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Pre Formulation and Formulation Studies on Cisplatin Nanoparticles Encompass Natural Polymer

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ABSTRACT

Our aim of this research work is to develop a cisplatin nanoparticles encompass natural polymer to facilitate the release of cisplatin in a more continued manner to progress therapeutic efficacy via the decrease of its toxicity. Pre formulation and formulation studies have been limited to studying the various physical characters of cisplatin nanoparticles encompass natural using a zeta nanosizer. The gumghatti polymer was designated in this study because of the high poly-cationic and biodegradable characters. Cisplatin nanoparticles encompass natural was prepared using the nanoprecipation technique and characterized using the Malvern zetasizer nano zs instrument, UK to find out the polydispersity index (pdi), zeta potential and particle size determination. The ideal nanoparticles were exhibiting +45.4 mV, 595.3 z.dnm and 0.6 pdi. The study concluded that cisplatin nanoparticles encompass natural can be formulated at an optimum concentration of 40 µg/ml of cisplatin entrapped in 2 mg/ml of aqueous solution of gumghatti in the presence of formaldehyde (0.1% v/v) as cross linker and identification of physical characterization of nanoparticles was established as a preliminary step in pre formulation and formulation studies to target cancer cells.

Keywords: Nano particles; specimen; Microscope; Cancer cells

INTRODUCTION

Cisplatin is a one of the most prescribed antitumor drug especially in ovarian, lung carcinoma, head and neck carcinomas, leukemia and testicular cancer. The pharmacological action of cisplatin is focusing to induce cytotoxic in tumor cells and causing cell death by interfering with the transcription mechanism of DNA, inducing apoptosis through the activation of signal transduction pathways such as the calcium channel, death receptor signaling and the activation of mitochondrial pathways. Though cisplatin is a successful therapy in various types of cancer, it reported paroxysmal enhancement of toxicity and the production of intrinsic resistance. ATP Binding Cassette (ABC) transporters are very common and the largest membrane transporter proteins responsible for the import and/or export of various substrates. Multidrug Resistance protein 1 (MDR1), functions as a pump to efflux a variety of drugs but not for cisplatin. Multidrug Resistant Associated Proteins (MRP) are responsible for the cisplatin efflux mechanism that leads to cisplatin resistance. Recently, many researchers have been exploring the efficacy of the biodegradable polymeric nanoparticle drug delivery system to overcome drug resistance in cancer. The aim is that the nanoparticles on the nano scale can easily target the specific cells, therefore general toxicities can be avoided. In this regard, chitosan, a polycationic polysaccharide polymer, abundantly available from crustacean shells has been reported for delivering drugs and vaccines. In this study, we aimed to formulate nanoparticles to target cancer cells in a simple cationic and anionic adherent interaction that can bind easily on the membrane of cancer cells and minimizes the general toxicity of cisplatin [1-5].

MATERIALS AND METHODS

Pre formulation study

The nanoparticles were characterized for that particle size, distribution width, surface area and zeta potential using particle size analyser.

Procedure for that bulk characterization

About 10 mg of pure chemicals were individually taken in the test tube containing distilled water and vortexed for 5 minutes route for that M dispersion.

Resultant dispersion was dropped in the sample cells of particle size analyser (malvern) till the preferred concentration was reached and measured the particle size, distribution width, surface area and uniformity. Resultant dispersion was taken in the zeta cell and the zp was assessed by means of zetasizer. The characterization experiments were performed in the triplicate [6].

Drug excipient compatibility studies for isothermal testing method

In this method, the samples were introduced in an elevated temperature amid or amid out moisture/water for a pre-determind interval. Subsequently, physical and chemical instabilities were studied using organoleptic parameters, structural changes and drug content.

Pure chemical, pure excipient, pure chemicals mixture and pure chemical-excipient mixture were taken in an individual glass vial (Tables 1 and 2).

Table 1: Observed characters of the bulk powder

Appearance	Crystalline material
Odour	Odorless
Colour	Whitish
Solubility	9.54 ± 0.26 mg/ml
Melting point	42ºC-44ºC
Absorbance	201 nm

Table 2: Samples for compatibility studies

S.No	Drug	Observation		
		Colour	Odour	Remarks
1	Cip	No significant colour change	Characteristic	Stable
2	Cip-surfactant	No significant colour change	Characteristic	Stable
3	Surfactant	No significant colour change	Characteristic	Stable

Physical instability

The organoleptic parameters (i.e. colour and texture) of the compatibility study samples were noted visually in prior for start the compatibility study. Subsequently, these organoleptic parameters were also noted visually at the finishing of the week 1, week 2, and week 3 and week 4.

