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FORMULATION AND EVALUATION OF CARBOPLATIN NANOPARTICLES BY IONIC GELATION METHOD

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ABSTRACT

A new development namely, controlled drug release dosage forms, has involved from the need for a prolonged drug effect, a better control of drug administration and the reduction of side effects. The controlled release delivery systems are those which deliver the drug in controlled manner over a specific period of time, so as to maintain plasma drug concentration within the therapeutic range. Carboplatin, a derivative of cisplatin, has far less nonhematologic toxicity, although myelosuppression may be slightly greater than that observed with cisplatin. Chitosan is a modified natural carbohydrate polymer prepared by the partial N- biopolymer derived from crustacean shells such as crabs, shrimps and lobsters. The Intranasal route is considered for drugs that are ineffective orally are used chronically require small doses and where rapid entry into the circulation is desired. In Ionic gelation method the chitosan nanoparticle was prepared by using sodium triphosphate as the cross-linking agent. From the result of present experimental investigation, it may be concluded that formulation F4 containing drug with polymer ratio was showing small vesicle size with desired release of Carboplatin. Hence F4 formulation was the optimized formulation. The optimize formulation was found to follow zero order pattern.

KEYWORDS: Carboplatin, Chitosan, Nanoparticles, Ionic gelation method, Intranasal drug delivery

INTRODUCTION

Drugs are rarely administered as pure chemical substances alone and are almost always given as formulated preparations or medicines (i.e. drug delivery systems or dosage forms). These can vary from relatively simple solutions to complex drug delivery systems through the use of appropriate additives or excipients in the formulations .It is the formulation additives that, among other things, solubilize, suspend, thicken, preserve, emulsify, modify dissolution, and improve to form various acceptable preparations or dosage forms[1,2]. Before a drug substance can be successfully formulated into a dosage forms, many factors must be considered. These can be broadly grouped into the following three categories.

• Biopharmaceutical considerations, including factors affecting the absorption of the drug substances from different administration routes.

• Drug factors, such as the physical and the chemical properties of the drug substances.

• Therapeutic considerations include consideration of the clinical indication to be treated and patient factors. High-quality and efficacious medicines will be formulated and prepared only when all these factors are considered and related to each other. This is the underlying principle of dosage form design. The goal is to

provide a therapeutic quantity of medicine(s) to the proper site in the body in order to achieve the desired effect and maintain such effect for the entire period of treatment. Hence, research continuously keeps on searching for ways to deliver drugs over an extended period of time, with a well-controlled release profile[4,5]. A new development namely, controlled drug release dosage forms, has involved from the need for a prolonged drug effect, a better control of drug administration and the reduction of side effects. In conventional drug delivery systems, the drug concentration in the blood rises when the drug is being administered, then peaks and declines almost to zero. Each individual drug has a maximum safe concentration and a minimum effective concentration. Fluctuations in plasma concentration may mean that drug levels may swing too high leading to toxic effects alternatively drug may fall too low leading to a lack of efficacy. Furthermore, the plasma drug concentration in a patient at a particular time depends on the compliance with the prescribed dosage interval. The controlled release delivery systems are those which deliver the drug in controlled manner over a specific period of time, so as to maintain plasma drug concentration within the therapeutic range[7]. The controlled release formulations offer numerous advantages over the conventional dosage forms which includes,

- Therapeutic Reduction in dosage frequency,
- Minimizing the adverse effects of the drug, by localizing it in the specific target area,
- Maintaining plasma concentration of the drug within range,
- Increasing efficiency of drug and provides better patient compliance and convenience.

These dosage forms could also preserve medications that are rapidly destroyed by the body.

