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Research

Formulation And Evaluation Of Cytarabine Microspheres For Sustained Drug Delivery

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Abstract

The Drug Cytarabine has short half life and hence requires frequent administration. Therefore the possible way for formulating a sustained release formulation of mucoadhesive microspheres. These formulations are prepared by solvent evaporation technique by using polymers HPMC15cps+Carbopol 934p and HPMC15000cps +Carbopol 934p. Various evaluation parameters assessed, with a view to obtain sustained release of Cytarabine. In the present study six formulations are formulated by using Sodium Alginate and HPMC15cps+Carbopol 934p and HPMC15000cps +Carbopol 934p various proportions. The prepared Cytarabine microspheres are then subjected to IR, SEM, particle size, % yield, Swelling Index, Micrometric, % Drug entrapment efficiency, *In-vitro* mucoadhesion test and *in vitro* dissolution studies. The IR Spectra revealed that, there is no interaction between the polymer and Cytarabine. Cytarabine microspheres are spherical in nature, which was confirmed by SEM. The Optimized formulation C3 was found to release the drug for 12 h (99.13%) and follows peppas drug release kinetics model in dissolution studies.

Keywords: Cytarabine, HPMC15cps +Carbopol 934p, HPMC15000cps+Carbopol 934p and solvent evaporation technique.

INTRODUCTION

Oral route drug administration is by far the most preferable route for taking medications. However, their short circulating half life and restricted absorption via a defined segment of intestine limits the therapeutic potential of many drugs. Such a pharmacokinetic limitation leads in many cases to frequent dosing of medication to achieve therapeutic effect. Rational approach to enhance bioavailability and improve pharmacokinetic and pharmacodynamics profile is to release the drug in a controlled manner and site specific manner.

One of the most challenging areas of research in pharmaceuticals is the development of novel delivery systems for the controlled release of drugs and their delivery at the targeted site in the body to minimize the side effects and enhance the therapeutic efficacy of drugs[2,3]. The basic principle behind the controlled drug delivery system is to optimize the biopharmaceutic, pharmacokinetic and pharmacodynamics properties of drug in such a way that its efficacy is maximized by reducing side effects, dose frequency and cure the disease in short time by using low amount of drug administered with the most suitable route [4,5, 6,7].

In 1997, first time microspheres were prepared for the sustained action of the drug. Since then, microparticles have proved to be good candidates for sustained and controlled release of drug and become an alternative of conventional or immediate release formulations. These particles are also a beneficial to deliver the active pharmaceutical ingredients which are pharmacologically active but are difficult to deliver due to limited solubility in water. In such type drugs, the attainment of required therapeutic concentrations of drug in the blood is problematic enabling to attain higher C_{max}, T_{max} and area under curve. Microsphere – based formulations can release a constant amount of drug in the blood or to target drugs to specific site in the body [8,9].

For many decades, medication of an acute disease or a chronic disease has been accomplished by delivering drugs to the patients via various pharmaceutical dosage forms like tablets, capsules, pills, creams, ointments, liquids, aerosols, injectables and suppositories as carriers. To achieve and then to maintain the concentration of drug administered within the therapeutically effective range needed for medication, it is often necessary to take this type of drug delivery systems several times in a day. This results in a fluctuated drug level and consequently undesirable toxicity and poor efficiency. This factor as well as other factors such as repetitive dosing and unpredictable absorption leads to the concept of controlled drug delivery systems. The word new or novel in the relation to drug delivery system is a search for something out of necessity. An appropriately designed sustained or controlled release drug delivery system can be major advance toward solving the problem associated with the existing drug delivery system.

The objective of controlled release drug delivery includes two important aspects namely spatial placement and temporal delivery of drug. Spatial placement relates to targeting a drug to a specific organ or tissue, while Temporal delivery refers to controlling the rate of drug delivery to the target tissue.

Oral controlled release dosage forms have been developed over the past three decades due to their considerable therapeutic advantages such as ease of administration, patient compliance and flexibility in formulation. However, this approach is be dilled with several physiological difficulties such as inability to restrain and locate the controlled drug delivery system within the desired region of the gastrointestinal tract (GIT) due to variable motility and relatively brief gastric emptying time (GET) in humans which normally averages 2-3 h through the major absorption zone, i.e., stomach and upper part of the intestine can result in incomplete drug release from the drug delivery system leading to reduced efficacy of the administered dose.[10,11]

