ABSTRACT SUMMARY: The purpose of this work is to prepare donepezil microspheres (DM) and evaluate its advantage as a sustained release delivery system administered as intramuscular injection. DM was prepared using poly (D,L-lactide-co-glycolide) (PLGA) by an oil-in-oil emulsion solvent evaporation technique. DM showed the loading of 24.88% (w/w) and yield 85% with mean particle size about 32.39 µm. In vitro release of DM showed that initially the release was slow, however after 6th day it followed zero order kinetics upto 14th day with 90% release for the optimized batch in Phosphate Buffer Saline (pH 7.4). These results implicated that DM as a sustained release delivery strategy could substitute for its oral formulation for therapy of AD.

INTRODUCTION: Donepezil Hydrochloride is a reversible and non-competitive cholinesterase inhibitor used to treat symptoms of mild to moderately severe Alzheimer’s disease. Microparticles based on biodegradable polymer have been extensively investigated as controlled release delivery system over the past three decades. Particles composed of poly (lactide-co-glycolide) (PLGA) have been used in various fields in life sciences, such as biomedicine, bioscience, biomaterial, and drug delivery systems (DDS).

EXPERIMENTAL METHODS: Preparation of microspheres: PLGA microspheres were prepared using oil-in-oil emulsification solvent evaporation technique. Briefly, suitable amount of polymer was dissolved in organic phase and sonicated. Drug was dissolved in polymer solution and sonicated (Phase 1). Phase 1 was injected into Phase 2 (Liquid paraffin and surfactant) under constant stirring. The emulsion was stirred under overhead stirrer until organic phase was evaporated. Microspheres were filtered and washed with n-Hexane to remove oil & surfactant. Microspheres were dried for 2-3 h under vacuum desiccator.

Optimization: Various parameters such as drug: polymer ratio and internal to external phase ratio were optimized using $3^2$ Factorial design with respect to % yield, particle size and % encapsulation efficiency. Effect of drug: polymer ratio on % Total drug content was studied. Also, the effect of % Surfactant concentration on % Encapsulation efficiency was studied.

Characterization:

1) Appearance and % Yield
2) Particle size and SEM: The particle size was determined using Optical microscopy. Morphology and microstructure of the selected formulations were studied using Scanning Electron Microscopy.
3) % Total Drug Content and % Encapsulation efficiency: The loading efficiency of drug in each formulation was determined spectrophotometrically.
4) DSC: Differential Scanning Calorimetry was performed to confirm drug encapsulation within the polymer matrix.
5) In-vitro release: In-vitro release kinetics was carried out using Water Bath Shaker at 37°C in Phosphate Buffer Saline pH 7.4.

RESULTS AND DISCUSSION:
Donepezil microspheres were found to be spherical in shape when observed under optical microscope. It was observed that drug loading was highest when drug: polymer ratio was 1:10 (Fig.1). 3-D Response plot of Drug: Polymer ratio and Int: Ext phase revealed that % encapsulation efficiency was highest when internal: external phase ratio was 1: 8.33 and drug: polymer ratio was 1:10 and 1: 12 (Fig.3C), % yield was highest when internal: external phase ratio was 1:16.66 and drug: polymer ratio was 1:10 (Fig.3A) while no significant effect was observed on particle size (Fig.3B). % surfactant conc was optimized and it was found
that % encapsulation efficiency was highest at 1 % concentration (Fig.2). Drug encapsulation within the polymer matrix was confirmed by DSC thermogram with absence of sharp drug peak in the formulated batch. SEM image revealed spherical smooth particles. From the in-vitro release study, it was found that initially up to fifth day the drug release was slow, however after 6th day it followed zero order kinetics up to 14th day with 90% release of DM (Fig.6).

CONCLUSION: Drug loaded PLGA Microspheres have been successfully formulated with sustained drug release over 15 days. Various product and process parameter have optimised using 3² Factorial designs to obtain high encapsulation efficiency and desired particle size. Thus, in conclusion long acting sustained release depot formulation has been developed to improve drug delivery, reduce dosing frequency and thus improved patient compliance in Alzheimer’s disease.

REFERENCES:

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