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Review article

Therapeutics

Preparation, characterization, and in-vitro evaluation of decitabine microspheres

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ABSTRACT

The main aim of any drug therapy is to achieve a desire concentration of the drug in blood or tissue, which is therapeutically effective and non-toxic for an extended period of time. This can be achieved by proper design of controlled-release dosage regimen. Various approaches have been developed for controlled release; Microspheres are the potential candidate for controlled release of drug. Decitabine microsphere were prepared with a coat consisting of alginate and polymer such as HPMC and Sodium alginate by Ionic cross-linking technique using CaCl_2 . The microspheres were evaluated with respect to the yield, particle size, Drug entrapment efficiency, in vitro drug release and stability. Microspheres were characterized by FTIR studies. It was found that the particle size and Drug entrapment efficiency of microspheres increases with increasing drug-to-polymer ratio.

Keywords: Decitabine, ionotropic gelation technique, HPMC, sodium alginate, FTIR studies, in vitro drug release studies.

INTRODUCTION

For many decades treatment of an acute disease or a chronic illness has been mostly accomplished by delivery of drugs to the patients using various pharmaceutical dosage forms, including tablets, capsules, pills, suppositories, creams, ointments, liquids, aerosols and injectables as drug carriers¹. Recently, several technical advancements have been made. They have resulted in the development of new techniques for drug delivery². These techniques are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and / or targeting the delivery of drug to a tissue³. Although these advancements have led to the development of several novel drug delivery systems that could revolutionize the method of medication and provide a number of therapeutic benefits, they also create some confusion in the terminology between “Controlled release” and “Sustained release.” Unfortunately, these terms have been often used interchangeably in the scientific literature

and technical presentations over the years⁴. The “microspheres” are characteristically free flowing powders consisting of proteins or synthetic polymers, which may be biodegradable, and ideally having a particle size less than 200 μm microspheres are, in strict sense, spherical empty particles⁵. The purpose of this study to formulation and evaluation of Decitabine microspheres for controlled release. The biocompatible polymers were used for the preparation of microsphere. Decitabine is used to treat myelodysplastic syndrome (a group of conditions in which the bone marrow produces blood cells that are misshapen and does not produce enough healthy blood cells). Decitabine is in a class of medications called hypomethylation agents.^{6,7} The resultant microspheres were characterized for their size, Morphology, Encapsulation Efficiency, and drug release. The Objective of the present study was to microencapsulate the Decitabine drug. It is used to treatment of hypomethylation agents. To provide controlled release and minimizing or eliminating local side effect by avoiding the drug release in the upper gastrointestinal track.

MATERIALS AND METHODS

Materials

Decitabine was collected as a gift sample from Hetero Drugs Ltd, Hyd, Tragacanth, Sodium alginate and various excipients were purchased from AR Chemicals, HYD.

FORMULATION DEVELOPMENT

METHODOLOGY

Compatibility studies Fourier transform infrared (FTIR) analysis

The FTIR analysis of the Decitabine was carried out for qualitative compound identification. To check the compatibility of the drug with various polymers, IR spectra of drug, polymers, and combination of the drug and polymers were taken on an FTIR spectrophotometer in the wave number region of 4000-400/cm⁸.

Table: 1 Formulation table of Decitabine microspheres

F. no	Decitabine (mg)	Sodium alginate	HPMC	Ethanol (ml)	CaCl ₂
F1	10	50	-	5	5%
F2	10	100	-	5	5%
F3	10	150	-	5	5%
F4	10	200	-	5	5%
F5	10	-	50	5	5%
F6	10	-	100	5	5%
F7	10	-	150	5	5%
F8	10	-	200	5	5%