The objective in designing a controlled release system is to deliver the drug at a rate necessary to achieve and maintain a constant drug blood level. This rate should be similar to that achieved by continuous intravenous infusion where a drug is provided to the patient at a rate just equal to its rate of elimination. This implies that the rate of delivery must be independent of the amount of drug remaining in the dosage form and constant over time, i.e release from the dosage form should follow zero-order kinetics.[12]

Definition and general description

Microspheres can be defined as solid, approximately spherical particles ranging in size from 1 to 1000 μm. They are made of polymeric, waxy, or other protective materials, that is, biodegradable synthetic polymers and modified natural products such as starches, gums, proteins, fats, and waxes. The natural polymers include albumin and gelatin9-10 the synthetic polymers include polylactic acid and polyglycolic acid. Fig. 1.2 shows two types of microspheres: Microcapsules, where the entrapped substance is completely surrounded by a distinct capsule wall, and micromatrices, where the entrapped substance is dispersed throughout the microsphere matrix.

The potential use of microspheres in the pharmaceutical industry has been considered since the 1960s for the following applications:

Taste and odor masking Conversion of oils and other liquids to solids for ease of handling Protection of drugs against the environment (moisture,light, heat, and/or oxidation) and vice versa (prevention of pain on injection) Delay of volatilization Separation of incompatible materials (other drugs or excipients such as buffers) Improvement of flow of powders Safe handling of toxic substances Aid in dispersion of water-insoluble substances in aqueous media,[13] and Production of sustained-release, controlled-release, and targeted medications Reduced dose dumping potential compared to large implantable devices Microencapsulation has also been used medically for the encapsulation of live cells and vaccines. Biocompatibility can be improved by the encapsulation of artificial cells and biomolecules such as peptides, proteins, and hormones, which can prevent unwanted immunological reactions that would lead to inactivation or rejection. Microspheres are used for isolating materials until their activity is needed. The biotechnology

industry employs microspheres to contain organisms and their recombinant products to aid in the isolation of these products.[14]

Microsphere carrier systems made from the naturally occurring biodegradable polymers have attracted considerable attention for several years in sustained drug delivery. Recently, dosage forms that can precisely control the release rates and target drugs to a specific body site have made an enormous impact in the formulation and development of novel drug delivery systems. Microspheres form an important part of such novel drug delivery systems[15]. Microspheres have varied applications and are prepared using assorted polymers. However; the success of these microspheres is limited owing to their short residence time at the site of absorption. So, various attempt have been made to increase the bioavailability as well as prolong the gastric residence time of dosage form in the stomach resulted in development of bio adhesive drug delivery system which will provide an intimate contact of the drug delivery system with the absorbing membranes[16]. This can be achieved by coupling mucoadhesion characteristics to microspheres and developing mucoadhesive microspheres. Mucoadhesive microspheres have advantages such as efficient absorption and enhanced bioavailability of drugs owing to a high surface-to-volume ratio, a much more intimate contact with the mucus layer, and specific targeting of drugs to the absorption site[17]. Gastric mucoadhesive drug delivery offers a number of applications for drugs having poor bioavailability because of narrow absorption window in the upper part of gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability.

MATERIALS AND METHODS

Materials

Cytarabine-Procured from Million Health Pharmaceuticals. provided by SURA LABS ,Dilsukhnagar, Hyderabad, HPMC15cps +Carbopol 934p (ratio)-Merk specialities Pvt Limited, Mumbai, HPMC15000cps + Carbopol 934p-Merk specialities Pvt Limited, Mumbai, Liquid paraffin (ml)-Merk specialities Pvt Limited,Mumbai, Span-80 (2%)-Merk specialities Pvt Limited,Mumbai.

Methodology

Preformulation studies

Spectroscopic studies

Preparation of 0.1n hcl (pH 1.2)

Take 8.5ml of HCl in a 1000ml volumetric flask and make up the volume with distilled water

Determination of λ_{MAX}

Weigh 10mg of Cytarabine and transferred into 10ml volumetric flask and dissolved in 10ml methanol (stock-I) to get concentration of 1000 µg/ml. From the stock-I take 1ml solution and make up 10ml with 0.1N HCL. From the second stock take 1ml solution and make up to 10ml with 0.1N HCL to get 10 µg/ml. Then scan from 200-400nm.

