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Research Article

FORMULATION AND EVALUATION OF NANOPARTICLES FOR ANTI-PSYCHOTIC DRUGS BY IONIC GELATION METHOD

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ABSTRACT

Antipsychotic drugs loaded chitosan nanoparticles (CS-NPs) were prepared by ionic gelation method using sodium tripolyphosphate (TPP) as cross-linking agent. The prepared nanoparticles were characterized for particles size, shape, zeta potential and encapsulation efficiency. Different ratios of drug: chitosan (1:1, 1:2, 1:3) and TPP at different concentrations (0.75%, 1%, 1.25%) were used. The particle size of the prepared nanoparticles (NPs) ranged between 73.0 ± 2.5nmto 291.3 ± 3.6 nm, zeta potential ranged from +22.7 ± 0.6 mV to +41.8 ± 0.3 mV, encapsulation efficiency ranged from 51±0.4% to 77±0.8%. By increasing the concentration of chitosan (CS), decrease in the particle size, zeta potential and encapsulation efficiency were observed and by further increasing the concentration of chitosan, increase in the particle size, zeta potential and encapsulation efficiency were observed. Among the entire formulations drug: chitosan ratio of 1:2 with 1% TPP showed better results. The studies suggested that the feasibility of formulating antipsychotic drugs loaded chitosan nanoparticles for the treatment of psychotic disorders.

KEY WORDS: *Nanoparticles, Antipsychotics, Schizophrenia, Chitosan, Ionic gelation.*

INTRODUCTION

Antipsychotics are the drugs used to reduce or relieve symptoms of psychosis (including delusions or hallucinations, as well as disordered thoughts), particularly in schizophrenia and bipolar disorder. Formerly known as major tranquilizers and neuroleptics, antipsychotic medications are the main class of drugs used to treat people with schizophrenia.Epidemiological studies report prevalence rates for psychiatric disorders varying from 9.5 to 370/1000 population in India. Despite variations in the design of studies, available data from the Indian studies suggested that about 20% of the adult population in the community is affected with one or the other psychiatric disorders [1]. Majority of the patients fall in the age group between 21 to 30 years (27.8%) of age, and 31 to40 years (26.7%) of age. Rest of the patients are inthe following age wise distribution: 0 to 10 years (0.8%), 11 to 20 years (17.2%), 41 to 50 years (16.7%), 51 to 60 years (7.6%), 61 to 70 years (3.1%), 71 to 80 years (0.5%). In the sample, maleto female ratio was found to be 3:2 and married to unmarried ratio was 4:3 [2]. Polymeric nanoparticles are particulate dispersions or solid particles with size range of 10-1000 nm. The drug is dissolved, entrapped, encapsulated or attached to a nanoparticle matrix. They represent a promising drug delivery system of controlled and targeted release. The use of polymeric nanoparticles for drug delivery is a strategy that aims to optimize therapeutic effects while minimizing adverse effects. Due to their small size, they exhibit unique physicochemical and biological properties [3]. In the recent years, many modern technologies have been established in the pharmaceutical research and development area. Use of polymeric drug nanoparticles is a universal approach to increase the therapeutic performance of poorly soluble drugs in any route of administration. Researchers have suggested that nanoparticles could be used in various psychiatric diseases like schizophrenia, endogenous depression and bipolar disorder [4]. Many of the drug substances have short half-lives, poor bioavailability, poor water solubility and extensive first-pass metabolism. Nanoparticles are one such universal approach to improve the pharmacokinetic profile of 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 [5]. Polymeric nanoparticulate drug delivery system offers numerous advantages over the conventional dosage forms. These include improved efficacy, reduced toxicity, and improved patient compliance. Nanoparticles are able to protect the drug from degradation, improve permeation/penetration of the drugs, and also control the release of the encapsulated or adsorbed drug. Among those various polymers used as drug carriers, chitosan and its derivatives are the most used polymers. Chitosan is a natural cationic polysaccharide prepared by partial deacetylation of chitin, a copolymer which is composed of glucosamine and N-acetyl glucosamine units. This cationic polymer is extensively used as carrier for drug delivery due to its biocompatibility and low toxicity [6]. The most widely developed method for preparation of chitosan nanoparticles is ionic gelation technique. Principle of this method is based on ionic interaction between positively charged primary amine group of chitosan and negatively charged groups of poly anion, such as sodium tripolyphosphate, the most widely used cross linking agent because of its nontoxic and multivalent characteristics. This physical cross-linking process not only avoids the use of chemical cross-linking agents and emulsifying agents which are often toxic to organisms, but also prevents the possibility of damage to drugs, particularly biological agents [7].