Chemical instability

Compatibility study samples were divided into two parts at the end of the week 4. Primary portion of the samples were utilized for record FT-IR spectrum and the second parts of the content, utilized for estimate the drug content [7-9].

Encapsulation efficiency of CIP nanoparticles

$$\textbf{Percentage Encapsulation Efficiency} = \frac{\textbf{Actual Drug Loading}}{\textbf{Theoretical Drug Loading}} \times \textbf{100}$$

An accurately weighed quantity of cip was sonicating in 10 ml of methanol for that 5 minutes and filter through 0.45 µl sintered glass filter. CIP concentration is analyzed by measuring the absorbance at 287 nm using UV-VIS spectrophotometer.

FT-IR analysis

About 2 mg of compatibility study samples were individually mixed thoroughly with 200 mg of potassium bromide (kbr-FT-IR grade). About 10 mg of FT-IR samples were individually taken in the transparent pellet using applied force under vacuum, which was scanned at 4000-400 cm^{-1} *via* FTIR. [10]

HPLC analysis

About 10 mg of compatibility study samples were individually assorted amid 10 ml of acetone and vortex for 300 seconds. Subsequently, samples were filtered using 0.22 µm membranes and analysed using the established hplc methods for CIP. The experiment was performed in triplicate.

Chromatographic conditions for CIP

- RP-HPLC amid isocratic elution amid 1.0 ml/min pace
- Moving phase; CH_3OH (filtered using 0.45 µm millipore filter prior to injecting)
- Sample injected 20 µl
- Detection wavelength; 370 nm
- Column used; Zorbax -C18 Column (250 mm × 4.6, 5 µm), at temperature of 35°C

Chromatographic conditions for excipients

- RP-HPLC amid isocratic elution amid 1.0 ml/min pace
- Non-stationary part; binary mixture methanol–water, 1:1 (V/V), adjusted to PH 2.8 amid phosphoric acid.
- Sample inejected; 20 µl
- Detection wavelength; 360 nm
- Column used; Zorbax Extend-C18 reverse-phase analytical column (150 mm × 46 mm, 5 µm particle pack), at temperature of 40°C

X- Ray diffraction technique

Can be utilized to taken as analysis of poly crystalline materials. A light emission a beam is sent in to the specimen and the way the pillar is scattered by the molecules in the way of the x-beam is considered. The scattered x-beams helpfully middle amid each other. This impedance can be taken a greater at utilizing Bragg's Law to decide different qualities of the precious stone or polycrystalline material.

Estimations are made in Angströms, 1 Angstrom=0.1 nm. However XRD can be tedious and requires a substantial volume of test. For example 1 mg of sample was weakened by 1% dimethyl sulfoxide dissolvable, which was kept in a specimen inlet and watch the readings [11-14].

Scanning electron microscope

- Put the sample on the aluminum holder stub utilizing a two folds sticky carbon tape
- Protecting samples must be situated amid either carbon or gold and electrically grounded. Gold covering is much conductive, however not useful for edx investigation. Additionally, utilize silver paint to electrically ground the specimen. Conductive samples needn't bother amid this procedure.
- In the event that you have many specimens resemble the other alike, record blemishes on the example stub or tests. It is difficult to perceive comparative specimens in the sem.
- At that point, totally dry the specimen in the drying boiler at 60ºC for not less than 3 hours relying upon the example conditions. The general guideline is that it is better on overnight in the drying stove [15].

Stacking the specimen into the sem holder

- Ensure that the valves of the two nitrogen gas tanks are open. In the event that there's insufficient nitrogen (less then 100 Psi).
- Press the vent catch situated at the show board of the microscope table.
- After a steady tapping sound (it might take around 1 moment to top off the load amid nitrogen), Fined the lever on the base of the entryway and tenderly draw the lever up and open the load entryway.
- Move the specimen mounting stage the distance around squeezing z-pivot down bolt key (situated on the console of the magnifying lens control table).
- Put the sample holder stubs on the mounting plates. Tall specimens ought to be found far from the left half of the chamber, where the auxiliary electron identifier exists. Utilizing the yellow long screwdriver fix the set screws for the mounting gaps. Two fold check whether the specimen holders are very much fixed.
- Ensure nothing acts as a burden to close the entryway. Delicately, shut the entryway and afterward press the Evac catch.
- Presently you will hear the sound of rotating pump. Sit tight for around 2 minutes until it shows the green light.
- Hold up around 30 minutes-45 minutes to accomplish high vacuum $<5 \times 10^{-5}$ pa [16-19].

