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FORMULATION AND EVALUATION OF GELATIN NANOPARTICLES OF ANTI-PSYCHOTIC DRUGS

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ABSTRACT

Antipsychotic drugs loaded gelatin nanoparticles (G-NPs) were prepared by desolvation method using acetone as solvent and glutaraldehyde as cross linking agent. The prepared gelatin nanoparticles were characterized for particle size, shape, zeta potential and encapsulation efficiency. Different ratios of drug:polymer (1:1, 1:2, 1:3), different concentrations of acetone (10ml,20ml,30ml) as solvent were used. The particle size distribution of prepared gelatin nanoparticles ranged from 105.0±0.2nm to 256.9±0.5nm. The zeta potential of the prepared gelatin nanoparticles ranged from 9.1±2.0mV to 14.8±0.4mV. The encapsulation efficiency of drug loaded G-NPs was ranged from 42±0.6% to 79±2.4%. By increasing the concentration of Gelatin (G) decrease in the particle size, increase in the zeta potential and encapsulation efficiency were observed and by further increasing the concentration of gelatin, increase in the particle size, decrease in the zeta potential and encapsulation efficiency were observed. Among all the formulations drug:polymer ratio of 1:2 with 20ml acetone as solvent and 100µl of 4% glutaraldehyde as cross linking agent showed better results for the treatment of psychotic disorders.

KEYWORDS: Nanoparticles, Antipsychotics, Schizophrenia, Gelatin, Desolvation.

INTRODUCTION

Antipsychotics are the drugs that are used for the treatment of psychiatric disorder such as schizophrenia, mania, and organic psychosis.[1] Formerly known as major tranquilizers and neuroleptics. Antipsychotic medications can help to calm and clear confusion in a person with acute psychosis within hours or days, but can take up to four or six weeks to reach their full effect. Combining antipsychotic medication with other therapy and support can help people to manage symptoms and improve quality of life.[2] Nanoparticles are used in various psychiatric diseases like schizophrenia, endogenous depression and bipolar disorder. This is mainly because of the small size of the nanoparticles. In neurology and psychiatry practice, one of the major challenges that physicians have so far been faced with, was inability of many medications to pass through blood-brain barrier.[3] Many of the drug substances have short half-life, poor bioavailability, poor water solubility and extensive first-pass metabolism. Preparation of nanoparticles is one such universal approach to improve the pharmacokinetic profile of drug, poorly water soluble, low bioavailable and high toxic drugs. Possible methods to avoid first-pass metabolism include transdermal, buccal, rectal and parenteral routes of administration.[4] Transdermal delivery provides a leading edge over injectables and oral routes by increasing patient compliance and avoiding first pass metabolism respectively. Transdermal delivery not only provides controlled, constant administration of the drug, but also allows continuous input of drugs with short biological half-lives and eliminates pulsed entry into systemic circulation, which often causes undesirable side effects. This method is capable of delivering drugs, the use of which would be limited due to poor oral bioavailability, side effects associated with high peaks or poor compliance due to the need for frequent administration.[5]

The aim of this work was to prepare gelatin nanoparticles (G-NPs) of antipsychotic drugs using the desolvation method and characterization of nanoparticles by determining their particle size, shape, surface charge, and drug entrapment efficiency.

MATERIALS AND METHODS

Materials

Quetiapine fumarate was a gift sample from Micro Labs Ltd, Bangalore. Ziprasidone HCL was a gift sample from Apotex Pharmachem, Bangalore. All other reagents and chemicals were of analytical grade.

Methods

Gelatin nanoparticles were prepared using three antipsychotic drugs Quetiapine fumarate (QC),

Ziprasidone HCL (ZC) and Paliperidone (PC) by desolvation method.

Preparation of Gelatin Nanoparticles (GNPs)[6]

GNPs of Quetiapine fumarate (QG), Ziprasidone HCL (ZG), Paliperidone (PG) were prepared by simple desolvation method. Aqueous solutions of gelatin in different concentrations were stirred on magnetic stirrer, to which accurately weighed amount of drug solution was added under constant heating temperature of 40^0C. To the gelatin drug solution, acetone was added drop-wise (desolvating agent), until the solution just becomes turbid. pH of the solution was adjusted to 2 ± 0.05 (by 1N HCl). 100µl of 4% glutaraldehyde was added as cross linking agent and stirred continuously at room temperature for 3 hrs. The nanoparticles samples were centrifuged at 12,000 rpm and 4ºC for 30 min using Eppendrof Ultracentrifuge 5430R. Nanoparticles were characterised by changing the parameters like concentration of gelatin, and quantity of acetone.

