were prepared by a hot melts microencapsulation approach byapplying various concentrations ration of Span 20, Span 80, Tween 20, and Tween 80. The drug release mechanism has been shown for every optimized formulation.

Keywords: Aripiprazole, solid lipid microparticles, Characterization

Introduction

Solid lipid microparticles (SLM)were introduced in the late 1990s, owing to potential drug carriers especially for the incorporation of the active drugs substance and acting as the sustained drug delivery system with a controlled release profile. Solid lipid microparticles are rapidly developed fields of technology with several important applications in drug delivery, research, and clinical medicines as well as in other varied areas [1]. SLM is spherical in shape and size varied from 1-1000 micrometer, and because of this property, it suspends in a given medium. It is a special size reliant Microparticles of solid lipids offer's Potential for growth improve latest medicinal drug [2]. The ability to insert drugs into microparticles carriers offers developed new drug delivery systems for site-based delivery. SLM reaches the targeted site and in a controlled manner and releases the drug in a controlled fashion and thus shows improved therapeutic effect in comparison to the conventional dosage form. The SLM drug delivery systems are prepared to obtain the sustained and controlled release of the drug at the active site to increase the bioavailability, enhance stability, and reduce the toxic effect of the drug at the targeted site [3]. The particle size of a drug of a hydrophobic drug such as aripiprazole could also be reduced in micro-size by incorporating into microparticles by preventing the drug particle from re-aggregate and forming larger particles. This also offers a larger surface area by reducing the particle size in the micrometer range [4]. The SLM is actually considered to become microspheres too. Microparticles are mainly

prepared by two types of polymers, especially natural polymers and synthetic polymers which support transportation of drugs at the active site. A natural polymer such as sodium alginate and ethylcellulose is obtained from acquired from brown marine algae commonly used in an oral and topical formulation. Theirbiocompatible, non-toxic and biodegradable nature necessitates their application in the formulation [5]. Because of colloidal property, SLM is used for different drug delivery routes like topical, oral, ophthalmic, subcutaneous, and intramuscular routes [6]. Now, this is the technique formed which is used to supply various types of drugs include antigen, antibiotics, Polymer microparticles are often either microspheres or microcapsules used. For the good of the Bioactive compound delivery [7]. While triglyceride and cholesterol are synthetic polymers that show the detrimental effect of incorporating peptides and proteins during the manufacturing of formulation. These polymers are biocompatible and non-toxic in nature. Microparticles are very wider in quality, spherical and Particulate uniformity, and distribution of particle size. The preparation of microparticles offers a range of techniques for the variety of opportunities to control various aspects of drug administration and facilitate the accurate delivery of a small quantity of the potent drug and avoid unexpected drug concentration at sites other than the targeted site. The behavior of the drug component can be changed according to need by coupling the drug to a carrier particle. The various components clearance kinetics, tissue distribution, metabolism, and interaction of drug are strongly dependent on the behavior of the carrier. The delivery system of medication is pre-based to obtain the primary goal of the Physical response medication with minimum That condition it's a side effect available via taking drugs in the general domain along with predetermining Pace and agreed on the interval of the Time in the skin [8]. Oral drug delivery systems are the most convenient route because of easy administration and more patient compliance. This is important to improve both the residence time as well as the release of drugs from the develop the oral doses forms [9]. The drug easily absorbed from the gastric intestinal tract and have a short half-life are eliminated faster from the bloodstream, to avoid this problem oral control drug delivery system develop with flow drug may be developed Then maintain the drug concentration steady in the serum for longer periods of time finally improve the bioavailability of drugs. An all-around planned controlled medication conveyance framework conquers a portion of the issues identified with customary treatment and upgrade the most extreme restorative viability, it becomes important to convey the medication to the target site in proper sum at the perfect time to maintain a strategic distance from the reaction and boost the helpful impacts. In a perfect world microsphere having a molecule size under 200µmand can be infused by an 18 or a needle with 20 numbers. Numerous strategies are utilized for the readiness of strong A homogenization of lipid microparticles (SLMs) system, dissolvable vanishing procedure, Solvent Extraction Technique, epitome strategy, stage Separation Strategy for Co-preservation, splash drying strategy, and some Much more. There it is are various systematic procedures utilized for the portrayal of A microsphere checking the Microscopy of particles method, differential filtering calorimetric strategy and Fourier changed infra-red spectroscopy (FTIR). The FTIR method is utilized for the portrayal of medication stacked detailing [10]. The in-vitro medication discharge was considered utilizing the rotator container strategy bushel technique which is portrayed in the fifth version of the European Pharmacopeia, with the assistance of disintegration mechanical assembly. The investigation can be done at 150 rpm in phosphate cradle arrangement of pH 7.4 at 37 °C [11].

1. Materials and methods

Aripiprazole was purchased from Almon Industries (Plot no:1801/02, Phase-IV, GIDC, Vithaludyog Nagar-388121) India. All other chemicals and reagents were of analytical grade.

Table 1. List of chemicals used along with their procurement sources.

S.NO	CHEMICAL	SOURCE
1.	Aripiprazole	Almon Industries.
2.	Stearic acid	RFCL Limited, New Delhi, India.
3.	Span 20	RFCL Limited, New Delhi, India.

4.	Span 80	RFCL Limited, New Delhi, India.
5.	Tween 20	Central drug house (CDH) Pvt. Ltd, New Delhi, India.
6.	Tween 80	Central drug house (CDH) Pvt. Ltd, New Delhi, India.
7.	Acetone	Central drug house (CDH) Pvt. Ltd, New Delhi, India.
8.	HCl	Central drug house (CDH) Pvt. Ltd, New Delhi, India.
9.	Ethanol	RFCL Limited, New Delhi (INDIA)

2. Preformulation study of Aripiprazole

Preformulation analysis in which we assess the physicochemical character of the active substance compound that could affects the drug performance and development of efficacious, safe and stable dosages from. It is a method of optimization, color, odor, taste, solubility, and the point of fusion, TLC, compatibility study, and Curve Calibration. All of these studies avoid the maximum chances of error during formulation or any kind of incompatibility.

3.1 Authentication of the procured aripiprazole

Procured aripiprazole was authenticated by measuring the melting point and by running the TLC of the drug solution.

3.2 Melting Point

The melting point of the aripiprazole process parameters for capillary fusion were determined. In this technique, one side of the capillary is fused by warming, and after that, the aripiprazole is filled in the capillary by another end and placed capillary in melting point device. The temperature was increased progressively points when aripiprazole begins to dissolve note that temperature with the assistance of a thermometer. This procedure is performed multiple times and compares the melting point of the sample with references various in literature.

3. Thin-layer chromatography (TLC)

Thin-layer chromatography is a qualitative technique. This procedure is used to isolate the target compound from the compound mixture, which has been used in capillary fusion process parameters. based on the compounding factor flows along with the plate. A compound can be identified by direct comparison with the known compound by measuring the R_f value of the sample. This is the ratio of the flow rate of the sample and solvent from the bottom. The TLC plate was fitted with Silica precoating G. A test solution spot was added to the silica plates (20x10cm) above 0.5cm from the bottom and placed in the TLC chamber, which was saturated with solvent system contains chloroform: benzene: ethanol (80:15:5). The plate is $3/4^{th}$ of his height from the edge and RF value measurement.

$$R_F \text{ Value} = \frac{\text{Distance travelled by the solute from the origin}}{\text{Distance travelled by the solvent from the origin}}$$

4. Estimation of Aripiprazole by UV-Spectrophotometer method

5.1 Preparation of calibration curve of Aripiprazole in 0.1 N HCl buffer (pH 1.2)

The absorption maxima (λ_{max}) of Aripiprazole in 0.1 N HCl medium was determined, UV-Spectrophotometer (SHIMADZU-1800) by using the drug solution within the range of 200-400nm. It was observed that the drug exhibited at the λ_{max} 219nm.

