e-ISSN: 2582-5208
International Research Journal of Modernization in Engineering Technology and Science
(Peer-Reviewed, Open Access, Fully Refereed International Journal)
Volume:06/Issue:11/November-2024 Impact Factor- 8.187 www.irjmets.com

MICROSPHERES FOR SUSTAINED RELEASE OF CISPLATIN: A COMPREHENSIVE FORMULATION & EVALUATION STUDY

Pathlavath Rashitha*1, G. Hari Kiriti Varma*2

*1,2Department Of Pharmaceutics, Teegala Krishna Reddy College Of Pharmacy, Medbowli, Meerpet, Saroornagar, Hyderabad, India.

Corresponding Author: Pathlavath Rashitha

Mail Id: Rathoderishi@Gmail.Com

ABSTRACT

The development of oral sustained or controlled release dosage form of Cisplatin has been an interested topic of research for a long period of time. Such drug is difficult to be delivered orally in a sustained or controlled release manner and, Due to its effectiveness and intensive use as a drug of choice in the treatment of headache, arthritis, numerous sustained and controlled release formulations of Cisplatin have been made and reported. Cisplatin microsphere were prepared with a coat consisting of alginate and polymer such as Xanthum gum and Sodium alginate by Ionic cross linking technique using $CaCl_2$. The microspheres were evaluated with respect to the yield, particle size, incorporation efficiency, in vitro drug release and stability. Microspheres were characterized by FTIR studies. It was found that the particle size and incorporation efficiency of microspheres increases with increasing drug-to-polymer ratio.

Keywords: Cisplatin, Ionotropic Gelation Technique, Xantham Gum, Sodium Alginate, FTIR Studies, In Vitro Drug Release Studies.

I. INTRODUCTION

Novel drug delivery system delivers a therapeutic substance to the target site in a well-controlled and sustained model. Microspheres or micro particles are defined as a free-flowing spherical particles consisting of polymer matrix and drug.[1] They consist of proteins or synthetic polymers which are biodegradable in nature having a particle size less than 200µm. Microspheres can be characterized as solid, approximately spherical particles with a diameter having between 1–1000µm, including dispersed drugs in certain solution or microcrystalline shape.[2] Micro particles used in skin applications required to benefit the release of the medication into the skin ensure that now the drug remains localized at the application. They act as a reservoir which releases an active ingredient over a longer period of time to maintain effective concentration of drug products in the skin while decreasing undesired side effects.[3] Ionotropic gelation technique is comparatively simple and has been applied for the encapsulation of a number of pharmaceuticals.[4] Cisplatin (cis-diamminedichloroplatinum(II), CDDP) is a platinum coordination complex that displays significant genotoxicity, mediated by covalent modification of DNA to form intrastrand crosslinks and other adducts. cisplatin remains one of the most widely used and effective anticancer agents for the treatment of a variety of solid tumours, including breast, liver, lung, ovarian, testicular, bladder, head and neck, small-cell and non-small-cell lung cancers, owing to its wide spectrum of anti-tumor activity.[5] However, non-selective distribution of the drug between normal and tumor tissue likely increases the impact of dose-limiting side effects including acute nephrotoxicity, myelosuppression, and chronic neurotoxicity. The therapeutic ratio is further compressed by tumours that display intrinsic cisplatin resistance or acquire resistance over the course of treatment. Toward overcoming these limitations, a wide range of microspheres drug carriers have been explored as drug delivery systems (DDSs) for cisplatin in order to promote preferential accumulation in cancer cells and thereby reduce adverse side effects.[6]

II. METHODOLOGY

MATERIALS

Cisplatin was obtained from Hetero labs, HYD. Sodium alginate and Xantham gum were procured from Synpharma Research Labs, Hyderabad. Other chemicals and the reagents used were of analytical grade.

e-ISSN: 2582-5208
International Research Journal of Modernization in Engineering Technology and Science
(Peer-Reviewed, Open Access, Fully Refereed International Journal)
Volume:06/Issue:11/November-2024 Impact Factor- 8.187 www.irjmets.com

FT-IR study[7]

The compatibility study assessed by FTIR spectroscopy was conducted on the raw materials, namely MTH, XG and their mixture, and also on the formulated microspheres. The spectra with a resolution of 4 cm^{-1}, using 10 scans, were then recorded in the range of 4000–500 cm^{-1} using a Fourier transform infrared spectrophotometer (Shimadzu, Tokyo, Japan).

