ORIGINAL ARTICLE

Design, Formulation, and Assessment of Pharmaceutical Co-Crystals on Antipsychotic Agent

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Abstract

Introduction: This study designed, developed, and evaluated long-acting olanzapine (OLA) formulations for schizophrenia and bipolar disorder therapy through parenteral route. The formulations were tested for appearance, particle size, drug entrapment effectiveness, surface morphology, pH, 15- and 30-day *in vitro* drug release, histopathology, and animal pharmacokinetics. **Materials and Methods:** Accelerated and controlled stability testing for the optimized final formulation lasted 6 and 12 months. The optimized OLA long-acting extended-release injectable microspheres formulation had a particle size of 37.80 ± 1.10 µm, 98.55 ± 1.28% drug entrapment efficiency, and 40.6 ± 7.14% and 98.9 ± 3.24% drug release at 15 and 30 days, respectively. **Results:** All batches were particle-free visually. All examined batches had pH levels ranging from 4.50 ± 0.05 to 6.22 ± 0.11. Compared to the positive control, OLA formulation histopathology shows no epithelial cell damage. The long-acting extended-release microsphere formulation of OLA demonstrated higher Cmax (49.4 ± 1.58 ng/mL) and Tmax (14.64 ± 3.49 days) compared to oral drug suspension (1.20 ± 0.32 days) and T1/2 (25 ± 2.96 days) compared to oral drug suspension (3.95 ± 0.59 days). The optimized long-acting extended-release injectable OLA microsphere formulation proved stable after 6 months in accelerated and 12 months under controlled conditions. **Conclusion:** In conclusion, quality by design-based development of long-acting extended-release injectable OLA microsphere *in situ* gel formulations showed plasma drug availability at controlled release for 30 days and can overcome the oral route administration drawback of these drugs.

Key words: Antipsychotic agent, assessment, co-crystal, design, formulation and pharmaceutical

INTRODUCTION

Drug co-crystal screening has become a widely used method to improve the physicochemical properties of an active pharmaceutical ingredient (API). An API co-crystallized with another or more co-crystal co-formers at a certain stoichiometric ratio through hydrogen bonds, van der Waals forces, or other non-covalent interactions, which the multiple components are both in the same crystal lattice, is a co-crystal. Researches on the application performance of drug co-crystals mainly focus on the following aspects: Improving drug solubility and dissolution rate; improving drug chemical stability; improving thermal stability; reducing the hygroscopicity; reducing photo degradation; improving the tablet ability; reducing the bitterness; improving the bioavailability; and improving the permeability.[1,2] ESTEVE laboratory announced the success of the Phase II clinical trial of tramadol and celecoxib co-crystals for the treatment of acute pain, and subsequently, the review article on drug combination therapy by European medicines agency made the multidrug co-crystals (MDC) become the superstar. MDC may have the potential advantages of synergy, complementary mechanisms, enhancing the solubility and dissolution of at least one component, and improving bioavailability. In the present work, to adjust the solubility and dissolution rate, we choose two insoluble polyphenols,

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resveratrol (RSV) and kaempferol (KAE), which have central nervous system activity, as coformer. The co-crystallization of olanzapine (OLA) with Resveratrol (RAV) and KAE was carried out by the solvent volatilization method, anti-solvent method, and liquid-assisted grinding method. We synthesized five co-crystals of OLA with RSV and KAE. The co-crystal structure was also characterized by powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC), thermogravimetric analysis, and attenuated total reflection Fourier's transform infrared spectroscopy (FTIR). Moreover, the dissolution behavior of two non-solvate co-crystals were studied at different pH medium.[3]

MATERIALS AND METHODS

Pre-formulation studies

Pre-formulation medication studies are crucial before formulation trials. Before formulation creation, drug samples must be tested for purity. In this study, drug samples were authenticated by appearance, color, solubility, ultraviolet (UV)-vis spectroscopy, melting point, DSC, and Fourier transform infrared (IR).[4]

Screening of co-crystal for OLA microspheres

The active component, extended-release polymer, emulsifier, viscosity modifier, pH modifier, isotonicity modifier, and vehicle make up the long-acting injectable OLA microsphere. Screening of the long-acting injectable OLA microsphere began with extended-release biocompatible, biodegradable polymer, then viscosity modifier, emulsifier, pH modifier, iconicity modifier, and vehicle. Pharmaceutically acceptable, non-irritant, non-sensitizing, and safe for human and animal administration were considered while choosing excipients.[5]

Compatibility study

The drug-excipient compatibility research used 1:5, 1:0.5, and 1:0.25 excipient-drug ratios. Triturating the excipients and medication in a mortar pestle in clear glass vials with rubber stoppers and aluminium crimps. Samples were at 40°C/75% relative humidity (RH) for 30 days. Physical observation and FTIR (Alpha II, Bruker, and Mumbai) testing were performed on exposed samples to determine excipient-drug compatibility.[6]

Formulation development

Long-acting OLA microspheres were made using the quasi-emulsion solvent diffusion process. Long-acting OLA microspheres were made in three steps. In Phase-I, purified water was stirred to dissolve polyvinyl alcohol (PVA), citric acid, sodium chloride, and sodium carboxymethyl cellulose (CMC). Phase II dissolves OLA API and polymer in dichloromethane and chloroform under continuous stirring. Phase II API and polymer solutions were added drop by drop to Phase I PVA solution using a syringe (Phase III). Citric acid or sodium hydroxide changed the final solution pH. The solution was chilled, filtered with Whatman No. 4, and dried. For further design of experiments (DOE) tests, dried solid microspheres were kept in high-density polyethylene (HDPE) bottles with screw tops [Table 1].[2]

Characterization and evaluation

The various parameters of long-acting OLA microspheres were analyzed by various characterization and evaluation techniques.