Chitosan

Chitosan is a modified natural carbohydrate polymer prepared by the partial N- biopolymer derived from crustacean shells such as crabs, shrimps and lobsters. Chitosan is also found in some microorganisms, yeast and fungi[9,10]. The primary unit in the chitin polymer is 2-deoxy-2- (acetyl amino) glucose. These units combined by ß-(1,4) glycosidic linkages, forming a long chain linear polymer. Although chitin is insoluble in most solvents, chitosan is soluble in most organic acidic solutions at pH less than 6.5 including formic, acetic, tartaric and citric acid. It is insoluble in phosphoric and sulfuric acid. Chitosan is available in a wide range of molecular weight and degree of deacetylation. Molecular weight and degree of deacetylation are the main factors affecting the particle size, particles formation and aggregation. In this project ionic gelation method is used for the formulation of nanoparticles. Preparation methods of chitosan (CS) micro/nanoparticles: Different methods have been used to prepare CS particulate systems. Selection of any of the methods depends upon factors such as particle size, thermal and chemical stability of the active agent, reproducibility of the release kinetic profiles, stability of the final product and residual toxicity associated with the final product. Different methods used in the preparation of CS micro/nanoparticles are discussed. However, selection of any of these methods depends upon the nature of the active molecule as well as the type of the delivery device[13].

Methods:

- Microemulsion method
- Coacervation/precipitation method
- Spray drying technique
- Emulsion droplet coalescence method
- Ionic Gelation method
- Reverse micellar method

Advantages of Nanoparticulate Drug Delivery System

- Simple and inexpensive to manufacture and scale-up.
- Reproducible and stable.
- Applicable to a broad category of drugs; small molecules, proteins and polynucleotides
- Ability to lyophilize
- Stable after administration
- Non-toxic

Pulmonary Drug Delivery System

The major function of the pulmonary system is the oxygenation of blood and the removal of carbon dioxide from the body. Breathing ventilates the respiratory tissue leading to gaseous exchange in the lungs. The

tissue is therefore specialized to present the largest available surface are within the protection of the thoracic cavity. The large oxygen requirement is necessary to support the high metabolic rate of mammals. The respiratory system in man is divided into the upper and lower respiratory tracts. The upper respiratory tract consists of the nose, nasal passages, paranasal passages, mouth, Eustachian tubes, the pharynx, the oesophages and the larynx. The trachea and bronchi are sometimes included as part of the upper respiratory tract. The lower respiratory tract consists of the true respiratory tissue, i.e. the air passages and alveoli[15,16]. Intranasal drug delivery. This route is considered for drugs that are ineffective orally are used chronically require small doses and where rapid entry into the circulation is desired. The rate of diffusion of the compounds through the nasal mucous membranes like other biological membranes is influenced by the physic chemical properties of the compound. However, *In-vivo* nasal absorption of compounds of molecular weight less than 300 is not significantly influenced by the physicochemical properties of the drug. Factors such as the size of the molecule and the ability of the compound to hydrogen bond with the component of the membrane are more important than lipophilicity and ionization state. The absorption of drugs from the nasal mucosa most probably takes place via the aqueous channels of the membrane[19-22]. Therefore, as long as the drug is in solution and the molecular size is small, the drug will be absorbed rapidly via the aqueous path of the membrane. The absorption from the nasal cavity decreases as the molecular size increases.

Carboplatin

Carboplatin, a derivative of cisplatin, has far less nonhematologic toxicity, although myelosuppression may be slightly greater than that observed with cisplatin. Carboplatin predominantly acts by attaching alkyl groups to the nucleotides, leading to the formation of monoadducts, and DNA fragmenting when repair enzymes attempt to correct the error. 2% of carboplatin's activity comes from DNA cross-linking from a base on one strand to a base on another, preventing DNA strands from separating for synthesis or transcription. Finally, carboplatin can induce a number of different mutations.

Applications : Neuroblastoma stage IV, Neuroectodermal tumors, Medulloblastoma, Rhabdomyosarcoma, Sarcoma, Germ cell tumor, Glioma, Astrocytoma, Retinoblastoma, Wilms Tumor, Liver tumors.

