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FORMULATION DEVELOPMENT AND IN-VITRO EVALUATION OF TETRAZOSIN LOADED CHITOSAN NANOPARTICLES FOR THE TREATMENT OF HYPERTENSION

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ABSTRACT

The purpose of this research was to prepare Tetrazosin loaded Chitosan Nanoparticles for controlled release of drug, to improve the solubility, reduce the dosing frequency, thereby increasing patient compliance to the therapy. Tetrazosin is formulated as Nanoparticles by ionic-gelation method using Chitosan as polymer, Sodium tripolyphosphate as a polyanionic agent (cross linking agent) and the lyophilized nanoparticles filled in hard gelatin capsules. The particle size analysis was done by Horriba scientific Nano SZ 100 particle size analyzer showed that mean particle size 188.3 nm and Z- Average 229.0 nm respectively. The Zeta potential study was done by Horriba scientific Nano SZ 100. The Zeta potential for the optimized formulations F5 was found to be 25.8mV and shows that the formulation is stable. Post formulation parameters (uniformity of weight, disintegration test, drug content, and in vitro drug release) for nano particulate capsules were evaluated. The results were found to be complying with official specifications. The dissolution data of the optimized formulation was fitted to various kinetic models and the formulation F5 was best fitted to Zero order kinetics. The slope of the Korsmeyer Peppas plot indicating the diffusion was Anomalous diffusion (Non-Fickian diffusion). From the overall results, it is clear that the formulations F5 containing 0.3% polymer concentration (Chitosan) is the optimal formulation, as it produces controlled drug release.

KEYWORDS: Chitosan Nanoparticles, particle size Zeta potential, kinetic study, Non-Fickian diffusion.

INTRODUCTION

A drug delivery system (DDS) is defined as a formulation or a device that enables the introduction of a therapeutic substance in the body and improves its efficacy and safety by controlling the rate, time and place of release of drugs in the body. This process includes the administration of the therapeutic product, the release of the active ingredients by the product, and the subsequent transport of the active ingredients across biological membrane.[1]

The objective of any drug delivery system is to deliver a therapeutic amount of drug to the sites of action and to maintain the desired amount of drug level in the tissue or the body that can elicit a desired pharmacological effect without causing any serious adverse reactions.

A perfect drug delivery system possesses two elements: the capacity to target and to control the release of drug. Targeting will ensure high efficiency of the drug and reduce the side effects, especially when dealing with drugs that are presumed to kill cancer cells but can also kill healthy cells when delivered to them. The side effects can be reduced or prevented by the control of drug release.[2]

Drawbacks associated with conventional dosage forms[3]

An ideal dosage regimen in the drug therapy of any disease is one which immediately attains the desired therapeutic concentration of drug in plasma and maintains it constant for the entire duration of treatment. This is possible through the administration of drug delivery system in a particular dose and at particular frequency. The frequency of administration or dose interval of any drugs depends upon its life or mean residence time and its therapeutic index. In most cases, dosing interval is much shorter than the half-life of the drug, resulting in number of limitations associated with such a conventional dosage form which are, A drug with short biological half-life which needs a close succession.

The uncontrolled fluctuation of drug level may leads to either below effective range or over the effective range.

Plasma concentration verses time profile of dosage form and it is difficult to achieve the steady state active drug level. The rise and fall of drug levels may give to accumulation of adverse effects, especially for a drug having less therapeutic index. To overcome the above

drawbacks, drug delivery system capable of controlling the rate of drug delivery, sustain the duration off therapeutics action or targeting the drug to a particular tissue was developed.

Terazosin is a member of quinazolines, a member of piperazines, a member of furans and a primary amino compound. It has a role as an antineoplastic agent, an antihypertensive agent and an alpha-adrenergic antagonist. It is chemically known as [4-(4-amino-6,7-dimethoxyquinazolin-2-yl)piperazin-1-yl]-(oxolan-2-yl)methanone.

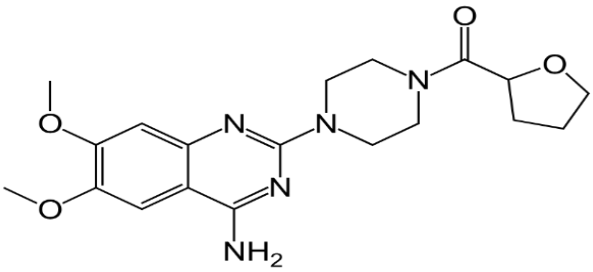

Fig. 1: Structure of Terazosin.