5.2 Preparation of stock solution

Weight accurately 100 mg of Aripiprazole and dissolved in 5ml of ethanol and make up the volume to 100 ml with 0.1N HCl (pH 1.2). As a result, the solution of concentration 1mg/ml was obtained.

5.3 Preparation of working standard

Take 10 ml of stock solution in a volumetric flask (100ml) and made up the volume with 0.1 (N) HCl, to obtain the solution of concentration of 100 µg/ml to obtain 5, 10, 15, 20, 25 and 30 µg/ml concentration of aripiprazole. Those dilutions and absorption were screened to obtain the calibration curve at 219 nm by using UV-Spectrometer were Plotted against concentration versus absorbance. Repeat the procedure three times, to get the average absorbance value.

5.4 Preparation of calibration curve of Aripiprazole in phosphate buffer (pH 7.4)

The absorption maxima (λ_{max}) of Aripiprazole in phosphate buffer of PH 7.4 was determined by using UV-spectrophotometer (SHIMADZU-1800) by scanning the drug solution within the range of 200-400 nm. It was observed that the drug exhibited at the λ_{max} 219 nm.

5.5 Preparation of stock solution:

Weight accurately 100 mg of Aripiprazole and dissolved in 5ml of methanol and made up the volume up to 100 ml with phosphate buffer of PH 7.4. As a result, the solution of concentration 1 mg/ml was obtained.

5.6 Preparation of working standard:

Take 10 ml of stock solution in a volumetric flask (100 ml) and made up the volume by phosphate buffer pH to obtain the solution of concentration of 100 µg/ml. Further dilutions were made of 100 µg/ml to obtain 5, 10, 15, 20, 25 and 30 µg/ml concentrations of aripiprazole. Such dilutions and absorbance were scanned to obtain the calibration curve at 219 nm by using UV-Spectrometer. The pacing curve was conceived against absorption concentration. Repeat the process three times, to get the average absorbance value.

5.7 Solubility study

Solubility of aripiprazole was performed using a mechanical shaker in 0.1N HCl, phosphate buffer (PH 7.4), and methanol by equilibrium solubility method.

5.8 Equilibrium solubility method:

Excess amount of aripiprazole was taken in a conical flask, which contains 25 ml of 0.1N HCl (PH 1.2), phosphate buffer (PH 7.4), and methanol separately. Put these conical flasks on a mechanical shaker for 1 hr at 37 °C. After that filter all the solutions and measure on UV-spectrophotometer at 219 nm. Then the amount of drug solubilized was calculated.

5.9 Compatibility studies

Determine FTIR spectroscopy was performed of drug-excipient interactions. The FTIR aripiprazole, stearic acid, and span 80 were taken in a ratio of (1:1:1) FTIR spectroscopy analyzed the powdered mixture. The individual spectrum of the drug was compared with the combined spectrum of drug and excipients.

5.10 Preparation of Solid lipid microparticles by hot-melt microencapsulation technique

Solid lipid Microparticles (SLMs) were prepared by using the hot-melt microencapsulation technique (which can be carried out by normal or phase inversion technique). Stearic acid (lipid) was melted in a beaker, by putting the beaker on a hot plate at 70°C. Aripiprazole was added to the melted Stearic acid under continuous stirring on a magnetic stirrer to form a hot melt mixture. The hot mixture was emulsified into an aqueous surfactant solution and was heated above the lipid melting point to form an oil/water emulsion. Different grades of surfactant (Span 20, Span 80, Span 80, and Tween 80) were used at different concentrations (0.5 ml 1 ml, 1.5 ml). The o/w emulsion was poured into a 100 ml of ice-cooled aqueous phase maintained at 2°C and was finally allowed to cool in an ice bath. Hardened microparticles were allowed to settle down and after 15 min the aqueous phase was decanted, microparticles were filtered, rinsed with water and freeze-dried.

5. Descibe:

Table 2. Table of composition of aripiprazole targeted Solid Lipid microparticles

Formulation	Drug (mg)	Stearic Acid (mg)	Surfactant (mL)
Using Span 20			
F1	100	2	0.5
F2	100	2	1
F3	100	2	1.5
Using Span 80			
F4	100	2	0.5
F5	100	2	1
F6	100	2	1.5
Using Tween 20			
F7	100	2	0.5
F8	100	2	1
F9	100	2	1.5
Using Tween 80			
F10	100	2	0.5
F11	100	2	1
F12	100	2	1.5

6. Characterization of the solid lipid microparticles

7.1 Encapsulation Efficiency

Aripiprazole loaded microparticles were crushed and extracted using ethanol by ultra-sonication method for 30 min. The supernatant containing unentrapped aripiprazole was withdrawn and measured UV spectrophotometrically at 219 nm against ethanol. The amount of aripiprazole entrapped in microparticles was calculated by the following equation [12].

$$\text{Encapsulation Efficiency} = \frac{\text{Mass of drug in microparticles}}{\text{Initial mass of drug}} \times 100$$

7.2 Determination of Percentage yield

The prepared microparticles firstly dried, then collect and weighed accurately. The actual weight of microparticles was divided by the total amount of all component which was used for the formulation of solid lipid microparticles [13].

$$\text{Percentage} = \frac{\text{Mass of drug in microparticles}}{\text{Initial mass of drug} + \text{Initial mass of polymer}} \times 100$$

7.3 Drug loading

Drug content of microparticles were determined on assayed spectrometrically (UV-1800 SHIMADZU) at the aripiprazole λmax 219nm. Each formulation was filtered and analyzed then drug content was determined by using the formula [14].

$$\text{Drug Loading} = \frac{\text{Mass of drug in Microparticles}}{\text{Mass of Microparticles}} \times 100$$

7.4 In-vitro release study

Dissolution test was done to determine the in-vitro drug release from a drug delivery system (dosages form). To perform the dissolution test USP type 2 (paddle type, SHIMADZU UV-1800) apparatus was used that contains 900 ml of phosphate buffer (pH 7.4), 0.1B HCl (pH1.2) dissolution medium with stirring speed 100rpm and at temperature 37±5ºC, the sink condition is maintained. The stirring must be constant and drug release start. The 5ml aliquots were withdrawn periodically and this was replaced with the same amount of fresh dissolution medium. The sample was analyzed spectrophotometrically (UV-1800 SHIMADZU) at the λ_{max} of 219 nm. The dissolution cumulative release versus time was plotted [15].

7.5 Particle size of microparticles

Particle size was analyzed by SEM. The particle size of microparticles formulation F3 was analyzed by SEM, which showed the average size of microparticles.

7.6 Particle shape of microparticles

The microparticles formulation F3 was visualized by scanning electron microscope (SEM Quanta 250 FEI Makers, Singapore) to assess the morphology of microparticles and surface characteristics. Samples were coated with gold-palladium under an argon atmosphere at room temperature and the morphology of microparticles was studied [16].

7.7 Release kinetics of aripiprazole from solid lipid microparticles

The in vitro release studies were fitted to various kinetic equations like zero-order, first-order, Higuchi's model, Korsmeyer-peppas model, and Hixson-Crowell cube-root models to find the mechanism of drug release from the SLM.