The aim of this work was to prepare chitosan-TPP nanoparticles of antipsychotic drugs using the ionic gelation method and characterization of nanoparticles by determining their particle size, shape, surface charge, and drug entrapment efficiency.

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MATERIALS AND METHODS

Materials:

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

Methods:

Chitosan nanoparticles were prepared using three antipsychotic drugs Quetiapine fumarate (QC), Ziprasidone HCL (ZC) and Paliperidone (PC) by ionic gelation method.

Chitosan-based nanoparticles preparation (CS-NPs):

Solutions of drug and polymer with drug and polymer in different ratios (1:1, 1:2, 1:3) were prepared by dissolving chitosan in 1% (v/v) glacial acetic acid and then the drug is added to the above solution with constant stirring on a magnetic stirrer at 1500 rpm for 30 min. To the above chitosan-drug solution, 5ml of aqueous TPP solution of different concentrations (0.75%, 1%, 1.25%) was added drop wise through a no.4 syringe needle. Then the solution was kept on constantmagnetic stirring (Remi Motors- RO-123, RPM- 1500) for 30 min, which led to the formation of nanoparticles. Subsequently, the pH was adjusted to 5.5 with the help of required amount of 1N HCl or NaOH. The nanoparticles were centrifuged at 12,000 rpm and at a temperature of 4ºC for 30 min using Eppendrof Ultracentrifuge 5430R to remove excessive amounts of TPP and unencapsulated drugs.

Table No. 1: Formulation consideration of chitosan nanoparticles with different concentration of TPP

S. No	Ingredients	QC1, ZC1, PC1	QC2, ZC2, PC2	QC3, ZC3, PC3
1	Drug: Polymer (Chitosan) mg	1:2	1:2	1:2
2	TPP (w/v)	0.75%	1%	1.25%
3	Tween 80 (v/v)	0.5%	0.5%	0.5%
4	Stirring speed (rpm)	1500	1500	1500

Table No. 2: Formulation consideration of chitosan nanoparticles with different concentration of Chitosan

S. No	Ingredients	QC4, ZC4, PC4	QC5, ZC5, PC5	QC6, ZC6, PC6
1	Drug: Polymer (Chitosan) mg	1:1	1:2	1:3
2	TPP (w/v)	1%	1%	1%
3	Tween 80 (v/v)	0.5%	0.5%	0.5%
4	Stirring speed (rpm)	1500	1500	1500

Characterization:

1. ***Shape and Surface Morphology:*** The shape and surface morphology of the chitosan naoparticles was visualized by scanning electron microscopy (SEM). 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.

2. ***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. 1ml 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.

3. ***Drug Entrapment Efficiency:*** The drug loaded nanoparticles were ultracentrifuged (Eppendrof) at 12,000 rpm and 4ºC for 30 min and the supernatant was assayed for non-bound drug concentration. The absorbance of the unencapsulated drug was determined in the supernatant using a UV-VIS spectrophotometer (UV-1800 Shimadzu) against plain chitosan nanoparticles as the blank which has also been prepared and treated similar to the drug-loaded nanoparticles. The analysis was carried out in triplicate and the mean was taken. The drug entrapment efficiency (EE) of the nanoparticles was calculated by the following equation.