Formulation table

Table 1: Formulation development of Cisplatin microspheres

F. no	Cisplatin	Sodium alginate	Xantham gum	$Cacl_2$
F1	100	1000	-	2%
F2	100	800	-	2%
F3	100	700	-	2%
F4	100	600	-	2%
F5	100	-	1000	2%
F6	100	-	800	2%
F7	100	-	700	2%
F8	100	-	600	2%

Method: Ionotropic gelation method[8]

Cisplatin microspheres were prepared by ionotropic gelation method. Two different solutions were prepared separately. In beaker suitable amount of polymers was mixed well with 100 ml water. In another beaker drug was dispersed into the suitable solvent. Drug solution poured into the polymeric solution with continuous stirring on magnetic stirrer. Then drug and polymer solution was added drop wise by using 22 G syringe having needle of 0.45 mm inner diameter from a height of about 5 cm into a beaker containing calcium chloride solution with continuous stirring on magnetic stirrer at 400 rpm for 2 h. Prepared microspheres were removed by filtration and washed with distilled water, vacuum dried and stored in well closed container for further use.

Evaluation of microspheres

Particle size analysis [9]

Particle size was determined by using an optical microscope under regular polarized light and the mean particle size was calculated by measuring 50-100 particles with the help of a calibrated ocular micrometre.

Shape and surface morphology[10]

Morphology of microspheres was investigated by using optical Leica microscopy. The photographs of the optimized formulations. The results of Leica microscope revealed that the microspheres of cisplatin combination with xantham gum as a polymer (F6) were spherical and their surface was smooth and devoid of cracks giving them a good appearance

Drug Entrapment Efficiency[11]

The drug Entrapment efficiency of Cisplatin microspheres was determined by taking accurately weighed 100mg of microspheres in a glass mortar and powdered by a glass pastel and treated with 100ml of Phosphate buffer of pH 7.4 in a closed volumetric flask and left over night. Then it was transferred into a 250ml beaker and stirred by magnetic stirrer using Teflon coated magnetic bead, the temperature was maintained at 37ºC ±0.5ºC. At the end of 1 hour, it was centrifuged and supernatant was filtered, the filtrate was analysed spectrophotometrically at 253 nm (Jasco- V-530). Dilution was done whenever required using Phosphate buffer pH 7.4, Corresponding drug concentrations in samples was calculated from calibration plot. Entrapment efficiency of the microspheres was calculated using the formula.

e-ISSN: 2582-5208
International Research Journal of Modernization in Engineering Technology and Science
(Peer-Reviewed, Open Access, Fully Refereed International Journal)
Volume:06/Issue:11/November-2024 Impact Factor- 8.187 www.irjmets.com

Drug entrapment efficiency (%) = Practical Drug content /Theoretical Drug content

X 100

Percentage Yield [12]

Percentage yield: The prepared microspheres were collected and weighed from different formulations. The measured weight was divided by the total amount of all non-volatile components which were used for the preparation of the microspheres.

Percentage Yield (%) = Actual weight of microspheres /Total weight of drug and polymer X 100

In-vitro drug release studies [13]

The in vitro dissolution study was carried out at two different pH values corresponding to simulated gastric media at pH 1.2 and intestinal media at pH 7.4 using a USP dissolution apparatus II, at the temperature of 37 ± 0.5 °C and the stirring speed of 100 rpm. An accurately weighted sample of microcapsules (100 mg) was introduced into the basket and placed in the dissolution medium. At defined time intervals, a 10 mL sample was withdrawn and filtered with a syringe filter (0.45 μm), and then replaced by the same volume with the dissolution medium. The samples obtained were then analyzed by UV–Vis (PerkinElmer Lambda 25) at the wavelength of 253 nm, after suitable dilution.

Kinetics of drug release studies [14]

Zero-order model Drug dissolution from dosage forms that do not disaggregate and release the drug slowly can be represented by the equation:

Q0ñ Qt = K0t

Rearrangement of equation (3) yields:

Qt= Q0+ K0t

where

Qt is the amount of drug dissolved in time t,

Q0is the initial amount of drug in the solution (most times, Q0= 0) and

K0 is the zero order release constant expressed in units of concentration/time.

To study the release kinetics, data obtained from in vitro drug release studies were plotted as cumulative amount of drug released versus time

First order Kinetics [15]

This model has also been used to describe absorption and/or elimination of some drugs, although it is difficult to conceptualize this mechanism on a theoretical basis. The release of the drug which followed first order kinetics can be expressed by the equation:

dB n = n Kc

dt where K is first order rate constant expressed in units of time-1. Equation can be expressed as:

Log C = log C0n Kt / 2.303

Where

C0 is the initial concentration of drug,

k is the first order rate constant, and

t is the time

The data obtained are plotted as log cumulative percentage of drug remaining vs. time which would yield a straight line with a slope of nK/2.303.