Preparation of Standard Calibration Curve of Cytarabine

1. 10 mg of Cytarabine was accurately weighed and dissolved in 10ml of methanol (Stock Solution – I) to get a concentration of 1000 µg/ml.
2. From the stock solution- I, 1ml of aliquots was taken and suitably diluted with 0.1N HCl (Stock Solution-II) to get concentrations of 100µg/ml.
3. From the stock solution- II, aliquots were taken and suitably diluted with 0.1N HCl (pH 1.2) to get concentrations in the range of 5 to 25µg/ml. The absorbance of these samples were analyzed by using UV-Visible Spectrophotometer at 272nm against reference solution 0.1N HCl (pH 1.2). The procedure repeated to pH 6.8 phosphate buffer and pH 7.4 phosphate buffer.

Method of preparation

Microspheres were prepared by emulsification solvent evaporation technique. Briefly, Cytarabine and polymers were mixed in 50ml distilled water. A different polymer ratio 1:1, 1:2 and 1:3 used to prepare the different formulations. Polymeric aqueous solution was made in which the drug was dispersed and then the solution was added drop wise into 150 ml of light liquid paraffin containing 2% span-80 as an emulsifying agent. The aqueous phase was emulsified in oily phase by stirring the system in a 500ml beaker, Constant stirring at 500 rpm was carried out using magnetic stirrer at 80ºC, stirring and heating were maintained for 4hrs, Until The aqueous phase was evaporated. The microspheres were washed 5 times with n-hexane, filtered through whattman's filter paper and dried in hot air oven at 50°C for 2 hours.

Characterization of microspheres

Table 1: Prepared formulation of Microspheres

INGREDIENTS	FORMULATION CODES					
	C1	C2	C3	C4	C5	C6
Cytarabine	100	100	100	100	100	100
HPMC15cps +Carbopol 934p (ratio)	1:1	1:2	1:3	-	-	-
HPMC15000cps + Carbopol 934p	-	-	-	1:1	1:2	1:3
Liquid paraffin (ml)	150	150	150	150	150	150
Span-80 (2%)	2	2	2	2	2	2

RESULTS AND DISCUSSION

Preformulation studies
Spectroscopic studies

Determination of λ_{max}

A solution of 10µg/ml of Cytarabine was scanned in the range of 200 to 400nm. The drug exhibited a λmax at 272 and 275nm in simulated gastric fluid pH 1.2 and pH 7.4 phosphate buffer respectively. Correlation between the concentration and absorbance was found to be near to 0.998, with a slope of 0.028 and intercept of 0.004.

Calibration curve of Cytarabine in simulated gastric fluid pH 1.2

Table 8.1 shows the calibration curve data of Cytarabine in simulated gastric fluid pH 1.2 at 272nm. Fig.8.1 shows the standard calibration curve with a regression value of 0.999, slope of 0.022 and intercept of 0.007 in simulated gastric fluid pH 1.2. The curve was found to be linear in the concentration range of 5-25µg/ml.

Table 2: Calibration curve data for Cytarabine in simulated gastric fluid pH 1.2

Concentration (µg /ml)	Absorbance
0	0
5	0.122
10	0.242
15	0.346
20	0.454
25	0.569

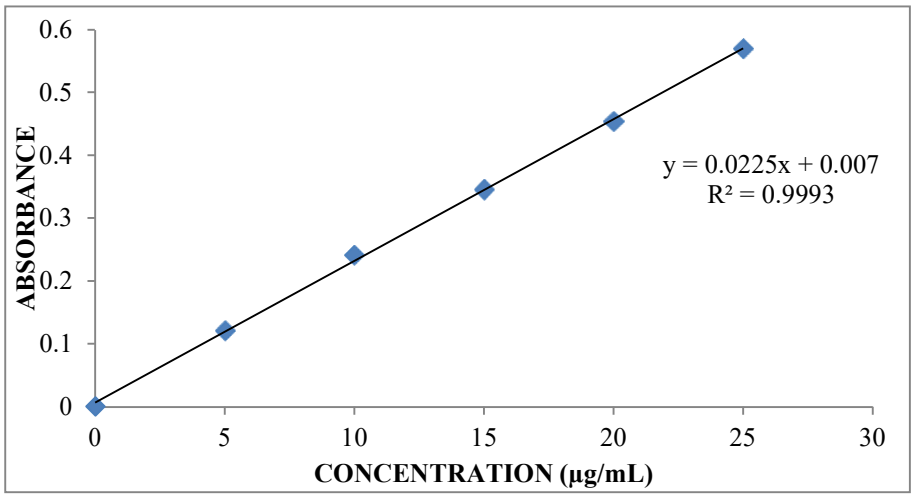

Fig 1 : Standard graph of Cytarabine in simulated gastric fluid pH 1.2

Calibration curve of Cytarabinein pH 7.4 phosphate buffer

Table 8.2 shows the calibration curve data of Cytarabine in pH 7.4 phosphate buffer at 275nm. Fig. 8.2 shows the standard calibration curve with a regression value of 0.999, slope of 0.027 and intercept of 0.007 in simulated gastric fluid pH 1.2. The curve was found to be linear in the concentration range of 5-25µg/ml.