MATERIALS AND EQUIPMENTS :

Carboplatin was a drug used to prepare the nanoparticle formulation which was purchased from Aarti industries, Boiser. The polymer like chitosan and poly {lactic co-glycolic acid} were purchased from sigma chemical company, USA. Then the excipients like Sodium tripolyphosphate, disodium hydrogen phosphate, potassium dihydrogen phosphate & sodium chloride were purchased from Sisco research laboratories PVT Ltd, Mumbai and S.D fine chemicals, Chennai.

Sartorius digital balance, Remi mechanical stirrer and Sigma ultra centrifuge were used as an equipment for the experiment. Then, further FT- IR with the model of Thermo Nicolet 320 avatar, UV Spectrophotometer with the model of Perkin Elmer lambda were used for the experiment. For the evaluation of structural morphology, the instrument Jeol version 1.1 JSM 6360, Japan were used and sonoplus sonicator is used for sonication[23].

EXPERIMENTAL METHODS

Preparation of Stock solution:

The standard stock solution was prepared by dissolving carboplatin in 0.1N HCl to make final concentration of 200µg/ml. Different aliquots were taken from the stock solution and diluted with 0.1N HCl separately to make series of concentration and the absorbance was measured at 276 nm.

Ionic Gelation Method

The use of complexation between oppositely charged macromolecules to prepare CS microspheres has attracted much attention because the process is very simple and mild. In addition, reversible physical cross linking by electrostatic interaction, instead of chemical cross linking, has been applied to avoid the possible toxicity of reagents and undesirable effects. Tripolyphosphate (TPP) is a polyanion, which can interact with the cationic CS by electrostatic forces. In the ionic gelation method, CS is dissolved in aqueous acidic solution to obtain the cation of CS. This solution is slowly added dropwise under constant stirring to polyanionic TPP solution. Due to complexation between oppositely charged species, CS undergoes ionic gelation and precipitates to form spherical particles[25]. However, TPP/CS microspheres formed have poor

mechanical strength thus limiting their usage in drug delivery.

PARTICLE SIZE MEASUREMENT

The particle size distribution of the white nanoparticles powder (F4) was determined by laser diffraction method using Microtrac Particle Size Analyzer (Bluewave model S4521). The samples were dispersed in the volume of water and the sizes of the nanoparticles were scanned by the refractive index at 30s run time.

DRUG CONTENT ESTIMATION

Yield of Nanoparticles was obtained by dividing the theoretical weight of polymer and drug used by the weight of nanoparticles obtained. The encapsulation efficiency was determined as follow, an accurately weight number of Nanoparticles was sonicated for 25 min. and centrifuged at 19000 rpm for 20 min. the absorbance of the supernatant was measured at 276 nm for Carboplatin.

The loading capacity and encapsulation efficiency were calculated as indicated below.

$$\text{Loading capacity} = \frac{\text{Total amount of Carboplatin– free Carboplatin}}{\text{Weight of nanoparticles}} \times 100$$

$$\text{Encapsulation efficiency} = \frac{\text{Total amount of Carboplatin– free Carboplatin}}{\text{Total amount of nanoparticles}} \times 100$$

In-Vitro Release Studies

In order to determine the Carboplatin release from chitosan NPs the drug – diffusion profile of the loaded copolymer nanoparticles was studied using dialysis membrane-70 (LA 3935MT, Himedia Laboratory Pvt. Ltd, Mumbai) The releases of the drug TP from Chitosan NPs were studied in pH 7.4 phosphate buffer. Drug loaded nanoparticles was placed in a dialysis membrane, and to this a little amount of dissolution medium was added, which was then sealed at both the ends. The dialysis bag was dipped into the receptor compartment containing the dissolution medium, which was stirred continuously at 100 rpm maintained at 37° C. The receptor compartment was closed to prevent evaporation of the dissolution medium. Samples were withdrawn at regular time intervals and the same volume was replaced with fresh dissolution medium. The samples were measured by UV Spectrophotometer at 276 nm against dummy nanoparticles as reagent blank which had also been prepared and treated similar to the drug loaded nanoparticles.

