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DEVELOPMENT AND CHARACTERIZATION OF DONEPEZIL MICROSPHERES BY USING IONOTROPIC GELATION TECHNIQUE

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ABSTRACT
Donepezil used to treatment of hypertention. Development the controlled release Donepezil microspheres using polymers in various formulations. These microspheres developed by utilizing the ionotropic gelationmethod. This makes Donepezil a better candidate for the formulate of CR dosage forms.The formulated were examined by release rate of the drug and further perform the stability data for selected or optimized formulation. The work was aimed to develop the controlled release Donepezil microspheres.

KEYWORDS: Donepezil, Ionotropic gelation, natural and synthetic polymers, microspheres, Franz diffusion cell, zero order kinetics.

1. INTRODUCTION
Microspheres are solid spherical particles ranging in size from 1-1000µm. They are spherical free flowing particles consisting of proteins or synthetic polymers. The microspheres are free flowing powders consisting of proteins or synthetic polymers, which are biodegradable in nature.[1] Microencapsulation is well known method to delay and modify drug release characteristics. For oral use, it has been employed to sustain the drug release and to reduce or eliminate gastrointestinal tract irritation.[2] It is a process of enclosing micron size particles of solid or liquid or gases in an inert shell resulting in the formation of microparticles or microcapsules or microspheres.[3] As multiparticulate drug delivery lead to wide and uniform distribution throughout GIT, a localized high concentration at a specific point may be avoided. In addition, multiparticulate delivery systems spread out more uniformly in the gastrointestinal tract. This results in more reproducible drug absorption and reduces local irritation when compared to single unit dosage form such as non disintegrating polymeric matrix tablets.[4] Donepezil Hydrochloride is a reversible and non-competitive cholinesterase inhibitor used to treat symptoms of mild to moderately severe Alzhiemer's disease.[5] The purpose of this study to prepare polymeric microsphere containing Donepezil by using Ionotropic gelation technique. The biocompatible polymers were use for the formulation of microsphere.

2. MATERIAL AND METHODS
2.1 Material
Donepezil was collected as a gift sample from Reddy's laboratories, Hyderabad and Sodium alginate, Xantham gum and eudragit were purchased from AR chemicals, Hyderabad.

2.2 METHODODOLOGY[6,7,8]
Drug excipient compatibility studies
Drug excipients compatibility studies were performed to know the compatibility of excipient with drug at accelerated conditions. The study was conducted by preparing homogenous mixture of excipients with drug and filled in HDPE bags and LDPE bags. Glass vials were exposed to 600 C and 400C/75 %RH for 4 weeks and LDPE bags were exposed to 400C±75 %RH for 4 weeks. Samples were observed periodically for any physical change.

Preparation and characterization of Donepezil microparticles

Formulation table

Table 1: Formulation development.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Drug	10	10	10	10	10	10	10	10
Sodium alginate	100	-	-	-	50	-	50	-
Xantham gum		100	-	-	50	-	-	50
HPMC			100	-	-	50	50	-
Eudradit	-	-		100	-	50	-	50
Methanol	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml
Cacl $_2$	5%	5%	5%	5%	5%	5%	5%	5%

Microspheres were prepared by using different ratios of Donepezil, sodium alginate, xanthan gum and eudragit. Sodium alginate was dissolved in deionized water to form a homogeneous solution (2% w/v). Sodium alginate and xanthan gum were dissolved separately with deionized water to get viscous and sticky solutions. The pure drug was dispersed in the solution of gum and then sodium alginate solution was added to it with vigorous stirring until formation of an even dispersion. The resulting dispersion was then extruded drop wise into the 100 ml calcium chloride solution (10% w/v) through a 23G syringe. The formed spheres were retained in the calcium chloride solution for 15 minutes to complete the formation of spherical rigid microspheres. They were collected by decantation, washed and dried at room temperature and subsequently stored in desiccators. Same procedures were repeated for all batches of formulation.

