Section A-Research Paper
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Preparation and Evaluation of Ifosphamide Loaded Microsponges for Treatment of Cancer

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Abstract:

Ifosphamide has a wide anticancer activity. The activity of Ifosphamide can be improved and its toxicity can be lowered by enhancing the relative specific accumulation in the tumor regions. The aim of this work was to develop Eudragit RS100 based Ifospphamide microsponges(MS). Oil in oil emulsion solvent diffusion method was used for the preparation of Ifosphamide sustained release Eudragit RS100 MS. MS were characterized for their encapsulation efficiency, production yield and drug polymer interaction, PXRD and Particle size visualized by scanning electron microscope (SEM). The results showed that all prepared MS were spherical in shape with several pores on their surfaces. The production yield was in 84±0.14. Entrapment efficiency was in 85% and particle size was (1 µm ± 0.03 µm and 5µm ± 0.21 µm). Fourier transform infrared revealed that there is no chemical interaction between Ifosphamide and Eudragit RS100. The results demonstrated that ifosphamide with Eudragit RS100 was successfully formulated.

Keywords: Ifospphamide microsponges, Eudragit RS100, scanning electron microscope.

Introduction:

Now a days to control the release rate of active pharmaceutical ingredient is the most challenging task in the pharmaceutical industry. So researcher concentrated on scheming different controlled release drug delivery systems to ameliorate efficacy and patient adherence.(1-2).

Ifosphamide is an oxazophosphorine alkylating agent. Its activation in the liver, Ifosfamide interferes with DNA through formation of phosphotriesters and DNA-DNA crosslinks, thereby inhibiting protein synthesis and DNA synthesis. Ifosfamide is cell cycle-specific, but cell cycle phase non-specific. Ifosfamide is an immunosuppressive agent. (3,4) Its oral absorbtion is 90-100% with time to peak is 1 hour.(5) Ifosphamide is activated by hepatic metabolism.

Microsponge Delivery System (MDS) is a special technology for controlled delivery of drug. MDS technique, a Microsponge delivery system is patented, highly cross-linked, porous, polymeric microspheres polymeric system composed of porous microspheresthat can capture wide range of actives and then release them into the site. (6-7).

Materials And Methods:

Materials

The drug Ifosphamide was obtained as gift sample from Neon Pharma, Mumbai. All other chemicals that were used in the experiment were of the analytical grade.

Methods

1) Determination of wavelength maxima (λmax) of Ifosphamide:

Determination of wavelength maxima (λmax) was done for Ifosphamide by UV Spectroscopy. A validated UV spectroscopy was acquire to quantify Ifosphamide content in the microsponges at a maximum wavelength of 240 nm. Initially, a stock solution (100 µg/ml) of Ifosphamide was prepared in ethanol. By using value of absorbance at absorption maxima, plotted a calibration curve using a series of standard solutions of Ifosphamide within the range of 2-10 µg/ml. A linear regression was applied to obtain linear equation (y = 0.1019x - 0.0386) with R^2 value of 0.9992. The inter- and intra-day variations were also checked.

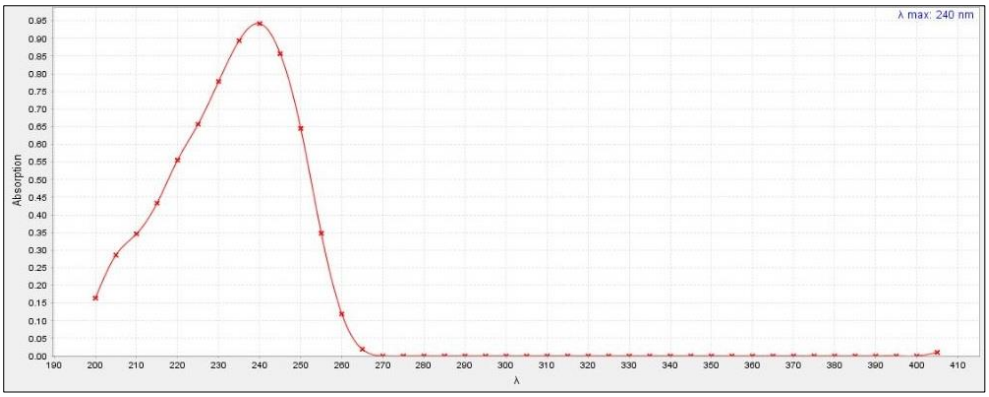

Figure 1: Wavelength Maxima of Ifosphamide (Absorption maxima 240 nm)