Appearance

The color of extended-release OLA microspheres was tested internally. Visual examination was done on the inspection booth's black-and-white surface. Powdered microspheres are white-off white in all investigated compositions.[7,8]

Particle size analysis

The extended-release OLA microspheres were examined using a scanning electron microscope (Nova Nano field emission gun scanning electron microscope [FEG-SEM] 450, FEI Ltd). Approximately 50 mg of extended-release OLA microspheres were dispersed in 1.0 mL of distilled water and 50 µL was added to the dispersion medium. Analyses were performed at 2000 revolutions per minute (RPM) in distilled water. Room-temperature observations were repeated 3 times. DOE experiments used the median particle size mean of three replicates as a response factor.[9,10]

Surface morphology

The surface morphology of extended-release OLA microspheres was examined using a scanning electron microscope (Nova Nano FEG-SEM 450, FEI Ltd). Approximately 50 mg of extended-release OLA microspheres were dispersed in 1.0 mL of distilled water and 50 µL was added to the dispersion medium. Analyses were performed at 2000 RPM in distilled water. Room-temperature observations were repeated 3 times.[11]

Drug entrapment efficiency

The microsphere drug entrapment percentage was calculated by high-performance liquid chromatography (HPLC) (Shimadzu Corporation, Japan). HPLC techniques for OLA estimation in Phosphate buffer pH 2.0: Acetonitrile (65:35) were developed. The spectrophotometric measurements were done using HPLC (Shimadzu, Japan). Development and analysis of both medicines were done at 225 nm

and 2.0 mL/min. At room temperature, three replicates were taken at each dissolution time point. DOE studies utilized the loaded drug's mean of three duplicate measurements as a response factor.[12,13]

Stability studies

A stability study was carried out as per International Council for Harmonization guideline Q1A (R2) 2003. The optimized OLA microsphere formulation was packed in a glass bottle sealed with a rubber cap and kept in the stability chamber at 40 ± 2°C and 75 ± 5% RH and 25 ± 2°C and 60 ± 5% RH. The samples were withdrawn at initial, 3 and 6 month intervals for accelerated conditions and initial, 6 month, and 12 month intervals for controlled conditions. The samples were analyzed for appearance, percent encapsulation efficiency (EE), pH, FTIR spectroscopy, and particle size analysis.[14-16]

RESULTS AND DISCUSSION

Pre-formulation study

Identification of procured drug samples and ensuring their properties was essential before initiating formulation development. The physicochemical characterization and identification of the received drug sample were characterized and found below results.

Appearance

The procured drug samples were evaluated for description and color. The received OLA was found to be a white to off-white crystal or crystalline powder with no characteristic odor which complies with the reported appearance of white to off-white crystalline powder, without odor. The description complies with the received certificate of analysis from the API supplier.

Solubility study

As per the United State pharmacopia (USP) descriptive term of solubility, the OLA was found practically insoluble in water (10 mg of drug insoluble in >1000 part of water) and freely soluble in methanol (10 mg of drug soluble in <1 part of methanol). The obtained solubility complies with the reported solubility. The reported solubility of OLA is ~ 0.0024 mg/mL in water and ~ 56.0 m/mL in methanol.

Identification by UV visible spectroscopy

The 50-ppm Acetate buffer pH 4.5: Methanol (70:30) solution of OLA was scanned over 200–400 nm using a UV-vis spectrophotometer. The OLA shows the maxima (λmax) at 216 nm. The obtained UV spectrum of OLA is depicted in Figure 1.

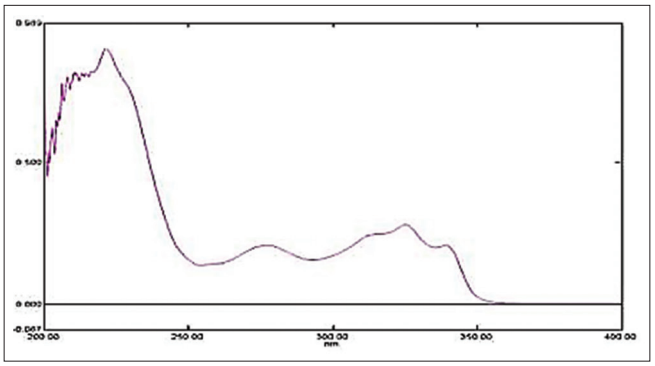

Figure 1: Ultraviolet spectrum of olanzapine in acetate buffer pH 4.5: Methanol (70:30)