Characterization of Microspheres[9,10,11,12]

The prepared microparticles were characterized for various parameters such as surface morphology of microspheres, drug entrapment efficiency, release rate of the drug and the result of different preparation and process variables such as drug to polymer ratio, type of polymer, speed, and compound of polymers were examined.

A. Yield of sustained microspheres

The Donepezil microparticles was calculated from the required amount of microspheres obtained divided by the total amount of all non-volatile components.

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

B. Particle size

Microspheres of particle was measured by optical microscopy. The eyepiece micrometer was calibrated using a stage micrometer. The microparticles were spread over a slide and imagine under an optical microscope using an eyepiece micrometer.

C. Surface morphology of the sustained release microspheres

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

D. Drug entrapment efficiency (DEE)

The required amount of drug entrapped was estimated by crushing 50 mg of Donepezil microspheres by using mortar and pestle. This microspheres powder sample was poured in to a 100 ml volumetric flask and add the 6.8 phosphate buffer. After that the solution was taken in to a beaker and sonicated in a bath sonicator for 2 hours. The solution was filtered and absorbance was measured after suitable dilutions spectrophotometrically at 268 nm against blank.

Formula

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

E. 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 Donepezil 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 analysed for the drug content spectrophotometrically using UV-Visible spectrophotometer (Lab India) at 262 nm against an appropriate blank. Three 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 release. The results are presented in tables and figures.

F. Mechanism of drug release

The obtained dissolution data was fitted into various kinetic models to understand the pattern of the drug release from sustained microspheres. The models used were zero order (equation 1) First order (equation 2) and Higuchi model (equation 3) and Koresmeyer Peppas model (equation 4).

i) zero order release kinetics

$R = K_o t$ -- (1)

R=cumulative percent drug release

Ko=zero order rate constant

ii) First order release kinetics

$\log C = \log C_o - K_1 t / 2.303$ -- (2)

where C = cumulative percent drug release

K_1 = first order rate constant

iii) Higuchi model

$R = K_H\ t^{0.5}$ -- (3)

Where R = cumulative percent drug release

K_H = higuchi model rate constant

iv) korsermeyer peppas model

$M\ t / M\ \alpha = K_k\ t^n$

$\log M\ t / M\ \alpha = \log K_k + n \log t$ -- (4)

where K_k = korsermeyer peppas rate constant

'M t / M α' is the fractional drug release, n = diffusional exponent, which characterizes the mechanism of drug release (Simon Benita, 2007).

Diffusional exponent (n)		Drug release mechanism
0.43	--	Fickian diffusion
0.43- 0.85	--	Anamolous (non- fickian) transport
0.85- 1	--	Case II transport
> 1	--	Supercase II transport

The obtained regression co-efficient (which neared 0.999) was used to understand the release pattern of the drug from the sustained release microspheres.

G. Stability studies

The optimised formulation was stored in a stability chamber at 40 ± 2^0c temperature and 75% ± 5% relative humidity. Samples were analysed at 3 months for drug loading and drug encapsulation.

3. RESULTS AND DISCUSSION

Drug and Excipient compatibility studies (FT-IR)

The compatibility between the drug and the selected lipid and other excipients was evaluated using FTIR peak matching method.