Higuchi model [16]

Higuchi described drug release as a diffusion process based on the Fick's law, square root time dependent. The simplified Higuchi equation is represented as

Qt=Kt ½

Where Qt = amount of drug released in time t,

K = Higuchi's constant

e-ISSN: 2582-5208
International Research Journal of Modernization in Engineering Technology and Science
(Peer-Reviewed, Open Access, Fully Refereed International Journal)
Volume:06/Issue:11/November-2024 Impact Factor- 8.187 www.irjmets.com

A linear relationship between amount of drug released (Q0 versus square root of time (t½) is observed if the drug release from the microspheres is diffusion controlled.

Korsmeyer-Peppas model[17]

Korsmeyer derived a simple relationship which described drug release from a polymeric system equation. To find out the mechanism of drug release, first 60% drug release data were fitted in Korsmeyer Peppas model.

Mt / M∞= KtnO

Where

Mt / M∞ is a fraction of drug released at time t,

k is the release rate constant and

n is the release exponent.

Stability studies [18]

Once the delivery system was developed, the practical utility of the formulation depends on the maintenance of the therapeutic efficacy throughout the shelf-life under different storage conditions. Various In vitro characterization parameters (physical appearance, entrapment efficacy, and drug release) of the microspheres were assessed after storage of the best formulations for 3 and 6 months at 40±2oC/ 75±5% RH according to ICH guidelines, and results were compared with those obtained before storage.

III. RESULTS AND DISCUSSION

Drug - excipient compatibility studies (FT-IR)

The compatibility between the API and the selected polymers and other excipients was evaluated using FTIR peak matching method. There was no appearance or disappearance of peaks in the drug-polymer mixture, which confirmed the absence of any chemical interaction between the drug, polymers and other chemicals.

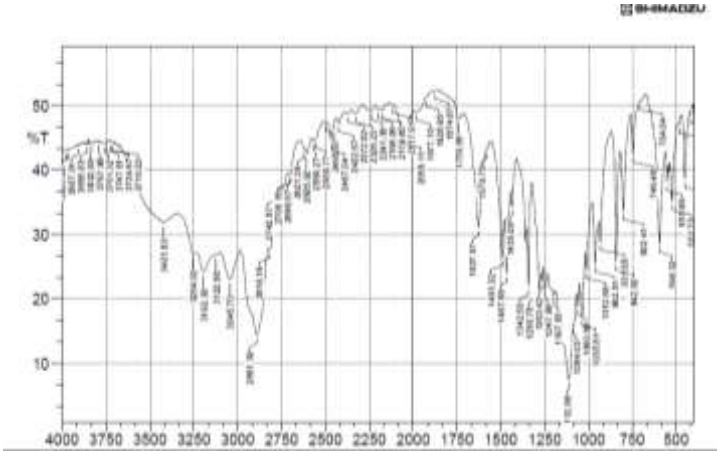

Fig 1: FT-IR Sample for Pure drug

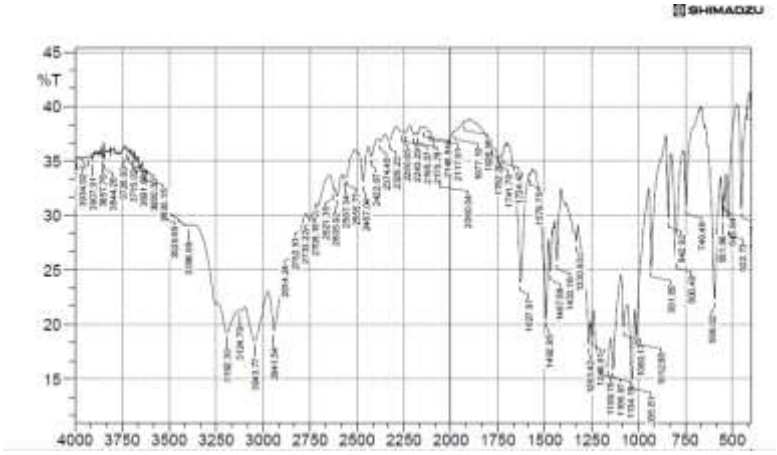

Fig 2: FT-IR Sample for Optimized formulation

e-ISSN: 2582-5208
International Research Journal of Modernization in Engineering Technology and Science
(Peer-Reviewed, Open Access, Fully Refereed International Journal)
Volume:06/Issue:11/November-2024 Impact Factor- 8.187 www.irjmets.com