Table 1: Formulation consideration of gelatin nanoparticles with different concentrations of acetone.

Sl.No	Ingredients	QG1, ZG1, PG1	QG2, ZG2, PG2	QG3, ZG3, PG3
1	Drug: Polymer (gelatin) mg	1:2	1:2	1:2
2	Acetone (ml)	10	20	30
3	Glutaraldehyde (µl)	100	100	100
4	Stirring speed (rpm)	600	600	600
5	Temperature (^{0}C)	40	40	40

Table 2: Formulation consideration of gelatin nanoparticles with different concentration of gelatin.

Sl.No	Ingredients	QG4, ZG4, PG4	QG5, ZG5, PG5	QG6, ZG6, PG6
1	Drug: Polymer (gelatin) mg	1:1	1:2	1:3
2	Acetone (ml)	20	20	20
3	Glutaraldehyde (µl)	100	100	100
4	Stirring speed (rpm)	600	600	600
5	Temperature (^{0}C)	40	40	40

Characterization of gelatin Nanoparticles

1. **Fourier transform infrared spectroscopy (FTIR):** Drug- excipient interaction plays a vital role in the release of drug from formulation. Fourier transform infrared spectroscopy (FTIR) has been used to study the physical and chemical interactions between drug and the excipients using KBr pellets method.
2. **Shape and Surface Morphology:** The shape and surface morphology of the gelatin naoparticles was visualized by scanning electron microscopy. The samples were prepared by lightly sprinkling nanoparticles on double-sided adhesive tape on an aluminum stub. The stubs were then coated with gold to a thickness of 200 to 500 Å under an argon atmosphere using a gold sputter module in a high vacuum evaporator. The samples were then randomly scanned and photomicrographs were taken at different magnifications with SEM.
3. **Particle Size and Zeta Potential Measurement:** The average particle size, polydispersity index (PDI) and Zeta Potential of the formulated nanoparticles were determined using HORIBA Scientific Nano Partica, nanoparticle analyzer SZ-100 at 25ºC. 1 ml of the sample of nanoparticles dispersion was placed in disposable cuvettes for particle size measurements. Samples were diluted with double distilled water. Each experiment was conducted in triplicate.
4. **Drug Entrapment Efficiency**: The drug loaded nanoparticles were ultracentrifuged (Eppendrof) at 12,000 rpm and 4^0C for 30 min and the supernatant was assayed for non-bound drug concentration. The absorbance of the unencapsulated drug was evaluated in the supernatant using a UV-VIS spectrophotometer (UV-1800 Shimadzu) against plain gelatin nanoparticles as the blank which have also been prepared and treated similarly to the drug-loaded nanoparticles. The analysis was carried out in triplicate and the mean was taken. The drug entrapment of the nanoparticles was calculated by the following equation.

$$EE = \frac{\text{Amount of total drug - Amount of free drug in supernatant}}{\text{Amount of total drug}} \times 100$$

5. **Total drug content:** The drug content for the drug loaded nanoparticles were determined by dissolving 1ml of the nanoparticle formulation in 9ml acetone and further dilutions were made with mobile phase. The amount of drug was estimated by HPLC method using C-18 column with flow rate of 1mL/min and injection of 20µL.

Chromatographic conditions for each drugs

Quetiapine fumarate[7]

Mobile phase: methanol: acetonitrile : phosphate buffer (pH 7) – (1:2:2)
UV detection: 254 nm
Retention time: 9min

Ziprasidone HCL[8]

Mobile phase: methanol: phosphate buffer (pH 3) – (60:40)
UV detection: 219 nm
Retention time: 15 min

Paliperidone[9]
Mobile phase: acetonitrile : phosphate buffer (pH 6) – (70:30)
UV detection: 237 nm
Retention time: 6 min

RESULTS

Drug-Excipients compatibility studies by FT-IR
The results of FT-IR spectroscopic analysis showed that there were no interactions between pure drugs and physical mixture.