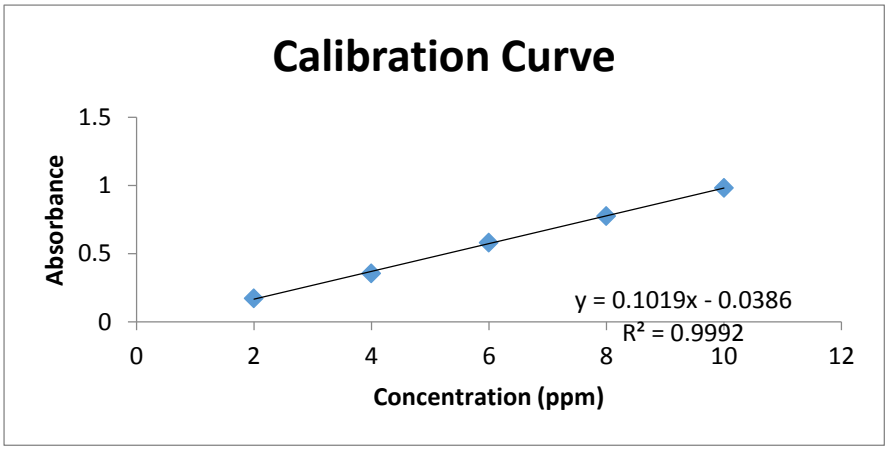

Figure 2: Calibration Curve of Ifosphamide

2) Fourier Transform Infra-Red Spectroscopy (FT-IR):

FT-IR spectra of Ifosphamide were recorded over wavelength range of 4000–500 cm^{-1} using an FT-IR spectrometer (Carry 630).

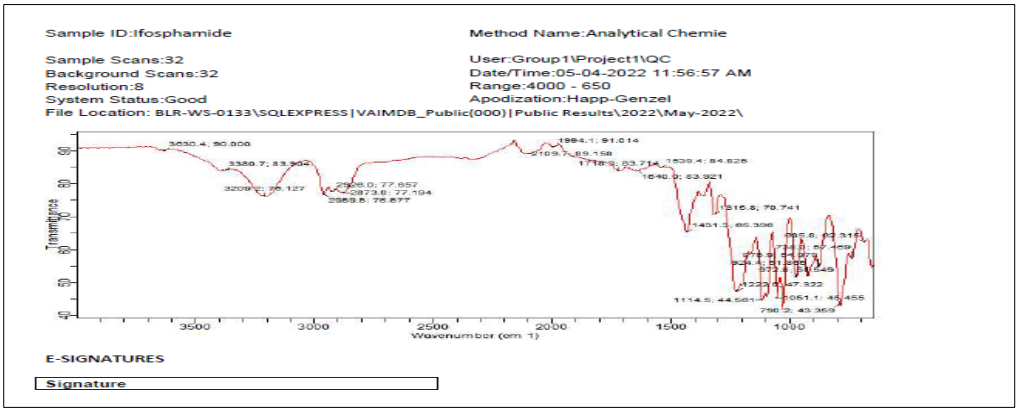

Figure 3: FTIR Spectra of Ifosphamide

Method of Preparation of Ifosphamide Sponges (8-11)