MATERIALS AND METHODS

Materials Used In Formulation

Tetrazosin collected from Active pharmaceutical, Bangalore; Chitosan 50k, Acetic acid, Sodium tripolyphosphate, Ethanol, Sodium Hydroxide and Distilled Water from Lab Chemicals, Chennai**,** and Potassium dihydrogen phosphate were collected from Merck specialities Pvt. Ltd, Mumbai.

Determination of Melting point[68]

The melting point of Tetrazosin was determined by the capillary tube method as per USP. A Sufficient quantity of Tetrazosin powder was filled into the capillary tube to give a compact column of 4-6 mm in height. The tube was introduced in electrical melting point apparatus and the temperature was raised. The temperature at which the last solid particle of Tetrazosin in the tube passed into liquid phase was noted as melting point.

Preparation of 6.8 pH Phosphate buffer[69]

0.2M solution of potassium dihydrogen phosphate was prepared by dissolving 27.218gm of substance in 1000ml of distilled water.0.2M solution of sodium hydroxide solution was prepared by dissolving 8gm of substance in 1000 ml of distilled water. 250 ml above prepared potassium dihydrogen phosphate solution & 112 ml of sodium hydroxide solution were mixed together and made up to 1000ml and pH was adjusted to 6.8.

Determination of lambda max (λ_{max})[32]

100 mg of Tetrazosin was weighed and transferred to 100ml of volumetric flask. The drug was dissolved in 10 ml of ethanol and volume was made up to 100ml using phosphate buffer pH 6.8 to obtain a stock solution of 1000µg/ml (stock solution I). 10ml of this stock solution was again diluted with phosphate buffer pH 6.8 up to 100ml to obtain a solution of 100µg/ml (stock solution II). From the stock solution-II, 10 ml was pipette out in 100ml volumetric flask. The volume was made up to 100 ml using phosphate buffer pH 6.8 get a concentration of 10µg/ml. this solution was then scanned at 200-400nm in UV-Visible spectrophotometer to attain the absorption maxima (λ_{max}).

Standard curve for Tetrazosin[33]

100 mg of Tetrazosin was weighed and transferred to 100ml of volumetric flask. The drug was dissolved in 10 ml of ethanol and volume was made up to 100ml using phosphate buffer pH 6.8 to obtain a stock solution of 1000µg/ml (stock solution I). 10ml of this stock solution was again diluted with phosphate buffer pH 6.8 up to 100ml to obtain a solution of 100µg/ml (stock solution II). From the stock solution-II 2, 4,6,8,10,12 ml were transferred to series of 100 ml volumetric flasks. The volume was made up with phosphate buffer pH 6.8. The absorbance of these solutions was measured at 268nm against the blank.

Solubility studies of pure Tetrazosin[70]

Solubility of Tetrazosin pure drug was tested in distilled water and phosphate buffer pH 6.8. An excess amount of Tetrazosin pure drug was added in the pertinent media. The mixtures were stirred in a mechanical shaker at speed 50 rpm for 24 hours and the temperature was maintained at 37±0.5ºC. Visual inspection was carefully made to ensure there were excess Tetrazosin solids in the mixture, indicating saturation had been reached. Then the mixtures were filtered using 0.45µm filter and filtrates were suitably diluted with same media. The absorbance of the solution was measured at 268nm in UV-Visible spectrophotometer.

Formulation Development

Preparation of Chitosan Nanoparticles – Ionic gelation Method[4,5,6]

The preparation of Chitosan nanoparticles was based on ionic interaction between positively charged Chitosan solution and negatively charged STPP solution, with and without drug and it was prepared in the presence of Tween 80 as a re-suspending agent to prevent particle aggregation, at ambient temperature while stirring and Chitosan solution were raised to pH 4.6 to 4.7. Seven formulations (F1,F2,F3,F4,F5,F6,F7) of Tetrazosin loaded Chitosan

nanoparticles were prepared by dissolving Tetrazosin in 30ml of Chitosan with varying concentrations (0.1,0.15,0.2,0.25,0.3,0.4,0.5%w/v) containing 0.5% w/v tween 80, TPP(0.1%w/v) was added drop wise under magnetic agitation(1000 rpm).The formed nanoparticle suspensions were lyophilized at -40^{o}C for 24hrs.

Table No.1: Composition of Nanoparticles.