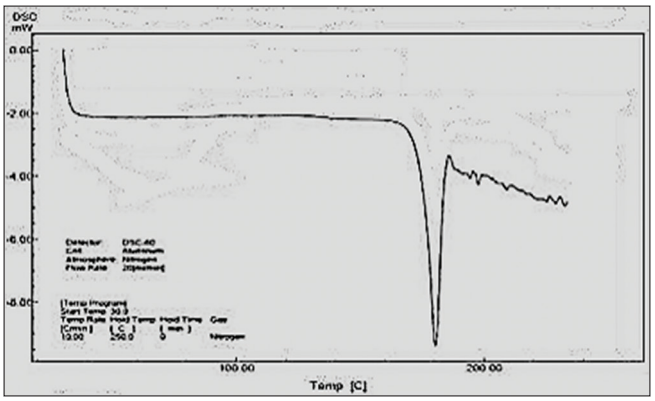

Figure 2: Differential scanning calorimetry thermogram of olanzapine

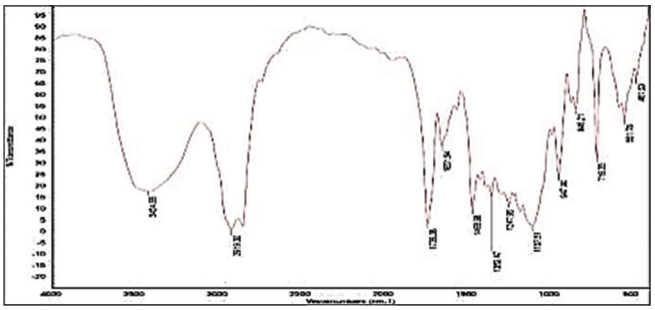

Figure 3: Reported Fourier's transform infrared spectroscopy spectrum

DSC

A DSC Q2000, thermal analysis instrument was employed to analyze the thermal behavior of the drug in the range of 30°C–300°C at a heating rate of 10°C/min under a nitrogen atmosphere. The DSC thermogram of OLA showed a sharp endothermic peak at 182.0°C. The obtained endothermic peak of OLA complies with the reported melting point of 179–183°C [Figure 2].

Identification by FTIR

The FTIR was carried out using Alpha II, Bruker spectrophotometer. The drug sample was placed directly on the diamond crystal plate and an IR scan of the drug was taken

Table 1: Plackett-Burman screening design of experiments for extended-release Olanzapine microsphere formulation

Batch ID	X1	X2	X3	X4	X5	X6
	Polymer conc.	Na-CMC conc.	Solvent volume	Stirring speed	Stirring time	Stirring temp
	% w/v	% w/v	mL	RPM	Hour	°C
OLA F1	24.0	7.0	50	1500	2	60
OLA F2	16.0	3.0	150	1500	4	40
OLA F3	16.0	7.0	150	1500	2	40
OLA F4	24.0	3.0	50	500	4	40
OLA F5	24.0	3.0	150	1500	4	60
OLA F6	16.0	7.0	150	500	4	60
OLA F7	16.0	3.0	50	500	2	40
OLA F8	16.0	7.0	50	500	4	60
OLA F9	24.0	7.0	150	500	2	40
OLAF10	24.0	3.0	150	500	2	60
OLAF11	16.0	3.0	50	1500	2	60
OLAF12	24.0	7.0	50	1500	4	40

[Figure 3]. The FTIR spectrum of the drug was obtained in the spectral region of 4000–500 cm^{-1}. The observed major IR peaks for OLA are summarized in Table 2 and the FTIR spectrum is shown in Figure 5a. The observed FTIR spectrum of the received sample was compared with the OLA reference spectrum. The received drug IR spectrum was found identical to the reference spectrum, as shown in Figure 5b.

Table 2: Observed and reported major transform infrared peaks of olanzapine

Functional group	Obtained wave number (cm^{-1})	Mode of vibration
-C-H	2940.09	Stretching
-C-H	2815.02	Stretching
-C=O	1650.14	Stretching

Screening of co-crystal and process parameters

Selection of extended-release polymer

The one factor at a time (OFAT) approach was used to test extended-release polymers and their effects on appearance and *in vitro* drug release. Different polymers were changed while keeping all other excipients, mixing speed, and mixing duration constant. Table 3 shows the composition and outcomes. RESOMER® RG 502 H was added at 8% w/v to OLA T1, along with sodium CMC, citric acid, sodium chloride, PVA, and process settings such 1000 RPM, 3 h, and 50°C. RESOMER® RG 752 H was added at 8% w/v to OLA T2, along with sodium CMC, citric acid, sodium chloride, PVA, and process parameters including stirring time (3 h), speed (1000 RPM), and temperature (50°C). Eudragit RL 100 was added at 8% w/v to sodium CMC, citric acid, sodium chloride, PVA, and process parameters including stirring speed (1000 RPM), time (3 h), and temperature (50°C) to make OLA T3. Eudragit RS 100 was added to OLA T4 at 8% w/v, along with sodium CMC, citric acid, sodium chloride, PVA, and process conditions such 1000 RPM, 3 h, and 50°C. RESOMER® C 209 was added at 8% w/v to OLA T5, along with Sodium CMC, citric acid, sodium chloride, PVA, and process settings such 1000 RPM, 3 h, and 50°C. Sodium CMC, citric acid, sodium chloride, PVA, and process parameters stirring speed (1000 RPM), stirring duration (3 h), and stirring temperature (50°C) were kept constant in OLA T6, which included 20% w/v Poloxamer Kolliphor P 407. Standard quasi-emulsion solvent diffusion was utilized to manufacture extended-release microspheres. Long-acting OLA microspheres were made in three steps. In Phase I, pure water was stirred to dissolve PVA, citric acid, sodium chloride, and CMC-Na. Phase II dissolves OLA API and polymer in dichloromethane and chloroform under continuous stirring. Phase II API and polymer solutions were added drop by drop to Phase I PVA solution using a syringe (Phase III). Citric acid or sodium hydroxide changed the final solution pH. The solution was chilled, filtered with Whatman No. 4, and dried. Standard screw-capped HDPE bottles held dry solid microspheres.