Ifosphamide loaded microsponges were prepared using oil in oil emulsion solvent diffusion technique. Eudragit RS 100 was dissolved in acetone, once a clear solution was obtained, 500 mg of Ifosphamide was added in addition to magnesium stearate (3% w/v solvent) and the whole mixture was kept in the ultrasonic bath for 5 minutes to obtain homogenous dispersion. Then the mixture was poured into 150 ml of liquid paraffin formerly cooled to 10°C ± 0.5°C while the use of mechanical stirrer for 45 minutes. The oil in oil emulsion formed was progressively warmed to 35°C ± 5°C and was stirred at this temperature for another 30 minutes. During this period of time, the acetone was entirely removed by diffusion into liquid paraffin and evaporated through the air/liquid interface. The solidified microsponges were purified, washed five times with 60 ml of n-hexane, dried at room temperature for 12 hours and stored in a desiccator for further Investigations.

Table 1 Composition of Microsponges

Formulation	Drug (mg)	Eudragit RS 100 (mg)
F1	500	500
F2	500	1000
F3	500	250
F4	500	1500
F5	500	166

Optimization :

StatEase 360^0 (Stat Ease Inc., USA), generated the design matrix of factors and optimized the microsponge particle method preparation. Optimization of the process depends on properly identifying controlling variables (factors). The software analysed the effects and interactions of factors against each independent variable/response and suggested the best-fit summary through response surface methodology (12). All the responses (yield, particle size, and %EE) are correlated with the factors and presented (figure 4 and 5). P Value was found to be less than 0.005, which is significant.

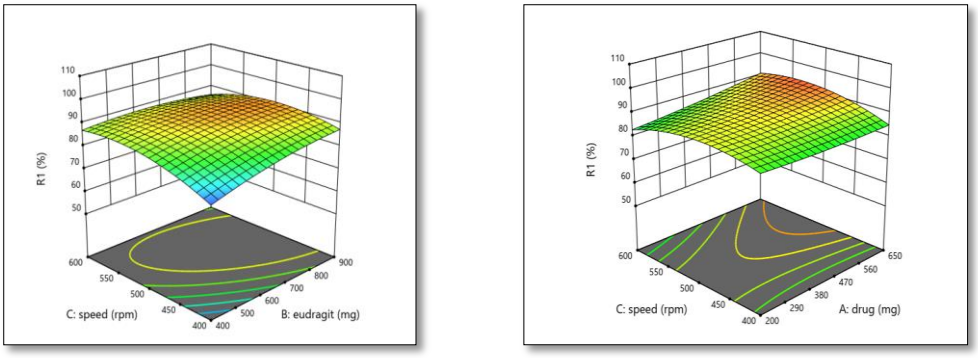

Figure 4: Three dimension plot for response 1(Stirring Speed vs Polymer and Stirring Speed vs Drug)

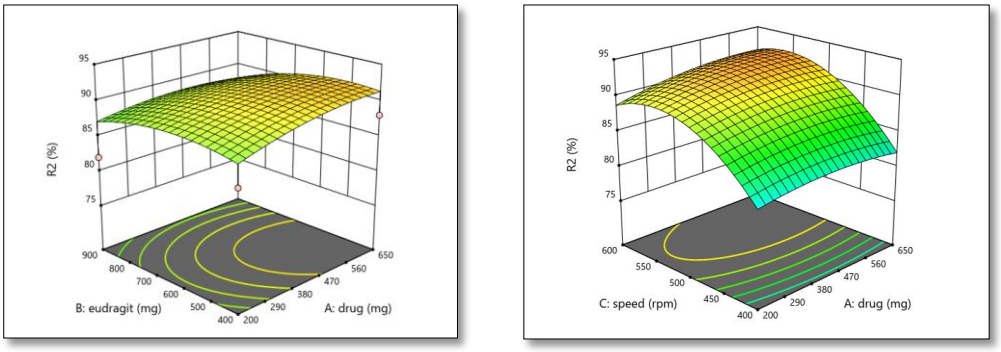

Figure 5: Three dimension plot for response 2 (Drug Vs Polymer and Stirring Speed Vs Drug)

Characterisation of Microsponges

Production Yield

The production yield for all microsponge formulations was calculated gravimetrically using the following equation,

Production yield (%) = weight of formulated sponge x 100 / weight of polymers and API

Production yield was reported with standard deviation values.