Formulation and Evaluation of sustained release Microspheres of Cisplatin

Characterization of microspheres

Surface topography by scanning electron microscopy (SEM)

Figure A shows SEM photograph of optimized microspheres at 100× magnification, at 1000× magnification. SEM photographs showed discrete, spherical microspheres. SEM photographs also showed the presence of drug crystal on the surface of microspheres revealing that the microspheres were having some rough surface**.** The drug crystals on microspheres were may be due to the presence of un entrapped drug in dispersion medium.

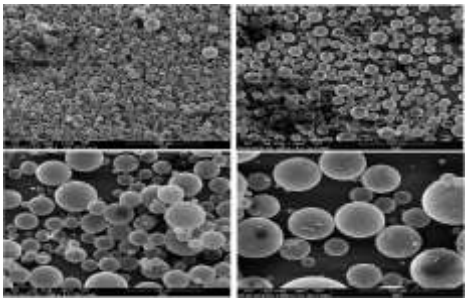

Fig 3: SEM photograph

The morphology of the prepared diverse types of microspheres was found to be virtually spherical in shape and have a rough surface, as illustrated in SEM photomicrographs of the microspheres.

Particle size:

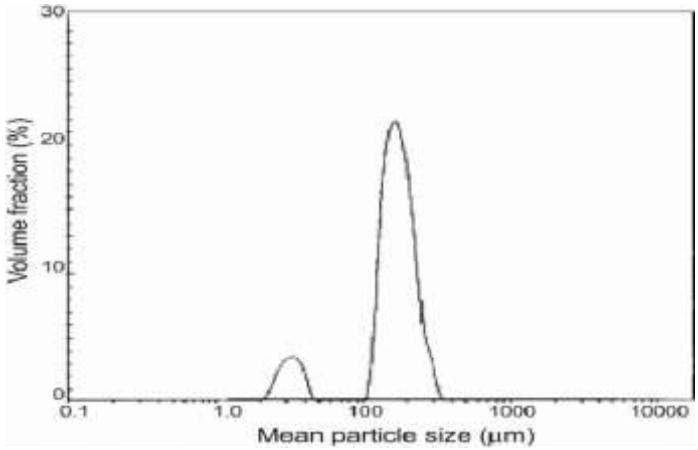

Fig 4: Particle size

The mean particle size of optimized cisplatin microspheres was found to be 602 micrometers.

Effect of formulation and process variables on Yield of sustained release microspheres, Particle size, Drug entrapment efficiency

Table 2: Effect of drug polymer ratio on Yield of microspheres, Particle size, Drug entrapment efficiency

Formulation code	%yield	Particle size	Drug Entrapment Efficiency
F1	80.32	536	84.65
F2	79.21	603	80.24
F3	76.25	587	79.52
F4	81.90	574	83.25
F5	83.21	521	86.35
F6	78.63	602	87.91
F7	74.21	582	84.93
F8	80.21	599	85.60

e-ISSN: 2582-5208
International Research Journal of Modernization in Engineering Technology and Science
(Peer-Reviewed, Open Access, Fully Refereed International Journal)
Volume:06/Issue:11/November-2024 Impact Factor- 8.187 www.irjmets.com

Drug release studies

Table 3: In vitro release data of film F_1 to F_8

Time (hrs.)	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8
0	0	0	0	0	0	0	0	0
1	23.69	25.93	22.17	20.14	21.34	23.93	22.13	23.61
2	38.46	39.63	38.93	35.19	34.56	32.16	34.92	31.69
3	47.12	48.25	45.21	44.63	43.61	42.39	40.21	41.36
4	55.13	59.53	55.10	52.31	53.19	52.01	51.20	50.21
5	69.86	68.14	65.90	64.82	63.52	60.20	61.39	61.50
6	73.89	73.14	71.20	73.15	72.90	75.93	74.36	73.15
7	82.15	80.21	82.61	83.64	82.13	83.16	84.16	82.34
8	90.32	91.17	93.15	92.22	93.67	95.76	94.38	93.12