Formulation	Chitosan (%w/v)	1% Aqueous acetic acid (ml)	Chitosan	DRUG (mg)	TWEEN 80 (%w/v)	TPP (%w/v)	Distilled water	TPP (mg)
F_1	0.10%	30ml	30	20	0.5	0.1	30	30
F_2	0.15%	30 ml	45	20	0.5	0.1	30	30
F_3	0.20%	30 ml	60	20	0.5	0.1	30	30
F_4	0.25%	30 ml	75	20	0.5	0.1	30	30
F_5	0.30%	30 ml	90	20	0.5	0.1	30	30
F_6	0.40%	30 ml	120	20	0.5	0.1	30	30
F_7	0.50%	30 ml	150	20	0.5	0.1	30	30

Characterization of tetrazosin loaded chitosan nanoparticle

Percentage yield[43]

The nanoaparticle yield was calculated according to the equation given below.

$$\text{Percentage yield (\%)} = \frac{\text{Practical yield}}{\text{Theoretical Yield}} * 100$$

Determination of Drug Content

Equivalent to 60 mg of the prepared formulation were weighed and dissolved in minimum quantity of ethanol mixture and made up to 100ml with phosphate buffer pH 6.8. The solution kept for 24 hours and filtered to separate fragments. Drug content was analyzed after suitable dilution by UV- Visible spectrophotometer at a wave length 268nm against phosphate buffer pH 6.8 as blank. From the absorbance the drug content in the batches were calculated.

Drug entrapment efficiency

For the determination of drug entrapment, the nanosuspension with known amount of drug was centrifuged at 4000 rpm for 15 minutes. The supernatant solution was separated. 5ml of supernatant was distributed with 100ml of phosphate buffer solution pH 6.8 and the absorbance was measured using UV-Visible spectrophotometer at 268nm using of phosphate buffer solution pH 6.8 as blank. The amount of drug unentrapped was calculated. The

percentage of entrapment efficiency was determined according to the following equation given below.

$$\% \text{ Drug Entrapment} = \frac{\text{total amount of drug} - \text{amount of unbound drug}}{\text{total amount of drug}} \times 100$$

Solubility Studies of Tetrazosin loaded Chitosan Nanoparticle

The solubility of the Tetrazosin loaded Chitosan nanoparticles formulations were tested in various medium (distilled water and phosphate buffer pH 6.8) by adding an excess amount of formulations. The mixtures were stirred in a mechanical shaker at speed 50 rpm for 24 hours at room temperature. Visual inspection was carefully made to ensure there were excess Tetrazosin solids in the mixture, indicating saturation had been reached. Then the mixtures were filtered using 0.45µm filter and filtrates were suitably diluted with same media. The absorbance of the solution was measured at 268nm in UV-Visible spectrophotometer.

***In vitro* drug release studies**

The *in vitro* release rate studies of Tetrazosin loaded Nanoparticles formulations were carried out by dissolution test apparatus USP Type-I (Basket). Tetrazosin loaded Chitosan Nanoparticles were filled in capsule and placed in a dissolution medium and rotated at 100rpm. 10 ml of samples were withdrawn predetermined intervals up to 12 h and replaced with equal amount of phosphate buffer pH 6.8 for further dissolution testing the absorbance determined by spectrophotometrically at 268nm.

FTIR study of optimized formulations

FT-IR spectra of optimized formulations of Chitosan Nanoparticle were recorded by grinding and dispersing the samples with micronized IR grade Potassium bromide powder and subjected to FT-IR measurement over the range of 4000- 400cm^{-1}.

Surface Morphology by SEM analysis

The Surface Morphology of the Chitosan nanoparticle can be measured by SEM at Anna University (Model Vega3 – Tescan, USA). Scanning Electron Microscopy was used to analyse particle size, shape and surface morphology of Nanoparticles. The sample was mounted directly onto the SEM sample holder using double sided sticking tape and image were recorded at different magnification at acceleration voltage of 10 kv using scanning electron microscope.

Particle size characterization

The samples of the optimized formulations were analyzed for their particle size using Horiba Scientific SZ-100 particle size analyzer, Particle size (Z-average diameter), Polydispersity index (as a measure of the width of the particle size distribution) of Tetrazosin loaded Chitosan Nanoparticles dispersion is performed by dynamic light scattering also known as photon correlation spectroscopy (PCS) using a Horiba Scientific Nano SZ-100 at 25°C.

Prior to measurements all samples were diluted using ultra – purified water to yield a suitable scattering intensity. The diluted nanoparticles dispersion was poured into the disposable sizing cuvette which is then placed in the cuvette holder of the instrument and analyzed. Air bubbles were removed from the capillary before measurement.