The zero-order rate describes where a drug is released independent of its concentration. To study the zero-order release kinetics, the release rate data are fitted to the following equation:

$Q = K_0 t$

Where Q is the fraction of drug released, K is the release rate constant and t is the release time.

The **first-order rate kinetic** describe in which the release is dependent on its concentration. The first-order release was determined by the following equation.

$$\log \log C = C_0 - \frac{Kt}{2.303}$$

Where C = amount of drug remaining at time t,

C_0= initial amount of the drug and

K = first-order rate constant (h^{-1}).

Higuchi release model indicates that the drug is released by a diffusion mechanism. To study the Higuchi release kinetics, the release rate data were fitted to the following equation:

$Q = K \cdot t_{1/2}$

Where Q is the amount of drug released, K is the release rate constant, and t is the release time.

The dissolution data were fitted to Korsmeyes Peppas equation release describe the exponent t is the release time. The dissolution data were fitted to Korsmeyes Peppas equation release describe the exponent n was calculated.
$M_t/M_\infty = K_p t^n$

Where M_t/M_∞ is the fraction of drug released at time t, K_p is the kinetic constant of the system, and n is the exponent characteristic of the transport. [17].

7. Results and discussion

8.1 Pre-formulation Studies

The drug powder was analysed for their physical appearance like colour, odour, texture and result shows colour was white to light yellow, odour found to be odourless and texture found to be smooth.

8.2 Thin layer chromatography

The TLC plate was prepared by precoating with Silica G. A spot of test solution was applied on the silica plate (20×10cm) above 0.5cm from the bottom and placed in the TLC chamber, which was saturated with a solvent system containing chloroform: benzene: ethanol (80:15:5) as shown in figure 1. The Rf Value of TLC (Aripiprazole) was found 0.88

Figure 1. TLC of Aripiprazole

8.3 Compatibility Study by FTIR [Fourier Transform Infra-Red Spectroscopy]

The FTIR spectra in the range of 4000-400 cm^{-1} were recorded. The sample was taken with KBr and then compressed into tablets. The drug KBr pellet was analyzed that will provide spectra.

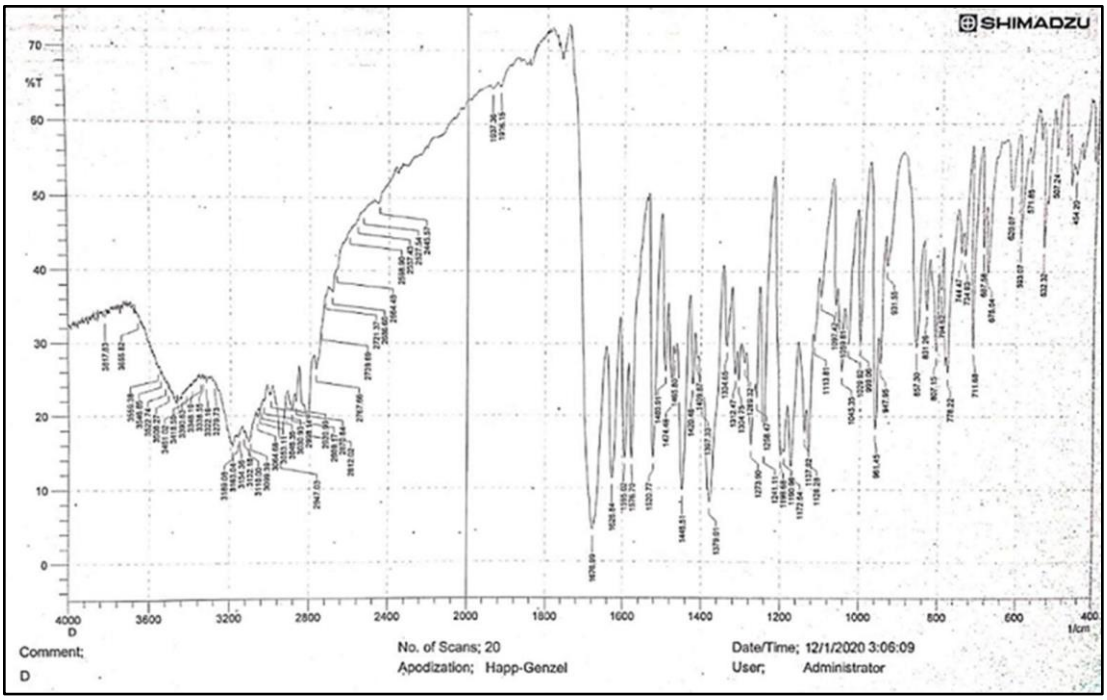

Figure 2. Reference FTIR Spectra of Aripiprazole (D)

Table 3. Interpretation of FTIR (drug)

Reported (cm^{-1})	**Wave No (cm^{-1})**	**Functional Group**	**Inference**
1676.99	cm^{-1}	CO	Stretching
3461.39	cm^{-1}	NH	Stretching

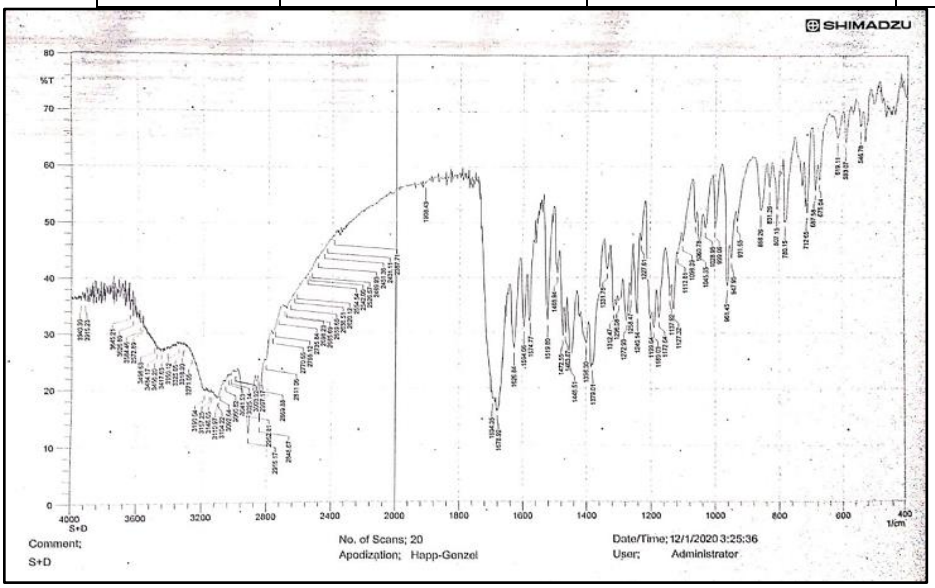

Figure 3. FTIR of Aripiprazole(D) + Stearic acid (S)

Table 4. Interpretation of FTIR Aripiprazole(D) + Stearic acid(S)

Reported (cm^{-1})	Wave No (cm^{-1})	Functional Group	Inference
1594.35	cm^{-1}	CO	Stretching
3484.17	cm^{-1}	NH	Stretching

8.4 Calibration Curve of Aripiprazole in 0.1 N HCl (pH 1.2)

Calibration curve of Aripiprazole was plotted in 0.1 N HCl (1.2pH) at λ_{max} 219nm medium by using UV-Spectrophotometer (SHIMADZU-1800). The results are shown in Table 5. A graph was plotted between concentration and absorbance. Regression coefficient was calculated R^2= 0.9981 as shown in figure 4.