Drug Release Kinetics

Zero order kinetics: The diffusion model of Carboplatin nanoparticles follows zero order kinetics. The graph is plotted time vs cumulative %drug release.

Higuchi plot: The graph is plotted on square root of time Vs cumulative % drug release.

RESULTS AND DISCUSSION

Preparation of Calibration Curve :

The standard stock solution was prepared by dissolving carboplatin in 0.1N HCl to make final concentration of 200µg/ml. Different aliquots were taken from the stock solution and diluted with 0.1N HCl separately to make series of concentration and the absorbance was measured at 276 nm.

Table 1: Absorbance of Carboplatin

S.No.	Concentration (µg/ml)	Absorbance at 276 nm
1.	20	0.1062
2.	40	0.1892
3.	60	0.2900
4.	80	0.3870
5.	100	0.4822

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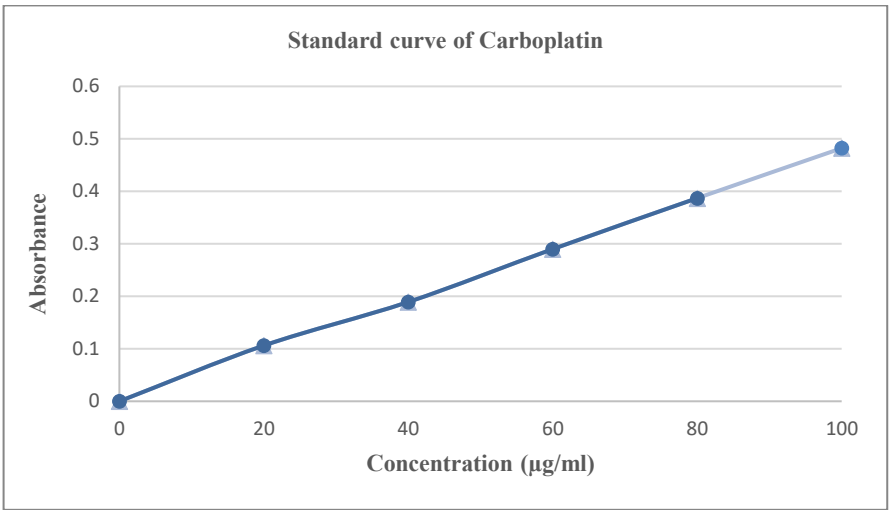

Figure 1: Standard curve of Carboplatin

Table 2: Composition of Carboplatin

S.No.	FORMULATION	DRUG (mg)	WATER SOLUBLE CHITOSAN (mg)	TPP (mg/ml)	PLGA (mg/ml)
1	F-1	20	10	4	0.25
2	F-2	20	20	4	0.25
3	F-3	20	30	4	0.25
4	F-4	20	40	4	0.25
5	F-5	20	50	4	0.25
6	F-6	20	60	4	0.25
7	F-7	20	70	4	0.25

Particle size analysis:

Particle size analysis was performed using laser diffraction method. Particle size was seems to be dependent on the method of preparation, chitosan concentration, etc. The particles prepared by ionic gelation method were in the range of 76 nm – 190 nm (Fig 14). Thus the method shows, as concentration of chitosan increases the particle size decreases.