1. IR spectra of Quetiapine Fumarate

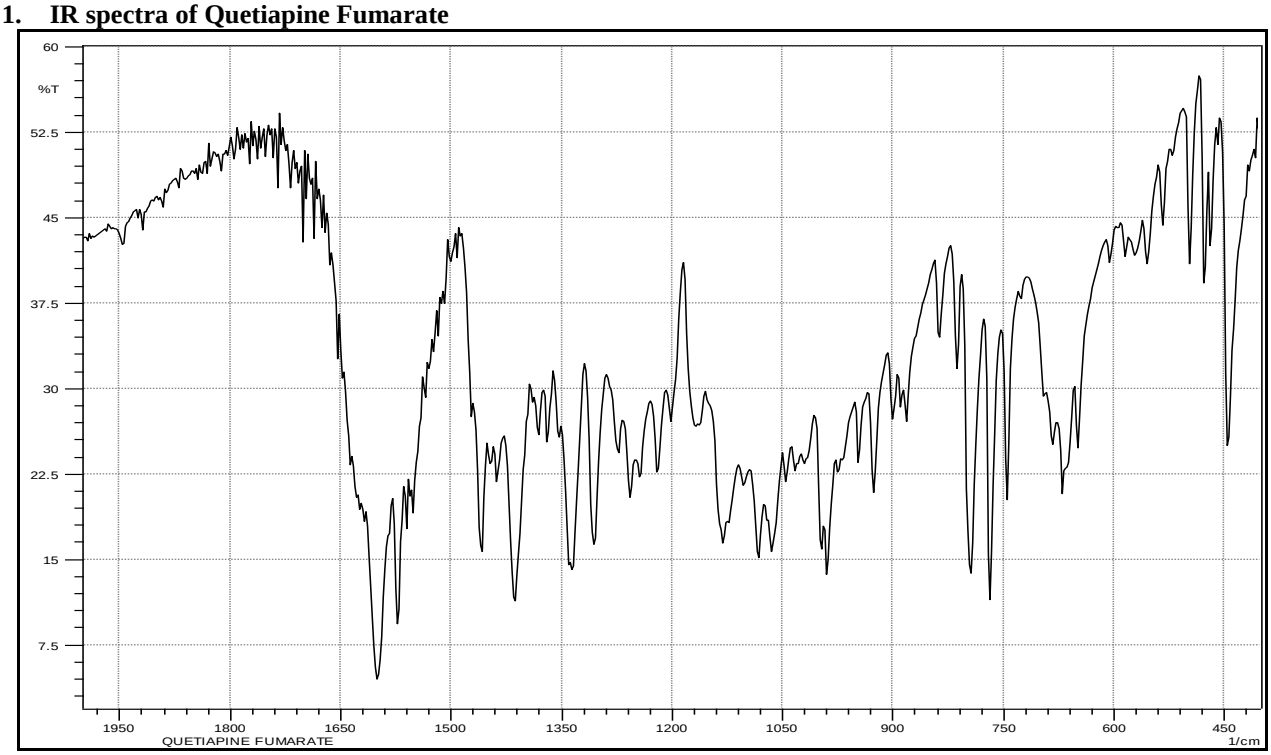

Fig. 1: FTIR spectra of pure drug Quetiapine Fumarate.

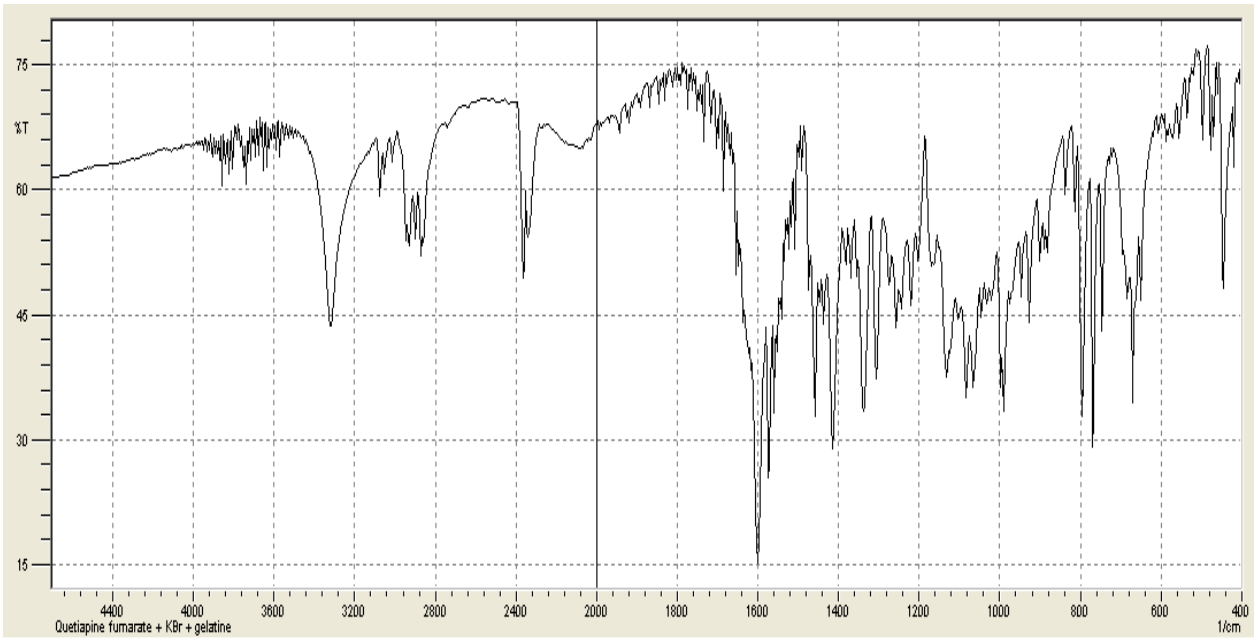

Fig. 2: FTIR spectra of physical mixture of Quetiapine Fumarate and gelatin.