Table 5. Absorbance of Aripiprazole at a series of concentration in 0.1N HCl (pH 1.2) at λ_{max} 219 nm

Sr. No.	Concentration (µg/ml)	Absorbance at λ_{max} 219nm
1	5	0.218 ± 0.094
2	10	0.452 ± 0.058
3	15	0.665 ± 0.072
4	20	0.884 ± 0.099
5	25	1.072 ± 0.088
6	30	1.251 ± 0.102

The values are expressed as means±SD, n=3

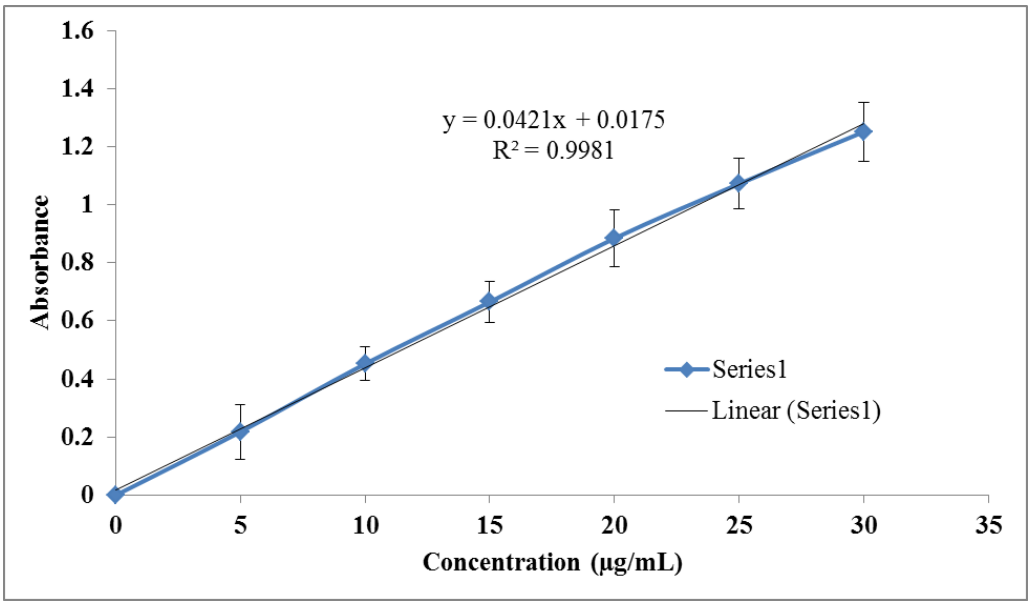

Figure 4. The standard plot of Aripiprazole in 0.1 N HCl (1.2 pH) at λmax at 219nm

8.5 Calibration curve of Aripiprazole in phosphate buffer (7.4 pH)

Calibration curve of aripiprazole was plotted in phosphate buffer (7.4 pH) at λmax 219nm and the results area shown in Table 6. A graph was plotted between concentration and absorbance. The regression coefficient was calculated as the R^2=0.9984 as shown in figure 5.

Table 6. Calibration curve data of Aripiprazole in Phosphate Buffer (7.4pH) at λ_{max} 219nm

Sr. No.	Concentration (µg/mL)	Absorbance at λmax 219nm
1	5	0.263 ± 0.085
2	10	0.462 ± 0.063
3	15	0.671 ± 0.054
4	20	0.860 ± 0.058
5	25	1.083 ± 0.074
6	30	1.323 ± 0.095

The values are expressed as means±SD, n=3

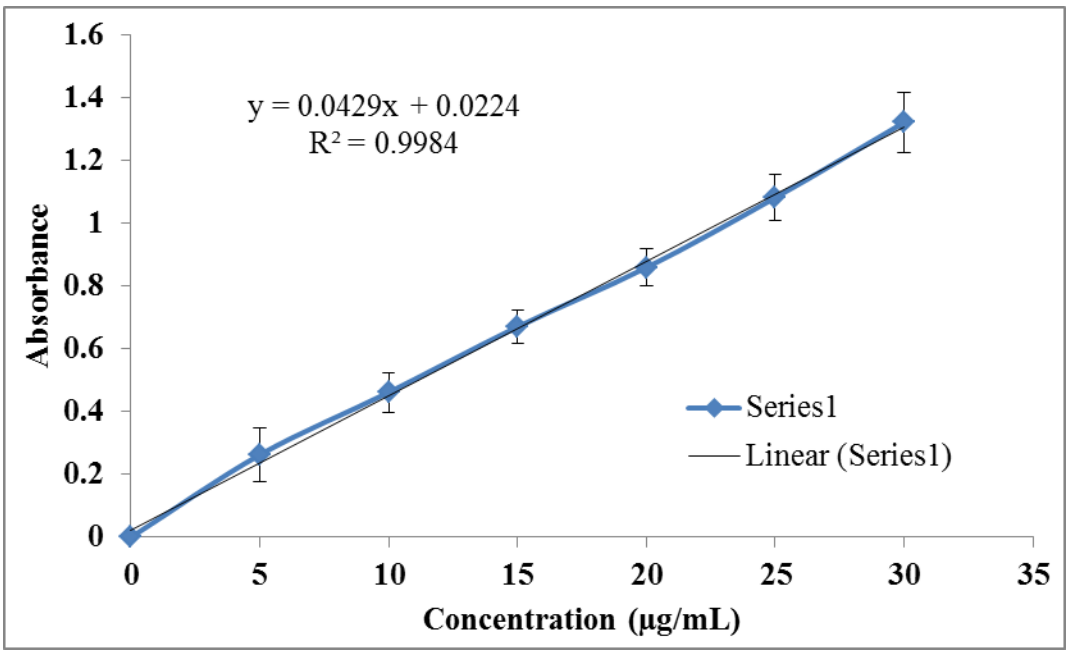

Figure 5. Calibration Curve of Aripiprazole in ethanol

Calibration curve of aripiprazole was plotted in ethanol at λ_{max}219nm and the results are shown in Table 11. A graph was plotted between concentration and absorbance. Regression coefficient was as R^2 = 0.9985 as shown in figure 6.

8.6 Standard plot of Aripiprazole in phosphate buffer (pH 7.4) at λ_{max} at 219 nm

Table 7. Calibration Curve data of Aripiprazole in Ethanol at λ_{max}219nm

S. No.	Concentration (µg/mL)	Absorbance at λ_{max} 219nm
1	5	0.222 ± 0.083
2	10	0.421 ± 0.072
3	15	0.661 ± 0.091
4	20	0.882 ± 0.062
5	25	1.063 ± 0.074
6	30	1.254 ± 0.083