Selection of viscosity modifying agent

The OFAT approach was used to screen viscosity modifying agents and their effects on appearance and viscosity. Different polymers were altered while maintaining all other excipients, mixing speed, and mixing duration constant. Table 4 shows the composition and outcomes. Sodium CMC was 2.0% w/v in OLA T7, along with RESOMER® RG 502 H, RESOMER® RG 752 H, citric acid, sodium chloride, PVA, and process conditions such 1000 RPM, 3 h, and 50°C. Sodium CMC was added to OLA T8 at 5% w/v, along with RESOMER® RG

Table 3: Screening of extended-release polymer

Ingredients	OLA T1 (%w/v)	OLA T2 (%w/v)	OLA T3 (%w/v)	OLA T4 (%w/v)	OLA T5 (%w/v)	OLA T6 (%w/v)
Olanzapine	4.0	4.0	4.0	4.0	4.0	4.0
RESOMER® RG 502 H	8.0	-	-	-	-	-
RESOMER® RG 752 H	-	8.0	-	-	-	-
Eudragit RL 100	-	-	8.0	-	-	-
Eudragit RS 100	-	-	-	8.0	-	-
RESOMER® C 209	-	-	-	-	8.0	-
Poloxamer Kolliphor P 407	-	-	-	-	-	20.0
Sodium carboxymethyl cellulose	5.0	5.0	5.0	5.0	5.0	5.0
Citric acid	0.5	0.5	0.5	0.5	0.5	0.5
Sodium chloride	0.4	0.4	0.4	0.4	0.4	0.4
Polyvinyl Alcohol	1.25	1.25	1.25	1.25	1.25	1.25
Dichloromethane	35 mL	35 mL	35 mL	35 mL	35 mL	35 mL
Chloroform	35 mL	35 mL	35 mL	35 mL	35 mL	35 mL
Purified water	30 mL	30 mL	30 mL	30 mL	30 mL	30 mL
Sodium hydroxide	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Appearance	Clear solution	Clear solution	Turbid solution	Turbid solution	Clear solution	Clear solution
In vitro dissolution*	Satisfactory	Satisfactory	Not satisfactory	Not satisfactory	Satisfactory	Not satisfactory

*Satisfactory: Drug release found for extended period of time suitable for long-acting injectables. Not satisfactory: Drug release not found for extended period of time suitable for long-acting injectables

Table 4: Screening of viscosity modifying agent

Ingredients	OLA T7 (%w/v)	OLA T8 (%w/v)	OLA T9 (%w/v)	OLA T10 (%w/v)
Olanzapine	4.0	4.0	4.0	4.0
RESOMER® RG 502 H	4.0	4.0	4.0	4.0
RESOMER® RG 752 H	4.0	4.0	4.0	4.0
Sodium CMC	2.0	5.0	-	-
Carbopol 974P	-	-	2.0	-
HPMC K4M	-	-	-	3.0
Citric acid	0.5	0.5	0.5	0.5
Sodium chloride	0.4	0.4	0.4	0.4
Polyvinyl alcohol	1.25	1.25	1.25	1.25
Dichloromethane	35 mL	35 mL	35 mL	35 mL
Chloroform	35 mL	35 mL	35 mL	35 mL
Purified water	30 mL	30 mL	30 mL	30 mL
Appearance	Clear solution	Clear solution	Precipitation of solution	Hazy solution
Viscosity (cps)	15.2±3.84	58.9±4.08	-	-

502 H, RESOMER® RG 752 H, citric acid, sodium chloride, PVA, and process parameters including stirring time (3 h), speed (1000 RPM), and temperature (50°C). Carbopol 974P was 2.0% w/v in OLA T9, along with RESOMER® RG 502 H, RESOMER® RG 752 H, citric acid, sodium chloride, PVA, and process parameters such as stirring time (3 h), speed (1000 RPM), and temperature (50°C). The formulation OLA T10 included 3.0% w/v HPMC K4M, RESOMER® RG 502 H, RESOMER® RG 752 H, citric acid, sodium chloride, PVA, and process parameters such as stirring time (3 h), speed (1000 RPM), and temperature (50°C). Standard quasi-emulsion solvent diffusion was utilized to manufacture extended-release microspheres. Long-acting OLA microspheres were made in three steps. Phase I included

stirring PVA, citric acid, sodium chloride, and sodium CMC or Carbopol 974P or HPMC K4M in filtered water. Phase II dissolves OLA API and polymer in dichloromethane and chloroform under continuous stirring. Phase II API and polymer solutions were added drop by drop to Phase I PVA solution using a syringe (Phase III). Citric acid or sodium hydroxide changed the final solution pH. The solution was chilled, filtered with Whatman No. 4, and dried. Standard screw-capped HDPE bottles held dry solid microspheres.