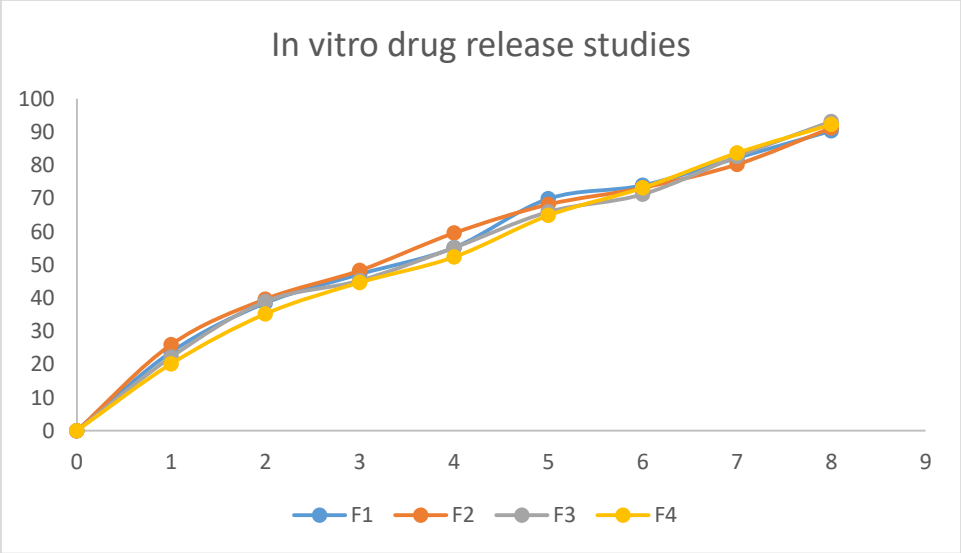

Fig 5: In vitro drug release of (F1- F4) formulation

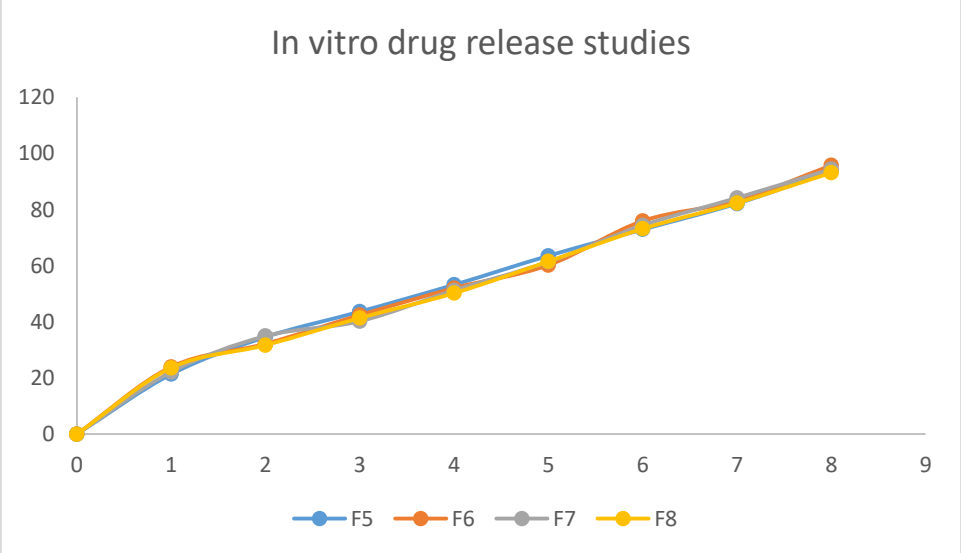

Fig 6: In vitro drug release of (F5- F8) formulation

e-ISSN: 2582-5208
International Research Journal of Modernization in Engineering Technology and Science
(Peer-Reviewed, Open Access, Fully Refereed International Journal)
Volume:06/Issue:11/November-2024 Impact Factor- 8.187 www.irjmets.com

Drug release kinetics:

All the 8 formulation of Cisplatin microspheres prepared were subjected to in vitro release studies these studies were carried out using dissolution cell apparatus.

The dissolution medium consisted of 10 ml of Standard buffer pH 7.4 period of time.