The values are expressed as means±SD, n=3

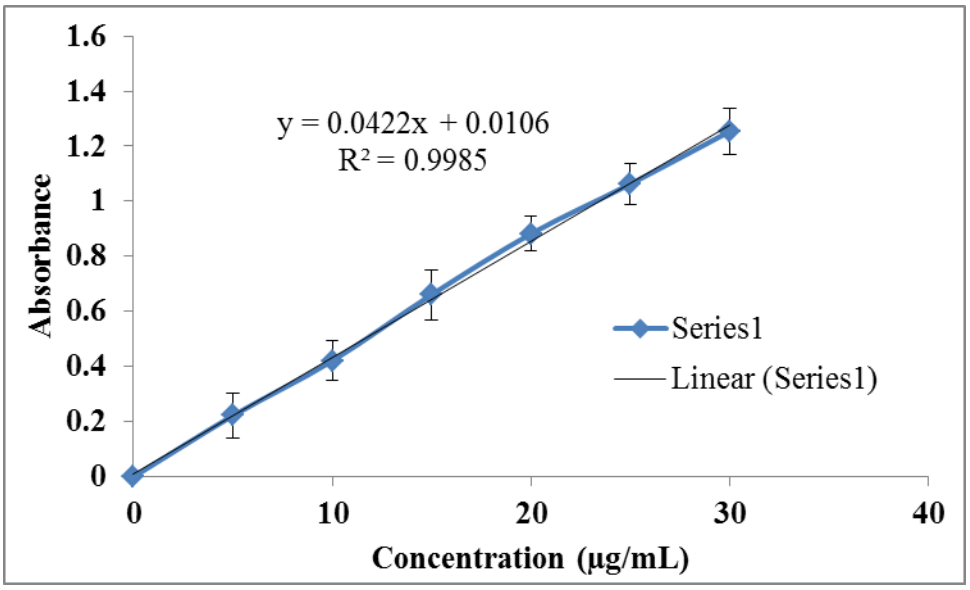

Figure 6. Standard Plot of Aripiprazole in Ethanol at 219nm

8.7 Solubility study of Aripiprazole

Solubility study of Aripiprazole was performed by using mechanical shaker in 0.1 N HCL (pH 1.2), phosphate buffer (pH 7.4) and methanol by equilibrium solubility method. The results are shown in Table 8.

Table 8. Solubility of Aripiprazole

S. NO.	Solubility Study	Concentration (mg/ml)
1.	0.1 N HCl	0.65 ± 0.061
2.	Phosphate Buffer	2.68 ± 0.039
3.	Ethanol	4.21 ± 0.056

The values are expressed as means±SD, n=3

8. Fabrication of microparticles

9.1 Development of aripiprazole loaded microparticles by hot-melt microencapsulation technique

Various batches of formulation were successfully formulated by using hot melt microencapsulation technique. In this technique, aripiprazole was taken with 2gm Stearic acid and a varied quantity of surfactant then melted in a beaker at 70ºC. Now o/w emulsion was formed and poured it a 100 ml of the ice-cooled aqueous phase was maintained at 2-5ºC and was finally allowed to cool in an ice bath.

9.2 Evaluation of developed solid lipid microparticles loaded with aripiprazole

Developed solid lipid microparticles were evaluated for various parameters. These are given below:

9.3 Drug loading, Percentage yield and entrapment efficiency

Drug loading, percentage yield, and entrapment efficiency were studied on twelve formulations. Assay for drug loading, percentage yield, and entrapment efficiency determination was done through UV spectrophotometer. The % drug loading was found to be 54.63 to 67.78%, Percentage yield was found 72.01 to 79.64 while entrapment efficiency was found to be 82.23 to 88.56 as given in table 9.

Table 9. Drug loading, entrapment efficiency, and percentage yield of different solid lipid microparticles loaded with aripiprazole

S. No.	Formulation Code	Drug loading (%)	Entrapment efficiency (%)	Percentage yield (%)
1	F1	53.34 ± 0.43	60.56 ± 0.85	82.37 ± 0.39
2	F2	68.27 ± 0.89	71.89 ± 0.34	85.69 ± 0.47
3	F3	72.71 ± 1.05	89.32 ± 0.76	89.38 ± 0.58
4	F4	40.00 ± 0.32	59.83 ± 0.94	72.45 ± 0.79
5	F5	54.46 ± 0.54	67.90 ± 0.34	74.56 ± 0.91
6	F6	74.65 ± 0.85	81.02 ± 0.87	79.78 ± 0.35
7	F7	20.12 ± 0.99	48.34 ± 1.54	53.45 ± 0.73
8	F8	35.93 ± 0.36	54.76 ± 0.34	60.05 ± 0.87
9	F9	47.20 ± 0.59	63.95 ± 0.54	66.21 ± 0.21
10	F10	20.00 ± 0.87	30.00 ± 0.87	60.07 ± 0.43
11	F11	21.49 ± 0.23	37.49 ± 0.23	68.56 ± 0.98
12	F12	25.50 ± 0.76	45.60 ± 0.76	72.89 ± 0.26

The values are expressed as means±SD, n=3

9.4 Weight Uniformity

Weight of individual formulations of aripiprazole was checked for weight uniformity. The average weight uniformity of SLMs is given in Table 10.

Table 10. Weight uniformity of individual Solid lipid microparticles (SLMs)

S. No.	Formulation code	Average weight (mg)
1.	F1	2790
2.	F2	2324

3.	F3	2921
4.	F4	2072
5.	F5	2177
6.	F6	2611
7.	F7	2245
8.	F8	2098
9.	F9	2181
10.	F10	2295
11.	F11	2130
12.	F12	2503

9.5 In-vitro drug release

In-vitro drug release study was carried out by using 0.1 N HCl (pH 1.2) and phosphate buffer (7.4 pH) was used as dissolution medium (900ml). Sample withdrawn from dissolution medium were then analysed through UV spectrophotometer at 219nm. Drug release profile of various formulations (F1-F3) of surfactant Tween 20, (F4-F6) of surfactant Tween 80 and, (F7-F9) of surfactant Span 20, (F10-F12) of surfactant Span 80 in Table 11and 12.

Table 11. In-vitro drug release of Aripiprazole micro particle formulation from (F1-F12)

Time (hr)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
0	0	0	0	0	0	0	0	0	0	0	0	0
1	11.23±0.38	12.32±0.32	23.2±0.56	8.79±0.78	9.01±0.85	11.03±0.49	2.21±0.27	10.56±0.2	17.5±0.81	1.59±0.08	1.88±0.12	3.07±0.54
2	15.85±0.67	20.74±0.84	39.56±0.64	12.56±0.89	13.98±0.64	34.85±0.67	13.59±0.84	14.85±0.67	26.4±0.97	8.62±0.66	2.95±0.76	10.18±0.90
3	25.79±0.59	35.47±0.56	48.75±0.38	28.02±0.34	15.44±0.67	42.5±0.89	15.78±0.64	15.98±0.98	32.2±021	18.02±0.28	3.27±0.94	19.06±0.35
4	37.23±0.81	40.65±1.22	60.89±0.94	38.52±0.56	16.79±0.94	55.85±0.29	17019±0.49	17.76±0.46	44.12±0.62	25.79±0.87	4.56±0.58	28.62±0.63
5	48.23±0.87	46.89±0.72	73.05±1.05	42.89±0.78	17.07±0.92	68.57±0.38	21.25±0.76	20.46±1.03	59.75±1.06	33.12±0.97	10.25±1.04	37.49±0.57
6	55.45±0.48	52.74±0.29	78.96±0.98	62.12±0.98	24.12±0.28	75.07±0.91	23.49±1.21	34.76±0.98	67.22±0.82	37.62±1.20	14.29±0.45	41.13±0.26
7	60.22±0.62	57.98±0.62	80.63±0.82	51.59±1.23	28.18±0.48	79.56±1.05	35.76±0.84	42.16±0.76	70.27±0.94	44.71±1.66	27.49±0.6	47.56±0.36
8	64.78±01.24	63.45±0.67	81.36±0.61	58.27±0.58	40.71±1.25	80.14±0.54	42.18±0.49	49.25±0.44	74.87±0.27	47.93±0.75	31.76±0.97	56.22±0.79