Method

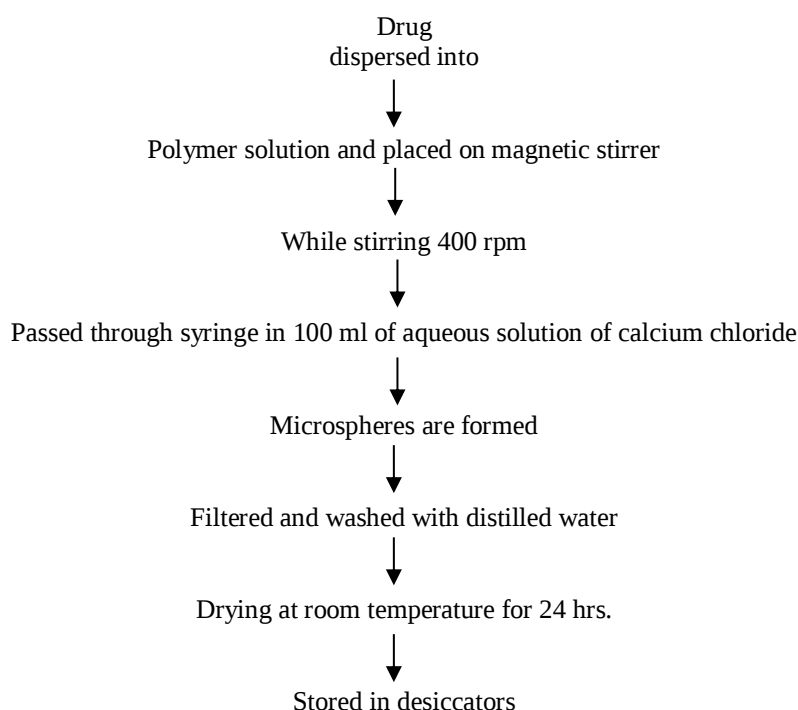


Fig 1: Schematic representation of preparation of microspheres of Decitabine

Evaluation of microspheres^{9,10,11}

The prepared sustained release microspheres were evaluated for various parameters such as yield, particle size, drug entrapment efficiency, evaluation of in vitro drug release and the effect of different formulation and process variables such as drug to polymer ratio, type of polymer, speed, and combination of polymers were studied.

Yield of microspheres

The yield of microspheres was calculated from the amount of microspheres obtained divided by the total amount of components

$$\% \text{ Yield} = \frac{\text{Actual weight of the microspheres}}{\text{Total weight of components}} \times 100$$

Particle size and shape

The particle size of the microspheres was measured by optical microscopy. The eyepiece micrometer was calibrated using a stage micrometer and the calibration factor was used further in the calculation of the size of microspheres. The microspheres were finely spread over a slide and visualized under an optical microscope using an eyepiece micrometer.

Surface morphology of the microspheres

The surface morphology of the sustained microspheres was studied with the aid of a Scanning Electron Microscope (SEM).

Drug entrapment efficiency (DEE)

The amount of drug entrapped was estimated by crushing 50 mg of microspheres using mortar and pestle, and extracting drug with aliquots of 7.4 pH buffer repeatedly. The extract was transferred to a 100 ml volumetric flask and the volume was made up using 6.8 pH buffer. The solution was taken in a beaker and sonicated in a bath sonicator for 2 hours. The solution was filtered and absorbance was measured after suitable dilutions spectrophotometrically at 244 nm against an appropriate blank¹². The amount of drug entrapped in the microspheres was calculated using the following formula

$$\text{DEE} = \frac{\text{Amount of drug actually present}}{\text{Theoretical drug load expected}} \times 100$$

In vitro drug release study

In vitro drug release studies were carried out for all formulations in Franz diffusion cell. Microspheres equivalent to 10 mg of Decitabine were poured into 5 ml aliquots were withdrawn at a predetermined intervals and equal volume of dissolution medium was replaced to maintain sink conditions. The necessary dilutions were made with 6.8 pH buffer and the solution was analyzed for the drug content spectrophotometrically using UV-Visible spectrophotometer (Lab India) at 244 nm against an appropriate blank. Trials were carried out for all formulations. From this cumulative percentage drug release was calculated and plotted against function of time to study the pattern of drug release¹³.