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

RESULTS

Surface morphology, Particle size and Zeta potential measurement of nanoparticles:

The morphological characters of drug loaded chitosan nanoparticles were determined. The particles were round in shape with a smooth appearance as shown in Fig 3. The particle size and zeta potential of the chitosan nanoparticles were analyzed by HORIBA scientific nano Partica, nanoparticle analyzer SZ-100. Six formulations were prepared with various concentrations of chitosan and TPP. The values for the average particle size, zeta potential, and polydispersity index and encapsulation efficiency are tabulated in Table 3.

Table No. 3: The values for the average particle size, zeta potential, polydispersity index and entrapment efficiency

S. No.	Formulation	Average particle size ± S.D	Zeta Potential ± S.D	Polydispersity Index ± S.D	Entrapment Efficiency ± S.D
1	QC 1	181.5 ± 2.6	23.1 ± 0.2	0.24 ± 0.12	61±2.8
2	QC 2	88.1 ± 2.4	27.2 ± 0.8	0.33 ± 0.13	75±1.9
3	QC 3	114.5 ± 1.3	24.1 ± 0.1	0.54 ± 0.2	52±0.5
4	QC 4	191.1 ± 2.6	22.7 ± 0.6	0.44 ± 0.38	69±1.6
5	QC 5	73.0 ± 2.5	41.8 ± 0.3	0.34 ± 0.12	77±0.8
6	QC 6	211.2 ± 0.6	36.7 ± 0.6	0.44 ± 0.3	67±1.8
7	ZC 1	176.9 ± 0.8	27.1 ± 1.0	0.58 ± 0.28	51±0.4
8	ZC 2	91.1 ± 1.5	37.7 ± 0.6	0.28 ± 0.32	79±1.7
9	ZC 3	190.3 ± 2.1	27.5 ± 0.9	0.44 ± 0.24	55±1.1
10	ZC 4	182.7 ± 2.6	36.6 ± 1.4	0.39 ± 0.34	57±1.7
11	ZC 5	83.5 ± 3.5	28.7 ± 2.3	0.23 ± 0.29	77±1.3
12	ZC 6	291.3 ± 3.6	32.5 ± 0.2	0.44 ± 0.24	60±1.5
13	PC 1	178.5 ± 1.5	24.1 ± 0.6	0.24 ± 0.17	61±2.1
14	PC 2	93.1 ± 2.4	29.2 ± 0.7	0.41 ± 0.32	73±1.5

15	PC 3	195.5 ± 1.7	31.1 ± 0.1	0.34 ± 0.29	54±0.1
16	PC 4	161.1 ± 2.3	32.7 ± 0.6	0.21 ± 0.18	69±1.3
17	PC 5	89.2 ± 2.5	31.1 ± 0.5	0.49 ± 0.23	75±0.9
18	PC 6	221.5 ± 0.2	33.8 ± 0.2	0.34 ± 0.21	57±1.1