2. IR spectra of Ziprasidone HCL

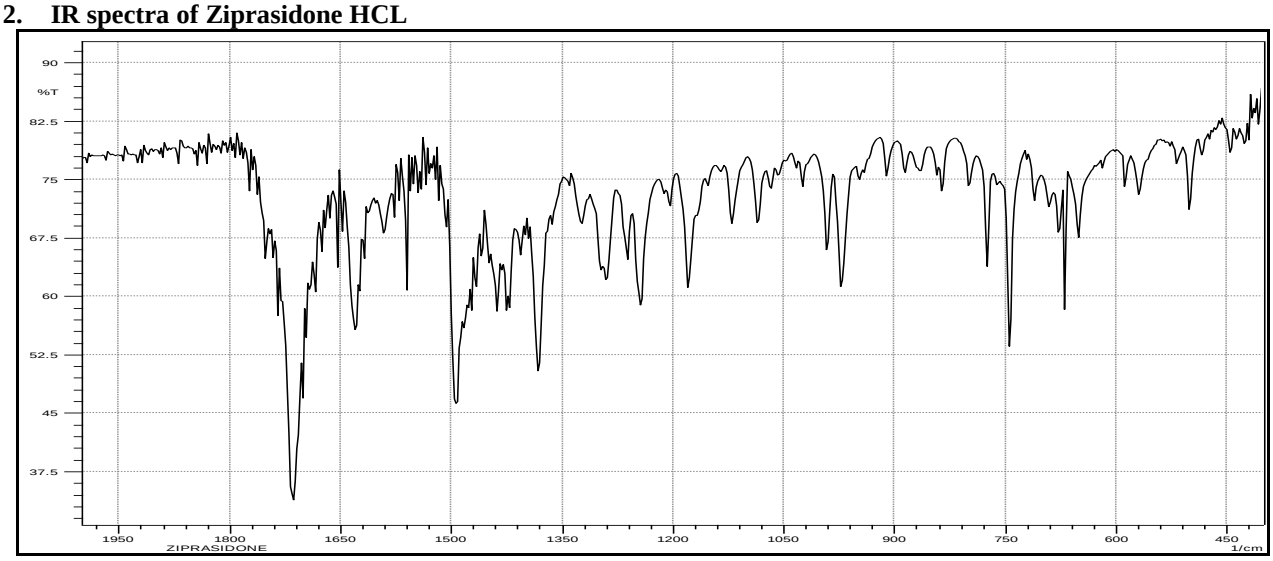

Fig. 3: FTIR spectra of pure drug Ziprasidone HCL.