Formulation study

Optimization of nanoparticle comprising CIP in gum Ghatti230

CIP was mixed amid water to prepare solution and add DMSO as cosolvent to make the inner phase more homogeneous. Then 150 mg of gum ghatti was dissolved in acetone and the solution was added to the drug to form dispersion. The content was stirred with magnetic stirrer at 2000 rpm for 60 minutes. The dispersion was add to 10 ml of aqueous ethanol solution (70%) after 5 minutes of mixing, the organic solvent was removed by evaporation at 38°C under normal pressure, nanoparticles were separated by using cooling centrifuge at 10,000 rpm for 20 min supernatant was removed and nanoparticles was washed amid water and dried at room temperature in a desicator. By following the above mentioned procedure five other batches of nanoparticles in the ratio of 1:1, 1:2, 1:3, 1:4 and 1:5 were prepared. However, there are several methods available for the formation of NPS *viz* desolvation method, dialysis method, ionic gelation method, nano precipitation method, direct solvent evaporation, salting out, supercritical fluid technology and spray drying. However, nano precipitation method is the most convenient and cost effective way to generate polymeric NPS [20,21].

Design of experiment

Fundamentally, utilization of factorial design for the optimization of a process allows testing of a large number of factors concomitantly and prevents the use of an unwanted number of runs or trials, thus it prevents material wastage and time consumption. Statistical design of experiment, is a perfect methodology to conduct and execute plan of experiments in order to extract the maximum amount of information amid limited number of inputs.

The most critical factors selected for the formulation along amid the proper selection of design of experiment input a tool proves to be superior. DOE identifies optimal formulation conditions for these NPS provide understanding of the underlying relationship. Most commonly applied screening designs is the Plackett-Burman Design (PBD) that evaluates large number of factors and identify critical one in a minimal number of trials. The utilization of Plackett-Burman experimental design paves the way for the study of numerous factors in a systematic and logical way to select optimized runs. The important significance of plackett-burman design method is quicker screening obtained amid minimum possible experimental runs [22].

By a large, number of run needed to probe the main effects are equal to 2 n or multiple of 4 in Plackett-Burman designs instead of 2 as in the relation of full-factorial designing. PBD screening design amid 12 experimental run was designed utilizing expert design (ver 9; stat-ease, inc, United States of America).

The linear equation of the model is given as

$$Y=B_0+B_1x_1+B_2x_2+B_3x_3+B_4x_4+B_5x_5+\cdots+B_nx_n$$

Where, Y is the responses,
B_0 is stable and
B_1....Bn are coefficient of factor X_1, X_2...X_n (Representing the consequence of every factor are amidin -1, +1).

Nevertheless, the process parameters which- includes consequently, PLB design was exploited to optimize the procedure parameter at lesser (-) and upper (+) level. The nanoparticle parameters such as APS (R1), PSU (R2) and SA (R3) are considered as relient variable. Twelve investigational runs exploiting 8 self-regulating progression variables at superior and inferior niche were generated exploiting expert desigining Version 9 [20-21].

Turning on the SEM

- At the point when vacuum achieves appropriate level, fiber light will be on.
- Turn the key change to on position. Presently the screen will be on.
- Check the status of dial positions. The increasing speed voltage ought to be 15 KV and spot size ought to be large and 1.
- Propelled clients; check the fiber outflow, shaft arrangement, gap arrangement and astigmatism.
- Go to the most minimal amplification (10X). Pick TV check mode.
- Discover your specimens utilizing trackball.
- Turn on the coarse concentration switch. Utilizing the concentration handle, change the working separation to 14 mm. Try not to get nearer than 6 mm. Your specimen may fine the goal focal point.
- Presently raise the specimen arrange gradually by squeezing Z-hub up key. In the meantime, Look the screen and discover the z-position where the picture is in core interest. Note down the z-position in the note pad.
- Then turn off the light (coarse).
- Change to the moderate sweep mode and increment amplification. On the off chance that the amplification is higher than 1000X, switch the spot size to medium. Utilize external concentration (medium) ring to center the picture.
- Propelled clients; if vital, increment or diminishing increasing speed voltage. For edx of a few materials, speeding up voltage of 25 kv might be important to produce higher vitality range of X-beam elimination. Present the vitality graph of different components glued at the lab divider.
- Squeeze variable secure to open a little factor window on the screen. Conform the measure of the screen and overlay it in the locale of intrigue. Center the picture inside the little screen utilizing external concentration ring and later inward concentration ring for fine core interest.
- Propelled clients: It is emphatically prescribed to stop the programmed control of splendor. Modify them physically by turning both dials counter clockwise the distance down amid the goal that pointer lights are altogether situated on left end (red shading). Begin rotate the dial in clockwise direction until brilliance marker begins to move right.
- Ensure that the examining velocity is set to S1. Just S1 filtering pace will permit electronic imaging procurement.
- Double tap the spirit symbol on the pc.
- Go to the file menu and select inclinations. Select your catalog under the organizer name "glen kowach" and input the specimen name ID number.
- Click picture set up symbol. Select the mapping alternative. Ordinary determination is 1024 and casing is 1. See the picture and modify the difference or potentially shine.
- Click ok to close the picture setup window.
- Click picture procure symbol to record the picture. Presently the product takes the control over sem and the screen will solidify. Try not to change any parameters amid the picture recording [23].