Polydispersity Index (PDI)

PDI indicates the width of the particle size distribution, which ranges from 0 to1. Monodisperse samples have a lower PDI value, whereas higher PDI value indicates a wider particle size distribution and the polydisperse nature of the samples can be calculated by following equation:

$$\mathbf{PDI = d/d\ avg}$$

Where,

d is the width of distribution donated by SD

d avg is the average particle size denoted by MV (nm) in particle size data sheet.

Zeta potential

Zeta Potential is a crucial factor to evaluate the stability of colloidal dispersion surface charge on the Tetrazosin loaded chitosan NPs were determined using Horiba Scientific Nano ZS100. 1 ml of sample of Tetrazosin suspension was filled in clear disposable zeta cell ensured there was no air bubble within the sample and the system was set at 25°C temperature and the test can be carried.

RELEASE KINETICS OF THE OPTIMIZED FORMULATIONS

Different kinetic models such as zero order (cumulative amount of drug released vs. time), first order (log cumulative percentage of drug remaining vs. time), Higuchi model (cumulative percentage of drug released vs. square root of time), Korsmeyer-Peppas model and Hixson Crowell model were applied to interpret the drug release kinetics from the

formulations. Based on the highest regression values for correlation coefficients for formulations, the best- fit model was decided.

To study the *in vitro* release kinetics of the optimized formulation, data obtained from dissolution study were plotted in various kinetics models.

- Zero-order
- First-order
- Higuchi
- Hixson-Crowell cube root law
- Korsmeyer-Peppas model

RESULTS AND DISCUSSION

Pre-Formulation Studies

The optimization of a formulation can be done only after a thorough investigation of its physicochemical properties of the drug and excipients. The drug and the polymer must be compatible for a successful formulation.

COMPATIBILITY STUDIES

Physical Compatibility study

Inference

The Physical compatibility study was performed for 3 months. There was no change of color therefore the drug and excipients are physically compatible with each other.

Chemical Compatibility Study

FT-IR spectroscopic study

FT-IR spectroscopy gives the possible information about the interaction between the drug and polymer. The results are follows

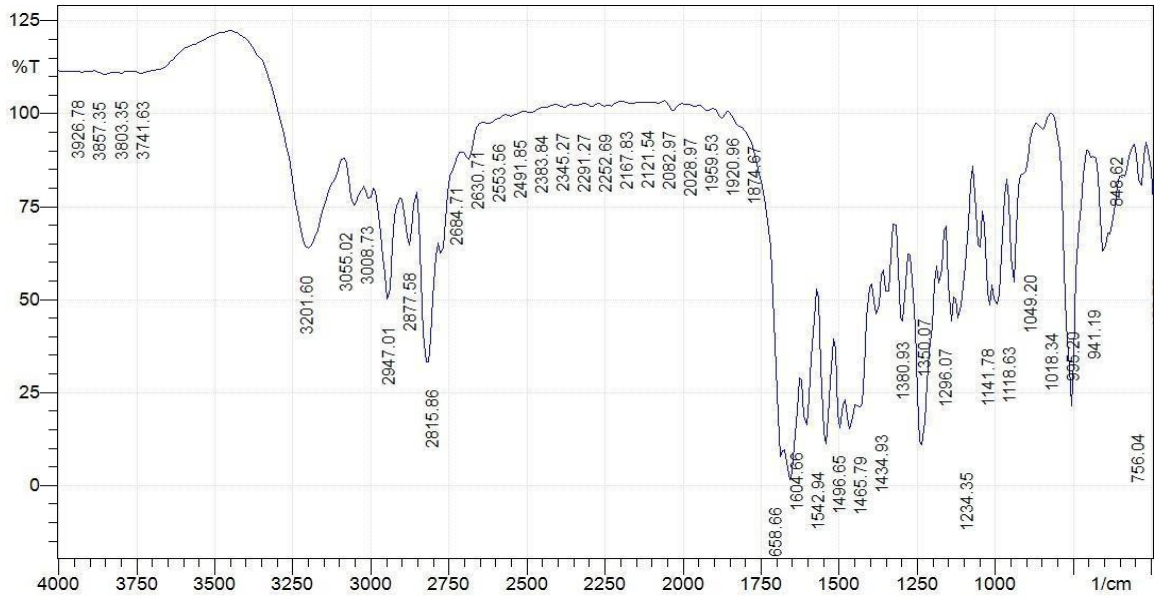

Figure 2: FT-IR spectrum of Tetrazosin.

MELTING POINT- The melting point of Tetrazosin was measured using capillary tube method in the range 157-158ºC.