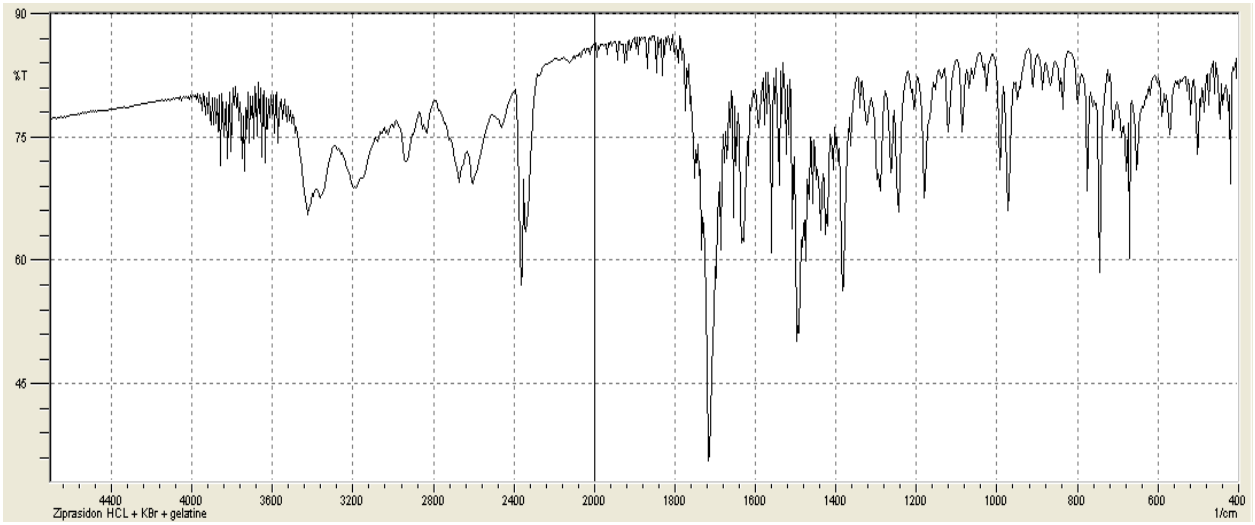

Fig. 4: FTIR spectra of physical mixture of Ziprasidone HCL and gelatin.

3. IR spectra of Paliperidone

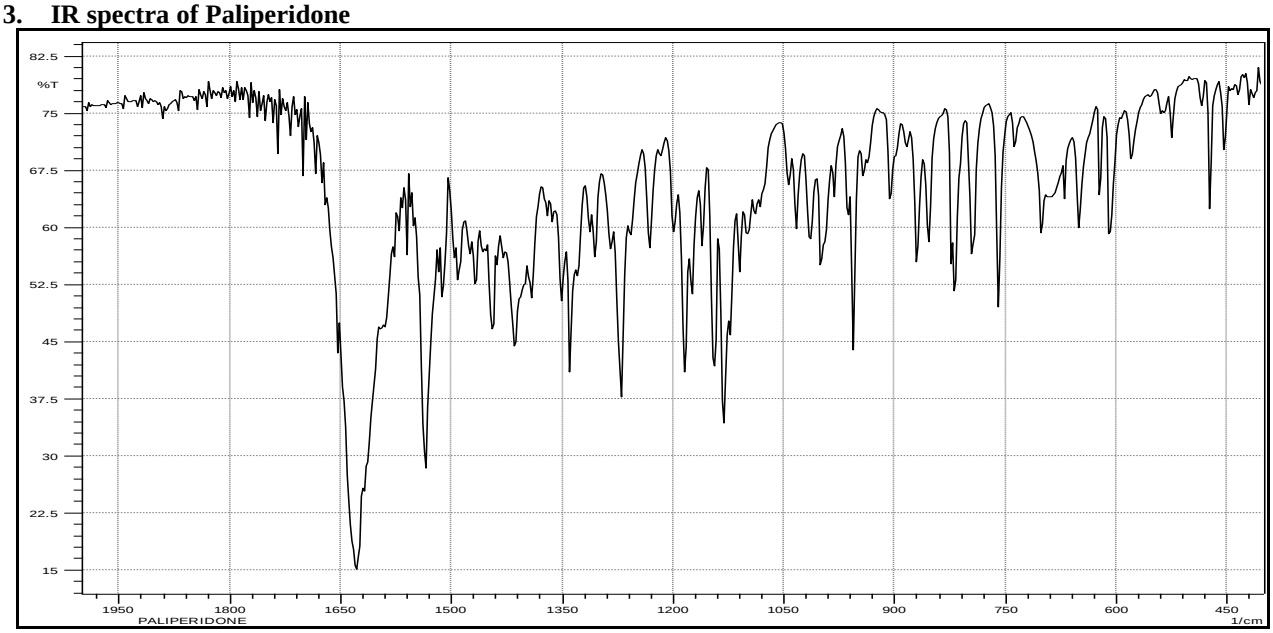

Fig. 5: FTIR spectra of pure drug Paliperidone.