Stability study

For long term studies about led at 25°C ± 2°C/40% RH ± 5% RH, extra testing at the moderate stockpiling condition ought to be executed as that depicted under the general case to assess the temperature impact at 30°C if huge change other than water loss happens amid the 6 months' trying at

the accelerated storage condition. Be that as it may, information ought to be given to exhibit that the drug products doesn't have-huge water misfortune all through the proposed timeframe of realistic usability if put away at 25°C and the reference relative moistness of 40% RH. Stability study of prepared CIP loaded nanoparticles were assessed as per the procedure mentioned in the chapter done and tabulated below. Stability study of the prepared CIP nanoparticles was done as per ICH guidelines. The long term stability study was performed at 5°C ± 3°C and 30°C ± 2°C, 65% ± 5% RH for initial, 15th, 30th, 45th and 60th day. Accelerated stability study performed at 40°C ± 2°C, 70% ± 5% RH for initial, 15th, 30th, 45th and 60th day.

RESULTS AND DISCUSSION

FTIR analysis

The FTIR spectrum of the samples kept at specific temperature has been analyzed under fourier transmission infrared spectroscopy and the results of the samples analyzed are as follows. Change the characteristics of peaks were observed in the compatibility study performed by the FTIR. Hence it indicated that no interaction between the drug and excipients. further the physical nature of the drug remained and observed no color changes when on stored in particular temperature for specified period of time (ICH mentioned) (Table 3) [24,25].

Table 3: Characterization of prepared nanoparticles

Options	Average particle size (nm)	Polydispersity index	Zeta potential (mV)
1	625.3	0.657	0.23
2	200.7	0.072	11.4
3	270	0.37	14.9
4	993	0.845	2.7
5	600	0.971	3.1
6	143.4	0.16	28.5
7	1005.8	0.602	1.16
8	199.1	0.24	9.5
9	1207.4	0.163	3.6
10	679.5	0.632	0.239
11	357.5	0.259	-0.078
12	238.9	0.79	8.65

Characterization of nanoparticles

Higher the particles in Brownian motion higher the steadiness of the novel nano formulation containing CIP. These charged particles one another obtain side in repelled against weak between particles prone to dipole interaction results of attractive force and then it prevents the agglomeration of particles altogether. The compound concentration, period of process, concentration of surface-active agent, organic section volume has inverse relationship there amid of zeta potential. Twelve experimental runs involving 10 process parameters at higher and lower levels were generated by Design-Expert Prepared dual loaded flavono polymeric Nanoparticles were characterized for average particle size, polydispersity index and zeta potential (Tables 4-12 and Figures 1-14).

Table 4: Indication ANOVA for evaluation of Zeta potential (mV)

Parameters	Numerical value		
P value	<0.0001		
P<0.05	Yes		
Number of groups	12		
F Value	10567		
R Squared	0.9997		
ANOVA table			
	Sum of square	**Difference**	**Mean of square**
Treatment (between columns)	3301	10	299.5
Residual (amidin columns)	0.6749	25	0.02814
Total	3308	37	-
Note: * indicates P value summary			

