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PREPARATION AND EVALUATION OF MICROPARTICLES CONTAINING CYCLOPHOSPHAMIDE FOR CONTROLLED RELEASE

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ABSTRACT
The present study aimed at preparation and Evaluation of microparticles for controlled release of Cyclophosphamide using blend of polymers in the treatment of Cancer. The microparticles of Cyclophosphamide were prepared by spray drying technique .The prepared microparticles were evaluated for drug polymer compatibility, the results shown that there were no significant interactions. The encapsulation efficacy was ranging from 69-90%. The *in-vitro* drug release studies indicate the release of drug in a controlled manner over a period of 12 hrs. It was found that the Cyclophosphamide release rate increased with a decreased amount of polymers. This can be adjusted by maintaining the concentration of the polymers. The formulation FD1 was found to be optimum formulation.

KEY WORDS: Cyclophosphamide, Cancer, spray drying, Controlled release.

INTRODUCTION
Controlled drug delivery systems containing polymeric carriers has gained increased interest in last two decades, because they can be fabricated into films, rods capsules and microparticles[1], they mask the unacceptable taste or odor of drugs, they stabilize drugs sensitive to oxygen, moisture or light, they eliminate incompatibilities among drugs.

Cyclophosphamide is an antineoplastic in the class of alkylating agents and is used to treat various forms of cancer. Alkylating agents are so named because of their ability to add alkyl groups to many electronegative groups under conditions present in cells. They stop tumor growth by cross-linking guanin bases in DNA double-helix strands - directly attacking DNA. This makes the strands unable to uncoil and separate. As this is necessary in DNA replication, the cells can no longer divide. In addition, these drugs add methyl or other alkyl groups onto molecules where they do not belong which in turn inhibits their correct utilization by base pairing and causes a miscoding of DNA. Alkylating agents are cell cycle-nonspecific. Alkylating agents work by three different mechanisms all of which achieve the same end result - disruption of DNA function and cell death.

METHODS
Preparation of microparticles
The microspheres were prepared by spray drying technique. Various formulations and process variables that could affect the preparation and properties of the microparticles were identified and optimized to get small, discrete and spherical microparticles. The formulation variables included concentration of drug: polymers ratio, amount of solvent used, types of excipients and its solubility.

Different parameters such as temperature of inlet air, drying temperature, concentration of different polymers and drug, feed rate, inlet air pressure and aspiration were optimized during the process. Optimum drying conditions were employed for the process i.e,

Inlet temperature	:	82°C
Feed-flow rate (ml/min)	:	5-6 ml/min
Compressed spray air flow	:	10 L/min
Air pressure	:	1.5 kg/cm^2

Table 1: Formulation chart of cyclophosphamide microparticles.

Ingredients	FA1	FA2	FB1	FB2	FC1	FC2	FC3	FC4	FD1	FD2	FE1	FE2
cyclophospamide (mg)	100	100	100	100	100	100	100	100	100	100	100	100
Polycarbophil (mg)	60	80	---	-----	----	-----	-----	-----	10	20	20	20
Chitosan-polycarbophil physical mixture(1:1) (mg)	----	-----	80	100	---	----	-----	-----	-----	----	---	---
IPEC (mg)	-----	-----	----	---	40	60	80	100	80	80	80	80
Chitosan (mg)	----	----	----	-----	----	----	----	---	10	20	20	20
SDC (mg)	----	----	-----	-----	---	----	----	----	----	----	3	4.5

Differential Scanning Calorimetry (DSC)

DSC is a technique in which the difference in heat flow between the sample and a reference is recorded versus temperature. All dynamic DSC studies were carried out on Du Pont thermal analyzer with 2010 DSC module. Calorimetric measurements were made with empty cell as the reference. The instrument was calibrated using high purity indium metal as standard. The dynamic scans were taken in nitrogen atmosphere at the heating rate of 10º C/Min. The runs were made in triplicate. The scanning temperature for reference pure drug and formulation are the same when dynamic measurements are performed, and hence the required heat energy for chemical transformation is directly recorded on a heat flow versus temperature graph. The energy is measured as Joules per kilocalorie.[5,6]

Drug loading and encapsulation efficiency

100 mg of microparticles were weighed and transferred to 100 ml volumetric flask containing pH 7.4 phosphate buffers. From this, 1 ml of solution was transferred to 10 ml volumetric flask and diluted up to the mark. Further 1 ml of this solution was diluted to 10 ml and absorbance was measured. The drug content was calculated by using the formula.[7,8]

$$\text{Amount of drug} = \frac{\text{Conc. from standard graph X dilution factor}}{1000}$$

Percentage encapsulation efficiency is found out by calculating the amount of drug present in 100 mg of microparticles. It is further calculated by using formula.

% Encapsulation Efficiency = b/a X100

Where, 'a' is the theoretical drug content and 'b' is the drug entrapped.

In vitro drug release studies

Release of Cyclophosphamide was determined using dissolution test apparatus USP type II at 100 rpm. The dissolution was studied using 900 ml of 0.1 N HCl, phosphate buffer 5.5, phosphate buffer pH 7.2. The temperature was maintained at 37±0.5°C. Aliquots (10 ml) of dissolution media were sampled at specified time intervals and replaced with fresh media immediately after sampling. Samples were analyzed for drug content by UV Visible spectroscopy.[9 10]

RESULTS AND DISCUSSION

Drug-excipient Compatibility Studies

The compatibility of drug and polymers under experimental conditions is important prerequisite before formulation. It is therefore necessary to confirm that the drug does not react with the polymers and excipients under experimental conditions and affect the shelf life of product or any other unwanted effects on the formulation. The DSC thermograms of the pure drug and formulation were taken, the obtained results indicates that there were no significant interactions between drug and polymer.