SOLUBILITY STUDY

The solubility study of Tetrazosin in different dissolution medium is performed by saturation solubility method.

Table 2: Saturation solubility of Tetrazosin in phosphate buffer pH 6.8 and Distilled water.

Medium	pH	Solubility (mg/ml)
Phosphate buffer pH 6.8	6.8	0.004093
Distilled water	7.0	0.000216

Inference

The solubility of the drug at pH 6.8 was significantly higher than in that of distilled water. Pure drug of Tetrazosin in distilled water and phosphate buffer pH 6.8 was found be insoluble.

DETERMINATION OF LAMBDA MAX (λ_{max}) FOR TETRAZOSIN

The maximum absorbance of the Tetrazosin was studied. The maximum absorbance of the Tetrazosin was found to be 268nm. Hence the wavelength of 268nm was selected for analysis of drug in dissolution media.

Calibration Curve For Tetrazosin

Table 3: Data for standard curve of Tetrazosin in Phosphate buffer pH 6.8.

S.No	Concentration (µg/ml)	Absorbance
1	0	0
2	2	0.115
3	4	0.2203
4	6	0.3445
5	8	0.4686
6	10	0.6035
7	12	0.7089

Mean ± SD (n=3)

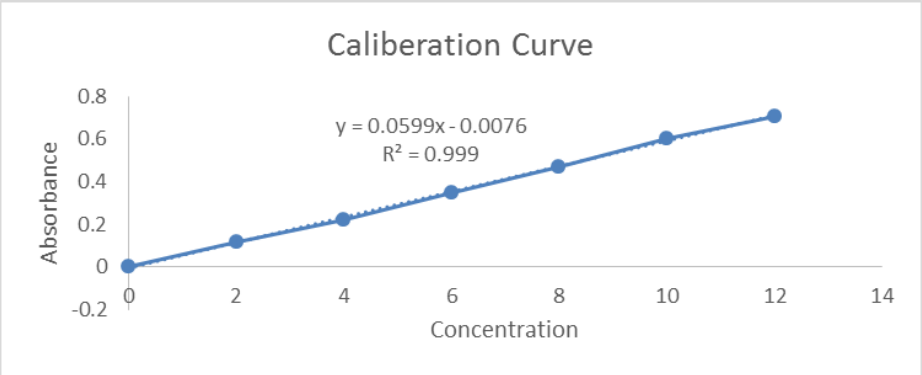

Figure 3: Standard curve of Tetrazosin in Phosphate buffer pH 6.8.

Inference

The constructed calibration curve of Tetrazosin in Phosphate buffer pH 6.8 is shown figure 9.5. It was found that the solutions show linearity (R^2 = 0.9995) in absorbance at a concentration of 2-12 µg/ml and obeys Beer-Lambert's law.

SOLUBILITY STUDIES OF TETRAZOSIN LOADED NANOPARTICLES

The solubility study of Chitosan Nanoparticles formulations in distilled water and phosphate buffer pH 6.8 were studied by saturation solubility method. The Nanoparticles formulations compared with pure and tabulated below.

Table 4: Solubility of Nanoparticles and Tetrazosin in various medium.

S. No	Formulation code	Solubility Medium	
		Distilled water pH 7 (mg/ml)	Phosphate buffer pH 6.8 (mg/ml)
1	Pure drug	0.000216	0.004093
2	F1	6.0998	6.9676
3	F2	6.7923	7.4355
4	F3	7.5888	8.7722

5	F4	7.9351	9.6748
6	F5	9.4933	13.251
7	F6	7.5190	8.1373
8	F7	6.4802	7.6360

Inference

The solubility of Tetrazosin in distilled water and phosphate buffer pH 6.8 were found to be 0.000216 mg/ml and 0.004093 mg/ml respectively. The solubility of all formulations was improved (from insoluble to slightly soluble) compared to pure drug of Tetrazosin. Among all the formulations F5 show higher solubility in distilled water and phosphate buffer pH 6.8.

Inference

Thus the solubility of formulation F5 in Distilled water and Phosphate buffer pH 6.8 were improved and compared with pure drug.