9	67.36±0.87	68.55±0.78	82.25±0.31	61.77±0.89	52.74±0.37	81.54±0.76	53.64±0.64	59.45±0.69	77.21±0.68	53.17±0.62	44.26±1.36	57.83±0.98
10	67.91±0.74	72.45±1.08	84.23±1.04	67.65±1.09	65.12±0.94	82.21±0.98	62.35±0.76	69.75±0.84	80.23±1.11	56.06±0.36	50.72±0.56	62.11±1.34
11	71.23±0.39	75.23±0.49	85.89±0.67	70.08±0.55	75.81±0.83	83.36±0.34	70.25±1.04	79.12±0.55	82.36±0.94	63.29±0.59	60.28±0.76	65.27±0.64
12	73.37±0.82	78.95±0.67	88.12±0.82	75.19±0.87	79.01±0.68	85.15±0.55	77.29±0.94	82.26±1.01	84.21±0.87	62.33±1.87	65.46±0.98	69.87±0.71

The values are expressed as means±SD, n=3

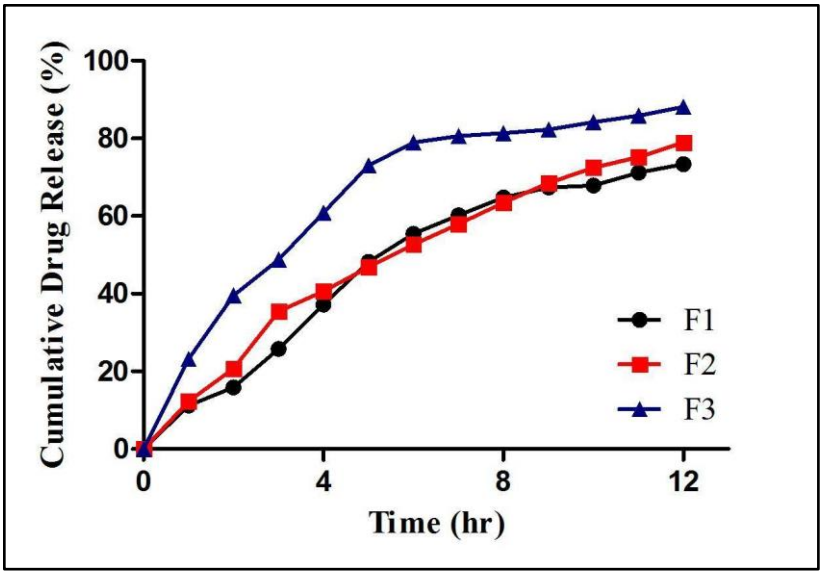

Figure 7. % Cumulative Drug Release of surfactant span 80 formulation (F1-F3)

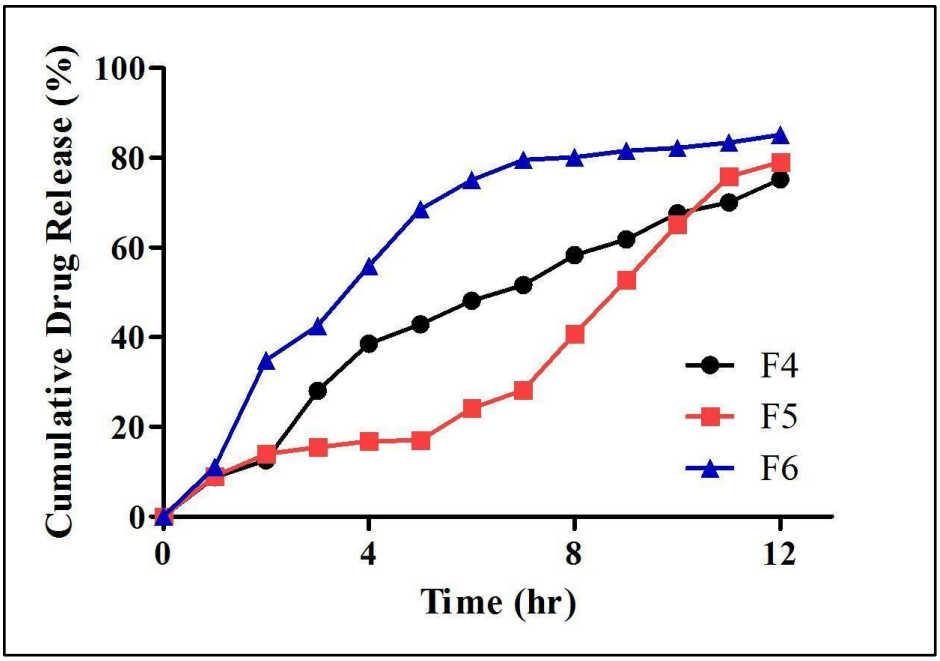

Figure 8. % Cumulative drug release of surfactant span 60 formulation (F4-F6)

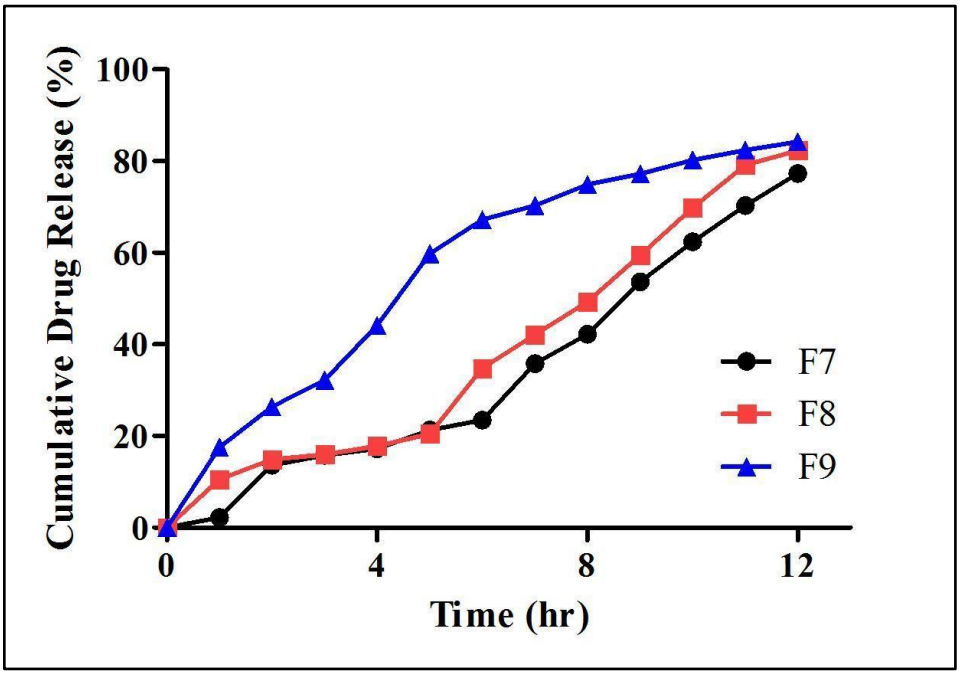

Figure 9. % Cumulative Drug Release of surfactant span 20 formulation (F7-F9)