Batch size study

The influence of batch size optimization on appearance was examined. Sample composition, batch size, and results are in Table 5. The formulation batch sizes of OLA T11, T12, and T13 were 25 mL, 50 mL, and 100 mL. Formulations OLA T11, OLA T12, and OLA T13 were made using RESOMER® RG 502 H, RESOMER® RG 752 H, sodium CMC, citric acid, sodium chloride, and PVA at 3 h, 1000 RPM, and 50°C. The research found no batch size influence on appearance. The study suggests manufacturing 25 mL–100 mL batches for this investigation.

Compatibility study

Physical observation (appearance)

The OLA compatibility study used RESOMER® RG 502 H Poly(D, L-lactide-co-glycolide) 50:50, 75:25, Eudragit RL 100, Eudragit RS 100, RESOMER® C 209 Poly (Caprolactone), Poloxamer Kolliphor P 407, and Sodium Carboxymethyl Cellulose, Citric Acid, and PVA in the ratios of 1:5 and 1:0.5. The samples' initial appearance before charging and after 40°C/75% RH exposure was examined and IR studied. All tested samples had white to off-white powder/granules before and after charging. The 40°C/75% RH sample was compared to the first sample for appearance. Table 6 shows initial and exposed sample appearance. The exposed sample looks the same as the first sample, proving excipients are drug-compatible.

Table 5: Screening of batch size

Ingredients	OLA T11 (%w/v)	OLA T12 (%w/v)	OLA T13 (%w/v)
Batch size	25 mL	50 mL	100 mL
Olanzapine	4.0	4.0	4.0
RESOMER® RG 502 H	4.0	4.0	4.0
RESOMER® RG 752 H	4.0	4.0	4.0
Sodium carboxymethyl cellulose	5.0	5.0	5.0
Citric acid	0.5	0.5	0.5
Sodium chloride	0.4	0.4	0.4
Polyvinyl alcohol	1.25	1.25	1.25
Dichloromethane	8.75 mL	17.5 mL	35.0 mL
Chloroform	8.75 mL	17.5 mL	35.0 mL
Purified water	7.5 mL	15.0 mL	30.0 mL
Stirring speed (rpm)	500	1000	1500
Stirring time (h)	2.0	3.0	4.0
Stirring temperature (°C)	40	50	60
Appearance	Clear solution	Clear solution	Clear solution

FTIR study

All exposed samples (40°C/75% RH, 1 month) had 4000–500 cm^{-1} FTIR spectra. Figure 4a-k show OLA and physical mixture IR spectra. See Table 5.8 for the main IR peaks of the pure drug and physical combination. From the IR spectra, the major peaks of OLA [Table 7] were not modified in the physical combination for all examined excipients, showing no substantial interaction between the two.

Table 6: Compatibility study of olanzapine with selected excipients

Drug (OLA)	Excipient	Ratio	Physical observation	
			Initial	1 Month 40°C/75% RH
OLA	Olanzapine (Pure drug)	-	White to off-white crystal or crystalline powder	No change
OLA	RESOMER® RG 502 H	1:5	White to off-white powder	
OLA	RESOMER® RG 752 H			
OLA	Eudragit RL 100			
OLA	Eudragit RS 100			
OLA	RESOMER® C 209 Poly (Caprolactone)			
OLA	Poloxamer Kolliphor P407		White to off-white granular Powder	
OLA	Sodium carboxymethyl cellulose	1:0.5	White to off-white powder	
OLA	Polyvinyl alcohol			
OLA	Citric acid			
OLA	Sodium chloride	1:0.25		