COMPARATIVE *IN VITRO* DRUG RELEASE FOR ALL FORMULATION

The formulated Nanoparticles preparation containing drug and polymer were evaluated for drug release and results were tabulated below

Table 5: *In vitro* drug release for all formulations

Time (h)	*In Vitro* Drug Release For Nanoparticles Formulations						
	F1	F2	F3	F4	F5	F6	F7
0.5	17.25	17.45	16.04	15.09	13.19	9.71	8.32
1	20.12	19.89	19.2	18.99	16.17	11.14	10.14
2	36.4	29.13	28.83	27.02	24.02	17.35	14.14
3	44.8	38.03	37.92	36.21	34.52	31.3	29.27
4	60.2	50.08	47.22	44.1	41.23	34.02	31.73
5	72.27	63.07	59.12	53.8	50.14	36.37	32.13
6	82.29	79.02	69.03	61.78	57.71	42.13	39.92
7	97.04	89.9	78.97	73.2	64.21	50.12	43.78
8	-	96.02	89.17	86.51	73.22	62.79	59.11
9	-	-	94.18	91.52	78.01	71.23	69.24
10	-	-	-	94.47	86.22	79.13	75.17
11	-	-	-	-	91.89	83.2	81.2
12	-	-	-	-	95.03	86.03	83.04

In-vitro Drug Release

The formulations F1 TO F7 were prepared using Chitosan as a polymer (0.1%, 0.15%, 0.2%, 0.25%, 0.3%, 0.4% and 0.5%) and the Sodium tripolyphosphate as a cross linking agent.

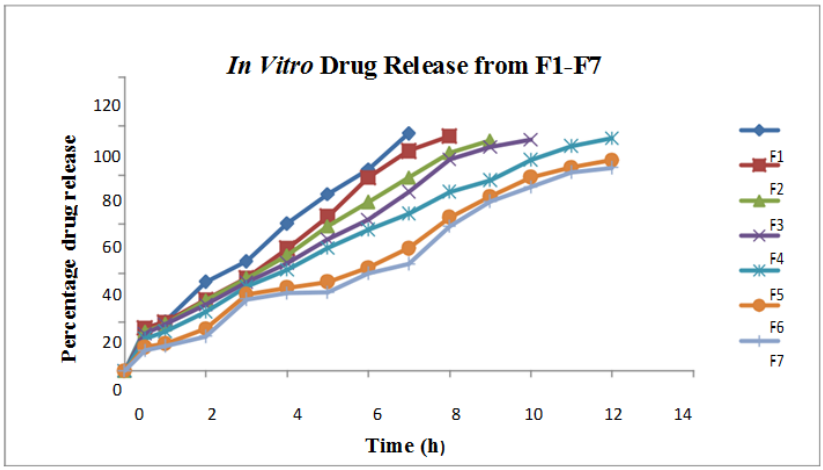

Figure 4: *In vitro* release study of Chitosan Nanoparticles (F1-F7).

Inference

- The in vitro drug release profile for formulated Tetrazosin loaded Chitosan Nanoparticles obtained from F1-F7 formulations were shown in figure 4.
- Among all the formulations F5 formulations shows 95.03% of drug release at the end of 12h in controlled manner. Thus F5 was selected as the optimized formulation.

CHARACTERIZATION OF OPTIMIZED TETRAZOSIN LOADED CHITOSAN NANOPARTICLES

FTIR Study of Optimized NPs

FTIR of optimized formulations of Tetrazosin loaded Chitosan Nanoparticles (F5)

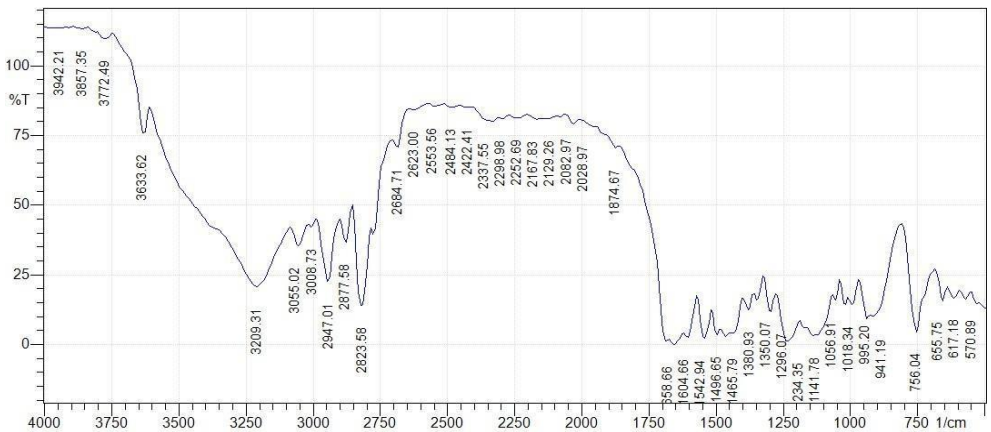

Figure 5: FT-IR spectral of Tetrazosin + Chitosan + Sodium tripolyphosphate.