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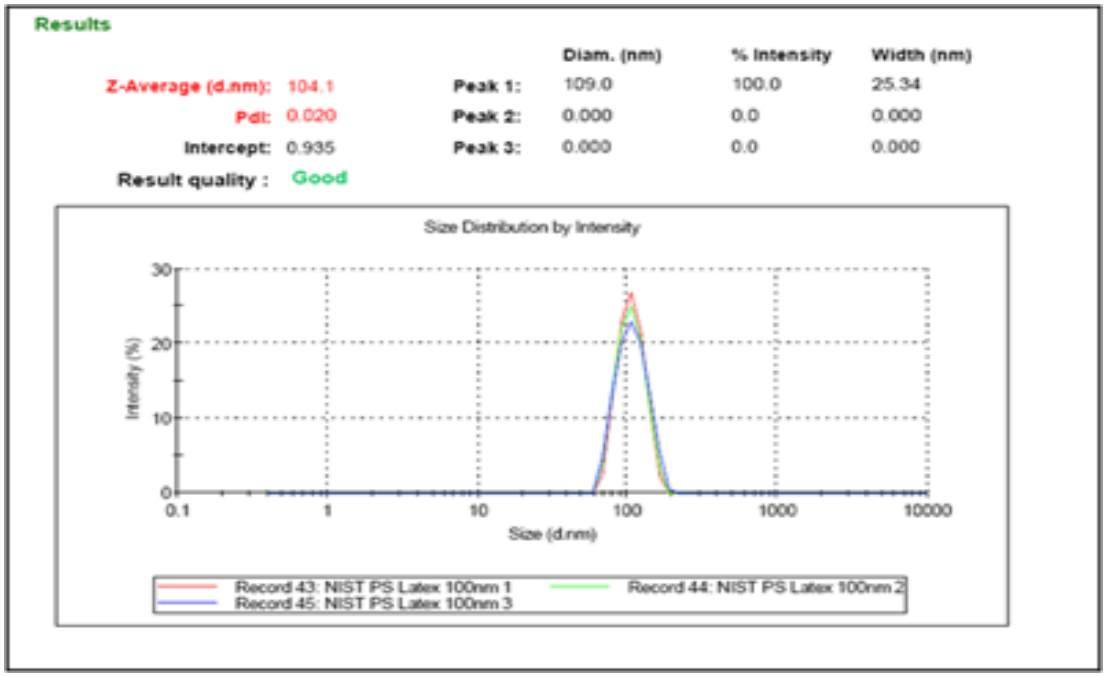

Figure 2: Measurement of Particle Size

SEM Analysis

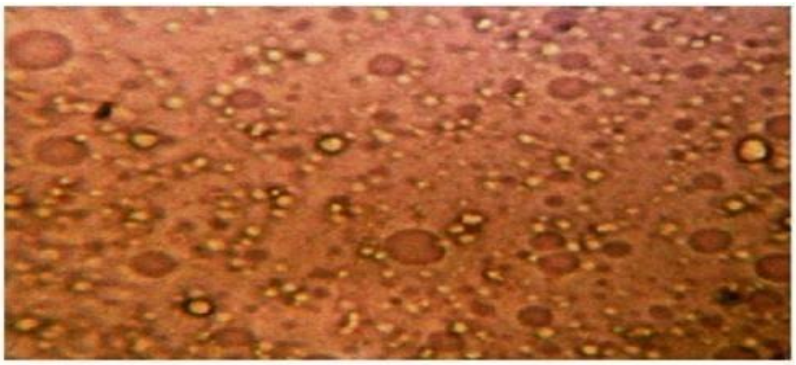

Figure 3: SEM image of Carboplatin loaded Chitosan Nanoparticles

Drug loading and entrapment efficiency:
The drug loading capacity was found to be between 70.19 and 78.53 % for the particles prepared by ionic gelation method (Table 9). Increasing the polymer amount leads to increase in chitosan concentration and viscous nature of the gelation medium.