Table 1: Production Yield

Formulation	Production Yield (%)
F1	74 ±0.30

F2	77±0.18
F3	84±0.14
F4	69±0.34
F5	54±0.34

Drug entrapment efficiency

Entrapment efficiency is measured by weighing 10 mg quantity of loaded sponges and mix with 50ml of ethyl alcohol. For extraction of drug it is kept on vortex mixer.for separation of residue it is centrifugated at 2000 rpm. The supernatant layer was separated and taken for UV analysis. The result were noted with value of standard deviation.

Table 2: Drug entrapment efficiency

Formulation	Entrapment Efficiency
F1	69 ± 0.31
F2	72 ± 0.21
F3	85 ± 0.24
F4	71 ± 0.19
F5	74 ± 0.12

X-ray diffraction (XRD)

X-ray diffraction patterns were recorded using X-ray diffraction system (PXRD). The equipment use for XRD is Rigaku model no: smart lab cu.15. KV. Made in Japan.

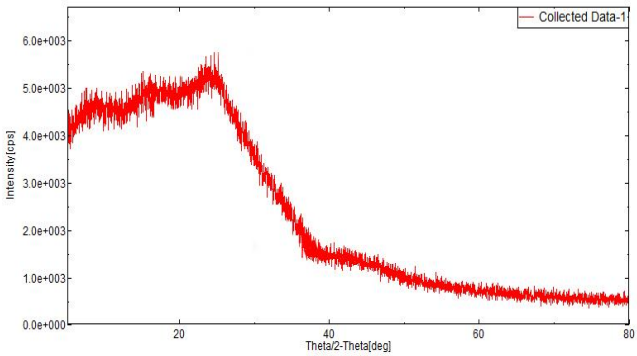

Figure 6 : XRD Spectra of Iphosfamide Sponges.

Fourier Transform Infra-Red Spectroscopy (FT-IR):

FT-IR spectra of Ifosphamide and ethyl cellulose physical mixture were recorded over wavelength range of 4000–500 cm−1 using an FT-IR spectrometer (Carry 650).