Table 3: Calibration curve data for Cytarabine in pH 7.4 phosphate buffer

CONCENTRATION (µg /ml)	ABSORBANCE
0	0
5	0.148
10	0.286
15	0.432
20	0.557
25	0.691

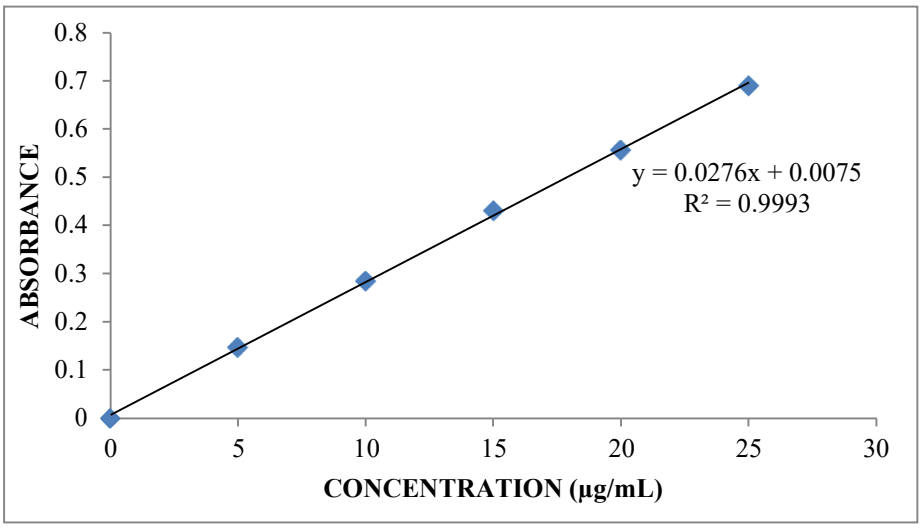

Fig 2: Standard graph of Cytarabine in pH 7.4 phosphate buffer

Evaluation and characterisation of microspheres

Micrometric Properties

The mean size increased with increasing polymer concentration which is due to a significant increase in the viscosity, thus leading to an increased droplet size and finally a higher microspheres size. Microspheres containing HPMC15cps +Carbopol 934p had a size range of 320.25 µm to 457.31µm. Microspheres containing HPMC15000cps + Carbopol 934p as copolymer exhibited a size range between 305.45 µm to 385.19µm.

The particle size data is presented in Tables 8.3. The effect of drug to polymer ratio on particle size is displayed in Figure. The particle size as well as % drug entrapment efficiency of the microspheres increased with increase in the polymer concentration.

The bulk density of formulation C1 to C6 containing HPMC15cps +Carbopol 934p and HPMC15000cps + Carbopol 934p formulation was in the range of 0.44 ± 0.03 to 0.55 ± 0.011 gm./cm^3 (as shown in table 8.3), Tapped density 0.50± 0.061 to 0.62 ± 0.011and hausners ratio 1.12 ± 0.015 to 1.16 ± 0.032.

The Carr's index of formulation C1 to C6 containing different grades of HPMC15cps +Carbopol 934p and HPMC15000cps + Carbopol 934p 11.29 ± 0.35 to 14.28 ± 0.47 respectively. The angle of repose of formulation C1 to C6 containing HPMC15cps +Carbopol 934p and HPMC15000cps + Carbopol 934p formulation was in the range <28.53 respectively (as shown in table 8.3) The values of Carr's index and angle of repose indicate good flow properties.

Table 4: Micromeritic property of floating microspheres of Cytarabine

Formulation code	Mean particle size	Bulk density ((gm./cm^3))	Tapped density (gm./cm^3)	Hauseners ratio	Carr's index	Angle of repose
C1	320.25	0.44 ± 0.03	0.50± 0.061	1.13 ± 0.012	12 ± 0.58	26.12 ± 0.1
C2	338.15	0.48 ± 0.06	0.56 ± 0.08	1.16 ± 0.032	14.28 ± 0.47	28.53 ± 0.57
C3	457.31	0.55 ± 0.08	0.62 ± 0.011	1.12 ± 0.015	11.29 ± 0.57	25.46 ± 0.57
C4	305.45	0.53 ± 0.09	0.61 ± 0.071	1.15 ± 0.021	13.1 ± 0.15	27.61 ± 0.63
C5	351.12	0.49 ± 0.01	0.56 ± 0.08	1.14 ± 0.012	12.5 ± 0.21	25.15 ± 0.58
C6	385.19	0.55 ± 0.011	0.62 ± 0.06	1.12 ± 0.023	11.29 ± 0.35	26.08 ± 0.51