Table 3: Entrapment efficiency

S.No.	FORMULATION	PERCENTAGE DRUG LOAD (W/W)
1	F1	77.53
2	F2	75.82

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3	F3	73.68
4	F4	70.19
5	F5	68.23
6	F6	65.12
7	F7	64.38

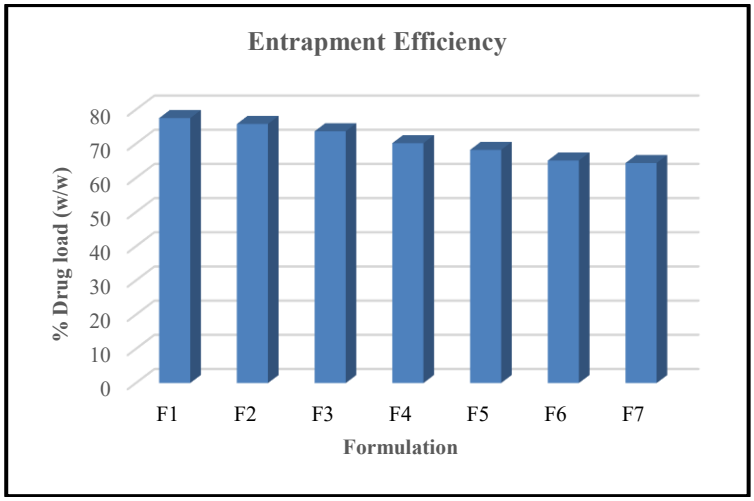

Figure 4: Entrapment efficiency

In-Vitro Drug Release Study

Table 4 : Comparative drug release of formulations

Time (hrs)	Cumulative Percentage Drug Release (%)						
	F1	F2	F3	F4	F5	F6	F7
0	0	0	0	0	0	0	0
2	12.18	14.72	15.97	16.54	16.98	15.47	14.87
4	25.13	29.13	31.62	32.07	36.87	39.76	30.65
6	36.26	38.72	43.72	47.9	49.98	50.86	41.32
8	49.52	52.37	56.43	62.80	65.34	66.09	59.05
10	62.81	64.42	69.11	75.49	73.76	72.78	71.54
12	68.63	71.89	76.03	88.12	87.52	85.38	83.92

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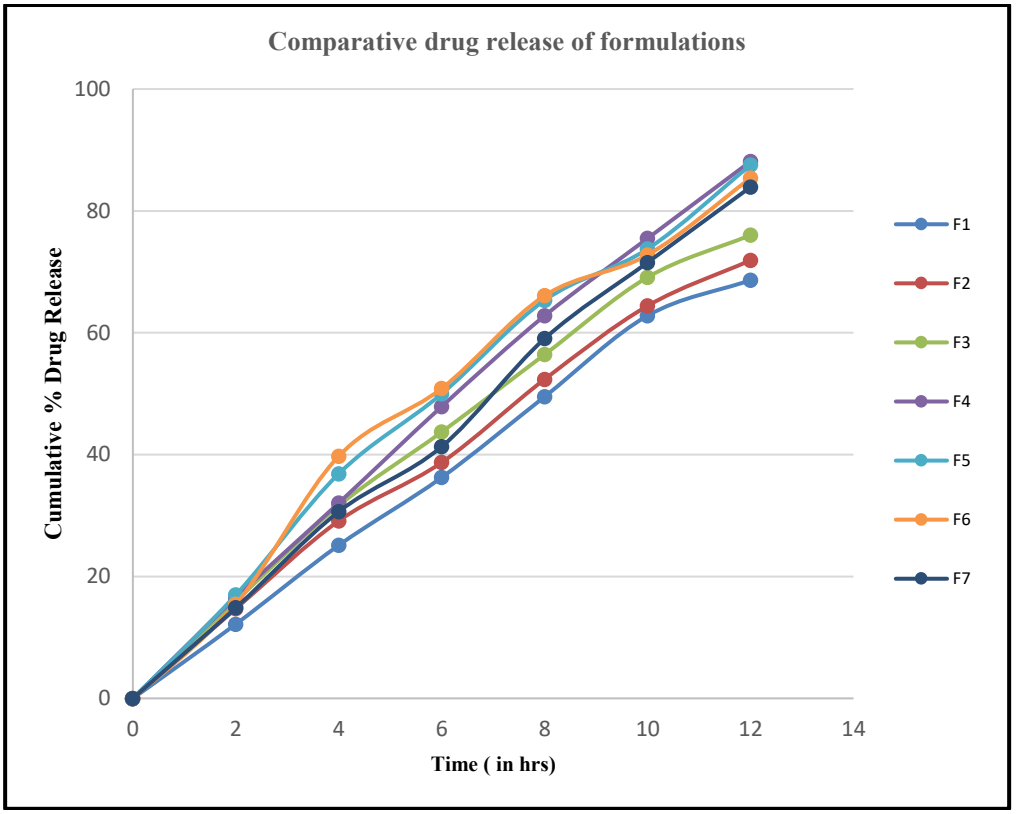