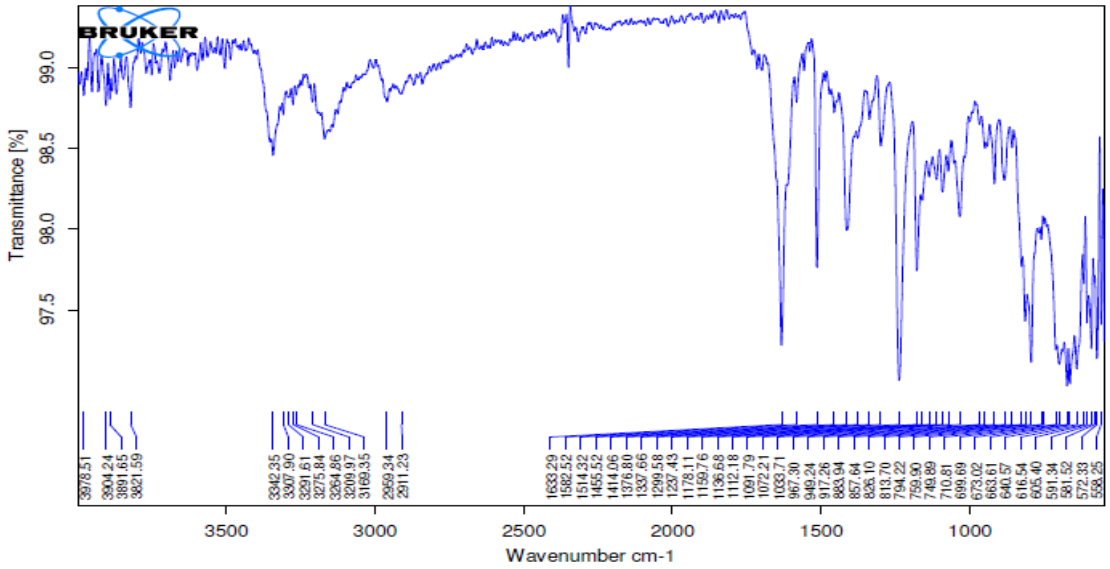

Fig. 1: FTIR spectra data for Donepezil.

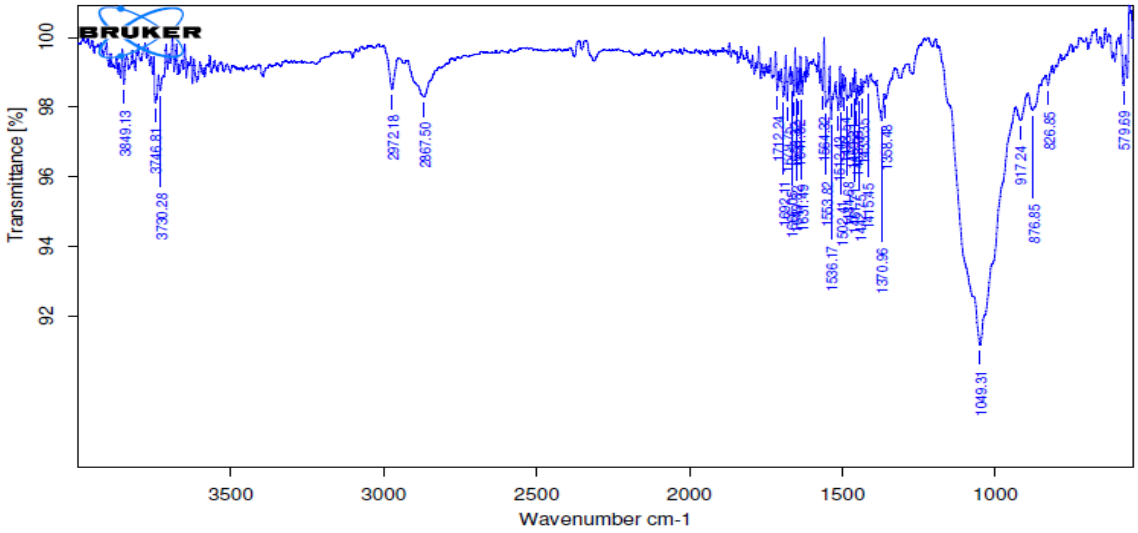

Fig. 2: FTIR Studies of optimized formulation.

Characterization of Donepezil microspheres

The formulated Donepezil microparticles were examined for different parameterss. 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 Donepezil from sustained microspheres were also studied.

Table 2: Effect of drug polymer ratio on Yield of microspheres, Particle size, Drug entrapment efficiency.

Formulation code	%yield	Particle size	Drug Entrapment Efficiency
F1	75.23	86.90	83.16
F2	78.21	84.21	89.23
F3	71.67	86.75	92.78
F4	74.15	87.25	88.93
F5	76.45	87.28	78.99
F6	77.50	83.15	89.74
F7	79.82	79.03	93.15
F8	81.23	82.10	91.45

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 unentrapped drug in dispersion medium.