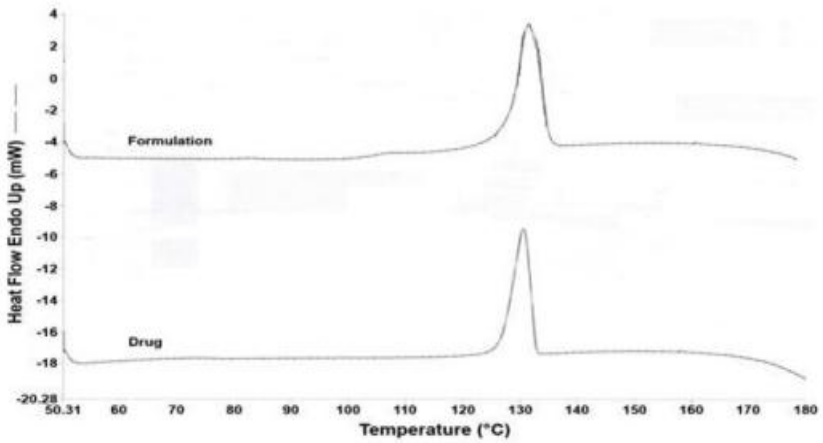

Figure 1: DSC Thermograms of pure drug and the formulation.

Drug loading and encapsulation efficiency

The test for drug content was carried out to ascertain uniform distribution of the drug in the formulation. Drug loading and entrapment efficiency increase with increase in the polymer concentration. From the results it can be inferred that there is a proper distribution of Cyclophosphamide in the microparticles and the deviation is within the acceptable limits. The decrease in the drug content in the product probably can be due to the loss of drug with the evaporation of the solvent.

Table 2: Drug loading and encapsulation efficiency of prepared microparticles.

Formulation	%Drug loading mean ± SD*	Encapsulation efficiency (%)
CA1	41.21 ± 0.36	71.10 ±0.26
CA2	39.42 ± 0.57	72.32 ± 0.33
CB1	41.32 ± 0.56	81.33 ± 1.05
CB2	37.50 ± 0.44	73.45 ± 0.33
CC1	45.23 ± 0.36	89.66 ± 0.56
CC2	40.21 ± 0.26	65.25 ±0.32
CC3	36.35 ± 0.33	69.20 ± 0.44
CC4	39.72 ± 0.42	76.40 ± 0.66
CD1	36.70 ± 0.38	70.70 ± 0.48
CD2	41.60 ± 0.44	84.42 ± 0.67
CE1	48.23 ± 0.36	90.66 ± 0.56
CE2	38.35 ± 0.33	79.20 ± 0.44

In- vitro drug dissolution

Release of Cyclophosphamide was determined using dissolution test apparatus USP type II at 100 rpm. The dissolution was studied using 900 ml of 0.1 N HCl, phosphate buffer 5.5, phosphate buffer pH 7.2. The temperature was maintained at 37±0.5°C. The sample were withdrawn at different time intervals 1,2,3,4,6,8,10 and 12hrs filtered through whatman filter paper and replaced equal volume of dissolution medium. Sample was suitably diluted and analyzed for Cyclophosphamide using UV-visible spectrophotometer. The percentage of Cyclophosphamide release was calculated.

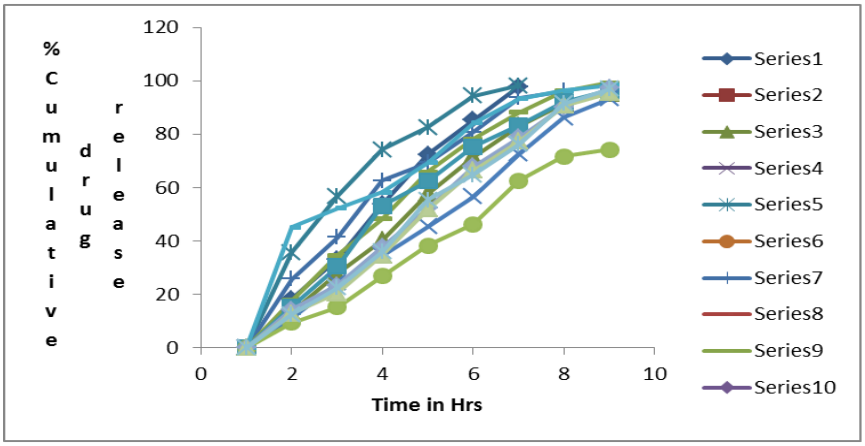

Figure 2: *In-vitro* drug release profile of the formulations.

CONCLUSION

The objective of this study was to prepare and evaluate microparticles loaded with Cyclophosphamide for controlled release using different ratios of drug to polymers and prepared microparticles were characterized. The method is simple, rapid, and economical and does not imply the use of toxic organic solvents. The method used was suitable for both water-soluble and insoluble drugs. The formulation (FD1) produced discrete spherical microparticles. The DSC thermogram obtained for the pure drug and formulation shows no significant shift in the endothermic peaks confirming the stability of the drug in the formulation.

From the results of drug loading and encapsulation efficiency, it can be inferred that there was a proper and uniform distribution of drug in the micro particles. The *in vitro* drug release data showed the release of a drug in a controlled manner.

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