Table 5: Observed and predicted value of size, P.D.I and zeta potential

Option	Average particle size		polydispersity index		Zeta potential	
	Ob	Pr	Ob	Pr	Ob	Pr
1	625.3	625.2	0.657	0.656	0.230	0.198
2	200.7	199.5	0.072	0.069	11.4	11.3
3	270.0	276.3	0.370	0.370	14.9	14.6
4	993.0	998.4	0.845	0.841	2.70	2.68
5	600.0	1299.1	0.971	0.975	3.10	3.23
6	143.4	142.3	0.160	0.161	28.5	29.0
7	1005.8	999.3	0.602	0.608	1.16	1.14
8	199.1	199.6	0.240	0.260	9.5	9.56
9	1207.4	1207.5	0.163	0.164	3.6	3.7
10	679.5	676.7	0.632	0.631	0.239	0.249
11	357.5	3584.2	0.259	0.260	-0.078	-0.072
12	238.9	237.6	0.790	0.791	8.65	8.53

Table 6: Parameters of the prepared nanoparticles

Options	Encapsulation Efficiency (EE)	Percentage Drug Loading (DL)	Percentage Yield
			(PY)
1	90.33 ± 0.781	64.33 ± 1.030	52.63 ± 0.063
2	91.66 ± 0.057	76.43 ± 0.052	43.76 ± 0.941
3	89.64 ± 0.064	53.66 ± 0.067	59.71 ± 0.045
4	86.03 ± 0.045	67.42 ± 0.850	49.37 ± 0.786
5	89.34 ± 0.890	69.33 ± 0.054	55.92 ± 0.871
6	93.56 ± 0.032	83.55 ± 0.053	76.54 ± 0.980
7	90.44 ± 1.030	75.33 ± 0.650	65.66 ± 0.094
8	78.56 ± 0.070	72.62 ± 0.072	48.33 ± 0.856
9	85.99 ± 0.750	62.54 ± 0.082	70.38 ± 0.83
10	83.45 ± 0.540	58.36 ± 0.069	60.87 ± 0.942
11	87.56 ± 0.067	63.47 ± 0.065	70.33 ± 0.673
12	90.22 ± 0.009	59.03 ± 0.032	50.33 ± 0.057

Table 7: Calibration curve

Concentration (µg/ml)	Absorbance (nm)
20	0.117
40	0.251
60	0.39
80	0.518
100	0.636

Table 8: Optimization process parameters at lower and higher levels code variables levels

Code	Variables	Levels	
		Lower (-)	**Higher (+)**
A	CIP (Drug)	100	105
B	Polymer quantity	150	200
C	Surfactant quantity	50	100
D	Aqueous solvent	10	20
E	Organic solvent	10	20
F	Stirring time	30	60
G	Stirring rate	1000	2000
H	Adding the component	Org to aqueous	Aqueous to org
I	Addition mode	All at once	Incremental
J	Stirring mode	Blade	Homogenizer

Table 9: Scheme of fabrication of CIP loaded nanoparticles by Plackett-Burman method

Drug	**Polymer**	**Surfactant**	**Aqueous**	**Organic**	**time**	**Stirring**	**Additing component**	**Addition Mode**
(mg)	**(mg)**	**(mg)**	**(ml)**	**(ml)**	**(min)**	**(rpm)**		
100	200	50	20	20	60	1000	O to A	All at once
100	200	50	20	20	30	2000	A to O	Incremental
105	150	100	20	20	30	1000	O to A	Incremental
105	150	50	20	10	60	2000	O to A	Incremental
100	150	100	10	20	60	1000	A to O	Incremental
100	150	100	20	10	60	2000	O to A	All at once
100	250	100	10	10	30	2000	O to A	Incremental
105	200	50	10	10	60	1000	A to O	Incremental
105	200	100	10	20	60	2000	O to A	All at once
105	150	50	10	20	30	2000	A to O	All at once
105	200	100	20	10	30	1000	A to O	All at once
100	150	50	10	10	30	1000	O to A	All at once

Table 10: Scheme of fabrication of CIP loaded nanoparticles by Plackett-Burman method higher (+) and lower (-) limits

Drug	**Polymer**	**Surfactant**	**Aqueous**	**Organic**	**time**	**Stirring**	**Additing component**	**Addition Mode**
(mg)	**(mg)**	**(mg)**	**(ml)**	**(ml)**	**(min)**	**(rpm)**		
100	200	50	20	20	60	1000	O to A	All at once
100	200	50	20	20	30	2000	A to O	Incremental
105	150	100	20	20	30	1000	O to A	Incremental
105	150	50	20	10	60	2000	O to A	Incremental
100	150	100	10	20	60	1000	A to O	Incremental
100	150	100	20	10	60	2000	O to A	All at once
100	250	100	10	10	30	2000	O to A	Incremental
105	200	50	10	10	60	1000	A to O	Incremental
105	200	100	10	20	60	2000	O to A	All at once
105	150	50	10	20	30	2000	A to O	All at once
105	200	100	20	10	30	1000	A to O	All at once
100	150	50	10	10	30	1000	O to A	All at once