Figure 5: Comparative drug release of formulations

In vitro drug release was studied for all 7 formulations. The studies were performed upto 12 hours for all formulations. The cumulative percentage release of formulation (F1, F2, F3, F4, F5, F6, F7) were found to be 68.63%, 71.89%, 76.03%, 82.19%, 87.52%, 85.38%, 83.92%.

As the concentration of chitosan water soluble polymer increases, the drug release gets decreases due to slow release of drug from the entrapped vesicles

The optimized formulation F4 has high amount of drug release due to good entrapment efficiency.

Drug Release Kinetics

Table 5: Zero Order Kinetics

S.No.	TIME (IN HOURS)	CUMULATIVE % DRUG RELEASE
1	0	0
2	2	16.54
3	4	32.07
4	6	47.9
5	8	62.80
6	10	75.49
7	12	82.19

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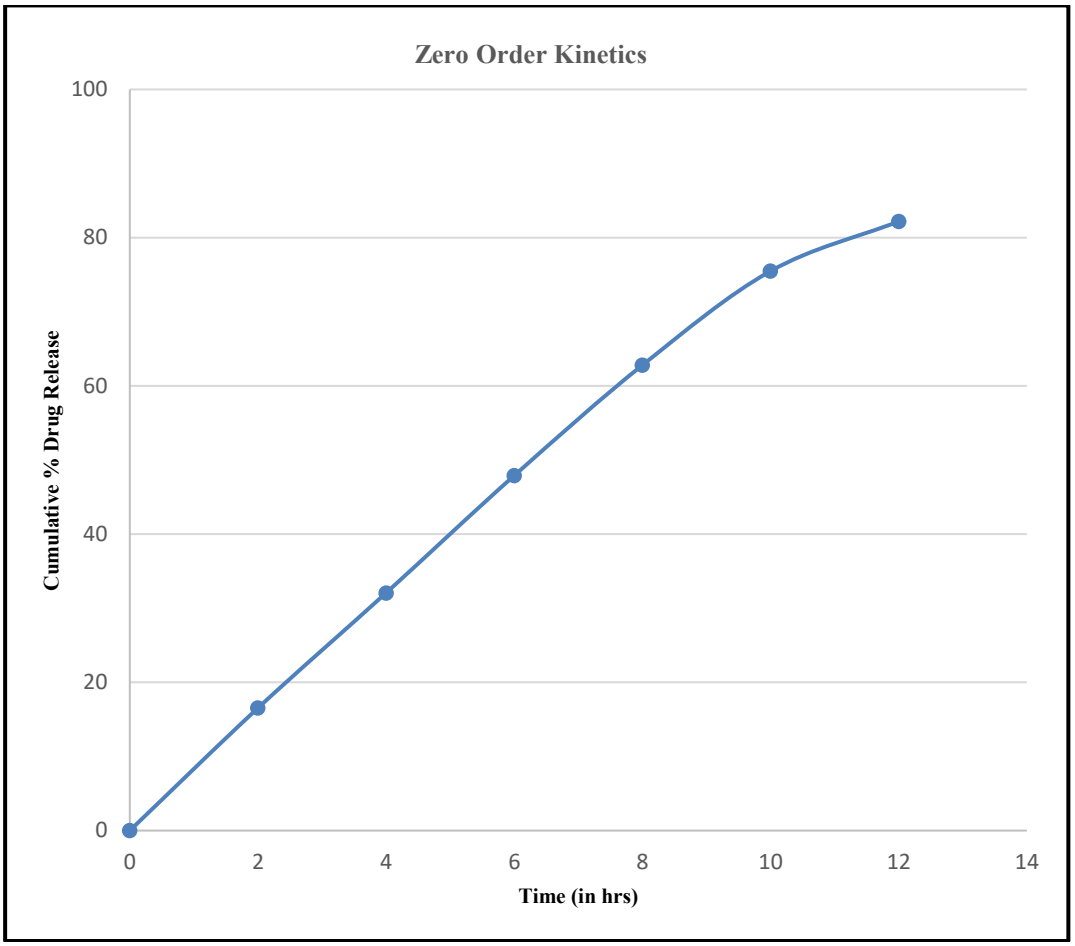