Stability studies

The success of an effective formulation can be evaluated only through stability studies. The purpose of stability testing is to

obtain a stable product which assures its safety and efficacy up to the end of shelf life at defined storage conditions and peak profile. The prepared Decitabine microspheres placed on plastic tubes containing desiccant and stored at ambient conditions, such as at room temperature, 40±2°C and refrigerator 2-8°C for a period of 90 days¹⁴.

RESULTS AND DISCUSSION

FT-IR Spectrum of Decitabine

FT-IR Spectra of Decitabine and F4 formulation were recorded. All these peaks have appeared in formulation and physical mixture, indicating no chemical interaction between Decitabine and polymer. It also confirmed that the stability of drug during microencapsulation process.

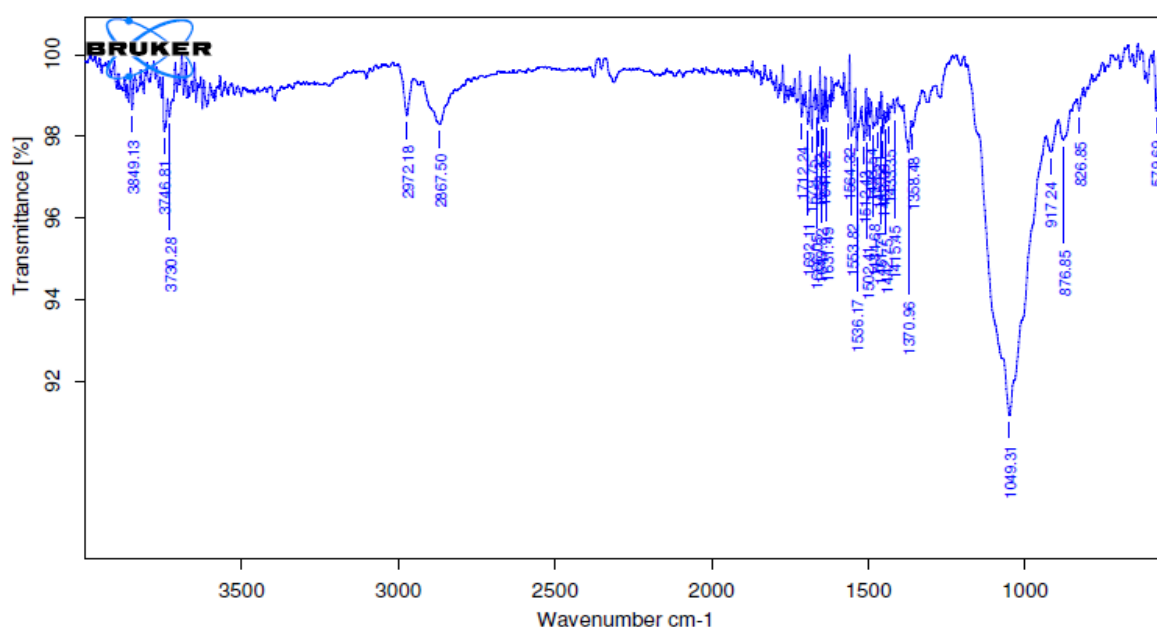


Fig 1: FTIR Studies of Decitabine

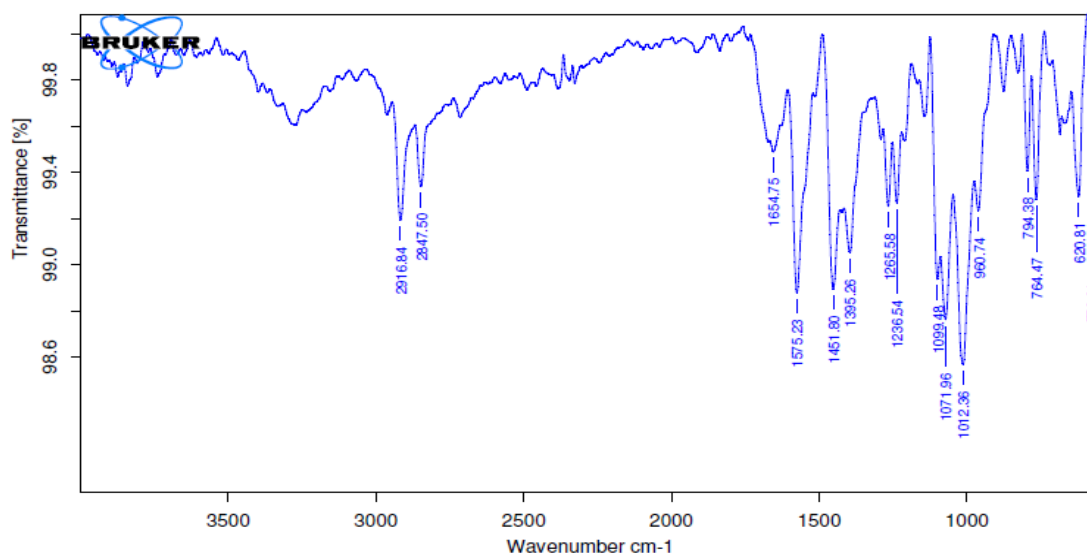


Fig 2: FTIR Studies of optimized formulation