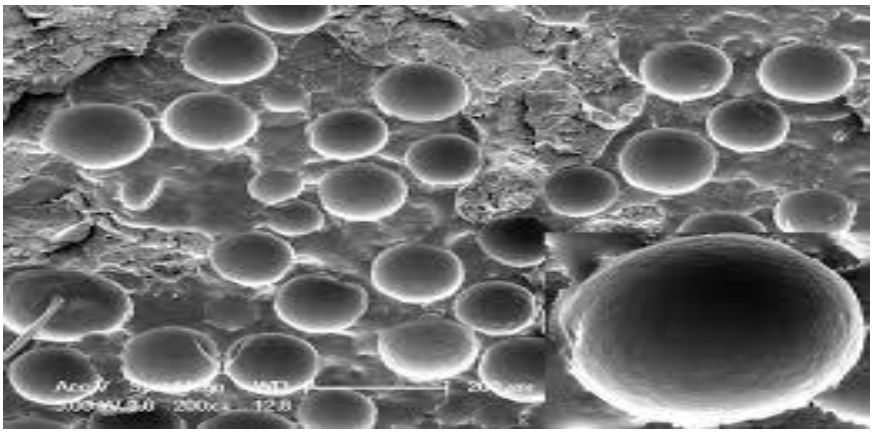

Fig. 3: SEM analysis of Microsphere.

Table 3: Drug release studies of all formulations.

TIME (hours)	F1	F 2	F3	F4	F5	F6	F7	F8
0	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
1	28.45	25.89	27.44	24.22	24.12	22.99	27.85	25.12
2	36.18	33.78	33.85	35.10	35.10	35.10	36.85	33.45
3	48.56	49.58	45.85	41.55	41.85	45.89	49.88	48.91
4	53.12	52.99	53.78	53.55	52.32	52.90	58.12	53.124
5	65.12	68.88	65.64	61.14	60.75	63.75	66.64	65.12
6	70.36	78.75	75.71	74.61	71.54	76.90	71.63	70.97
7	81.86	86.71	82.99	84.81	80.12	85.06	88.96	87.14
8	90.56	91.58	93.65	95.61	93.61	92.85	98.65	97.77

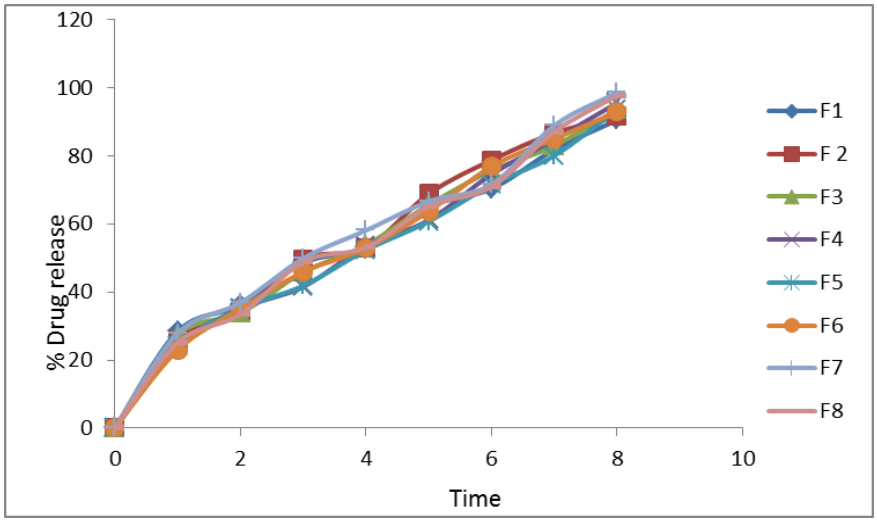

Fig. 4: Comparative Dissolution profile of F1-F8.