Percentage yield

It was observed that as the polymer ratio in the formulation increases, the product yield also increases. The low percentage yield in some formulations may be due to blocking of needle and wastage of the drug-polymer solution, adhesion of polymer solution to the magnetic bead and microspheres lost during the washing process. The percentage yield was found to be in the range of 86.15 to 98.17 % for microspheres containing HPMC15cps +Carbopol 934p, 82.24 to 95.12 % for microspheres containing HPMC15000cps + Carbopol 934p.

Drug entrapment efficiency

Percentage Drug entrapment efficiency of Cytarabine ranged from 76.29 to 98.38 % for microspheres containing HPMC15cps +Carbopol 934p, 80.77 to 93.54% for microspheres containing HPMC15000cps + Carbopol 934p. The drug entrapment efficiency of the prepared microspheres increased progressively with an increase in proportion of the respective polymers. Increase in the polymer concentration increases the viscosity of the dispersed phase. The particle size increases exponentially with viscosity. The higher viscosity of the polymer solution at the highest polymer concentration would be expected to decrease the diffusion of the drug into the external phase which would result in higher entrapment efficiency. The % drug entrapment efficiency of the prepared microspheres is displayed in Table 8.4, and displayed in Figures.

Table 6: Percentage yield and percentage drug entrapment efficiency of the prepared microspheres

S.No.	Formulation code	% yield	Drug Content (mg)	% Drug entrapment efficiency
1	C1	86.15	90.40	76.29
2	C2	90.60	92.83	85.14
3	C3	98.17	97.10	98.38
4	C4	82.24	83.91	80.77
5	C5	86.46	89.73	90.16

6	C6	95.12	92.50	93.54

Swelling studies

The swelling ratio is expressed as the percentage of water in the hydrogel at any instant during swelling. Swellability is an important characteristic as it affects mucoadhesion as well as drug release profiles of polymeric drug delivery systems. Swellability is an indicative parameter for rapid availability of drug solution for diffusion with greater flux. Swellability data revealed that amount of polymer plays an important role in solvent transfer. It can be concluded from the data shown in Table 8.5 that with an increase in polymer concentration, the percentage of swelling also increases.

Table 7: Swelling studies

S.NO.	Formulation Code	Initial (wt)	Final (wt)	Percentage Swelling
1	C1	15	18.65	80.42
2	C2	15	17.15	87.46
3	C3	15	16.01	93.69
4	C4	15	19.71	76.10
5	C5	15	17.36	86.40
6	C6	15	16.09	93.22

***In-vitro* mucoadhesion test**

As the polymer to drug ratio increased, microspheres containing HPMC15cps +Carbopol 934p exhibited % mucoadhesion ranging from 53.41 to 90.14 %, microspheres containing HPMC15000cps+Carbopol 934p exhibited % mucoadhesion ranging from 62.78 to 87.63%. The results of *in-vitro* mucoadhesion test are compiled in Table 8.6. Comparative depiction of % mucoadhesion is depicted in Fig.8.5 and 8.6.

Table 8: Percentage mucoadhesion of the prepared microspheres

S.NO.	FORMULATION CODE	No. OF MICROSPHERES		PERCENTAGE MUCOADHESION
		INITIAL	FINAL	
1	C1	15	10.31	53.41
2	C2	15	13.47	71.51
3	C3	15	14.96	90.14
4	C4	15	11.85	62.78
5	C5	15	13.41	70.14
6	C6	15	14.28	87.63

***In-vitro* drug release studies**

Dissolution studies of all the formulations were carried out using dissolution apparatus USP type I. The dissolution studies were conducted by using dissolution media, pH 1.2. The results of the *in-vitro* dissolution studies of formulations C1 to C6 are shown in table. The plots of Cumulative percentage drug release Vs Time. Figure shows the comparison of % CDR for formulations C1 to C3, figure for formulations C4 to C6.

The formulations C1, C2 and C3 containing HPMC15cps+Carbopol 934p showed a maximum release of 96.14 % at 9 hours, 97.82 % after 10 hours and 99.13 % after 12 hours respectively.