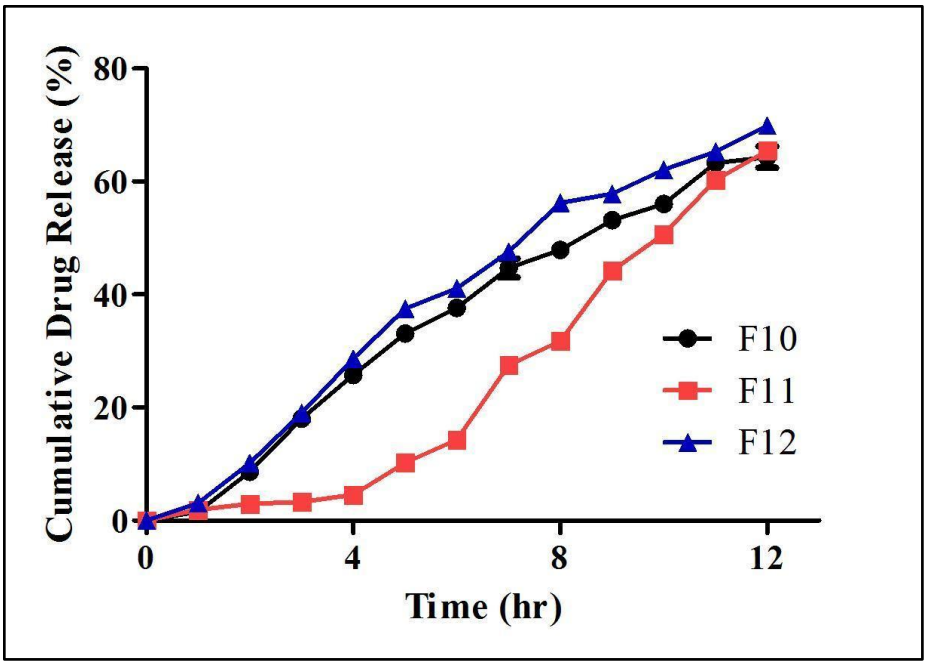

Figure 10. Percentage Cumulative Drug Release of surfactant Tween 80 formulations (F10-F12)

Table 12. In-vitro drug release of best four formulations (F3, F6, F9, and F12)

Hour(hr)	F3	F6	F9	F12
0	0	0	0	0
1	23.2±0.56	11.03±0.49	17.5±0.81	3.07±0.54
2	39.56±0.64	34.85±0.87	26.4±0.67	10.18±0.90
3	48.75±0.38	42.5±0.38	32.2±0.47	19.06±0.25
4	60.89±0.94	55.85±0.290	44.12±0.28	28.62±0.63
5	73.05±1.05	68.57±0.68	59.75±1.05	37.49±0.57
6	78.96±0.98	75.07±0.91	67.22±0.98	41.13±0.26
7	80.63±0.82	79.56±0.47	70.27±0.82	47.56±0.65
8	81.36±0.61	80.14±0.67	74.87±0.61	52.22±0.36
9	82.25±0.38	81.54±0.28	77.21±0.38	57.83±0.79
10	84.23±1.04	82.21±1.11	80.23±1.04	62.11±0.18
11	85.89±0.67	83.36±0.67	82.36±0.67	65.27±1.36
12	88.12±0.82	85.15±0.82	84.21±0.82	69.87±0.71

The values are expressed as means±SD, n=3

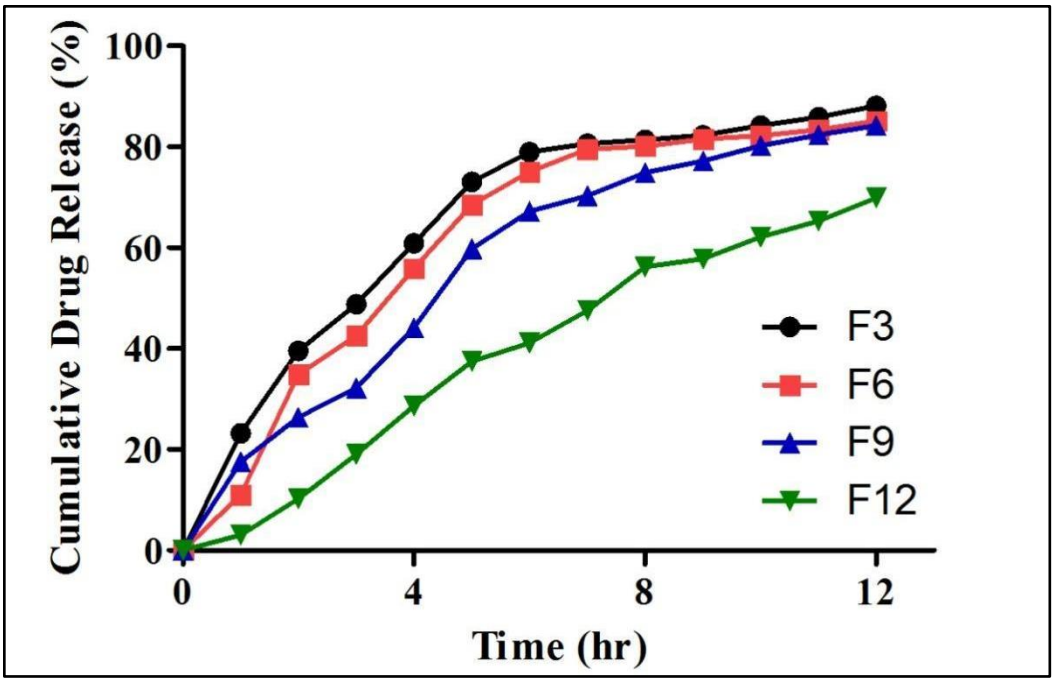

Figure 11.% Cumulative Drug Release of the best four formulations (F3, F6, F9, and F12)

Based on encapsulation efficiency, percentage yield, and percentage drug release the optimized formulations are F3 and F2. Therefore, the F3 formulation was selected for measuring the size and shape of the microparticles.

9.6 Kinetic release of Aripiprazole loaded microparticles

Different models were applied on release of F3 formulation and the best-fitted method was found to be the Higuchi method.

Table 13. Kinetic assessment of aripiprazole loaded microparticles (F3)

Formulation Code	**Correlation co-coefficient (R^2)value**			
	Zero order	**First order**	**Higuchi type**	**Korsmeyer Pepper Model**
F3	0.8955	0.8311	0.9221	0.8719

9.7 Particle size and Zeta Potential of microparticles

The particle size and zeta potential of microparticles formulations F3 was analyzed by Malvern Zeta-Sizer, which shows the average size of microparticles, which are within the range of 18.70- 22.31 µm. The results of zeta potential on the surface of microparticles are shown in Figure 12