Figure 6: Zero order Kinetics

Table 6: Higuchi Plot

S.No.	Time (In Square)	Cumulative % Drug Release
1	0	0
2	4	16.54
3	16	32.07
4	36	47.9
5	64	62.80
6	100	75.49
7	144	82.19

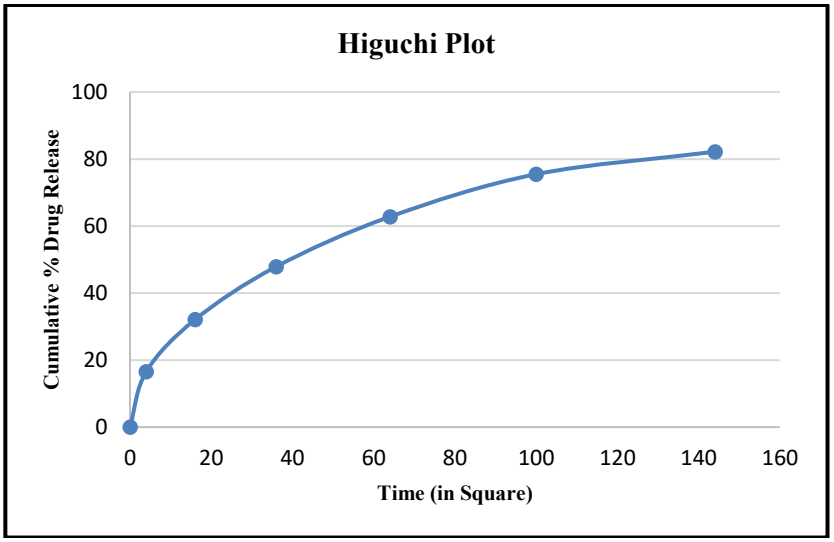

Figure 7: Higuchi plot

Kinetics Studies

ZERO ORDER KINETICS	HIGUCHI PLOT
R^2	R^2
0.99	0.96

Table 14: Kinetic studies

SUMMARY AND CONCLUSION

In this study we have taken effort to prepare nanoparticle formulation by ionic gelation method. In the Pre formulation studies the compatibility of the drug with polymer was evaluated by FT-IR techniques, it was found that carboplatin was compatible with chitosan. In Ionic gelation method the chitosan nanoparticle were prepared by using sodium triphosphate as the cross linking agent. From the result of present experimental investigation it may be concluded that formulation F4 containing drug with polymer ratio was showing small vesicle size with desired release of Carboplatin. Hence F4 formulation was the optimized formulation. The optimize formulation was found to follow zero order pattern. So we can conclude that nanoparticles could be used as drug carrier for carboplatin also to sustain the effect for longer duration.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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