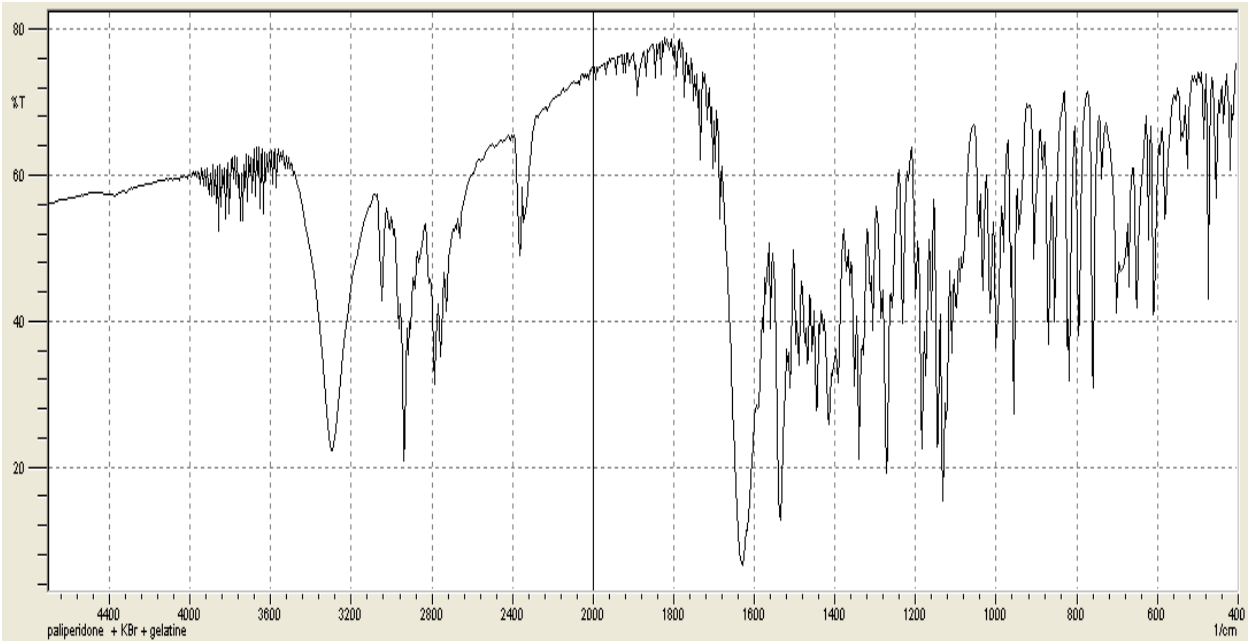

Fig. 6: FTIR spectra of physical mixture of Paliperidone and gelatin.

Surface Morphology, Particle size and Zeta Potential Measurement of nanoparticles

The morphology of drug loaded gelatin nanoparticles was irregular in shape with a rough surface as shown in Figure 9. The particle size and zeta potential of the gelatin nanoparticles were analyzed by HORIBA scientific nano Partica, nanoparticle analyzer SZ-100. Six formulations were prepared with various concentrations of gelatin and acetone. The values for the average particle size, zeta potential, polydispersity index and encapsulation efficiency are tabulated in Table 3.

Table 3: The values for the average particle size, zeta potential, polydispersity index and entrapment efficiency.

Sl.No.	Formulation	Average particle size ± S.D	Zeta Potential ± S.D	Polydispersity Index ± S.D	Entrapment Efficiency ± S.D
1	QG 1	211.5 ± 1.4	9.5 ± 0.3	0.67 ± 1.4	46±0.5
2	QG 2	105.0 ± 0.2	14.8 ± 0.4	0.40 ± 0.8	79±2.4
3	QG 3	171.6 ± 2.4	11.3 ± 2.2	0.76 ± 1.3	54±1.4
4	QG 4	256.9 ± 0.5	10.2 ± 1.6	0.79 ± 0.7	42±0.6
5	QG 5	108.5 ± 0.9	14.2 ± 1.2	0.46 ± 1.4	79±0.7
6	QG 6	201.2 ± 1.8	11.3 ± 1.6	0.75 ± 1.8	53±1.9
7	ZG 1	240.1 ± 1.6	12.1 ± 0.4	0.63 ± 1.4	49±1.5
8	ZG 2	111.8 ± 2.5	13.7 ± 2.3	0.47 ± 0.5	67±1.7
9	ZG 3	193.3 ± 1.9	10.2 ± 1.8	0.84 ± 0.3	56±1.7
10	ZG 4	182.7 ± 2.2	11.6 ± 1.5	0.72 ± 1.6	59±2.1
11	ZG 5	113.5 ± 1.8	13.5 ± 1.4	0.42 ± 0.7	67±1.6
12	ZG 6	191.3 ± 2.1	10.5 ± 1.6	0.79 ± 0.5	49±0.5
13	PG 1	218.5 ± 1.3	9.1 ± 2.0	0.85 ± 1.8	58±0.7
14	PG 2	116.1 ± 2.7	12.2 ± 0.9	0.57 ± 0.9	74±1.3
15	PG 3	199.5 ± 2.9	11.1 ± 0.7	0.78 ± 1.5	43±0.8
16	PG 4	226.1 ± 1.5	11.7 ± 1.1	0.65 ± 1.7	51±1.4
17	PG 5	118.2 ± 1.2	12.1 ± 1.3	0.49 ± 0.4	73±1.9
18	PG 6	189.5 ± 1.6	10.8 ± 1.4	0.74 ± 1.9	47±2.1

n=3; Values are mean ± standard deviation

HORIBA Scientific

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SZ-100

201603221426000.nsz

Measurement Results

Date	:	Saturday, December 03, 2016 3:36:26 PM
Measurement Type	:	Particle Size
Sample Name	:	QG 2
Scattering Angle	:	173
Temperature of the Holder	:	25.2 °C
Dispersion Medium Viscosity	:	0.891 mPa·s
Transmission Intensity before Meas.	:	34845
Distribution Form	:	Standard
Distribution Form(Dispersity)	:	Polydisperse
Representation of Result	:	Scattering Light Intensity
Count Rate	:	1221 kCPS