The formulations C4, C5 and C6 containing HPMC15000cps+Carbopol 934p showed a maximum release of 95.93% after 9 hours, 96.85% after 11 hours and 97.12% after 12 hours respectively.

This shows that more sustained release was observed with the increase in percentage of polymers. As the polymer to drug ratio was increased the extent of drug release increased.

Table 9: *In-vitro* drug release data of Cytarabine microspheres

TIME (H)	CUMULATIVE PRECENT OF DRUG RELEASED					
	C1	C2	C3	C4	C5	C6
0	0	0	0	0	0	0

1	19.72	17.53	13.98	25.19	11.20	08.91
2	30.90	27.19	23.51	32.25	18.86	13.58
3	35.45	32.26	30.60	39.13	23.32	18.16
4	43.83	38.37	35.19	46.56	31.12	25.93
5	55.42	45.20	41.99	50.83	37.28	31.75
6	60.01	50.12	48.45	66.93	43.67	39.54
7	79.95	68.86	53.72	78.54	50.49	43.83
8	87.50	77.10	60.02	90.17	56.53	58.76
9	96.14	85.23	65.14	95.93	62.68	65.12
10		97.82	71.23		88.94	79.43
11			89.27		96.85	91.86
12			99.13			97.12

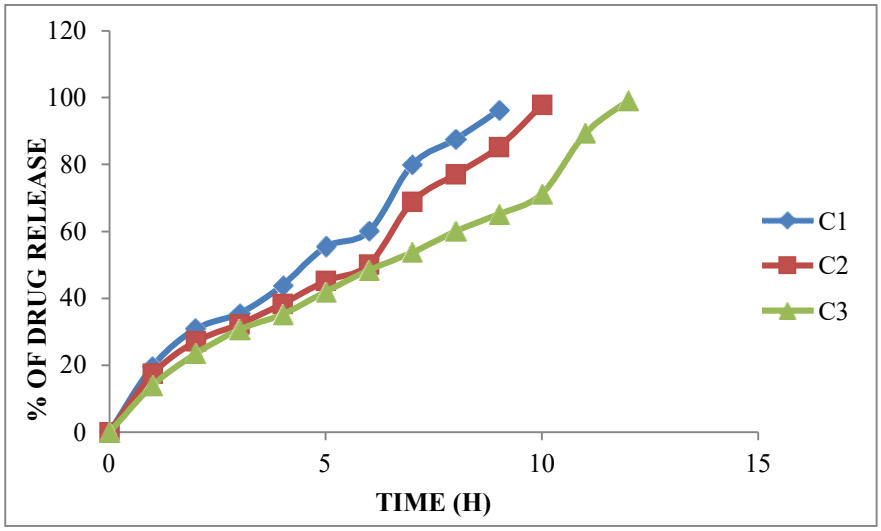

Fig 3: *In-Vitro* drug release profile of Cytarabine microspheres containing HPMC15cps +Carbopol 934p

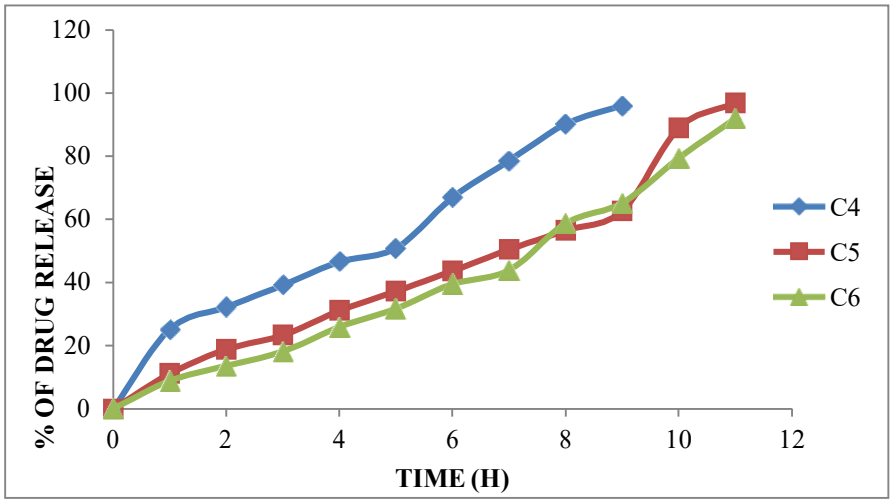

Fig 4: *In-Vitro* drug release profile of Cytarabine microspheres containing HPMC15000cps + Carbopol 934p