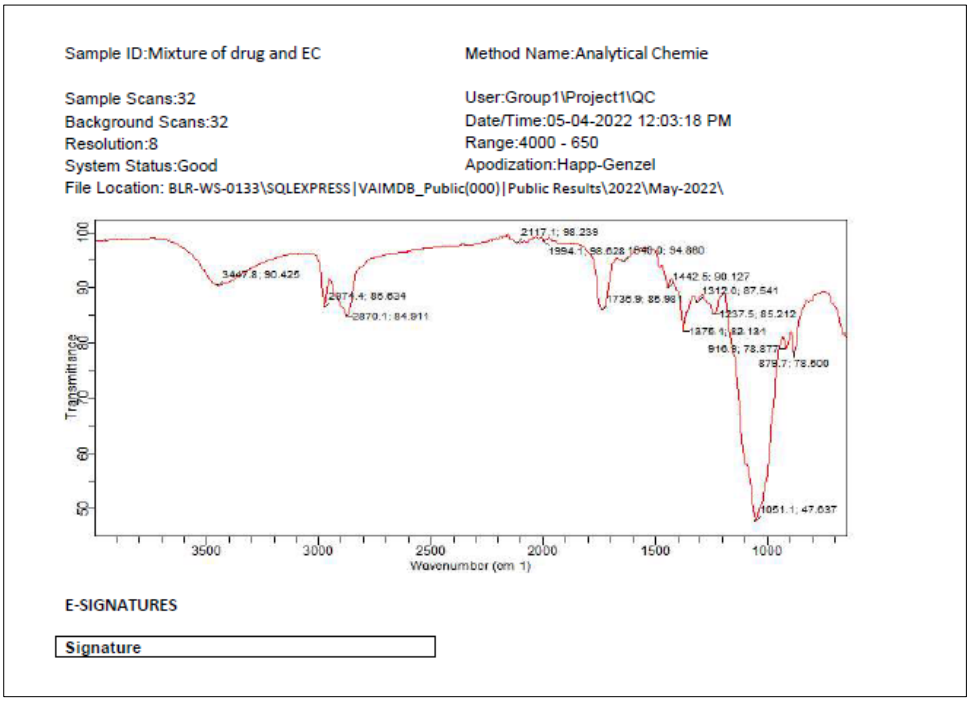

Figure 7 : Ifosphamide Microsponges

Scanning electron microscopy (SEM)

Microsonges were evaluated for morphology by a Carl Zeiss model Supra 55 scanning electron microscopy (Germany). Samples were attached to stub by using conductive carbon tape. Fix the stub properly to sample holder. Samples were carefully prepared to ensure particles are not crushed.

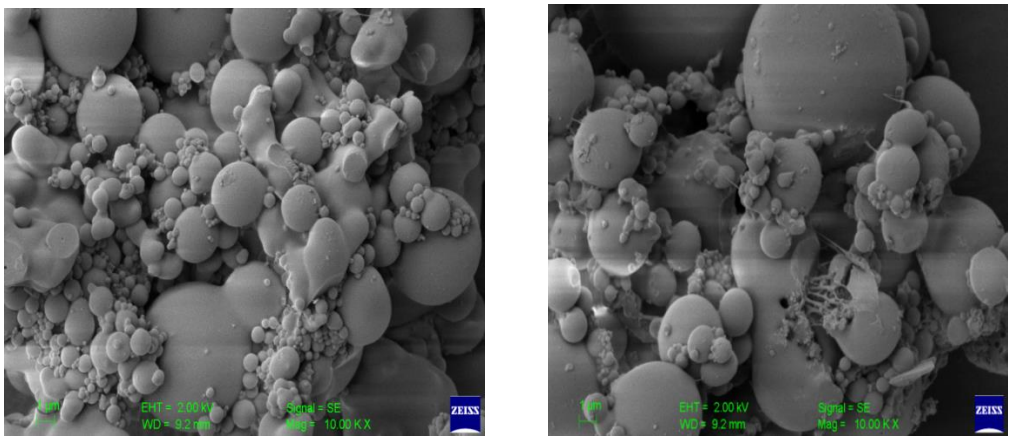

Figure 8: SEM Images of Ifosphamide

Result and Discussion:

Ifosphamide microsponges were prepared using oil in oil emulsion solvent diffusion technique. Microsponges are spontaneously prepared when internal phase (polymeric phase) is introduced in the external phase (paraffin solution) under constant stirring with mechanical stirring. This process involves evaporation of organic solvent, thus allowing the polymeric blend to form a spherical porous particles engulfing drug molecules.

Different microsponge formulations F1 to F5 are studied for entrapment efficacy and production yield is summarised in table 3.

Table 3: Production yields and high entrapment efficiency

Formulation	Theoretical drug contents (mg)	Entrapment efficiency (%)	Production Yield (%)
F1	500	69	74
F2	500	72	77
F3	500	85	84
F4	500	71	69
F5	500	74	54

The microsponges were prepared by oil in oil emulsion solvent diffusion technique. Various characterizations that were carried out include entrapment efficiency, percentage yield, particle size determination. SEM images indicates hollow particles for all formulation. Surface resembled core shell particles as per the SEM image. FTIR spectroscopy indicate no possible interaction between Ifosphamide and polymers in microsponges. PXRD specra indicate that the prepared microsponge is amorphous in nature. 2ɵ value indicate drug is stable in throughout process. Statistical analyses of batches and surface response studies were done to understand the effect of various independent variables on the dependent variables.

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