The results obtaining in vitro release studies were plotted in different model of data treatment as follows:

- Cumulative percent drug released vs. time (zero order rate kinetics)
- Log cumulative percent drug retained vs. time (First Order rate Kinetics)
- Cumulative percent drug released vs. square root of time (Higuchi's
- Classical Diffusion Equation)
- Log of cumulative % release Vs log time (Peppas Exponential Equation)

Zero order kinetics

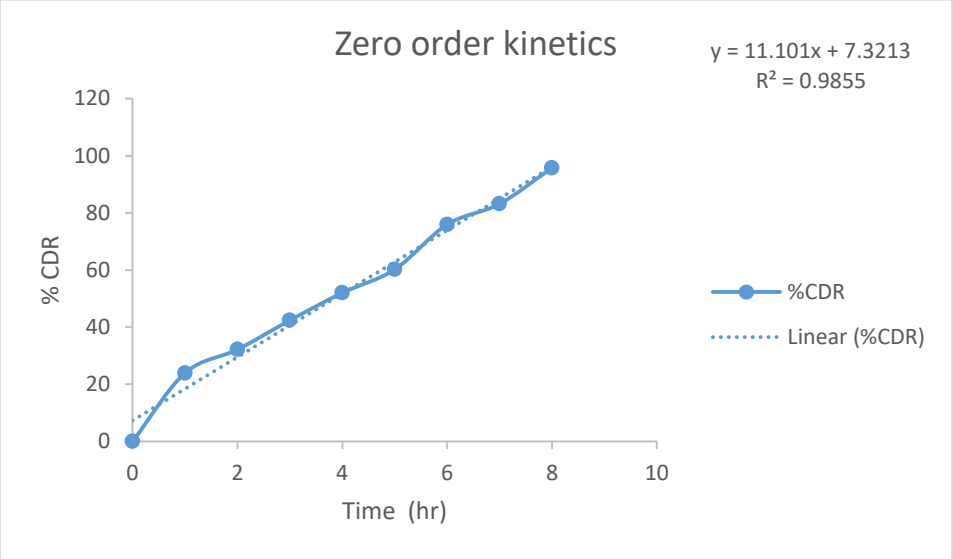

Fig 7: Zero order kinetics of optimized formulation

First order kinetics

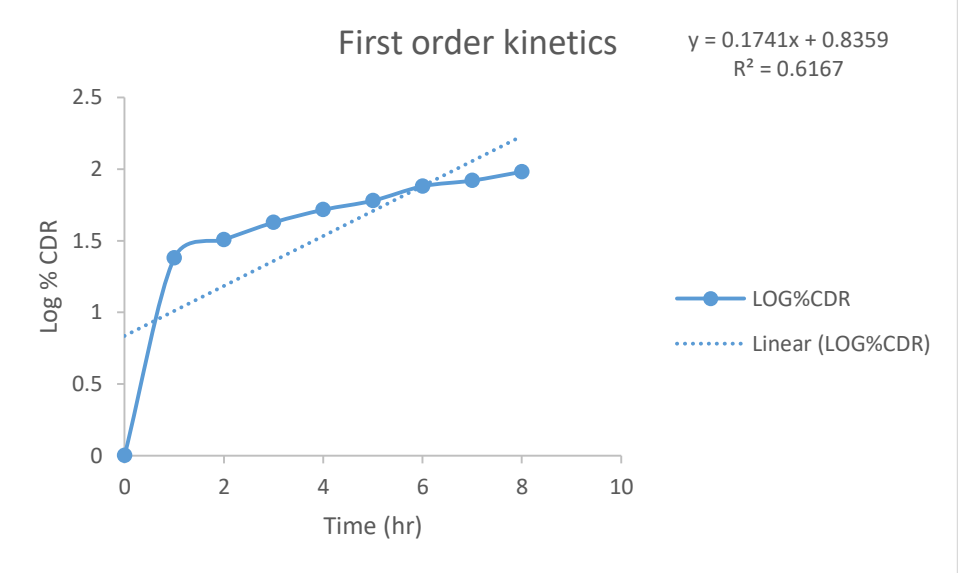

Fig 8: First order kinetics of optimized formulation

e-ISSN: 2582-5208
International Research Journal of Modernization in Engineering Technology and Science
(Peer-Reviewed, Open Access, Fully Refereed International Journal)
Volume:06/Issue:11/November-2024 Impact Factor- 8.187 www.irjmets.com