***In-vitro* drug release kinetics**

For understanding the mechanism of drug release and release rate kinetics of the drug from dosage form, the *in-vitro* drug dissolution data obtained was fitted to various mathematical models such as zero order, First order,

Higuchi matrix, and Krosmeyer-Peppas model. The values are compiled in Table 8.9. The coefficient of determination (R^2) was used as an indicator of the best fitting for each of the models considered. The kinetic data analysis of all the formulations reached higher coefficient of determination with the peppas drug release model whereas release exponent value (n) ranged from 0.983. From the coefficient of determination and release exponent values, it can be suggested that the mechanism of drug release follows Korsmeyer-Peppas model along with non-Fickian diffusion mechanism which leading to the conclusion that a release mechanism of drug followed combination of diffusion and spheres erosion.

Table 10: Release kinetics studies of the optimized formulation (C3)

CUMULATIVE (%)	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATI	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
13.98	1	1.000	1.146	0.000	1.935	13.980	0.0715	-0.854	86.02	4.642	4.414	0.227
23.51	2	1.414	1.371	0.301	1.884	11.755	0.0425	-0.629	76.49	4.642	4.245	0.397
30.6	3	1.732	1.486	0.477	1.841	10.200	0.0327	-0.514	69.4	4.642	4.109	0.532
35.19	4	2.000	1.546	0.602	1.812	8.798	0.0284	-0.454	64.81	4.642	4.017	0.625
41.99	5	2.236	1.623	0.699	1.764	8.398	0.0238	-0.377	58.01	4.642	3.871	0.770
48.45	6	2.449	1.685	0.778	1.712	8.075	0.0206	-0.315	51.55	4.642	3.722	0.920
53.72	7	2.646	1.730	0.845	1.665	7.674	0.0186	-0.270	46.28	4.642	3.590	1.051
60.02	8	2.828	1.778	0.903	1.602	7.503	0.0167	-0.222	39.98	4.642	3.419	1.222
65.14	9	3.000	1.814	0.954	1.542	7.238	0.0154	-0.186	34.86	4.642	3.267	1.375
71.23	10	3.162	1.853	1.000	1.459	7.123	0.0140	-0.147	28.77	4.642	3.064	1.577
89.27	11	3.317	1.951	1.041	1.031	8.115	0.0112	-0.049	10.73	4.642	2.206	2.436
99.13	12	3.464	1.996	1.079	-0.060	8.261	0.0101	-0.004	0.87	4.642	0.955	3.687

Compatibility studies

Drug polymer compatibility studies were carried out using Fourier Transform Infra Red spectroscopy to establish any possible interaction of Drug with the polymers used in the formulation. The FT-IR spectra of the formulations were compared with the FTIR spectra of the pure drug.