n=3; Values are mean ± standard deviation

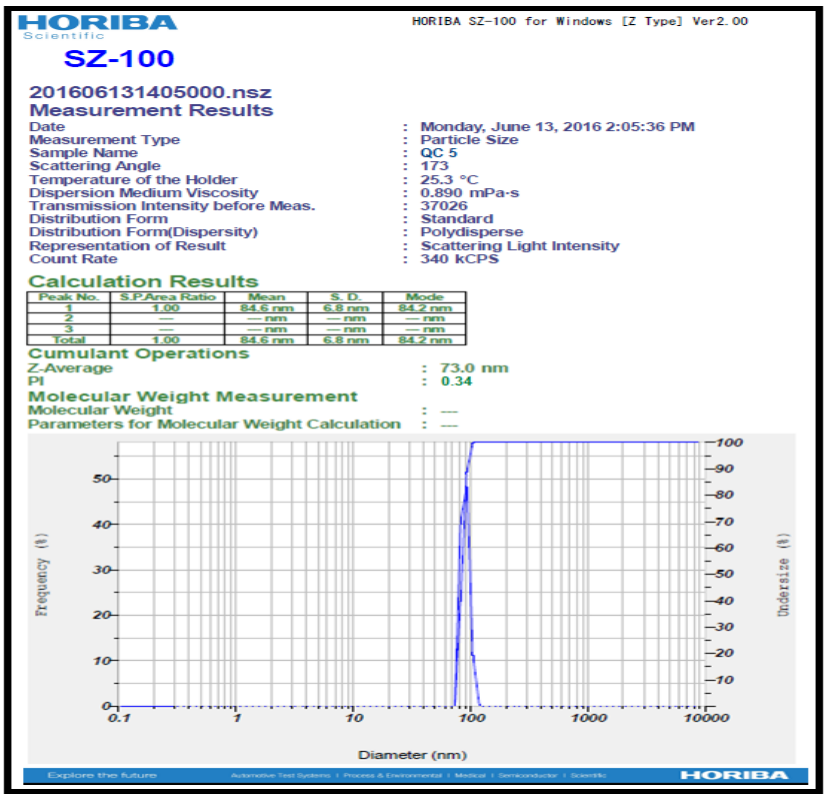

Fig. 1: Particle size analysis

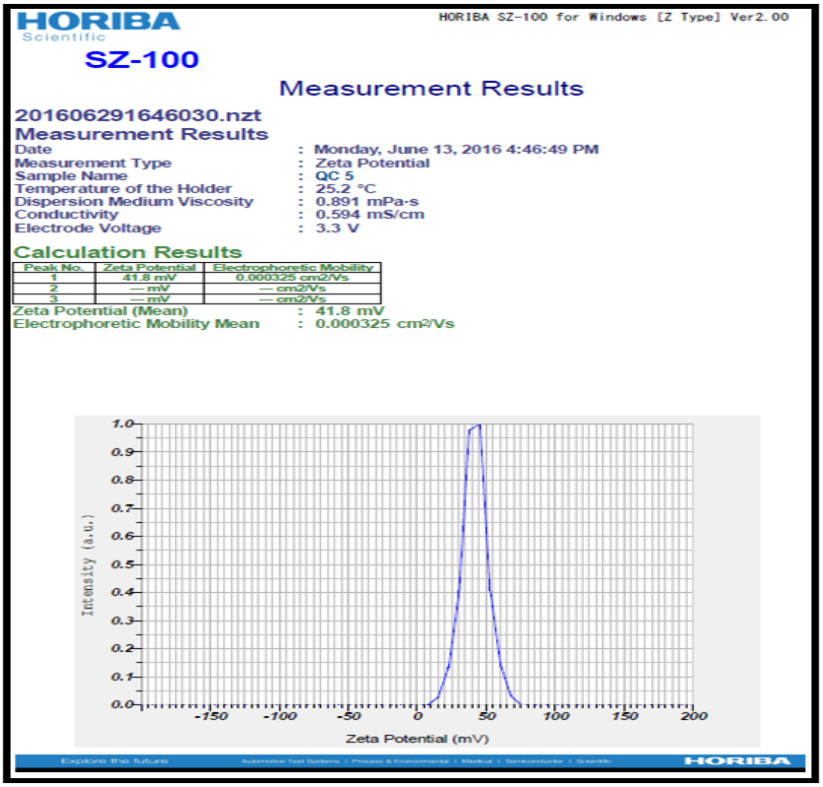

Fig. 2: Zeta potential analysis

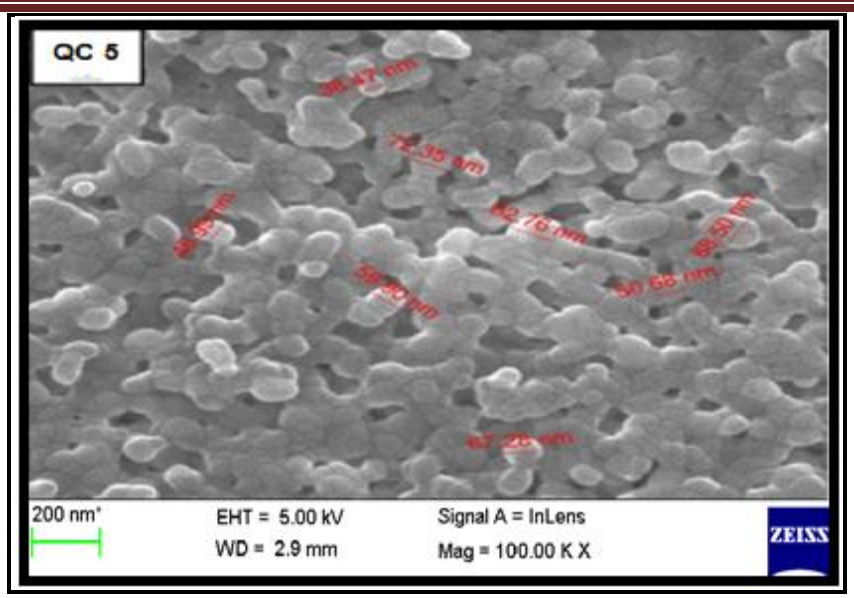

Fig. 3: SEM images of Quetiapine Fumarate (QC 5) loaded CS-NPs.

DISCUSSION

The drug loaded chitosan nanoparticles were successfully formulated by ionic gelation method using Quetiapin efumarate, Paliperidone and Ziprasidone HCL. The particle size distribution of prepared CS nanoparticles ranged from 73.0 ± 2.5nmto 291.3 ± 3.6 nm. By increasing the concentration of CS 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, the particle size increased. The zeta potential of the prepared CS nanoparticles was ranged from +22.7 ± 0.6 mV to +41.8 ± 0.3 mV. Zeta value increases with increase in the concentration of CS. The encapsulation efficiency of drug loaded CS-NPs ranged from 51±0.4%to 77±0.8%. By increasing the chitosan concentration increase in encapsulation was observed. The optimum formulation of Quetiapine fumarate (QP5) containing drug and polymer in the ratio of 1:2 with 1% TPP showed better results. The size of the nanoparticles was 73.0 ± 2.5 nm (Figure:1), zeta potential +41.8 ± 0.3 mV (Figure:2), indicated the good colloidal stability of the prepared CS-NPs. The encapsulation