Higuchi model

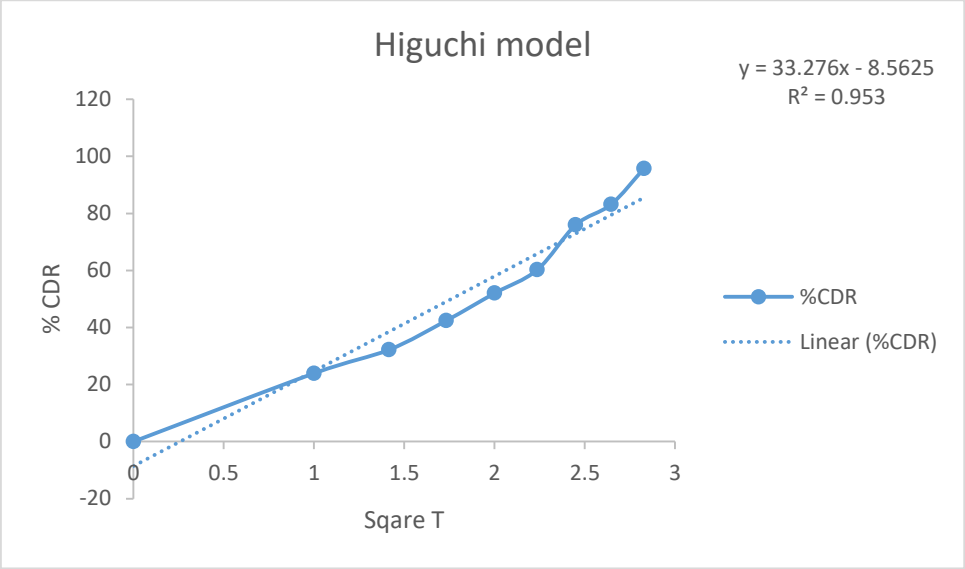

Fig 9: Higuchi model of optimized formulation

korsmeyer peppas

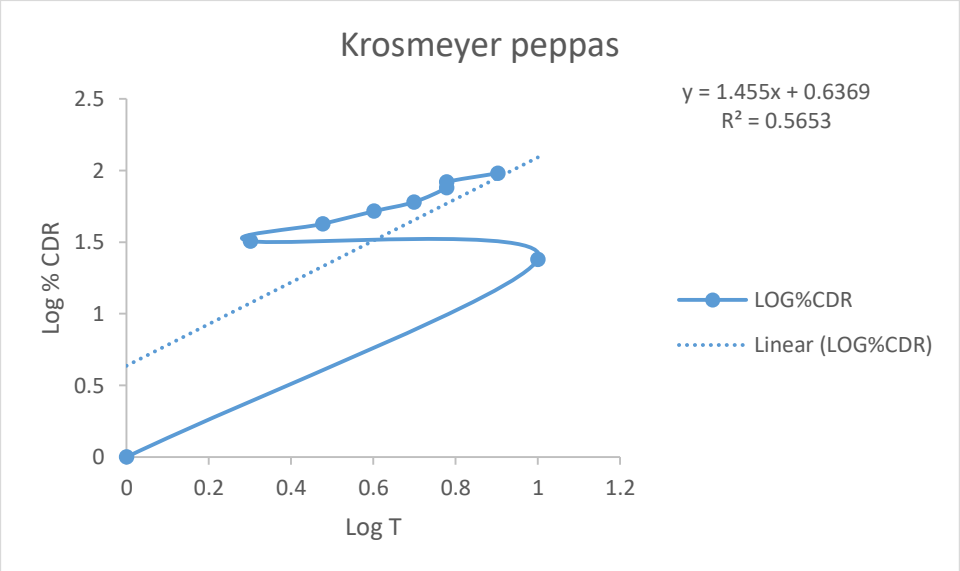

Fig 10: korsmeyer peppas of optimized formulation

The values of in vitro release were attempted to fit into various mathematical models. Plots of zero order, first order, Higuchi matrix, Pappas were respectively.

Regression values are higher with Zero order release kinetics. Therefore all the Cisplatin microspheres Zero order release kinetics.

The table indicates that r^2 values are higher for Higuchi's model compared for all the formulation. Hence cisplatin release from all the microspheres followed dissolution rate controlled mechanism

Stability studies

There was no significant change in physical and chemical properties of the Microspheres optimized formulation after 90 days. Parameters quantified at various time intervals were shown.

e-ISSN: 2582-5208
International Research Journal of Modernization in Engineering Technology and Science
(Peer-Reviewed, Open Access, Fully Refereed International Journal)
Volume:06/Issue:11/November-2024 Impact Factor- 8.187 www.irjmets.com

Table 4: Results of stability studies of optimized formulation

F. Code	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F-6	**25⁰C/60%RH % Release**	95.76	95.85	94.63	93.25	**Not less than 85 %**
F-6	**30⁰C/75% RH % Release**	95.76	95.74	94.53	93.12	**Not less than 85 %**
F-6	**40⁰C/75% RH % Release**	95.76	95.60	94.45	93.10	**Not less than 85 %**