Table 11: Optimized formula for the fabrication of CIP loaded Gum ghatti nanoparticles

Trials	Drug (mg)	Polymer (mg)	Surfactant (mg)	Aqueous solvent (ml)	Organic solvent (ml)	Stirring time (min)	Stirring rate (rpm)	Additing component	Addition Mode	Stirring Mode
6	100	150	100	20	10	60	2000	O to A	All at once	B

Table 12: Optimized formula for the fabrication of CIP nanoparticles higher and lower limits

Trials	Drug (mg)	Polymer (mg)	Surfactant (mg)	Aqueous solvent (ml)	Organic solvent (ml)	Stirring time (min)	Stirring (rpm)	Additing component	Addition Mode	Stirring Mode
6	-	-	+	+	-	+	+	-	-	B

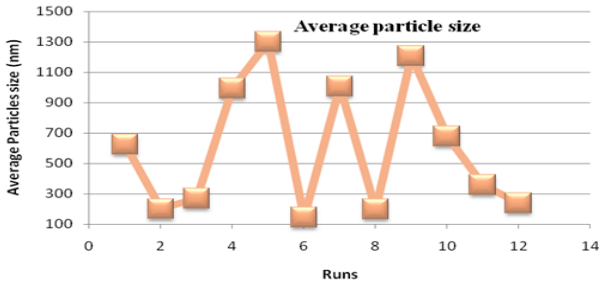

Figure 1: Average particle size for the all 14 runs

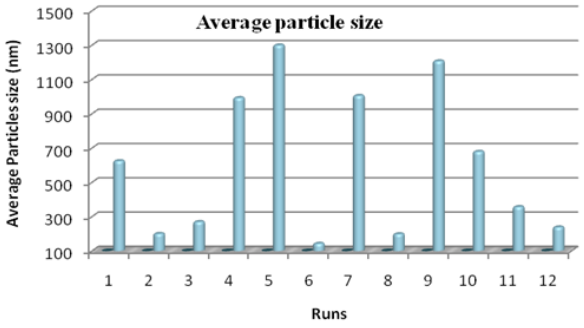

Figure 2: Average particle size for all the 12 runs

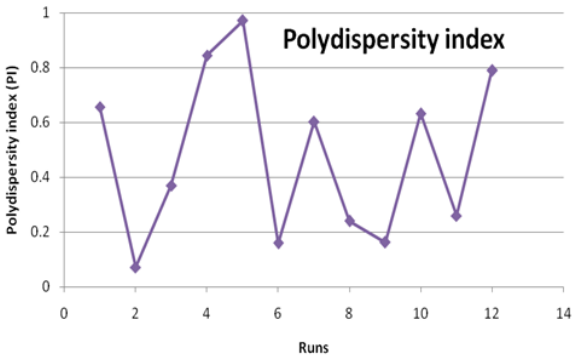

Figure 3: Scheme of average particle size for all the 12 runs

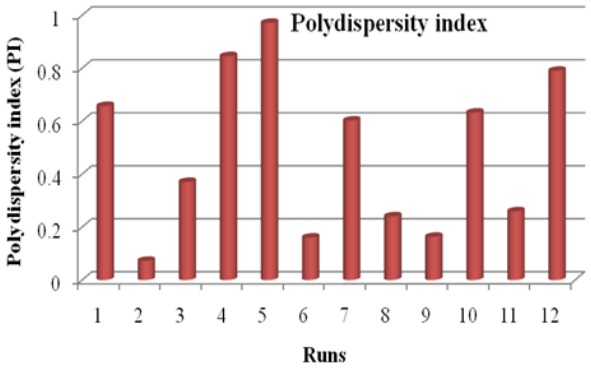

Figure 4: Polydispersity index of all the 12 runs