Release kinetics

The mechanism of Donepezil release from microspheres was studied by fitting the data obtained from *in-vitro* release studies into zero-order, first-order, Higuchi's, korsermeyer peppas kinetic models.

On application of different release kinetic models mentioned earlier, it was found that optimized formulations showed better fitting with the zero-order release and korsermeyer peppas model.

Zero order kinetics

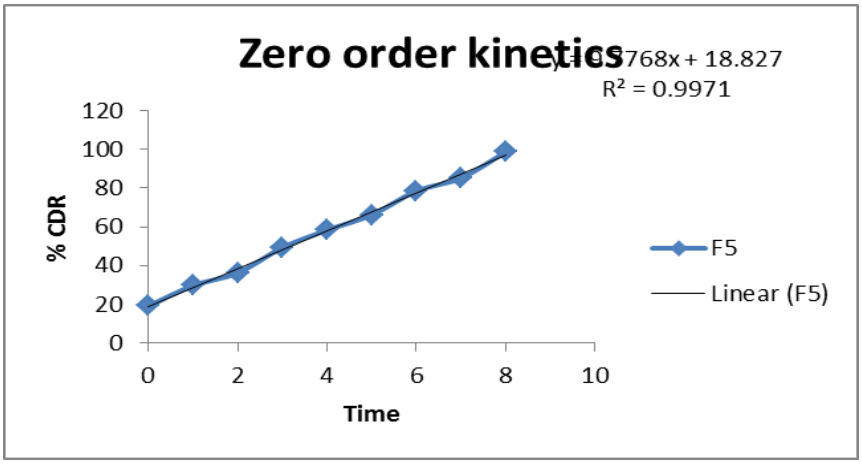

Fig. 5: Zero order plot for optimized formula.

First order kinetics

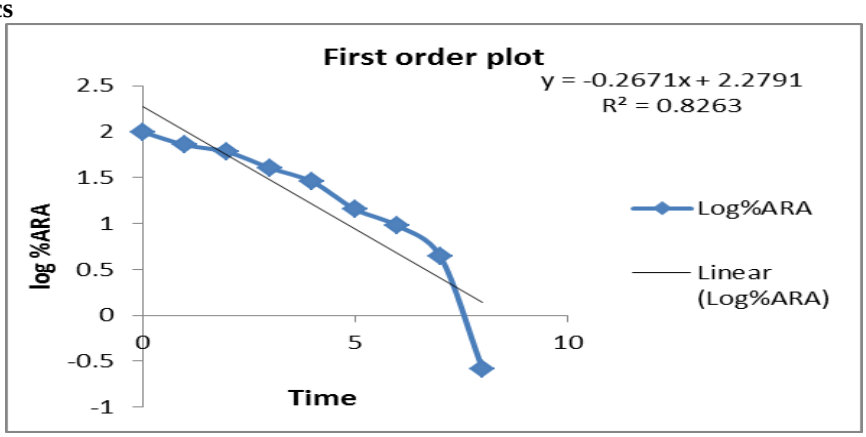

Fig. 6: First order for optimized formula.

Higuchi model

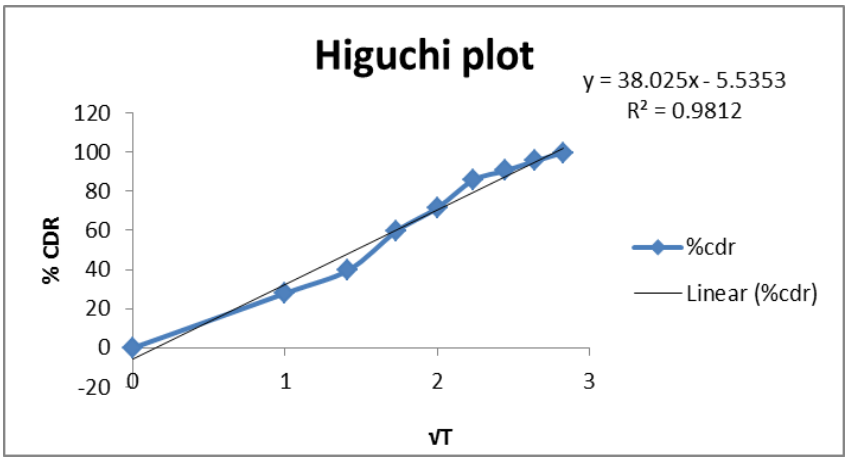

Fig. 7: Higuchi plot for optimized formula.