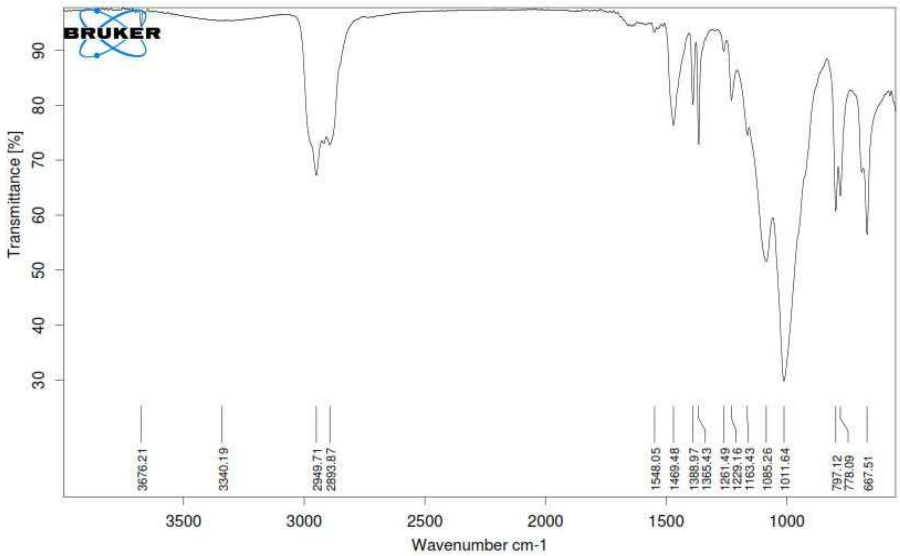

Fig 5: FT-IR spectra of Pure drug

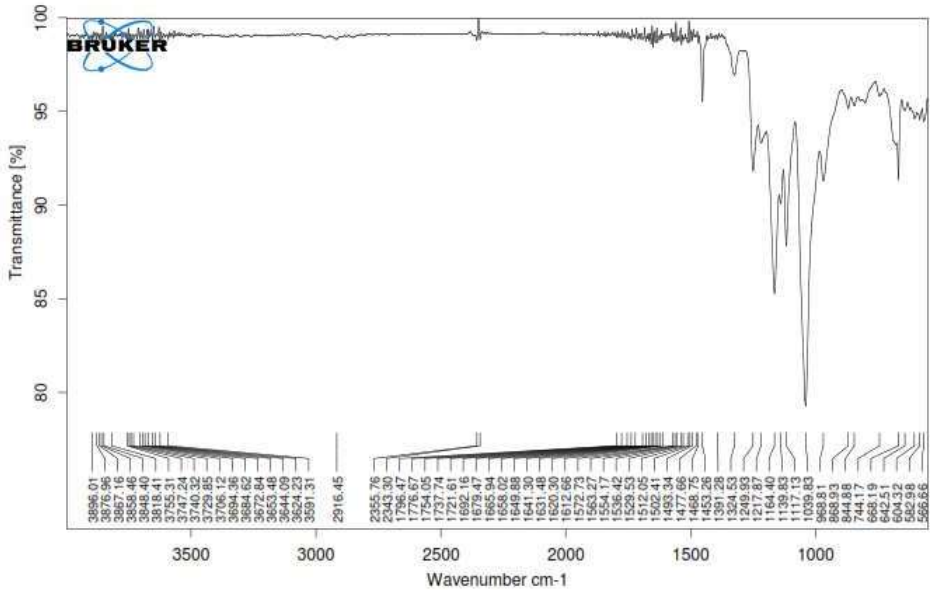

Fig 6: FT-IR spectra of Optimised formulation

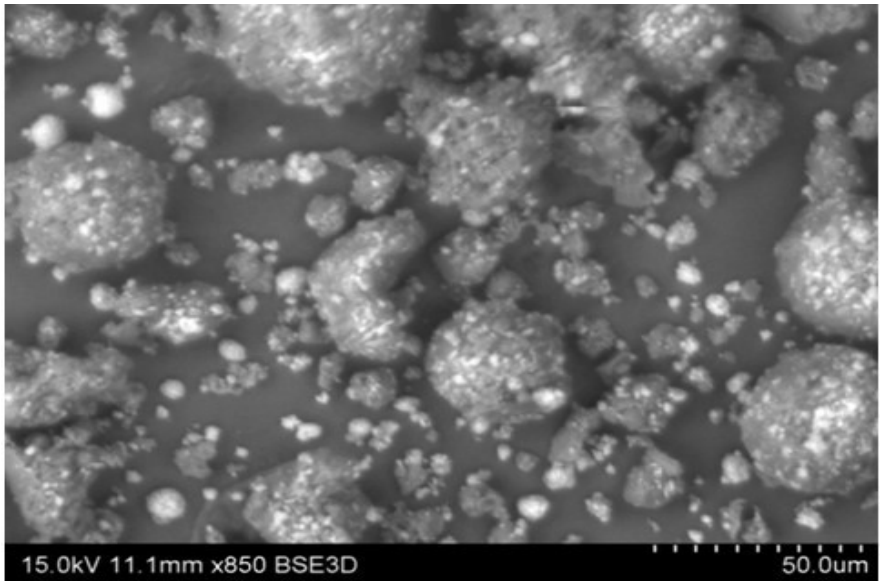

Fig 7: SEM of Optimised formulation

CONCLUSION

Cytarabine loaded microspheres were prepared solvent evaporation technique. Six batches of formulations, of drug: polymer ratio i.e. 1:1,1:2 and 1:3, were prepared and evaluated for particle size, % yield, drug content, drug entrapment efficiency, Swelling studies, *In-vitro* mucoadhesion test, *in vitro* drug release and Flow property had shown satisfactory results. The IR Spectra's revealed that, there is no interaction between polymer and Cytarabine. The polymer used is compatible with the Cytarabine. The basis of release data and graphical analysis formulation C3 showed a good sustained release profile with maximum entrapment efficiency because of high polymer concentration. Hence, from all the above obtained data it can be summarized that it is possible to formulate a promising sustained release mucoadhecive microspheres of Cytarabine by solvent evaporation technique using an ideal polymer like HPMC15cps +Carbopol 934p.

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