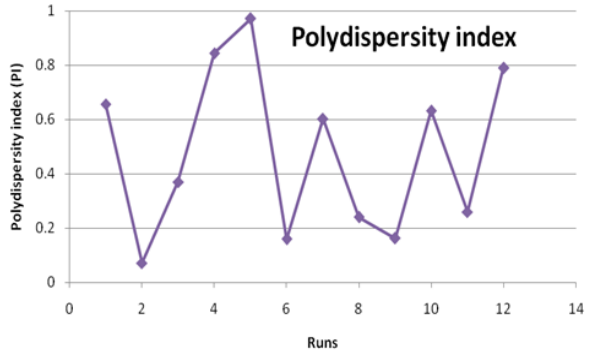

Figure 5: Scheme of polydispersity index for all the 12 runs

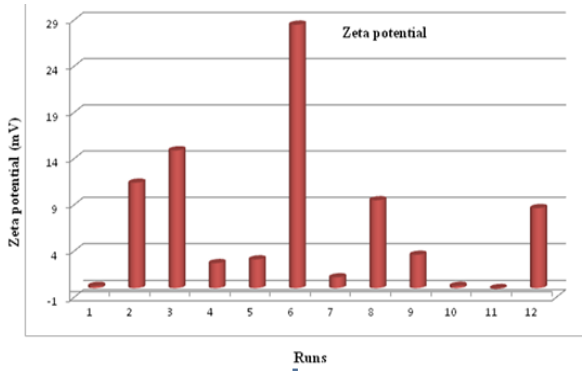

Figure 6: Zeta potential of all the runs

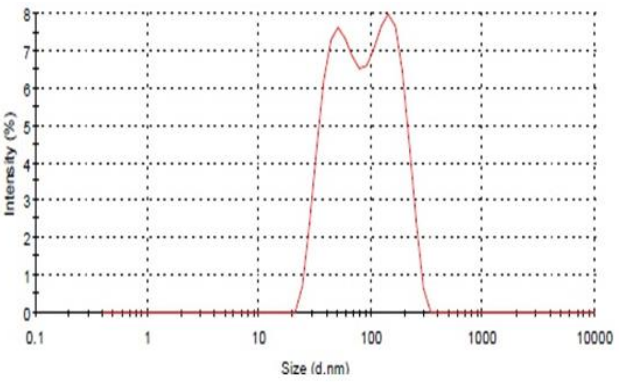

Figure 7: Scheme of zeta potential of all runs

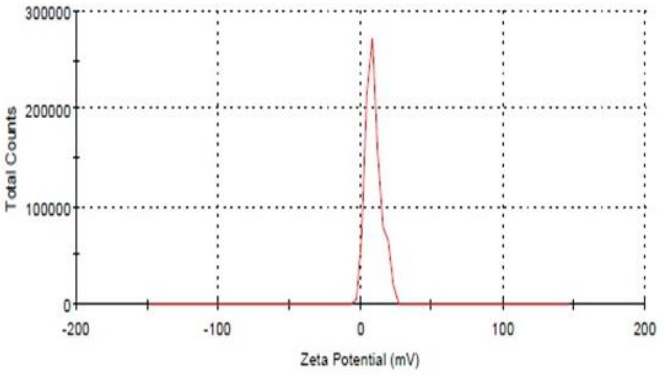

Figure 8: Distribution of nanoparticles of trail 6

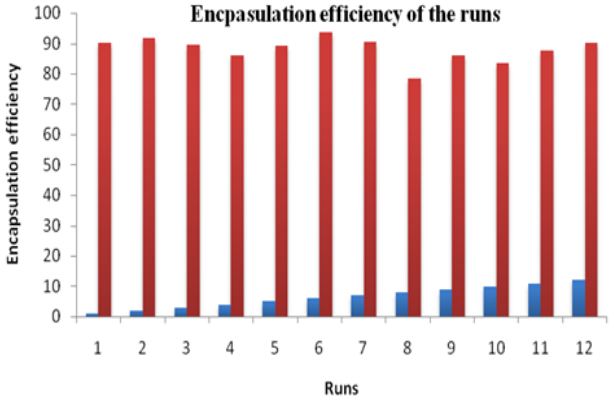

Figure 9: Encapsulation of CIP nanoparticles 12 runs

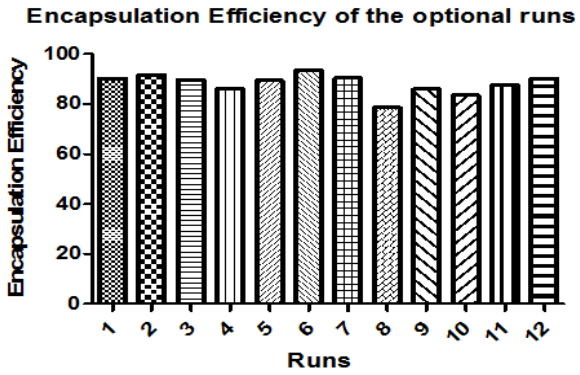

Figure 10: Scheme of encapsulation efficiency of the CIP nanoparticles

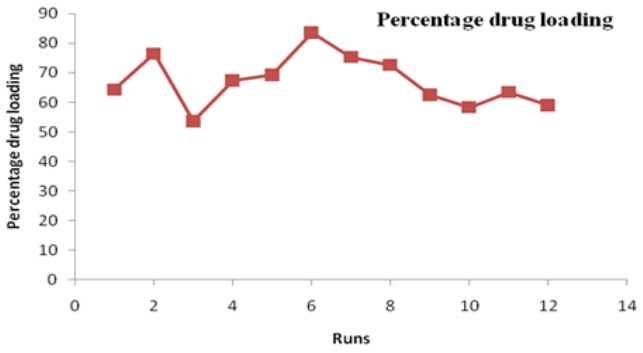

Figure 11: Percentage drug loading of the CIP nanoparticles (12 runs)

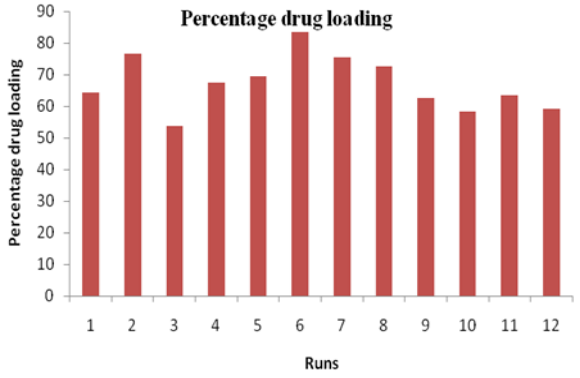

Figure 12: Scheme of drug loading of the CIP nanoparticles (12 runs)

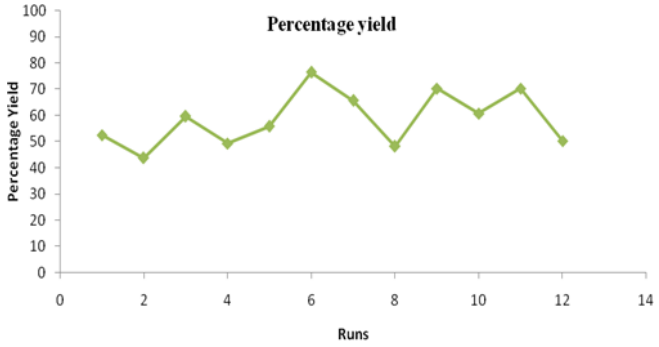

Figure 13: Percentage yield of the CIP nanoparticles (12 runs)

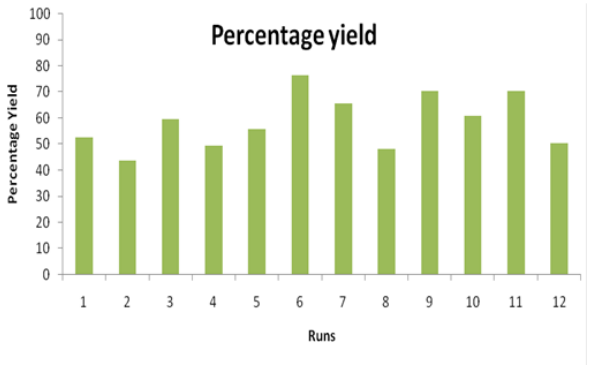

Figure 14: Scheme of percentage yield of the CIP nanoparticles (12 runs)

CONCLUSION

Cisplatin combined gumghatti nanoparticle preparations using nanoprecipation method have successfully produced particles of which sizes ranging from 80 nm-475 nm. The formulation and preformulation studies results were best respectively. This result shows that cisplatin combined gumghatti nanoparticle it may have anticancer activity and further carried out anticancer activity on *in vitro* and *in vivo.* It is concluded that the nanoparticles on the nano scale can easily target the specific cells, therefore general toxicities can be avoided. In this regard, chitosan, a polycationic polysaccharide polymer, abundantly available from crustacean shells has been reported for delivering drugs and vaccines. In this study, nanoparticles are target cancer cells in a simple cationic and anionic adherent interaction that can bind easily on the membrane of cancer cells and minimizes the general toxicity of cisplatin.

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