Characterization of microspheres

Surface topography by scanning electron microscopy (SEM)

Figure 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 an entrapped drug in dispersion medium.

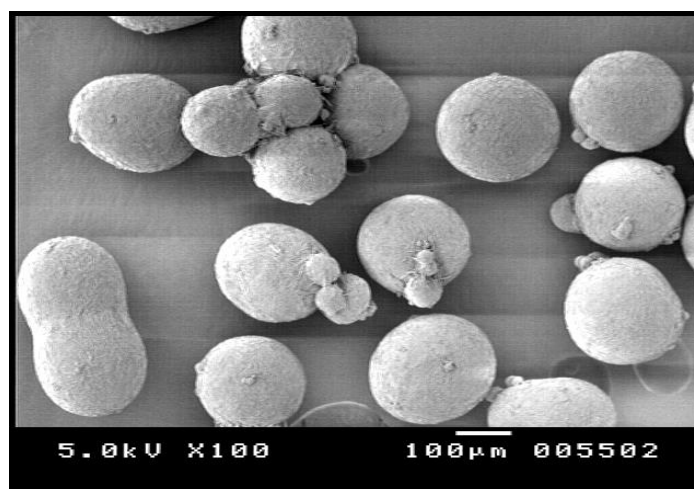


Fig 3: SEM photograph of Decitabine sat 100x and 1000x magnification.

Formulation and Evaluation of Microspheres of Decitabine

Optimization of formulation variables

Therefore, the optimized conditions for the formulation of microspheres were:

Results of the evaluation parameters of formulated controlled release microspheres

The prepared controlled release microspheres were evaluated for various parameters such as yield, drug entrapment efficiency, particle size, and *in vitro* drug release. And effect of preparation and process variables such as drug polymer ratio, speed, type of polymer and combination of polymers on particle size, yield, entrapment efficiency, and *in-vitro* release of Decitabine microspheres were also studied.