Kross mayer peppas

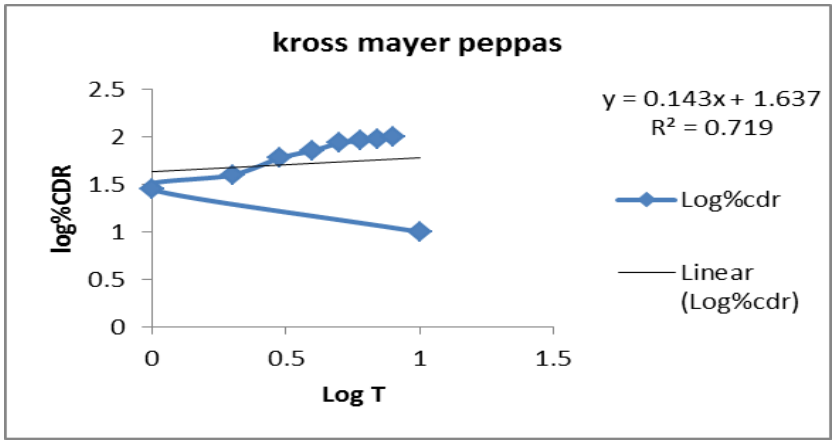

Fig. 8: Korsmayer peppas plot for optimized formula.

The drug release from the donepezil microspheres was found to follow Zero order release based on the "r" value obtained for Zero order (0.997) and first order (0.826) for F5 formulation. Also, the drug release mechanism was found to be "Diffusion" based on the "r" value of 0.981 obtained for Higuchi's plot. Similarly, the drug release mechanism was found to be of Anomalous diffusion mechanism based on the "n" value of 0.719 obtained for Peppa's equation.

Table 4: Drug release kinetics.

S.no	Kinetic model	R^2 value
1	Zero order kinetics	0.997
2	First order kinetics	0.826
3	Higuchi model	0.981
4	Krossmayer peppas	0.719

Stability studies

Optimized formulations F7 was selected for accelerated stability studies as per ICH guidelines. The patches were observed for color, appearance and flexibility for a period of three months. The folding endurance, weight, drug content, % cumulative drug release of the formulation was found to be decreasing. This decrease may be attributed to the harsh environment (40^0C) maintained during the studies. The results are tabulated in table 25.

Table 5: Stability studies of optimized formulations at 40 ± 2 ^{0}C and 75 ± 5% RH for 3 months.

Formulation Code	Initial	1st Month	2nd Month	3rd Month
F7	98.65	98.66	98.70	98.74
F7	98.65	98.70	98.71	98.75
F7	98.65	98.75	98.78	98.80

Table-: Stability study of Optimized Formulation.

4. CONCLUSION

The research study was to prevent extensive metabolism of the drug and consequently to enhance the bioavailability of the drug. It is from the Donepezil microparticles. These Donepezil particles are used to treatment of Alzheimers. The Donepezil microparticles were prepared by ionotropic gelation method using synthetic polymer such as natural and synthetic polymers. These polymer as retarding polymers and evaluated for parameters like particle size, drug loading. Microspheres morphology was evaluated by SEM.

The yield and entrapment efficiency was high for Sodium alginate microspheres were Particle size, entrapment efficiency and production yield were affect by the type of polymer, polymer concentration, stirring speed and combination of polymers. *In vitro* dissolution of optimized formulations of various Polymer in pH 6.8 formulations are releasing the drug up to 8 hrs.

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