SCANNING ELECTRON MICROSCOPE (SEM) ANALYSIS

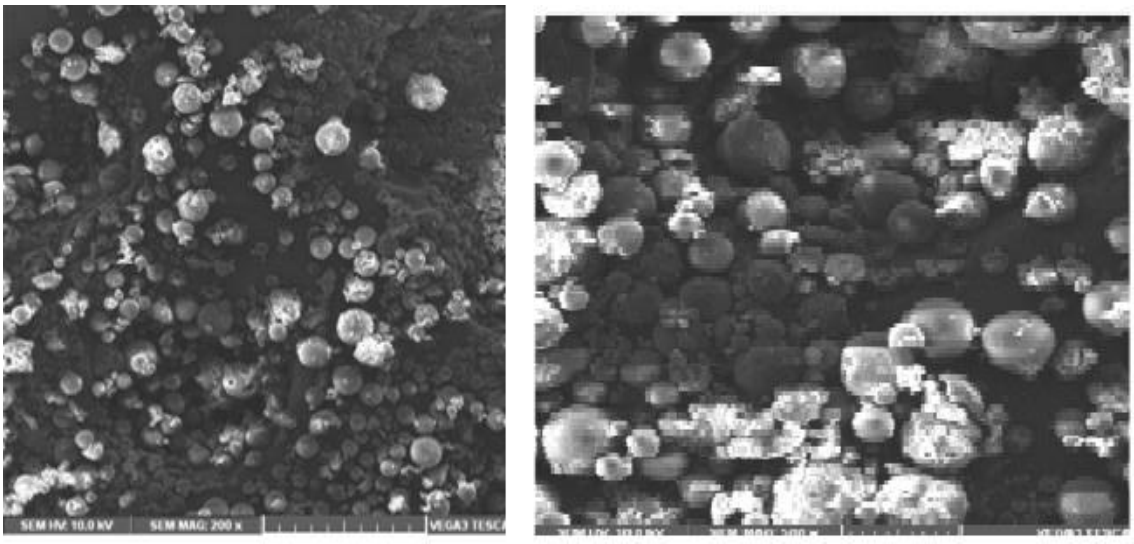

Figure 6: SEM Image of optimized formulation F5.

Inference

- The shape and surface morphology of optimized formulations F5 was observed in scanning electron microscope.

PREFORMULATION STUDIES OF OPTIMIZED NPs

After lyophilisation the preformulation studies of optimized Chitosan Nanoparticles formulations were carried out to check the flow property. The optimized formulation F5 are evaluated for flow property and the results are shown in table 6.

Table 6: Flow property measurements of optimized NPs.

Formulation code	Bulk density (g/ml)	Tapped density (g/ml)	Carr's Index (%)	Hausner's ratio	Angle of repose (Ɵ)
Pure drug	0.2013±0.000531	0.29393±0.001247	32.75±0.3657	1.49±0.008165	51.14±1.3609
F5	0.3356±0.000245	0.3885±0.000327	13.62±0.00474	1.16±0.00471	33.20±0.1087

Mean ± SD (n=3)

Inference

The above results reveal that the optimized formulation F5 shows good flow property compared with Tetrazosin pure drug.

RELEASE KINETIC OF OPTIMIZED FORMULATION

RELEASE KINETIC OF C-NPs. F5

Table No. 7: Release Kinetics of C-NPs.F5.

Time (h)	% Cum. Drug Release	% Cum. Drug Remaining	Log % Cum. Drug Remaining	Square root of time	Log time	Log % Cum. Drug Release	cubic root of % drug Remaining
0	0	100	2	0	∞	∞	4.6416
0.5	13.19	86.81	1.9386	0.70711	-0.30103	1.1202	4.4278
1	16.17	83.83	1.9234	1	0	1.2087	4.3766
2	24.02	75.98	1.8807	1.4142	0.30103	1.3805	4.2355
3	34.52	65.48	1.8161	1.73205	0.4771	1.53807	4.0306
4	3.6806	58.77	1.7692	2	0.60205	1.6152	3.8879
5	50.14	49.86	1.6978	2.23607	0.69897	1.70018	3.6806
6	57.71	42.29	1.6262	2.44949	0.7782	1.76125	3.4840
7	64.21	35.79	1.5538	2.64575	0.8451	1.8076	3.2955
8	73.22	26.78	1.4278	2.82843	0.9031	1.8646	2.9918
9	78.02	21.99	1.3422	3	0.9542	1.89215	2.8016
10	86.22	13.78	1.1393	3.162278	1	1.9356	2.3975
11	91.89	8.11	0.9090	3.316625	1.04139	1.96327	2.0091
12	95.03	4.97	0.6964	3.46410	1.07918	1.97786	1.7066

Kinetic study

The coefficient of determination (R^2) was taken as criteria for choosing the most appropriate model. The R^2 values of various models are given in table 9.