Calculation Results

Peak No.	S.P.Area Ratio	Mean	S. D.	Mode
1	1.00	139.9 nm	45.9 nm	125.7 nm
2	---	--- nm	--- nm	--- nm
3	---	--- nm	--- nm	--- nm
Total	1.00	139.9 nm	45.9 nm	125.7 nm

Cumulant Operations

Z-Average	:	105.0 nm
PI	:	0.402

Molecular Weight Measurement

Molecular Weight	:	---
Parameters for Molecular Weight Calculation	:	---

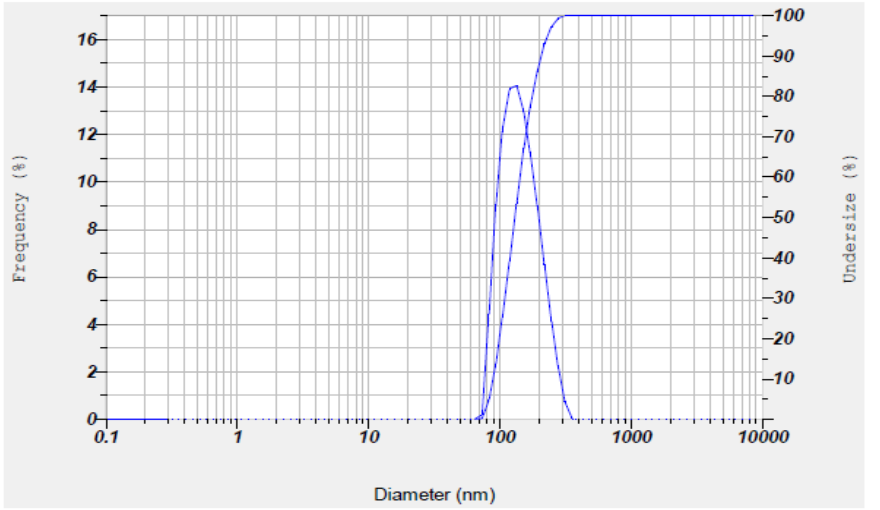

Fig. 7: Particle size analysis.

Measurement Results

201701061741003.nzt

Measurement Results

Date	:	Saturday, December 03, 2016 3:29:48 PM
Measurement Type	:	Zeta Potential
Sample Name	:	QG 2
Temperature of the holder	:	25.3 °C
Viscosity of the dispersion medium	:	0.890 mPa·s
Conductivity	:	20.645 mS/cm
Electrode Voltage	:	1.3 V

Calculation Results

Peak No.	Zeta Potential	Electrophoretic Mobility
1	14.8 mV	0.000115 cm2/Vs
2	--- mV	--- cm2/Vs
3	--- mV	--- cm2/Vs

Zeta Potential (Mean)	:	14.8 mV
Electrophoretic Mobility mean	:	0.000115 cm^2/Vs

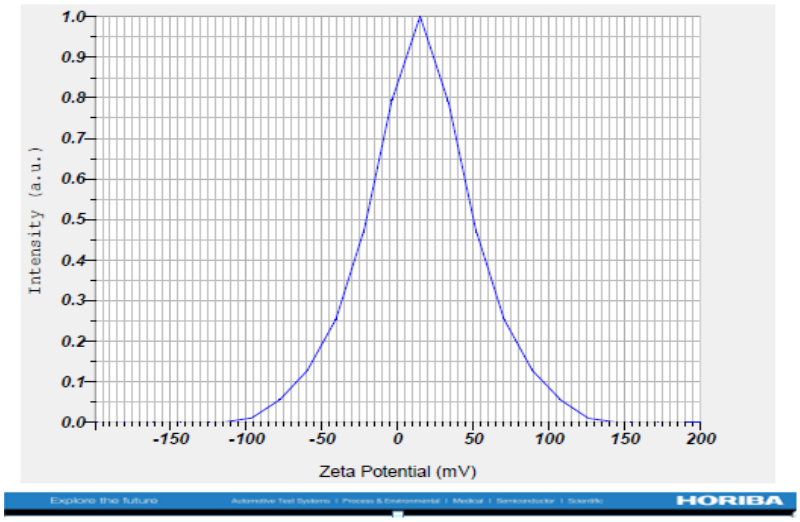

Fig. 8: Zeta potential analysis.