OLA: Olanzapine

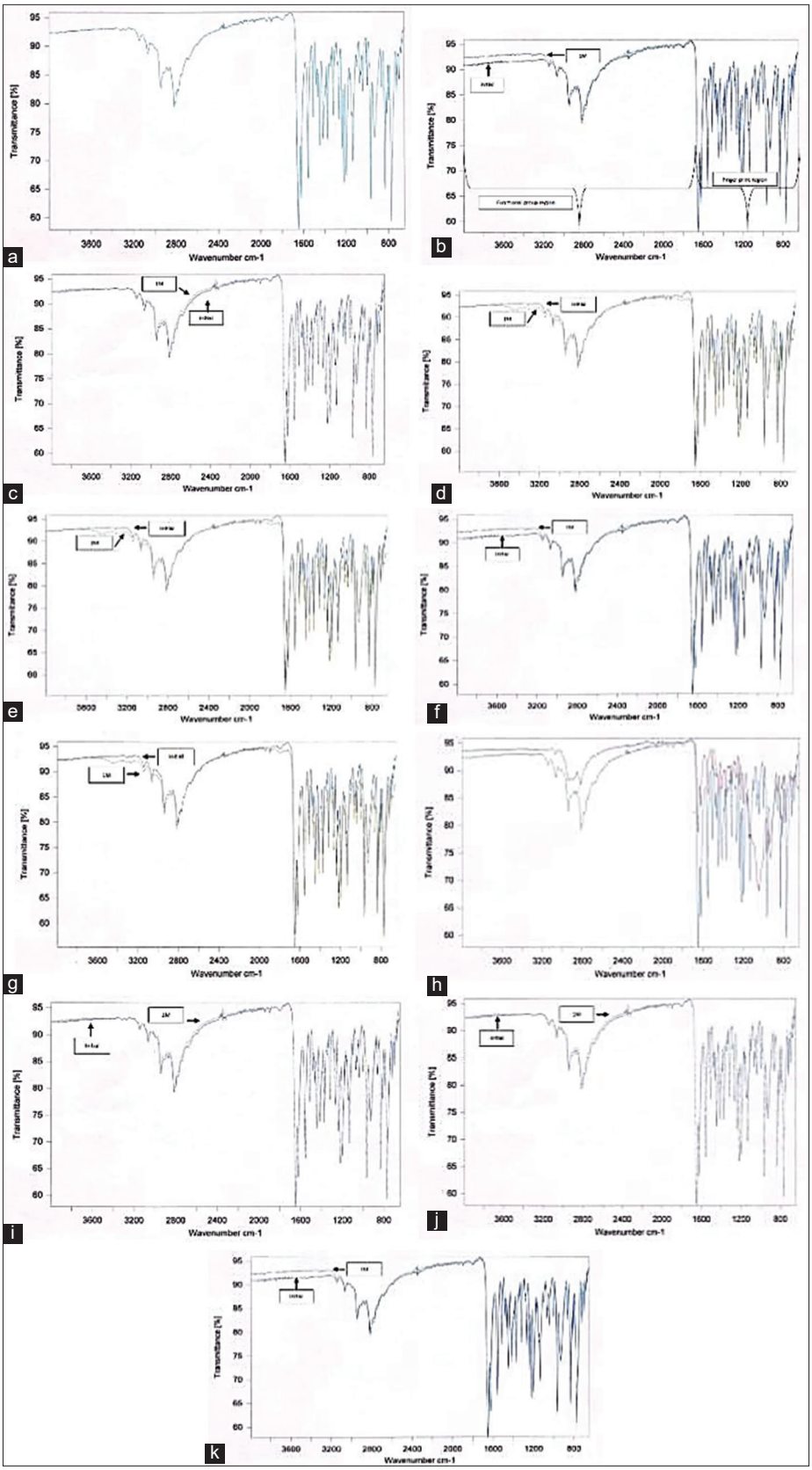

Figure 4: infrared spectrum of (a) pure drug olanzapine (OLA) (Initial), (b) OLA+RESOMER® RG 502 H, (c) OLA+RESOMER® RG 752 H, (d) OLA+Eudragit RL 100, (e) OLA+Eudragit RS 100, (f) OLA+RESOMER® C 209 Poly (Caprolactone), (g) OLA+PoloxamerKolliphor P 407, (h) OLA+Sodium Carboxy Methyl Cellulose, (i) OLA+Citric Acid, (j) OLA+PVA, and (k) OLA+Sodium Chloride

Characterization and evaluation

The various parameters of long-acting extended-release OLA microsphere formulations were analyzed using different characterization techniques. The evaluation parameters and results are discussed in the below sections.

Appearance

Visual appearance is a typical quality control test for medication safety and quality. Particulate particles in the product may cause patient noncompliance. The trial batch formulations and optimized formulation OLA FO-13 were particulate-free, making them safe to administer. Table 8 shows appearance results. All trial batch formulations from OLA-F1 to OLA-F12 were particle-free. The optimized OLA FO-13 formulation was particle-free.

Table 7: Principal peaks in IR spectra of olanzapine and physical mixtures

Sample	Wave No. (cm^{-1})
Pure drug (OLA, Initial)	2940.09, 2815.02, 1650.14
OLA+RESOMER RG 502 H (1:5)	2981.11, 2839.09, 1665.25
OLA+RESOMER RG 752 H (1:5)	2980.90, 2837.51, 1658.33
OLA+Eudragit RL 100 (1:5)	2931.26, 2829.44, 1641.67
OLA+Eudragit RS 100 (1:5)	2932.87, 2832.73, 1645.31
OLA+RESOMER® C 209 Poly (Caprolactone) (1:5)	2987.67, 2822.64, 1669.42
OLA+PoloxamerKolliphor P 407 (1:5)	2943.11, 2827.99, 1654.38
OLA+Sodium Carboxymethyl Cellulose (1:0.5)	2932.28, 2819.40, 1653.27
OLA+Citric Acid (1:0.5)	2950.11, 2817.26, 1651.85
OLA+polyvinyl alcohol (1:0.5)	2954.21, 2814.94, 1654.87
OLA+Sodium Chloride (1:0.25)	2940.56, 2818.21, 1655.59

OLA: Olanzapine

Table 8: Visual appearance and clarity results

Batch ID	Observation
Trial batches OLA-F1–OLA-F12	Free-flowing, free from particulate matter
Optimized batch, OLA FO-13	Free-flowing, free from particulate matter

FTIR and DSC analysis

FTIR and DSC analysis of final optimized formulation was important analysis to confirm the stability of OLA API into the formulation. Figure 5a and b shows about FTIR comparison of final optimized formulation (b) compared against pure drug OLA. Figure 6a and b shows about DSC thermogram comparison of final optimized formulation (b) compared against pure drug OLA.