Table R^2 Values of F5 in various kinetic models.

Kinetic Models	Coefficient of determination (R^2) F5
Zero order	0.9878
First order	0.9216
Korsmeyer and Peppas	0.985
Higuchi	0.9717
Hixson crowell	0.9771

The in vitro release of optimized formulation F5 are fit into various kinetic models to find out the mechanism of drug release from Tetrazosin loaded Chitosan Nanoparticles Thus, the release kinetics of the optimized formulation was best fitted into Higuchi model that showed zero order drug release with anomalous diffusion (Non Fickian diffusion) mechanism.

SUMMARY AND CONCLUSION

The purpose of this research was to prepare Tetrazosin loaded Chitosan Nanoparticles for controlled release of drug, to improve the solubility, reduce the dosing frequency, thereby

increasing patient compliance to the therapy. Tetrazosin is formulated as Nanoparticles by ionic-gelation method using Chitosan as polymer, Sodium tripolyphosphate as a polyanionic agent (cross linking agent) and the lyophilized nanoparticles filled in hard gelatin capsules. The preformulation studies like melting point, determination of absorption maximum (268nm) were performed and the results evident that the drug and excipients are stable, safe and effective within the range. Physical compatibility study showed that the drug and excipients were physically compatible with each other. The chemical compatibility studies of Tetrazosin with excipients were physically analyzed by using FTIR Spectrometer. The results of the FTIR study proved that there was no interaction between the drug and polymer. Standard graph was drawn for Tetrazosin and it was found that the solutions show linearity (0.9995) and obeyed Beer – Lambert's law. Tetrazosin loaded Chitosan Nanopaticles prepared by ionic-gelation method using Chitosan as a polymer in different concentration (0.1%, 0.15%, 0.2%, 0.25%, 0.3%, 0.4%, and 0.5%). Sodium tripolyphosphate as a polyanionic agent (cross linking agent), Tween 80 as a deaggregating agent. All seven formulations characterized for percentage yield which found to be within the range of 78.84% to 87.25% and the entrapment efficiency of the formulations was observed between 83.40% to 93.15%. The results showed that the increase in polymer concentration, increase the entrapment efficiency. The entrapment efficiency was found to be higher in F5- 93.15% comparatively with other formulations. The Solubility analysis of Tetrazosin was carried out before and after formulation in distilled water and phosphate buffer pH 6.8. The results show that the solubility profile is improved after formulations (from insoluble to slightly soluble) compared with pure drug. Thus the solubility of formulation F5 in distilled water and phosphate buffer pH 6.8 were improved (9.4933 mg/ml and 13.251 mg/ml) respectively. The in vitro release study was carried out for all seven formulations. The percentage of drug release in formulation F5 was found to be 95.03% at the end of 12h and the release profile was in controlled manner comparatively with other formulations.Based on the higher entrapment efficiency, drug content and prolonged in vitro drug release F5 was selected as optimized formulation.

The FTIR studies of optimized formulation F5 shows there was no change in the individual peaks of the drug and the excipients. It concludes that there was no chemical interaction between the drug and excipients. The optimized formulations F5 are characterized for SEM analysis, particle size analysis and zeta potential. The SEM image showed that nanoparticles were spherical with smooth surface. The particle size analysis was done by Horriba scientific

Nano SZ 100 particle size analyzer showed that mean particle size 188.3 nm and Z- Average 229.0 nm respectively. The Zeta potential study was done by Horriba scientific Nano SZ 100. The Zeta potential for the optimized formulations F5 was found to be 25.8mV and shows that the formulation is stable. Post formulation parameters (uniformity of weight, disintegration test, drug content, and in vitro drug release) for nano particulate capsules were evaluated. The results were found to be complying with official specifications. The dissolution data of the optimized formulation was fitted to various kinetic models and the formulation F5 was best fitted to Zero order kinetics. The slope of the Korsmeyer Peppas plot indicating the diffusion was Anomalous diffusion (Non-Fickian diffusion). From the overall results, it is clear that the formulations F5 containing 0.3% polymer concentration (Chitosan) is the optimal formulation, as it produces controlled drug release.

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