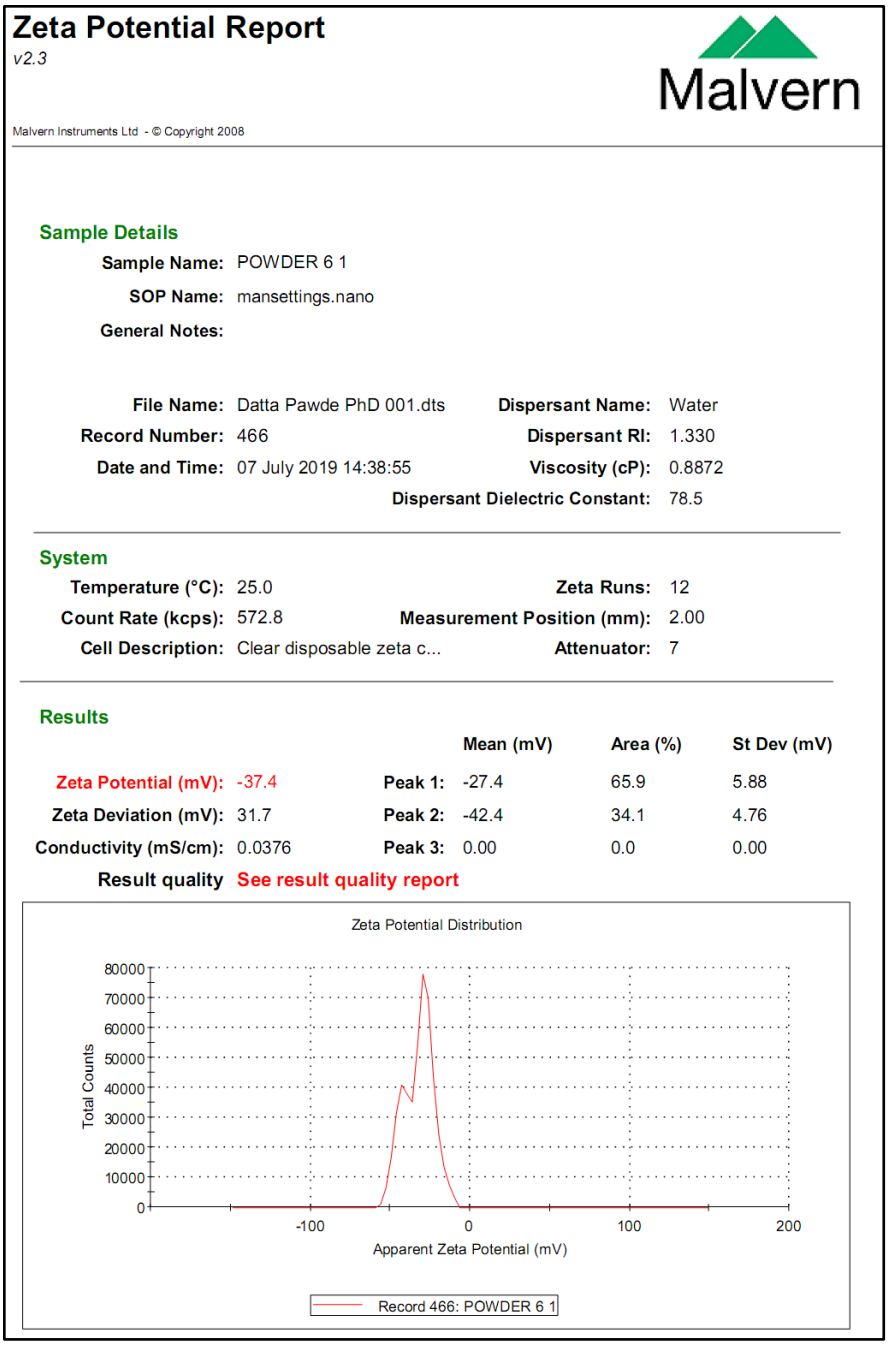

Figure 12. Zeta potential value of solid lipid microparticles (F6)

9.8 Morphology of solid lipid microparticles

Morphology of solid lipid microparticles was studied using scanning electron microscopy (SEM). It was observed by SEM analysis that the optimized F3 formulation was smooth and spherical in shape. The outer surface of SLM is shown in Figure 23.

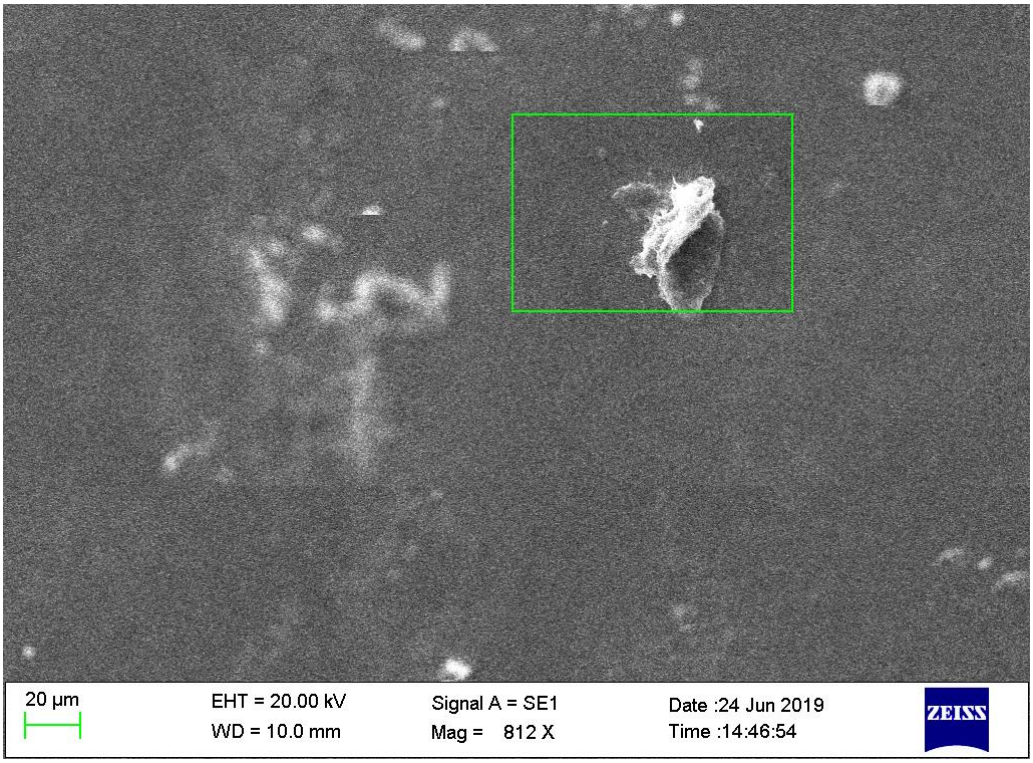

Figure 13. SEM image of Aripiprazole solid lipid microparticles

9. Discussion

Aripiprazole microparticles were designed with the objective of controlled and targeted release of drugs to the brain. Therefore, stearic acid polymer with various grades of surfactant (Span 20, Span 80, Tween 20, and Tween 80) was chosen which assists the drug transportation and which also ensures the targeted effect. The identification of the procured drug was done by melting point determination which was found to be in the reference value range obtained from the literature. Thin-layer chromatography was also performed and the R_f value of the drug was almost the same as reported in the literature confirmed the identity of the drug. The identification of the drug was further confirmed by its FTIR spectroscopy in which the spectrum was analyzed to confirm the presence of various functional groups present in aripiprazole and it same reported in the literature.

Figure 4, 5 and 6 shows the standard calibration curve with regression value of 0.9981 for 1.2 pH [0.1 N HCl], 0.9984 for 7.4 [phosphate buffer] and 0.9985 for ethanol. The curves were found to be linear in the range of 5-3µg/ml. at λ_{max} of 219nm. During the drug-excipient compatibility study by FTIR, there was no change in the major peaks. This suggested that there was no interaction between drug and excipient. Regarding solubility studies in different media as shown in table 8, it was found that the solubility of aripiprazole was more in ethanol (4.21 ± 0.056) as compared to Phosphate Buffer pH 7.4 (2.68 ± 0.039) than pH 1.2 0.1N HCl (0.65±0.06). It was observed that the result of percentage yield and drug loading were within the limit with respect to variation of surfactant concentration of same formulations encapsulation efficiency of all formulations lies 82.23% to 67.78% and table 9 showed the results of each formulation. The in-vitro drug release pattern of aripiprazole was carried out and shown in Figure 7, 8, 9, 10, and 11, and Table 12 and 13 shows the pattern of drug release. F3 formulation showed maximum release up to 86.23%. The SPAN 80 containing microparticles of aripiprazole offered a high degree of positive results in relation to its constant drug release. The experimental design was optimized by using Hot melt microencapsulation technique. Figure 11 shows the average size of F3 formulations i.e., 23.70µm. The results of SEM revealed the smooth and spherical structure of microparticles.

Conclusion

We have optimized the drug-loaded formulation and showed several characterizations including size analysis, drug release kinetics, zeta potential, and surface morphology of drug-loaded carrier.

Conflict of Interest

None

Funding

None

Acknowledgement

We are thankful to our Institutions for giving us the opportunity.

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