Particle size

OLA microsphere formulation effectiveness depends on particle size. Drug release from formulations depends on microsphere particle size. Very tiny particles (100 µm) cause variance in medication release from formulations. For the long-acting injectable formulation, the recommended particle size was 10–100 µm. Table 9 shows the formulation and optimized batch results. All formulations had particle sizes ranging from 26.112 ± 0.50 µm (Batch ID: OLA-F8) to 43.667 ± 0.78 µm (Batch ID: OLA-F6). The standard deviation was good. Successful operating ranges and design space formulation resulted in a particle size of 27.80 ± 1.10 µm for the optimized batch.

Surface morphology

Microsphere surface morphologies explain drug-polymer cross-linking. Anisotropic microcrystalline whiskers match the nanospheres or spherical crystal structure of amorphous particles. Materials research relies on morphology the study of size, shape, and structure. Microsphere formulations depend on surface morphology since shape influences physical and chemical characteristics. All formed testing batches had rough, spherical surfaces. Figures 7 and 8 illustrate optimized batch OLA microsphere surface shape FO-13.

Drug entrapment efficiency

Drug EE is a crucial drug product property that affects formulation drug availability and *in vivo* efficiency. The

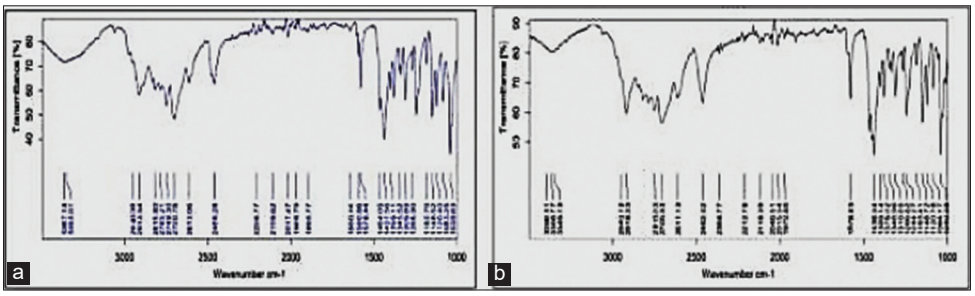

Figure 5: (a) Fourier's transform infrared spectroscopy (FTIR) spectrum of olanzapine pure drug and (b) FTIR spectrum of Brexpirazole long-acting microsphere final optimized formulation

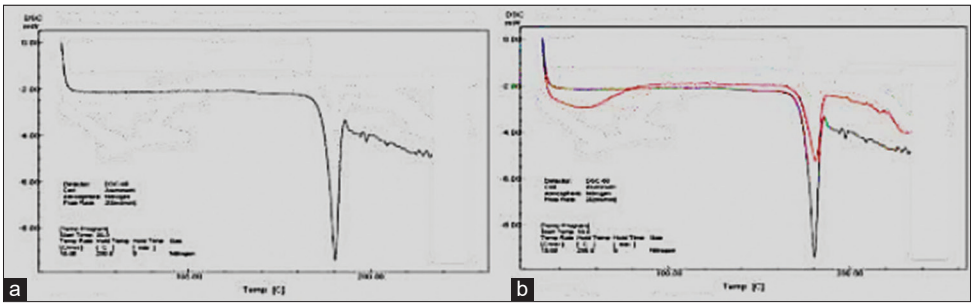

Figure 6: (a) Differential scanning calorimetry (DSC) thermogram of olanzapine pure drug and (b) DSC thermogram of brexpirazole long-acting microsphere final optimized formulation

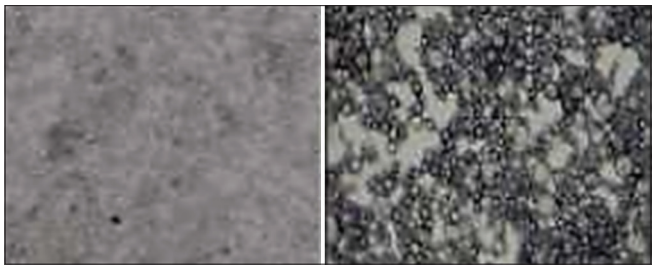

Figure 7: Optical microscopic images of RESOMER® RG 752-based microspheres ×10 magnification

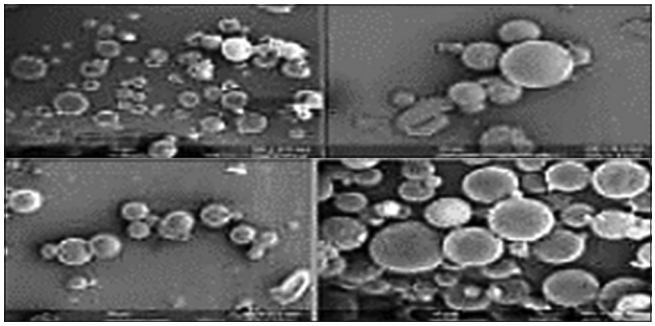

Figure 8: Scanning electron microscope images of RESOMER® RG 752-based batch microsphere formulations at different magnification

drug entrapment goal was determined using the USP general standard (90–110% of label claims), ensuring medication safety and effectiveness. Table 10 shows the formulation and optimized batch results. All examined formulations had particle sizes ranging from 86.2 ± 1.15% (OLA-F9) to 96.2 ± 2.78% (OLA-F3). The medicine EE met 90–110% of label promises in most forms. All formulas had acceptable standard deviations. The optimized batch had a particle size of 98.55 ± 1.28%, based on satisfactory operating ranges and design space formulation.