efficiency was 77±0.8%. Tween 80 also provides steric stabilization to the nanoparticles. For Paliperidone (PC5) and Ziprasidone HCL (ZC5) formulations, where drug and polymer in the ratio of 1:2 with 1% TPP showed better results. The particle size of nanoparticles was 89.2 ± 2.5 nm and 83.5 ± 3.5 nm, zeta potential +31.1 ± 0.5mV and +28.7 ± 2.3mV and encapsulation efficiency was 75±0.9% and 77±1.3%for Paliperidone (PC5) and Ziprasidone HCL (ZC5) respectively.

CONCLUSION

The drug loaded chitosan nanoparticles were successfully formulated by ionic gelation method using Quetiapine fumarate (QC5), Paliperidone (PC5) and Ziprasidone HCL (ZC5) and characterized using the HORIBA scientific nano Partica, nanoparticle analyzer SZ-100. Drug : polymer in the ratio of 1:2 with 1% TPP are considered as best formulations compared to other formulations as they showed better characteristics like particle size 73.0 ± 2.5 nm, 89.2 ± 2.5 nm and 83.5 ± 3.5 nm, zeta potential +41.8 ± 0.3 mV, +31.1 ± 0.5mV and +28.7 ± 2.3mV and encapsulation efficiency of 77±0.8%, 75±0.9% and 77±1.3% respectively. The shape and surface morphology of the drug loaded chitosan nanoparticles was visualized by scanning electron microscopy (SEM). The nanoparticles were spherical in shape and have a smooth surface.

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