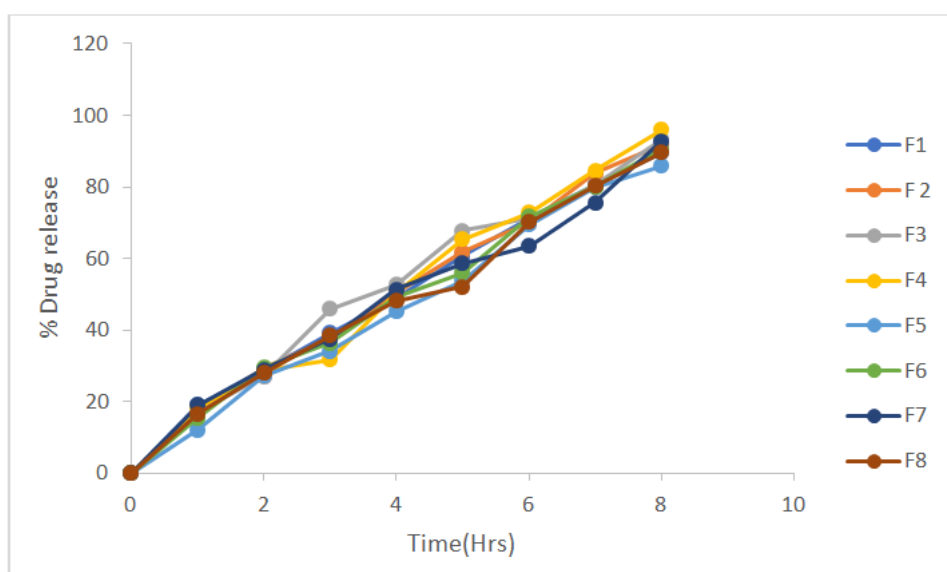
Table 2: Evaluation parameters of microspheres

Formulation code	%Yield	Particle size	Drug Entrapment Efficiency
F1	72.22	128.64	82.93
F2	78.19	140.25	84.23
F3	71.82	136.63	88.46
F4	74.82	129.52	92.62
F5	73.56	128.64	76.24
F6	75.24	124.12	78.26
F7	82.16	126.72	80.32
F8	83.56	132.54	82.56

Drug release studies

Table 3: Cumulative %drug release

Time(hrs)	F1	F 2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	19.1	16.98	17.15	18.31	12.2	15.5	18.96	16.55
2	28.66	29.23	26.98	28.55	27.18	29.56	28.92	27.94
3	39.12	37.68	45.86	31.78	34.22	36.45	37.55	38.45
4	48.73	50.36	52.68	50.27	45.18	49.25	51.44	48.24
5	60.64	61.85	67.85	65.28	53.81	55.98	58.55	52.15
6	71.19	69.94	71.25	72.85	69.46	71.65	63.56	70.22
7	80.68	83.86	80.45	84.64	79.92	80.15	75.72	80.25
8	89.69	91.63	93.36	95.98	85.88	90.55	92.86	89.62

**Fig 4: Cumulative percentage drug released Vs Time Curves of microspheres F1–F 8 in P^H 7.4 buffer.**

Here, keeping drug ratio constant and varied polymer ratio as the polymer concentration increases viscosity; this influences the interaction between disperse phase and dispersion medium that affects the size distribution of particle. And F4 formulation shows good results when compared to other formulations. Above graph indicates that %Drug release of F4 formulation shows better drug release when compared with other formulations.

Stability Study

There was no significant change in physical and chemical properties of the formulation F-4 after 3 Months. Parameters quantified at various time intervals were shown;

Table 4: Results of stability studies of optimized formulation F-4

Formulation Code	Parameters	Initial	1 st Month	2 nd Month	3 rd Month	Limits as per Specifications
F-4	25°C/60%RH % Release	95.98	95.26	95.24	95.18	Not less than 85 %
F-4	30°C/75% RH % Release	95.98	95.24	95.21	95.15	Not less than 85 %
F-4	40°C/75% RH % Release	95.98	95.23	95.20	95.18	Not less than 85 %

CONCLUSION

The present study was to prevent extensive metabolism of the drug and consequently to increase the bioavailability of the drug improve patient compliance, decreases toxicity, and increase efficacy in the form of microspheres. Attempt has been made to prepare controlled release microspheres of Decitabine, these microspheres are used to treat myelodysplastic syndrome. The microspheres were prepared by Iontropic gelation technique method using 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. Microsphere's morphology was evaluated by SEM. The yield and entrapment efficiency were high for Sodium alginate polymers. 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. F4 formulation shows better drug release when compared with other formulations.

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