Stability study

The improved OLA microsphere formulation was stable for 6 months at 40 ± 2°C and 75 ± 5% RH (accelerated condition) and up to 12 months at 25 ± 2°C and 60 ± 5% RH (controlled condition). No visible changes were made

Table 9: Results of particle size for studied formulations

S. No.	Batch ID	Particle size (µm) (Mean±SD) (*n*=3)
1	OLA-F1	30.247±0.87
2	OLA-F2	37.552±0.70
3	OLA-F3	38.875±0.08
4	OLA-F4	29.884±0.64
5	OLA-F5	31.589±0.55
6	OLA-F6	43.667±0.78
7	OLA-F7	34.902±0.09
8	OLA-F8	26.112±0.50
9	OLA-F9	28.994±0.13
10	OLA-F10	40.265±0.99
11	OLA-F11	35.866±0.65
12	OLA-F12	31.492±0.49
13	OLA-FO13	37.800±1.10

Table 10: Outcomes of drug entrapment efficiency for studied formulations

S. No.	Batch ID	DEE (%) (Mean±SD) (*n*=3)
1	OLA-F1	91.6±1.67
2	OLA-F2	95.4±1.05
3	OLA-F3	96.2±2.78
4	OLA-F4	87.5±1.11
5	OLA-F5	94.8±0.75
6	OLA-F6	92.1±1.66
7	OLA-F7	88.3±2.89
8	OLA-F8	90.9±3.07
9	OLA-F9	86.2±1.15
10	OLA-F10	93.3±2.99
11	OLA-F11	91.7±2.45
12	OLA-F12	92.4±1.24
13	OLA-FO13	98.5±1.28

OLA: Olanzapine

Table 11: Stability study results of olanzapine optimized microsphere formulation

Condition		Accelerated		Controlled	
Storage condition		40±2°C/75±5% RH		25±2°C/60±5% RH	
Period	**Initial**	**3 months**	**6 months**	**6 months**	**12 months**
Appearance	White-off-white colored powdered microspheres				
% EE	98.55±1.28	96.10±1.88	99.05±2.35	97.88±1.12	96.09±1.5
pH	5.77±0.14	6.15±0.09	5.25±0.12	5.95±0.11	5.80±0.17
Fourier's transform infrared spectroscopy	2980.90, 2837.51, 1658.33	2977.23, 2849.00, 1661.42	2991.95, 2855.69, 1672.40	2982.63, 2832.33, 1659.08	2987.55, 2841.37, 1649.07
Particle size analysis	37.80±1.10	36.751±3.5	38.987±2.6	35.987±1.15	39.30±2.6

Mean±standard deviation (*n*=3)

to the formulation during stability testing. The student's *t*-test showed no changes in pH, FTIR, particle size, or drug EE throughout stability experiments. Optimized OLA microsphere formulation remained stable at 40 ± 2°C and 75 ± 5% RH (accelerated condition) and up to 12 months at 25 ± 2°C and 60 ± 5% RH (controlled condition). Table 11 shows optimized batch OLA FO-13 stability values.

CONCLUSION

Co-crystallization provides one of the most encouraging methods to improve physicochemical properties of drug substances. OLA co-crystals were prepared using p-hydroxybenzoic acid and saccharin sodium by solvent evaporation method. This method of laboratory scale to prepare co-crystal scan be transformed to potentially large scale continuous production method. The co-crystals, prepared using equimolar concentration of drug and coformer, were confirmed by characterization techniques such as melting point, solubility studies, dissolution studies, FTIR, DSC, PXRD, and SEM studies. Orodispersible tablets (ODTs) of paliperidone co-crystals efficiently and successfully formulated by employing superdisintegrants addition method to generate prima face evidence. Detailed insight is given on the mechanism of co-crystallization and working of ODTs. The prepared tablets complied for pharmacopoeial and non-pharmacopoeial tests. It is anticipated that this data will certainly become a suitable platform for further development of paliperidone ODTs.[17,18] Co-crystallization offers one of the most promising approaches to improve physicochemical properties of APIs. A wide range of options exist to prepare co-crystals ranging from routine laboratory scale synthesis methods to potentially large scale continuous production methods. This review offers standard descriptions and examples of established and emerging co-crystal preparation routes. Moreover, detailed insight is given on the proposed mechanisms of co-crystallization in different techniques. As co-crystals continue to gain interest and prove their value, the range of demonstrated co-crystal application areas continues to expand. All demonstrated application areas for pharmaceutical co-crystals are included in this review with the aim of highlighting the wide ranging potential of these materials. It is anticipated that co-crystals will become more and more routine in pharmaceutical development as their benefits continue to be demonstrated and routine routes of manufacturing are proven.[19,20]

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