IV. CONCLUSION

Attempt has been made to prepare sustained release microspheres of cisplatin, a highly water soluble drug. These microspheres are used to treat advanced cancer of the bladder, ovaries, or testicles. The microspheres were prepared by Ionotropic gelation technique method using natural polymers as retarding polymers and evaluated for parameters like percentage yield, particle size, entrapment efficiency and the effect of preparation and process variables such as drug polymer ratio, speed, type of polymer and combination of polymers on evaluated parameters. Microspheres morphology was evaluated by SEM. The yield and entrapment efficiency was high for Sodium alginate microspheres were Particle size, entrapment efficiency and production yield were influenced by the type of polymer, polymer concentration, stirring speed and combination of polymers. In vitro dissolution of optimized formulations of various Polymer in pH 7.4 formulations are releasing the drug up to 8 hrs. Hence, it is concluded that cisplatin polymeric microspheres can be selected for the development of sustained drug delivery system for potential therapeutic uses and thereby improve the bioavailability

V. REFERENCES

[1] Niculescu-Duvaz I, Springer CJ. Antibody-directed enzyme prodrug therapy (ADEPT): a review. Advanced Drug Delivery Reviews 1997; 26: 151-72.

[2] Wheate NJ, Walker S, Craig GE, Oun R. The status of platinum anticancer drugs in the clinic and in clinical trials. Dalton Trans. 2010;39:8113–8127.

[3] Ali I, A Wani W, Saleem K, Haque A. Platinum compounds: a hope for future cancer chemotherapy. Anti-Cancer Agents Med Chem. 2013;13:296–306.

[4] Hartmann JT, Lipp HP. Toxicity of platinum compounds. Expert Opin Pharmacother. 2003;4:889–901.

[5] Sastry J, Kellie SJ. Severe neurotoxicity, ototoxicity and nephrotoxicity following high-dose cisplatin and amifostine. Pediatr Hematol Oncol. 2005;22:441–445.

[6] Alagusundaram.M, Microspheres as a Novel Drug Delivery Sysytem - A Review, International Journal of Chem Tech Research, 2009, 1 (3), Page 526-534. 10.

[7] M. Okubo, Production of submicron-size monodisperse polymer particles having aldehyde groups by seeded aldol condensation polymerization, Colloid and Polymer Science, 1993, 271, Pages109–113. 11.

[8] Pawan Chaware, Bioadhesive Microspheres: A Review On Preparation And In-Vitro Characterization, World Journal of Pharmaceutical Research, 4, (2), 423-436.

[9] Farah Hamad Farah, et. al., Magnetic Microspheres: A Novel Drug Delivery System, Analytical and Pharmaceutical Research, 2016 3 (5), Page 1-10.

[10] Jagtap Yogesh Mukund, et. al., Floating microspheres: a review, Brazilian Journal of Pharmaceutical Sciences, 2012, 48 (1), Page 17-30.

[11] Urs Häfeli, Review: Radioactive Microspheres for Medical Applicationsm, Cleveland Clinic Foundation, Radiation Oncology Department T28, page 1-29.

[12] Lachman LA, Liberman HA, Kanig JL. The Theory and Practice of Industrial Pharmacy. Varghese Publishng House, Mumbai, India: 1991, 3rd edition; P-414-415.

[13] Ando S, Putnam D, Pack DW, and Langer R. PLGA Microspheres Containing Plasmid DNA: Preservation of Super coiled DNA via Cry preparation and Carbohydrate Stabilization. J. Pharmaceut. Sci.1998;88(1): 126– 130.

[14] Ketie Saralidze, Polymeric Microspheres for Medical Applications, Materials, 2010, 3, Page 3537-3564.

[15] E Veena Rani, Preparation and Evaluation of Aspirin Loaded Microspheres by Solvent Evaporation Technique, Journal of Medicine and Biology, 2019, 1 (1), Page 27- 32.

[16] Saravana Kumar K, A Review on Microsphere for Novel drug delivery System, Journal of Pharmacy Research, 2012, 5(1), Page 420-424.

[17] Sanjay dey, Formulation and Optimization of Sustained Release Stavudine Microspheres Using Response Surface Methodology, International Scholarly Research Notices, 2011, pages 1-7.

[18] Gaurav kumar R. Agrawal, Formulation, physicochemical characterization and in vitro evaluation of human insulin-loaded microspheres as potential oral carrier, Prog Biomater (2017) 6:125–136.