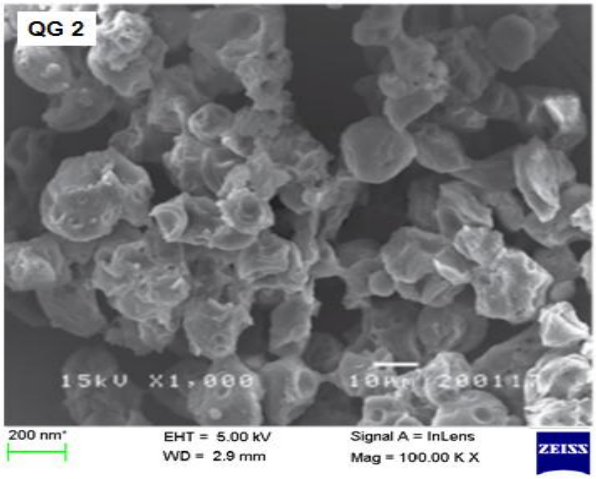

Figure 9: SEM images of Quetiapine Fumarate (QA 2) loaded G-NPs.

Table 4: The values for the total drug content using HPLC method.

Sl.No.	Formulation code	Drug content ± S.D (%)
1	QG2	92.87±1.4
2	ZG2	88.76±1.6
3	PG2	90.65±1.4

n=3; Values are mean ± standard deviation

DISCUSSION

Drug-loaded gelatin nanoparticles (G-NPs) were successfully formulated by using desolvation method with different ratio of drug : polymer (1:1, 1:2, 1:3), different concentrations of acetone as solvent and characterized using the HORIBA scientific nano Partica, nanoparticle analyzer SZ-100. Drug excipient compatibility studies were carried out using FTIR and DSC, and it was observed that there was no interaction between the drug and polymer. The particle size distribution of prepared gelatin nanoparticles ranged from 105.0 ± 0.2nm to 256.9 ± 0.5nm. By increasing the concentration of gelatin from 1:1 to 1:2 ratio, decrease in particle size was observed and by further increasing the concentration from 1:2 to 1:3 ratio, increase in the particle size was observed. By increasing the volume of acetone decrease in particle size was observed and by further increasing the volume of the acetone, the particle size increases. The zeta potential of the prepared gelatin nanoparticles ranged from 9.1 ± 2.0 to 14.8 ± 0.4 mV. The encapsulation efficiency of drug loaded G-NPs was ranged from 42±0.6 to 79±2.4%. By increasing the gelatin concentration, increase in encapsulation was observed. The optimum ratio of drug : polymer was identified as 1:2 with 20ml of acetone (QG 2) and 100µl of 4% glutaraldehyde as cross linking agent. The particle size of nanoparticles was 105.0 ± 0.2 nm showed in (Figure:7), zeta potential 14.8 ± 0.4 mV showed in (Figure:8), encapsulation efficiency was 79±2.4% and drug content of 92.87±1.4%. For Paliperidone (PG2) and Ziprasidone HCL (ZG2) formulations, where drug and polymer in the ratio of 1:2 with 20ml of acetone and 100µl of 4% glutaraldehyde as cross linking agent showed better results. The particle size of nanoparticles was 116.1 ± 2.7nm and 111.8 ± 2.5nm, zeta potential 12.2 ± 0.9mV and 13.7 ± 2.3mV, encapsulation efficiency was 74±1.3% and 67±1.7% and the total drug content was found to be 90.65±1.4% and 88.76±1.6% respectively.

CONCLUSION

The drug loaded Gelatin nanoparticles prepared using Quetiapine fumarate (QG2), Paliperidone (PG2) and Ziprasidone HCL (ZG2) containing drug : polymer in the ratio of 1:2 (QG2) with 20ml of acetone as solvent and 100µl of 4% glutaraldehyde as cross linking agent are considered as best formulations compared to other formulations with particle size of 105.0 ± 0.2 nm, zeta potential of 14.8 ± 0.4 mV and entrapment efficiency of 79±2.4%. The shape and surface morphology of the drug loaded gelatin nanoparticles were visualized by scanning electron microscopy (SEM). The nanoparticles were irregular in shape and have a rough surface. Among all the formulations QG 2 was selected as the best

formulation based on particle size, zeta potential and encapsulation efficiency.

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